



Title: A 2-Part, Randomized, Double-Blind and Open-Label, Placebo and Active-Comparator Controlled Trial to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics for TAK-906 in Subjects With Diabetes Mellitus and Gastroparesis or With Idiopathic Gastroparesis

NCT Number: NCT03268941

Protocol Approve Date: 14 December 2017

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## **TAKEDA PHARMACEUTICALS**

### **PROTOCOL**

**TAK-906-1002: A 2-Part, Randomized, Double-Blind and Open-Label, Placebo and Active-Comparator Controlled Trial to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics for TAK-906 in Subjects With Diabetes Mellitus and Gastroparesis or With Idiopathic Gastroparesis**

**Study Identifier:** TAK-906-1002

**Compound:** TAK-906 maleate

**Version/Amendment Number:** 04 **Date:** 14 December 2017

#### **Amendment History:**

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## 1.0 TRIAL SUMMARY

<b>Name of Sponsor:</b> Millennium Pharmaceuticals, Inc. (Takeda Global Research and Development –United States)	<b>Compound:</b> TAK-906 maleate
<b>Study Identifier:</b> TAK-906-1002	<b>Phase:</b> 2a
<b>Protocol Title:</b> TAK-906-1002: A 2-Part, Randomized, Double-Blind and Open-Label, Placebo and Active-Comparator Controlled Trial to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics for TAK-906 in Subjects With Diabetes Mellitus and Gastroparesis or With Idiopathic Gastroparesis	
<p><b>Trial Design:</b></p> <p>This is a randomized, double blind and open-label, placebo and active-comparator controlled trial to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) for TAK-906 in subjects with diabetes mellitus and gastroparesis (DG), or idiopathic gastroparesis (IG). The trial will consist of 2 parts and is designed to allow all enrolled subjects to participate in each part of the study, at the discretion of the investigator. Subjects may decline participation at any time during the study.</p> <p>In Part 1, approximately 48 subjects will be randomized into 1 of 3 active treatment arms (ie, orally [PO] TAK-906 maleate 5 mg twice daily [BID], 25 mg BID or 100 mg BID) or a matching placebo BID arm in a double-dummy manner for 9 consecutive days, for a total of 17 doses (ie, BID Days 1 to 8 and morning dose on Day 9). All trial drug dosing will be under fasted conditions. Gastrointestinal (GI) emptying will be evaluated following a test meal using a <sup>13</sup>C-Spirulina gastric emptying breath test (GEBT), and GI emptying and motility will also be evaluated using SmartPill technology. Blood samples for assessment of TAK-906 concentrations will be collected at scheduled time points from predose on Day 1 to 48 hours after Day 7 dose. Blood samples for assessment of prolactin concentrations in serum will be collected at Screening and scheduled time points from Day -2 to 48 hours after Day 7 dose. Subject randomization will be stratified by the underlying condition, ie, DG versus IG.</p> <p>Approximately 18 subjects who completed Part 1 of the study (and following a minimum 7-day washout from the last dose in Part 1) will be enrolled into Part 2 of the study. At the discretion of the investigator approximately 6 subjects will receive TAK-906 maleate 25 mg with and without food in an open-label crossover design over 2 periods (ie, fed, fasted). Blood samples for assessment of TAK 906 concentrations will be collected from predose to 48 hours after each dose of TAK-906 maleate. Furthermore, up to an additional 12 subjects who completed Part 1 of the study will be enrolled at the discretion of the investigator to participate in the evaluation of TAK-906 vs active comparator metoclopramide to confirm the responsiveness of the GEBT test. Subject will be blinded to treatment until all subjects have completed Part 1. Blood samples for assessment of TAK-906 or metoclopramide concentrations will be collected at scheduled time points from predose on Day 1 to 48 hours postdose.</p> <p>Key safety and tolerability will be assessed during Parts 1 and 2 through physical examinations, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory assessments, as well as collection of serious and nonserious adverse events (AEs).</p> <p>After completion of the trial (or following subject withdrawal), all subjects will return for a Follow-up Visit 10 to 14 days after their last dose of study medication.</p>	
<p><b>Trial Primary Objective:</b></p> <ul style="list-style-type: none"> <li>To evaluate safety and tolerability of TAK-906 in subjects with gastroparesis (GP).</li> </ul> <p><b>Trial Secondary Objectives:</b></p> <ul style="list-style-type: none"> <li>To assess the prolactin PK/PD relationship in subjects with GP.</li> <li>To demonstrate the effect of TAK-906 on GEBT.</li> </ul>	
<b>Trial Subject Population:</b> Male and female subjects aged 18 to 75 years, inclusive, with DG or IG.	

<b>Planned Number of Subjects:</b> Part 1: 48 Part 2: 18	<b>Planned Number of Sites:</b> The study is being conducted at multiple sites in the United States
<b>Dose Levels:</b> <b>Part 1</b> TAK-906 maleate 5 mg BID TAK-906 maleate 25 mg BID TAK-906 maleate 100 mg BID matching placebo BID <b>Part 2:</b> TAK-906 maleate 25 mg once daily (QD) Metoclopramide 10 mg QD	<b>Route of Administration:</b> PO
<b>Duration of Treatment:</b> Part 1: 9 days (ie, Days 1-8 BID; Day 9 QD in am) Part 2: 8 days (single dose fed and fasted with 7-day washout between doses) Part 2: 3 days (metoclopramide)	<b>Planned Trial Duration:</b> Approximately 8 Weeks
<b>Main Criteria for Inclusion:</b> Male and female subjects aged 18 to 75 years, inclusive, diagnosed with documented slow gastric emptying (GE) and a minimum of 3-month history of symptoms consistent with GP, which may include: postprandial fullness or nausea, vomiting, abdominal pain, loss of appetite, and early satiety.	
<b>Main Criteria for Exclusion:</b> The subject must be excluded from participating in the study if the subject: <ol style="list-style-type: none"> <li>Subjects who have a history of clinically significant endocrine (apart from diabetes mellitus), GI (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases will be excluded from the trial.</li> <li>Has acute severe gastroenteritis and pronounced dehydration in the 48 hours prior to Screening, gastric pacemaker, chronic parenteral feeding or persistent severe vomiting.</li> <li>Has a known disturbance of small intestinal absorption, exocrine pancreatic function liver metabolism, and pulmonary function.</li> <li>Has a history of anorexia nervosa or bulimia.</li> <li>Has a history of additional risk factors for Torsade de Pointes (eg, heart failure, hypokalemia, family history of Long QT Syndrome), evidence of cardiac autonomic neuropathy, eg, lack of respiratory rate variation upon deep breathing.</li> <li>Previous history of bezoars (the presence of retained liquid, bile, or small amounts of poorly organized food residue is permitted).</li> <li>Difficulty swallowing solid food or pills.</li> <li>Prior surgery involving the luminal gastrointestinal tract (cholecystectomy, appendectomy, and hysterectomy are permitted if performed &gt;3 months prior to SmartPill test).</li> <li>Any abdominal or pelvic surgery within the past 3 months.</li> <li>Known or history of inflammatory bowel disease.</li> <li>Has active diverticulitis, diverticular stricture, and other intestinal strictures.</li> <li>Lactating or pregnant women as determined by positive serum <math>\beta</math>-human chorionic gonadotropin (hCG) test at Screening and within 24 hours of the first dose.</li> </ol>	



**Main Criteria for Evaluation and Analyses:**

The primary safety endpoint of the study is key safety and tolerability as assessed through physical examinations, vital signs, ECG, and laboratory assessments as well as collection of serious and nonserious AEs. The following secondary endpoints will be assessed through evaluation of the following parameters:

- The change in serum prolactin from Baseline to Day 1 at time of first occurrence of maximum plasma concentration ( $t_{max}$ ) for TAK-906 following administration with TAK-906 maleate vs placebo.
- The change from Baseline to Day 7 in GEBT gastric half-emptying time as measured by the  $^{13}\text{C}$  Spirulina GEBT following a multiple doses of TAK-906 maleate vs placebo.
- The change from Baseline to Day 1 in GEBT gastric half-emptying time as measured by the  $^{13}\text{C}$  Spirulina GEBT following single dose administration of TAK-906 maleate vs placebo.
- The percent change from Baseline to Day 7 in GE time as measured by the SmartPill.
- Pharmacokinetics: Plasma PK parameters for TAK-906 (Part 1).

**Statistical Considerations:**

The primary, secondary, and exploratory endpoints will be analyzed in randomized subjects in Part 1 or enrolled subjects in Part 2 who received at least 1 dose of study drug.

For each of the following, change in prolactin, change in GEBT gastric half-emptying time, change in SmartPill GE time and change in Company Confidential Information

[REDACTED] endpoints, a linear model will be fit; the model will include fixed effects of stratification factor, regimen (dose level), a random effect of subject, and a covariate of baseline value. Pairwise comparisons will be performed within this linear model, with the point estimate and 95% confidence interval (CI) derived.

If there is a significant departure from the assumptions underlying the linear model, nonparametric analyses will be performed. Pairwise comparisons will be made via Wilcoxon Rank Sum tests along with Hodges-Lehmann estimate and 95% CI.

**Sample Size Justification:**

Assuming a standard deviation (SD) of 20% for the percent change from Baseline in GEBT gastric half-emptying time, a total of approximately 48 subjects (12 per treatment group) is sufficient to achieve around 80% power to detect a difference of 25% between TAK-906 doses and placebo in the GEBT by a 2-sample t-test with a 2-sided significance level of 0.05.

## **1.1 Protocol Amendment No. 04 Summary of Changes**

### **Rationale for Amendment 04**

This document describes the changes in reference to the protocol incorporating Amendment No. 04.

The primary reason for this amendment is to correct and clarify errors and omissions. Minor grammatical, editorial, and formatting changes are included for clarification purposes only. For specific descriptions of where the changes are located, see [Appendix A](#).

### **Changes in Amendment 04:**

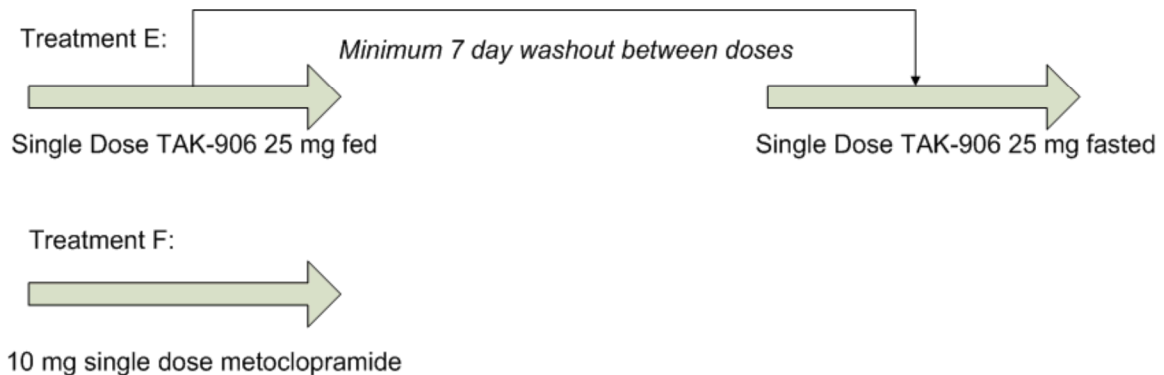
1. Changed the body mass index criteria for eligibility.

## 2.0 STUDY SCHEMATIC

### PART 1



### PART 2



QD=once daily.

### 3.0 SCHEDULE OF STUDY PROCEDURES

Part 1 (Treatment Groups A, B, C, and D)																
	Day													Early Termina- tion	Follow- Up Visit (a)	
	Screen- ing Day -28 to Day-3	- 2	-1	Pre- dose Day 1	1	2	3	4	5	6	7	8	9			
Administrative procedures																
Informed consent	X															
Inclusion/exclusion criteria	X	X		X												
Medical history/demographics	X															
Prior and concomitant medication review	-----Continuous Review-----															
Clinical procedures/assessments																
Full physical examination (b)	X			X								X		X	X	
Height	X															
Weight	X			X (c)								X (c)		X	X	
Body mass index	X															
Semi-recumbent vital signs (heart rate, systolic and diastolic blood pressure)	X			X (d)	X (d)			X (d)				X (d)		X	X	
Vital signs (respiratory and heart rates, oral [floor of the mouth]/tympanic temperature)	X			X (e)										X	X	
12-lead ECG Standard	X (e)			X (e)	X (f)			X (f)	X (f)			X (f)		X	X	
TAK-906 maleate / placebo administration (g)					X	X	X	X	X	X	X	X	X			
GEBT (h)	X		X		X						X					
SmartPill ingestion (post-test meal)			X								X					
Sliding scale insulin administration				X	-----X											
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Part 1 (Treatment Groups A, B, C, and D)															
	Day														
	Screen- ing Day -28 to Day-3	- 2	-1	Pre- dose Day 1	1	2	3	4	5	6	7	8	9	Early Termina- tion	Follow- Up Visit (a)
Company Confidential Information															
AE Monitoring	-----Continuous Monitoring-----														
Laboratory procedures/assessments															
Hematology	X			X (j)								X (j)		X	X
Urinalysis	X			X (j)								X (j)		X	X
Serum chemistry	X			X (j)								X (j)		X	X
Fingerstick glucose (k)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hemoglobin A1c (HbA1c)	X														
β-human chorionic gonadotropin (hCG)	X		X								X			X	X
Serum follicle stimulating hormone (FSH)	X														
Urine drug screen (l)	X														
Hepatitis screen	X														
Human immunodeficiency virus (HIV) Screen	X														
Blood samples for deoxyribose nucleic acid (DNA) pharmacogenomics (PGx)		X													
PK evaluations															
Plasma samples for TAK-906 PK (m)				X-----											
PD evaluations															
Serum samples for PD (n)	X	X		X-----X						X-----X					
Other															
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Test meal (p)	X		X		X			X			X				
Standard meals (q)			X		X			X			X				

- (a) Follow-up visit will occur approximately 14 days after the last dose of trial drug received. For example, if the subject does not continue to Part 2 or prematurely discontinues at any time during the study. Subjects who complete Part 1 and continue to Part 2 will not complete a 14-day follow-up, but will follow the 7-day washout procedure.
- (b) Predose Day 1 physical examination may be done within approximately 48 hours predose Day 1 and 24 hours post Day 7 am dose.
- (c) Weight will be obtained Predose Day 1 and 24 hours postdose Day 7.

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- (d) Vital sign measurements will occur:
- Predose Day 1 and 90 minutes postdose.
  - Predose Day 4.
  - 24 hours post AM dose on Day 7.
- (e) Vital signs and 12-Lead ECG will be performed within approximately 1 hour predose on Day 1. The Screening ECG must include 60-second deep inspiration and expiration to exclude autonomic neuropathy.
- (f) 12-lead ECG on Days 1, 4, and 5 will be obtained at 90 minutes (1.5 hour) post AM Dose. The 12-Lead ECG on Day 8 will be performed 24 hours after the Day 7 AM dose.
- (g) TAK-906 or matching placebo will be administered as a witnessed dose at approximately 0700-0800 and at approximately 1500-1600. On Day 9, only the morning dose will be administered.
- (h) GEBT in Part 1 will be performed at Screening (unless one was performed within 12 months that showed delay in GE) and Day -1, starting with breath sample collection before the test meal (2 samples), after the test meal at 15-minute intervals through 60 minutes post meal, and then at 30 minute intervals until 4 hours post meal. GEBT will be performed on Days 1 and 7 with breath sample collection before the test meal (2 samples), after the test meal at 15-minute intervals through 60 minutes post meal, and then at 30 minute intervals until 4 hours post meal (5 hours postdose).
- (i) **Company Confidential Information**
- (j) Predose hematology, chemistry and urinalysis test may be done within approximately 24 hours predose Day 1 and 24 hours following the Day 7 dose.
- (k) Diabetes mellitus only: If the subject is confined to the CRU (optional), fingerstick glucose measurements will be obtained up to 3 times per day (pre-AM dose, pre-lunch, pre-dinner). At all other times (washout and nonconfinement) the subject will obtain a fingerstick glucose measurement pre-breakfast and at bedtime. Pre-test meal values must be below 270 mg/dL. If glucose is above 270 mg/dL prior to the GEBT, a sliding scale insulin administration should be implemented.
- (l) A urine drug screen will be obtained at Screening.
- (m) Plasma for PK TAK-906 will be obtained:
- Day 1: Predose, 0.5, 1, 1.5, 2, 4, and 8 hours post morning dose.
  - Day 2-6: just before morning dose.
  - Day 7: Predose, 0.5, 1, 1.5, 2, 4, 8, 24, and 48 hours post morning dose.
- (n) Serum for PD (prolactin concentrations) will be obtained:
- Screening (local laboratory for inclusion/exclusion ONLY).
  - Day -2.
  - Day 1: Predose, 1, 1.5, 2, 4, and 8, 24 hours post morning dose.
  - Day 7: Predose, 1, 1.5, 2, 4, 8, 24, and 48 hours post morning dose.
- (o) **Company Confidential Information**
- (p) For GEBT and SmartPill evaluation. On dosing days, the test meal will be administered 1 hour post the AM dose. The test meal will consist of 100 mg <sup>13</sup>C-Splatensis, 27 g freeze-dried egg mix, 6 saltine crackers, and 180 mL of water. The caloric content of the meal is 238 kcal, and the meal has a balanced composition of 16.9 g carbohydrates, 14.4 g protein, and 11.2 g fat.
- (q) Lunch will be administered approximately 5 hours post AM dose. If the subject is confined to the clinical research unit (CRU) (optional), dinner will be provided 2-3 hours post PM dose. The meals on Day -1, 1, 4 and 7 will be standard.

Part 2

Part 2 (Treatment E [Periods 1 and 2] and Treatment F)													
	Day	Day 1	Hours										Early Termina- tion
	-1	Predose	0	0.5	1	1.5	2	4	8	24	48		Follow- Up Visit (a)
Administrative procedures													
Prior and concomitant medication review													
Clinical procedures/assessments	-----Continuous Review-----												
Full physical examination (b)		X										X	X
Semi-recumbent vital signs (heart rate, systolic and diastolic blood pressure)		X (c)				X						X	X
Vital signs (respiratory rate, oral [floor of the mouth]/tympanic temperature)		X (c)									X	X	X
12-lead ECG standard		X (c)				X						X	X
TAK-906 maleate or metoclopramide administration (d)			X										
Sliding scale insulin as needed (e)	X												
Company Confidential Information													
AE Monitoring	-----Continuous Monitoring-----												
Laboratory procedures/assessments													
Fingerstick glucose (e)	X	-----X											
hCG	X											X	X
PK evaluations													
Company Confidential Information													
Plasma samples for metoclopramide PK (Group F)		X		X	X	X	X	X	X	X	X		
Other													
Company Confidential Information													
High fat breakfast (Group E) (h)		X											
Standard meals (i)			X	-----X									

(a) Follow-up visit will occur approximately 14 days after the last dose of trial drug received in Part 2 or if the prematurely discontinues at any time during the study. Else, a 7-day washout separates each dosing period (ie, fed, fasted) in Part 2 food-effect arm (Group E).

(b) Predose Day 1 physical examination may be done within approximately 48 hours predose Day 1.

(c) Vital signs and 12-lead ECG will be performed within approximately 1 hour predose on Day 1.

(d) Subjects will be given either a single-dose of 25 mg TAK-906 with a high fat breakfast or in the fasted state (Treatment Group E) or 10 mg metoclopramide (1 hour before test meal) (Treatment Group F). TAK-906 or metoclopramide will be administered as a witnessed dose at approximately 0700-0800.

(e) Diabetes mellitus only: If the subject is confined to the CRU, fingerstick glucose measurements will be obtained up to 3 times per day (pre-AM dose, pre-lunch, pre-dinner). At all other times (washout and nonconfinement) the subject will obtain a fingerstick glucose measurement pre-breakfast and at bedtime. Pre-test meal values must be below 270 mg/dL. If glucose is above 270 mg/dL prior to the GEBT, a sliding scale insulin administration should be implemented.

(f) Company Confidential Information

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(g) Company Confidential Information

(h) Subjects will be given either a single-dose TAK-906 maleate 25 mg between 0700 and 0800 (after at least an 8-hour fast) approximately 30 minutes after the start of a high-fat breakfast, or in the fasted state, ie, Period 1 or 2 (Group E).

(i) If the subject is confined to the CRU, lunch will be administered approximately 5 hours post AM dose, dinner will be provided 2-3 hours post PM dose.

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## 4.0 INTRODUCTION

### 4.1 Background

The overall program strategy is to develop TAK-906 for patients with gastroparesis (GP), a disorder of the stomach characterized by delayed gastric emptying (GE) in the absence of mechanical obstruction. Symptoms are chronic with episodic symptom exacerbation [1]. These symptoms may include nausea, vomiting, early satiety, abdominal pain, and postprandial fullness. The prevalence of gastroparesis in the United States (US) is 24.2 per 100,000 [2]. In cases of chronic gastroparesis, diabetic (29%), postsurgical (13%), and idiopathic (36%) etiologies comprise the majority of cases in the tertiary referral setting [3]. Currently in the United States, there exists a large unmet medical need because there are no approved therapies for the chronic treatment of diabetic gastroparesis. Validated targets for gastroparesis are the D<sub>2</sub> and D<sub>3</sub> dopamine (DA) receptors. The D<sub>2</sub> receptor antagonist metoclopramide is indicated for the short-term treatment of acute and recurrent diabetic gastroparesis 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 extrapyramidal symptoms (EPS) [4]. EPS are caused by the blockade of DA D<sub>2</sub> receptors in the dorsal striatum and thus are potential side effects of all centrally-penetrant drugs that share this mechanism of action, particularly selective DA D<sub>2</sub> 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 and as such, the United States package insert includes a black box warning regarding the chronic use of metoclopramide for longer than 12 weeks [5].

Domperidone is a peripherally-acting DA D<sub>2</sub>/D<sub>3</sub> receptor antagonist marketed for use as an anti-emetic and prokinetic agent in a number of countries worldwide, although not in the United States due to its cardiovascular safety profile which includes a risk for drug-induced long QT syndrome, torsades de pointes, and sudden cardiac death [6].

DA receptor antagonists are effective in the treatment of delayed GE and GP symptoms because of the role of D<sub>2</sub> and D<sub>3</sub> receptors in the upper gastrointestinal (GI) tract and in the area postrema which controls vomiting [7-9]. Both of these areas are outside of the blood brain barrier. Therefore, a peripherally-selective D<sub>2</sub>/D<sub>3</sub> antagonist could achieve the desired efficacy without the undesired central nervous system (CNS) effects [10,11]. TAK-906 is a peripherally selective (ie, very limited penetration of the blood brain barrier) DA D<sub>2</sub>/D<sub>3</sub> receptor antagonist. It demonstrated suitable pharmacokinetic (PK) and pharmacodynamic (PD) activity in a phase 1 trial in healthy volunteers without the CNS liabilities of metoclopramide or cardiac liabilities associated with domperidone. Therefore TAK-906 is expected to reduce nausea and vomiting, and to have prokinetic effects, without the side effects which restrict the use of other D<sub>2</sub>/D<sub>3</sub> antagonist.

TAK-906 shows rapid absorption. Half-life following a single oral (PO) dose averaged approximately 4 hours when administered in the fasted state. Food had a significant impact on reducing the exposure to TAK-906.

To date, there are no development and reproductive toxicity data available for TAK-906.

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

In conclusion, TAK-906 maleate is a promising therapeutic for the treatment of gastroparesis.

#### **4.2 Rationale for the Proposed Trial**

There are approximately 13 million patients with GP in United States, European Union, and Japan. The most common causes are idiopathic (~36%) and diabetes (~29%). TAK-906 is a D<sub>2</sub>/D<sub>3</sub> DA antagonist belonging to a class of prokinetic drugs (eg, domperidone and metoclopramide) shown to be effective in the treatment of GP.

This proof-of-concept trial is designed to evaluate the safety, PK, and PD for TAK-906 in the population intended for compound development, ie, subjects with diabetic gastroparesis (DG) or idiopathic gastroparesis (IG). For a small proof-of-concept trial, it is prudent to limit the trial population to reduce variability, and to focus on the target trial population for phase 3. This trial will evaluate the effect of TAK-906 and metoclopramide on GE and the symptoms of GP using the instruments proposed for later stage development. In addition, this study will evaluate the effect of food on the PK of TAK-906 in the GP population.

#### **4.3 Benefit/Risk Profile**

There is no expected clinical benefit to the trial participants.

In vitro, TAK-906 showed no potential for cytochrome P-450 (CYP) enzyme inhibition (2C9, 2C19, and 3A4) or induction (3A4). To date, no drug-drug interaction data are available for hormonal contraceptive use during TAK-906 administration. Additionally, since full reproductive toxicity studies have not been completed to date, the combination of caution and the use of highly effective double-barrier contraceptives ([Appendix E](#)) in a short study provide an adequate safe guard against pregnancy during the dosing period.

Potential risks are based on clinical findings, the mechanism of action, and nonclinical findings. Also, there is minimal risk associated with study procedures including scheduled, periodic phlebotomy (limited to <500 mL), and noninvasive procedures including vital sign assessments and electrocardiograms (ECGs).

There is a very small risk for the SmartPill to be lodged in the gastrointestinal (GI) tract. While most will eventually pass, there is a risk that it may need to be removed surgically.

For the subjects with diabetes, there is a possibility that the glucose control may be disrupted because of the fasting and the study medication. This is transient and can usually be managed proactively through closer glucose monitoring.

The principal mitigation for these risks include appropriate selection of the study populations, the clinical research unit (CRU) study setting permitting close monitoring and rapid institution of appropriate care as needed, appropriate specified monitoring procedures, and utilization of experienced staff trained in study procedures.

Overall, the risk:benefit profile is considered appropriate for this trial.

## 5.0 TRIAL OBJECTIVES AND ENDPOINTS

### 5.1 Hypotheses

- Multiple twice daily (BID) administration of TAK-906 maleate in subjects with GP will be safe and well tolerated, based on an assessment of clinical and laboratory adverse events (AEs), to permit continued clinical investigation.
- Following the first dose, 1 or more well-tolerated doses of TAK-906 maleate will result in a 3-fold increase in serum prolactin at the maximum observed concentration ( $C_{max}$ ) of serum prolactin as compared with Baseline for each period. Moreover, no clinical evidence of prolactinemia will be observed following multiple doses in any dose groups.
- Following treatment with TAK-906 maleate, a  $D_2/D_3$  antagonist, at least 1 dose of TAK-906 maleate is superior to placebo for improving GE as measured by GE time using the gastric emptying breath test (GEBT). A difference between TAK-906 and placebo of 25% is expected.
- Following treatment with TAK-906 maleate, a  $D_2/D_3$  antagonist, at least 1 dose of TAK-906 maleate is superior to placebo for improving GE as measured by GE time using the SmartPill. A difference between TAK-906 and placebo of 25% is expected.
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### 5.2 Trial Objectives

#### 5.2.1 Trial Primary Objective

The primary objective of the study is:

- To evaluate the safety and tolerability of TAK-906 in subjects with GP.

#### 5.2.2 Trial Secondary Objectives

The secondary objective(s) of the study are:

- To assess the prolactin PK/PD relationship in subjects with GP.
- To demonstrate the effect of TAK-906 on GEBT.

#### 5.2.3 Trial Exploratory Objectives

Exploratory objectives of this study are:

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## 5.3 Endpoints

### 5.3.1 Primary Safety Endpoint

The primary safety endpoint of the study is key safety and tolerability as assessed through physical examinations, vital signs, ECG, and laboratory assessments, as well as collection of serious and nonserious AEs.

### 5.3.2 Secondary Endpoints

Secondary endpoints include:

1. The change in serum prolactin from Baseline to Day 1 at time of first occurrence of  $C_{\max}$  ( $t_{\max}$ ) for TAK-906 following administration with TAK-906 maleate vs placebo.
2. The change from Baseline to Day 7 in GEBT gastric half-emptying time as measured by the  $^{13}\text{C}$  Spirulina GEBT following multiple doses of TAK-906 maleate vs placebo.
3. The change from Baseline to Day 1 in GEBT gastric half-emptying time as measured by the  $^{13}\text{C}$  Spirulina GEBT following single dose administration of TAK-906 maleate vs placebo.
4. The percent change from Baseline to Day 7 in GE time as measured by the SmartPill.
5. Pharmacokinetics: Plasma PK parameters for TAK-906 (Part 1).

### 5.3.3 Exploratory Endpoints

Exploratory endpoints will be assessed through the following parameters:

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## 6.0 TRIAL DESIGN AND DESCRIPTION

### 6.1 Trial Design

This is a phase 2a, randomized, double-blind and open-label, placebo and active-comparator controlled trial to evaluate the safety, PK, and PD for TAK-906 in subjects with DG or IG. The trial will consist of 2 parts and is designed to allow all enrolled subjects to participate in each part of the study, at the discretion of the investigator. Subjects may decline participation at any time during the study.

Subjects will include men and women aged 18 to 75 years, inclusive, with DG or IG who have been diagnosed with documented slow GE and a minimum of 3-month history of symptoms consistent with GP, including postprandial fullness or nausea, vomiting, abdominal pain, loss of appetite, and early satiety.

#### 6.1.1 Part 1

As shown in [Table 6.a](#), approximately 48 subjects will be randomized into 1 of 3 active treatment arms or a placebo arm to receive trial drug in a double-dummy manner for 9 consecutive days, for a total of 17 doses (ie, BID Days 1 to 8 and morning dose on Day 9). All trial drug dosing will be under fasted conditions.

**Table 6.a Doses for Part 1**

Treatment Group	N (a)	Trial Drug
A	12	TAK 906 maleate 5 mg BID
B	12	TAK 906 maleate 25 mg BID
C	12	TAK 906 maleate 100 mg BID
D	12	Placebo BID

(a) A minimum of 4 DG and IG in each treatment arm.

GE will be evaluated following a test meal using a GEBT, and GE and motility will also be evaluated using SmartPill technology.

Subjects will be weaned off all medications to treat GP or the symptoms of GP at least 10 days prior to assessment of GP on Day -1. A GEBT will be performed during Screening to confirm eligibility. If a subject has had a scintigraphy or GEBT within the last 12 months that showed delayed in GE, this may be considered and a screening GEBT would not be required.

A baseline GEBT will be performed on Day -1, and repeated on Days 1 and 7. An 8-hour fast is required prior to each GEBT. The GEBT performed on Day -1 will not be used to confirm eligibility. A second noninvasive measure of GE and motility will be performed concurrently with the GEBT at Baseline (Day -1) in the form of SmartPill motility monitoring, and repeated on Day 7. This will serve as a second validated quantitative measure of GE.

Prior to each GEBT and/or SmartPill assessment, subjects will be required to fast the evening before the dose (from 2300), and return to the CRU for witnessed doses on each subsequent day of

dosing. This procedure will be repeated for the Days 1 (GEBT) and 7 (GEBT and SmartPill) procedures.

The first dose of trial medication should be given between approximately 0700 and 0800 (after at least an 8-hour fast) and the subject will remain fasted, with the exception of the trial meal at 1 hour post AM dose, until 4 hours post-test meal (5 hours postdose). After the test meal, breath samples will be collected at 15 minute intervals through 60 minutes post meal, with the remaining samples collected at 30 minute intervals until 4 hours post meal (5 hours postdose). On Days 2 through 8, trial medication will be given BID in the morning as a witnessed dose at the CRU (approximately 0700 and 0800) an hour prior to breakfast and 8 hours later in the afternoon (approximately 1500 and 1600), 2 hours after the last meal and at least an hour before the next meal. On Day 9 the trial medication will be given only in the morning.

An overview of the diet/meal considerations relative to dosing, GEBT, and SmartPill are presented in Section 7.4.1.

The dosing period will be for 9 days and total of 17 doses (ie, BID Days 1 to 8 and morning dose on Day 9).

To assess GP symptoms, Company Confidential Information



Blood samples for assessment of TAK-906 concentrations in plasma will be collected at scheduled time points from predose on Day 1 to 48 hours after Day 7 dose.

Blood samples for assessment of prolactin concentrations in serum will be collected at Screening and scheduled time points from Day -2 to 48 hours after Day 7 dose.

### 6.1.2 Part 2

An assessment of the food effect on PK of TAK-906, and separately, a comparison of TAK-906 to an active comparator (metoclopramide) will be assessed in Part 2, the open-label period of the study. All subjects who participated in Part 1 of the study are eligible to participate in all treatment groups in Part 2 following a minimum 7-day washout from the last dose in Part 1. Approximately 18 subjects who completed Part 1 of the study will be enrolled into Part 2 of the study. At the discretion of the investigator, approximately 6 subjects will be enrolled in Treatment Group E (food effect), and they will receive TAK-906 maleate 25 mg with and without food in a crossover design. A minimum 7-day washout will separate the doses in each period. An additional 12 subjects who complete Part 1 of the study will be enrolled at the discretion of the investigator in Treatment Group F (active comparator). In Treatment Group F, a known promotility agent in the form of metoclopramide will serve as an active comparator to confirm the responsiveness of the GEBT test. All subjects will remain blinded until all subjects have completed Part 1 of the study.

Blood samples for assessment of TAK-906 or metoclopramide concentrations will be collected at scheduled time points from predose on Day 1 to 48 hours postdose.

**Table 6.b Doses for Part 2**

Treatment Group	N (a)	Trial Drug	
		Period 1 (a)	Period 2 (a)
E	~ 6	Single dose TAK-906 maleate 25 mg Fed	Single dose TAK-906 maleate 25 mg Fasted
F (b)	~ 12	Single dose metoclopramide 10 mg	

(a) There will be a minimum of 7 days washout between doses in Periods 1 and 2.

(b) A minimum of 4 subjects with DG and 4 subjects IG will be enrolled.

A GEBT will be performed for Day -1 and Day 1 for the metoclopramide group. An 8-hour fast is required prior to each GEBT. The GEBT performed on Day -1 will not be used to confirm eligibility.

Subjects may take rescue medication for nausea under the circumstances described in Section 8.1.2.

## 6.2 Rationale for Trial Design, Dose, and Endpoints

### 6.2.1 Rationale of Trial Design

This study was designed as a randomized, double-blind (Part 1) and open-label (Part 2), placebo and active-comparator controlled study in men and women with DG or IG. Since diabetes mellitus affects both genders, it is important to include both men and women into the study. In a review of the prevalence of gastroparesis in Olmsted County, Minnesota from 1996 to 2006, it was found that almost 70% of patients were women. Since GP is a complication of diabetes mellitus, it is anticipated that many of these patients would be of child bearing age, and therefore, it is important to test early whether these patients are likely to benefit from therapies such as TAK906 [12]. Additionally, the recent approval of an instrument (GEBT) that doesn't require radiation removes another potential barrier for the inclusion of women.

For Part 1 of the study, which has 3 TAK-906 maleate arms and 1 placebo arm, a parallel design was selected as it was determined more likely facilitate trial recruitment and retention. For Part 2 food effect, PK is an objective measure of response; thus open-label design is acceptable. For Part 2 metoclopramide arm, a known promotility agent in the form of metoclopramide 10 mg and known to demonstrate a promotility effect even following a single dose, will serve as an active comparator to confirm the responsiveness of the GEBT test.

### 6.2.2 Rationale for Dose

Data from the phase 1 single- and multiple-ascending dose (SAD and MAD) trial in healthy volunteers were used to select doses for the phase 2a trial. Several considerations were given to dose selection: safety, tolerability, PK, and PD (prolactin). Prolactin has been used as a measure of



target engagement. The plasma TAK-906-prolactin concentration relationship was characterized and was used to estimate prolactin concentrations for several dosing regimens (BID fasted). The maximum dose selected (100 mg BID) is predicted to be associated with nearly maximum prolactin production at steady state. This dose was also shown to be safe and well tolerated. The half maximal effective concentration (EC<sub>50</sub>) estimate for TAK-906-prolactin concentration relationship is estimated to be approximately 5 mg BID; therefore this dose is the lowest dose selected.

A dose of TAK-906 maleate 25 mg was selected for testing food effect to allow direct comparison with data collected in food-effect portion of the phase 1 SAD study in healthy subjects.

Metoclopramide 10 mg was selected for a comparator as it has a similar mechanism of action to TAK-906 and is currently indicated to treat GP in diabetic patients.

### 6.2.3 Rationale for Endpoints

The PK, PD, and safety measurements in this study are used widely and are recognized as reliable, accurate, and relevant.

DA inhibits prolactin production by pituitary lactotroph cells. Thus, when the D<sub>2</sub> receptor is inhibited, serum prolactin levels rise and can serve as a marker for D<sub>2</sub> DA receptor engagement.

The hallmark of patients with GP is delayed GE, therefore the intended benefit from TAK-906 therapy is an improvement in GE. There are a number of modalities to objectively measure GE. Radiographic scintigraphy is the most established and widely published, but it is associated with significant amount of radiation exposure and requires access to centers knowledgeable in the techniques to standardize across centers. Two other validated tests to assess GE are GEBT and SmartPill motility capsule. The GEBT is a nonradioactive, noninvasive, PO administered test for measuring the rate of solid phase GE in adults. The GEBT has been validated against the gold standard reference method of gastric scintigraphy. SmartPill is an ingestible capsule that measures pressure, pH and temperature as it travels through the GI tract to assess GI motility. SmartPill eliminates radiation exposure and is the only motility test that provides a complete transit profile of the GI tract. It provides an additional element of data to support the promotility effect of TAK-906.

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#### **6.2.4 Critical Procedures Based on Trial Objectives: Timing of Procedures**

For this trial, timing of the SmartPill, GEBT, and timing of meals relative to study drug administration are critical procedures. Specifically:

- The SmartPill capsule should be ingested immediately following the completion of the test meal at Baseline (Day -1) and Day 7.
- At any predose and postdose time point, GEBT and timing of meals needs to be collected as close to the exact time point as possible.
- All other procedures should be completed as close as possible, either before or after the prescribed/scheduled time.
- The order of priority can be changed during the trial with joint agreement of the investigator and the sponsor.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

#### **6.3 Trial Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters**

This is a phase 2a assessment of TAK-906 maleate in humans, and the PK, PD, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of phase 2a clinical trials. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined below may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects.

Every effort should be made for all subjects to participate in the SmartPill assessment; however, if a subject does not meet the Inclusion/Exclusion criteria for the SmartPill but is otherwise eligible to participate in the clinical study, this test may be optional following discussion with the sponsor.

Some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose/exposure detailed in Section 6.2.2, may not exceed those currently outlined.

- The dose may be changed in Part 2.
- Part 2 may be omitted.
- Lengthening of the washout Parts 1 and 2.
- Decrease of the washout period between doses if supported by safety and PK evidence.

- In the event a subject is unable to swallow the SmartPill they may continue participation in the study.
- Additional subjects may be entered into Part 2 of the study up to approximately 12 subjects.
- Rescue medications given around ECGs and routine blood draws are permitted.

The PK/PD sampling scheme currently outlined in the protocol may be modified during the trial based on newly available PK or PD data (eg, to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional PD markers.

Up to an additional 50 mL of blood may be drawn for PK and/or PD analyses. This may include repeat samples or modified PK/PD time points based on emerging data. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his/her participation in the entire trial.

The timing of planned safety procedures for assessment (eg, vital signs, ECG, safety laboratory tests, etc) currently outlined in the protocol may be modified during the trial based on newly available safety, tolerability, PK, or PD data (eg, to obtain data closer to the time of peak plasma concentrations). These changes will not increase the number of trial procedures for a given subject during his/her participation in the entire trial.

Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information (eg, adding creatinine kinase to serum chemistry panel that was already drawn).

It is understood that the current trial may employ some or none of the alterations described above. Any alteration made to this protocol to meet the trial objectives must be detailed by the sponsor in a letter to the Trial File and forwarded to the investigator for retention. The letter must be forwarded to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

## **6.4 Trial Beginning and End/Completion**

### **6.4.1 Definition of Beginning of the Trial**

The overall trial begins when the first subject signs the trial informed consent form.

### **6.4.2 Definition of End of the Trial**

The overall trial ends when the last subject completes the last planned or follow-up visit/interaction associated with a planned visit (this can be a phone contact), discontinues from the trial or is lost to follow-up (ie, the investigator is unable to contact the subject).

### **6.4.3 Definition of Trial Discontinuation**

A primary objective of this early phase 2a trial is to identify dose and/or dosing regimen that achieves PK, PD, and/or biologic targets in humans based on preclinical or early clinical data. Therefore, it is possible that trial subjects may not receive all doses specified in the protocol

if this objective is achieved at lower dose levels in this trial. This would not be defined as early termination of the trial, but rather an earlier than anticipated achievement of the trial objective(s) or trial completion

- A finding (eg, PK, PD, efficacy, biologic targets) from another nonclinical or clinical trial using the trial treatment(s) results in the trial being stopped for a nonsafety-related reason.
- Data from comparator(s), drug(s) of the same class, or methodology(ies) used in this trial become available and results in the trial being stopped for a nonsafety-related reason.
- The trial is stopped because of nonscientific and nonsafety reasons, such as slow enrollment.

Trial discontinuation because of safety reasons:

- Early trial termination because of unanticipated concerns of safety to the trial subjects arising from clinical or preclinical trials with the trial treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this trial.

#### *6.4.3.1 Criteria for Premature Termination or Suspension of the Trial or Trial Sites*

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

#### *6.4.3.2 Procedures for Premature Termination or Suspension of the Trial or the Participation of Trial Site(s)*

In the event that the sponsor, an IRB, or regulatory authority elects to terminate or suspend the trial or the participation of an investigational site, a trial-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or trial suspension.

## 7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

### 7.1 Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Understand the study procedures and agree to participate by providing written informed consent.
2. Be willing and able to comply with all study procedures and restrictions.
3. Has a documented diagnosis of diabetic gastroparesis or idiopathic gastroparesis.
4. Be man or a woman aged 18 to 75 years, inclusive, at the Screening Visit.
5. Have a body mass index (BMI)  $\geq 18$  and  $\leq 40$  (kg/m<sup>2</sup>) at the Screening Visit.
6. Be a nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months prior to trial drug administration of the initial dose of trial drug/invasive procedure.
7. Be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead ECG, and vital sign measurements performed at the Screening Visit and prior to administration of the initial dose of trial drug/invasive procedure.
8. Has a QT interval with Fridericia correction method (QTcF) interval  $<450$  mSec (men)  $<475$  mSec (women).
9. Has a serum prolactin  $<2\times$  upper limit of normal (ULN) at Screening.
10. Has an alanine aminotransferase (ALT) and aspartate aminotransferase (AST)  $<1.5\times$ ULN; bilirubin  $\leq 1.5\times$ ULN (except Gilbert syndrome).
11. Meet the following birth control requirements:
  - Is a man who is sterile or agrees to use a highly reliable double-barrier method of contraception\*, including a condom with spermicide, from trial drug administration on the first day of the first dose until 31 days after the last dose of trial drug administration. No restrictions are required for a vasectomized man provided the subject is at least 1 year post-bilateral vasectomy procedure prior to trial drug administration on first day of the first dose. A man whose vasectomy procedure was performed less than 1 year prior to trial drug administration on the first day of the first dose must follow the same restrictions as a nonvasectomized male. Appropriate documentation of surgical procedure should be provided.
  - Is a man who agrees to not donate sperm from trial drug administration on the first day of the first dose until 31 days after the last dose of trial drug administration.
  - Is a woman of childbearing potential who agrees to use a highly effective double-barrier method of contraception\* from signing of informed consent throughout the duration of the study and until 31 days after the after the last dose.

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- Is a woman with no childbearing potential, defined by at least 1 of the following criteria:
  - a) Postmenopausal (defined as 12 months of spontaneous amenorrhea in women aged >45 years, 6 months of spontaneous amenorrhea in females aged >45 years with serum follicle-stimulating hormone (FSH) levels >40 mIU/mL). Appropriate documentation of FSH levels is required.
  - b) Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.
  - c) Had a tubal ligation with appropriate documentation of surgical procedure.
  - d) Has a congenital condition resulting in no uterus.

\*Details of contraception and pregnancy procedures are found in [Appendix E](#).

12. Has symptoms for GP (ie, chronic postprandial fullness, abdominal pain, postprandial nausea, vomiting, loss of appetite and/or early satiety) the past 3 months.
13. Has documented slow GE, with delayed GE by GEBT at Screening defined as  $\geq 80$ th percentile. Note: If a subject has had a documented scintigraphy or GEBT within the last 12 months that confirms the diagnosis of delayed GE, a screening GEBT would not be required.
14. Has nausea subscale (of ANMS-GCSI-DD) symptom score  $\geq 2$  at least 3 of 7 days during Screening.
15. Has glycosylated hemoglobin (HbA1c) <10% (for diabetes mellitus only).

Note: Given the biological variability of glycemic parameters, subjects with a value that does not meet the above criteria, but is within 0.2% HbA1c of the qualifying range may, at the discretion of the investigator, have a repeat determination performed and use as a qualifying parameter in lieu of the original value.

## 7.2 Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Subjects who have a history of clinically significant endocrine (apart from diabetes mellitus), GI (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases will be excluded from the trial.
2. Has participated in another investigational trial within 4 weeks prior to the pretrial (Screening) visit. The 4-week window will be derived from the date of the last trial procedure and/or AE related to the trial procedure in the previous trial to the pretrial/Screening Visit of the current trial.
3. Is an employee or immediate family member (eg, spouse, parent, child, sibling) of the clinical site or of the sponsor.

4. Has acute severe gastroenteritis and pronounced dehydration in the 48 hours prior to Screening, gastric pacemaker, chronic parenteral feeding or persistent severe vomiting.
5. Has a known disturbance of small intestinal absorption, exocrine pancreatic function, liver metabolism, and pulmonary function.
6. Has a history of anorexia nervosa or bulimia.
7. Has a history of additional risk factors for Torsade de Pointes (eg, heart failure, hypokalemia, family history of Long QT Syndrome), evidence of cardiac autonomic neuropathy, eg, lack of respiratory rate variation upon deep breathing.
8. Previous history of bezoars (the presence of retained liquid, bile, or small amounts of poorly organized food residue is permitted).
9. Difficulty swallowing solid food or pills.
10. Prior surgery involving the luminal GI tract (cholecystectomy, appendectomy, and hysterectomy are permitted if performed >3 months prior to SmartPill test).
11. Any abdominal or pelvic surgery within the past 3 months.
12. Known or history of inflammatory bowel disease.
13. Has active diverticulitis, diverticular stricture, and other intestinal strictures.
14. Has active ongoing cancer. In addition, subjects with a history of cancer who have received treatment within the last 5 years are not eligible to screen.
15. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription or nonprescription drugs or food.
16. Has a hypersensitivity to Spirulina, egg, milk, bread, or jam, or wheat allergens.
17. Has a positive alcohol or drug screen.
18. Lactating or pregnant women as determined by positive human chorionic gonadotropin (hCG) test at Screening and within 24 hours of the first dose.
19. Is breastfeeding or has breastfed in approximately the last 6 months.
20. Is positive for hepatitis B surface antigen (HBsAg), hepatitis C antibodies, or human immunodeficiency virus (HIV) (confirmatory testing is allowed; most sensitive test should take precedence).
21. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial Screening Visit.
22. Is unable and/or unwilling to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies beginning approximately at least 10 days prior to assessment of GP on Day -1, throughout the trial (including washout intervals

between treatment periods), until the posttrial visit. There may be certain medications that are permitted. See Section 7.3.

Note: Hormone replacement therapy (HRT) and thyroid dysfunction: HRT are allowed (eg, levothyroxine, continuous HRT), but subjects should be on stable regimen for at least 6 weeks, and are expected to remain on that stable regimen during the treatment period and through 14 days after the last dose of trial drug.

23. Chronic daily use of nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen, etc).
24. Uses medications that prolong the QT/ corrected QT interval.
25. Has a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce] per day).
26. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
27. Has a substance-abuse disorder.
28. Has a consistent fasting glucose of approximately  $\geq 270$  mg/dL (14.99 mmol/L) during any visit up to and including the randomization visit (Period 1 Day 1 predose).  
  
Note: If the subject meets this exclusion criterion AND the investigator believes that the value is not consistent with the subject's current self-monitoring blood glucose values, the subject should not be excluded at this time. The visit can be repeated within 5 to 7 days.
29. Has had diabetic ketoacidosis (within the prior 4 weeks).
30. Use of cardiac medical devices such as pacemakers and defibrillators (bladder stimulators, spinal stimulators, medication infusion devices, insulin pumps, continuous glucose monitors) are permitted.
31. Subject is unable or unwilling to comply with the study rules, regulations, and procedures.

### **7.3 Excluded Medications, Supplements, Dietary Products**

#### **7.3.1 Prohibited Medications**

##### *7.3.1.1 Medications Which May Alter Gastric pH (for SmartPill)*

1. Proton pump inhibitors (omeprazole, lansoprazole, esomeprazole, dexlansoprazole, pantoprazole, rabeprazole) for 7 days prior to study, including the day of SmartPill ingestion.
2. Histamine2 receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine) for 3 days prior to study including the day of SmartPill ingestion.
3. Antacids (containing magnesium, aluminium, or calcium carbonate) for 1 day prior to study including the day of SmartPill ingestion.

#### *7.3.1.2 Medications That May Affect Gastrointestinal Motility*

The following medications must be discontinued at least 10 days prior to assessment of GP on Day -1, including the day of SmartPill ingestion (if subject develops nausea to the degree that study discontinuation is contemplated, he or she may take promethazine, prochlorperazine, or ondansetron as rescue antiemetics in doses recommended by the site investigator):

1. Prokinetic agents (metoclopramide, domperidone, erythromycin, azithromycin, bethanechol, pyridostigmine).
2. Narcotic analgesics (codeine, hydrocodone, oxycodone, methadone, fentanyl, etc).
3. Anticholinergic agents (dicyclomine, hyoscyamine, scopolamine).
4. Cannabinoids (dronabinol, marijuana).

#### *7.3.1.3 Medications to Treat Nausea*

The following medications must be discontinued at least 10 days prior to assessment of GP on Day -1, including the day of SmartPill ingestion:

1. Aprepitant, dolasetron, granisetron, ondansetron, palonosetron, and prochlorperazine.

### **7.3.2 Permitted Medications**

Prescription medications for maintenance of stabilized conditions (eg, hyperlipidemia, thyroid disease, chronic anxiety or depression, birth control, etc) are permitted if the condition and the dose are stable for 3 months prior to study participation.



Use of excluded agents (prescription or nonprescription) or dietary products is outline in [Table 7.a](#).

**Table 7.a Excluded Medications, Supplements, and Dietary Products**

Category	Between Screening and Enrollment (Days -28 to Predose [Day 1])	Randomization Post-Enrollment (Day 1) to Follow-up
<b>Tobacco- and nicotine-containing products</b>	Completely restricted	Completely restricted
<b>Cannabis products</b>	Completely restricted	Completely restricted
<b>Alcohol</b>	Completely restricted 7 days before dosing	Completely restricted 7 days before dosing At all other times no more than 3 units/day
<b>Xanthine and/or caffeine</b>	Completely restricted 48 hours before dosing	Completely restricted 48 hours before dosing At all other times no more than 6 units/day
<b>Medications</b>	Completely restricted 7 days before dosing	Completely restricted (a)
<b>Food substance</b>		
• Grapefruit / grapefruit juice	Completely restricted 7 days before dosing	Completely restricted
• Fruit	No restriction	No restriction
• Fruit juice	No restriction	Dosing will occur without consumption of fruit juice. Fruit juice is restricted 4 hours after dosing.
• Mustard green (b)	Completely restricted 7 days before dosing	Completely restricted
• Charbroiled meat	Completely restricted 7 days before dosing	Completely restricted

(a) Occasional use of acetaminophen/paracetamol ( $\leq 1$  g/day) or other medication as approved by Takeda on a case-by-case basis is allowed.

(b) Mustard green family includes kale, broccoli, watercress, collard greens, kohlrabi, Brussel sprouts, and mustard. Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

## 7.4 Diet, Fluid, Activity

### 7.4.1 Diet and Fluid

An overview of the diet/meal considerations relative to dosing, GEBT, and SmartPill are shown in [Table 7.b](#).

Before each GEBT and/or SmartPill assessment in Part 1, subjects will be required to fast from 2300 the evening before and return to the CRU for witnessed doses on each subsequent day of dosing. This procedure will be repeated for the Day 7 (SmartPill and GEBT) procedures.

The first dose of trial medication should be given between approximately 0700 and 0800 (after at least an 8-hour fast) and the subject will remain fasted (with the exception of the test meal at 1 hour post AM dose) until 4 hours post trial meal (5 hours postdose).

After the test meal (1 hour postdose), breath samples will be collected at scheduled intervals until 4 hours postdose. On Days 2 through 8, trial medication will be given BID in the morning as a

witnessed dose at the CRU (approximately 700 and 800 AM), an hour prior to breakfast, and 8 hours later in the afternoon (approximately 1500 and 1600), 2 hours after the last meal, and at least 1 hour before the next meal. On Day 9 the trial medication will be given only in the morning.

**Table 7.b Timing of Meals Relative to Dosing and Procedures**

Part 1			
Day -1			
Time	Witnessed Dose	GEBT & SmartPill	Meal
~7:00-8:00	No dose	X	Test meal (a)
~8:00-9:00			
~9:00-10:00			CRU Standard Lunch (b)
~13:00-14:00			
~15:00-16:00	No dose		CRU Standard Dinner (b)
~16:00-17:00			
Day 1			
Time	Witnessed Dose	GEBT	Meal
~7:00-8:00	X	X	Test meal (a)
~8:00-9:00			
~9:00-10:00			CRU Standard Lunch (b)
~13:00-14:00			
~15:00-16:00			CRU Standard Dinner (b)
~16:00-17:00			
Days 2 - 6			
Time	Witnessed Dose		Meal
~7:00-8:00	X		Breakfast ad lib (b)
~8:00-9:00			
~13:00-14:00			Lunch ad lib (b)
~15:00-16:00			
~16:00-17:00			Dinner ad lib (b)
Day 7			
Time	Witnessed Dose	GEBT & SmartPill	Meal
~7:00-8:00	X	X	Test meal (a)
~8:00-9:00			
~9:00-10:00			CRU Standard Lunch (b)
~13:00-14:00			
~15:00-16:00			CRU Standard Dinner (b)
~16:00-17:00			
Days 8 and 9			
Time	Witnessed Dose		Meal
~7:00-8:00	X		Breakfast ad lib (b)
~8:00-9:00			
~13:00-14:00			Lunch ad lib (b)
~15:00-16:00			
~16:00-17:00	X (no evening dose on Day 9)		Dinner ad lib (b)

(a) The test meal will consist of 100 mg  $^{13}\text{C}$  –Splatensis, 27 g freeze-dried egg mix, 6 saltine crackers, and 180 mL of water. The caloric content of the meal is 238 kcal, and the meal has a balanced composition of 16.9 g carbohydrates, 14.4 g protein, and 11.2 g fat. The nature and size of the meal were selected to ensure stability at room temperature, palatability, and calorie content that would be consumed entirely, even by patients with suspected gastroparesis and upper abdominal symptoms.

(b) Standardized meal will be provided if the subject is confined to the CRU (optional).

For the food effect portion in Part 2, the dose of trial medication should be given between 0700 and 0800 (after at least an 8-hour fast) approximately 30 minutes after the start of a high-fat breakfast.

For metoclopramide portion in Part 2, an 8-hour fast is required prior to each GEBT performed for Day -1 and Day 1 for the metoclopramide group. On Day 1, metoclopramide should be given between approximately 0700 and 0800 and the subject will remain fasted until the test meal at 1 hour post metoclopramide dose and until 4 hours post trial meal (5 hours postdose). After the test meal (1 hour postdose), breath samples will be collected at scheduled intervals until 4 hours post test meal.

#### **7.4.2 Activity**

Subjects will avoid unaccustomed strenuous physical activity (eg, weight lifting, running, bicycling) from the Screening Visit until the Follow-up visit.

#### **7.5 Criteria for Discontinuation or Withdrawal of a Subject**

1. The subject experiences 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.

2. Liver Function Test (LFT) Abnormalities

In multidose studies, trial 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 10.2.8.4), if the following circumstances occur at any time during trial 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 >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. Significant protocol deviation. The discovery 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.
  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 documentation.
  5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the trial. The reason for withdrawal, if provided, should be recorded in the electronic case report form (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 because of an AE should not be recorded in the “voluntary withdrawal” category).

6. Trial termination. The sponsor, IRB, or regulatory agency terminates the trial.

#### **7.6 Procedures for Discontinuation or Withdrawal of a Subject**

The investigator may discontinue a subject’s trial participation at any time during the trial when the subject meets the trial termination 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 trial. Should a subject’s participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

#### **7.7 Subject Replacement**

If a subject discontinues from the trial, a replacement subject may be enrolled, if deemed appropriate by the investigator and sponsor. The trial site should contact the sponsor for the replacement subject’s treatment assignment and allocation number.

## 8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

### 8.1 Clinical Trial Drug

#### 8.1.1 Trial Drugs

In this protocol, the term study medication refers to all or any of the drugs defined below. TAK-906 maleate capsules and matching placebo capsules for PO administration will be provided to the investigator by the sponsor.

Details regarding the composition and extemporaneous preparation of the active ingredient are found in the Pharmacy Manual, Compounding Instructions, and/or similar documents. Clinical trial drug will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the sponsor needs to be contacted before dosing.

##### 8.1.1.1 TAK-906 maleate

TAK-906 capsules, consists of TAK-906 maleate, nominally 5 or 25 mg in TAK-906 maleate per capsule, along with microcrystalline cellulose, National Formulary (NF) (PH102), sodium starch glycolate, NF and magnesium stearate, NF. All filled into size 3 hard gelatin capsule. All capsules have the same appearance.

Dose	5 mg Capsule	25 mg Capsule	Placebo Capsule
Placebo	0	0	4
5 mg	1	0	3
25 mg	0	1	3
100 mg	0	4	0

All doses will be overencapsulated to have a similar appearance to placebo.

##### 8.1.1.2 Placebo

A matching placebo is identical to the TAK-906 maleate capsule presentations (ie, overencapsulation) except for an equal amount of microcrystalline cellulose NF in place of TAK-906 maleate.

##### 8.1.1.3 Metoclopramide

Metoclopramide 10 mg will be administered according to product prescribing information [5].

### 8.1.2 Use of Rescue Medication

Subjects may take rescue medication for nausea under the following circumstance:

During screening, subjects may receive up to 2 doses per day of anti-nausea medication (eg, ondansetron), but only *after* the subject has reported a nausea subscore  $\geq 2$ . Similarly, anti-nausea medication may be used from Days 1 through 7 only if the nausea subscore is  $\geq 2$ . All doses of rescue medications will be documented and tabulated.

Rescue medications given around ECGs and routine blood draws are permitted.

Metoclopramide will not be allowed to be used as a rescue medication from Day -3.

### **8.1.3 Clinical Study Drug Labeling**

Clinical trial drug packaging will be affixed with a clinical label in accordance with regulatory requirements.

### **8.1.4 Clinical Study Drug Inventory and Storage**

Clinical trial drug must be stored in a secure, limited-access location under the storage conditions specified on the label. Inventory (receipt and dispensing) of trial drug must be recorded by an authorized person at the trial site.

### **8.1.5 Clinical Study Drug Blinding**

Part 1 is the double-blind portion of the trial. The trial drug blind is maintained through a randomization schedule held by authorized persons only.

Part 2 is the open label portion of the trial; therefore, the sponsor, investigator, and subject will know the treatment administered.

### **8.1.6 Randomization Code Creation and Storage**

Takeda Development Center Americas, Inc. Analytical Sciences Department or designee will generate the randomization schedule. Subject randomization will be stratified by the underlying condition, ie, DG versus IG. All randomization information will be stored in a secured area, accessible only by authorized personnel.

### **8.1.7 Clinical Trial Blind Maintenance/Unblinding Procedure**

Part 1:

The investigational drug blind is maintained through a randomization schedule held by authorized personnel only.

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

### **8.1.8 Accountability and Destruction of Sponsor-Supplied Drugs**

The investigator is responsible for keeping accurate records of the clinical trial drug received from the sponsor or designee, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the trial. For all trial sites, the local country sponsor personnel or

designee will provide appropriate documentation that must be completed for clinical trial drug accountability, return, and destruction.

#### **8.1.9 Ancillary Supplies**

All ancillary supplies will be provided by either the site or Takeda, based upon availability. If provided by Takeda, unused ancillary supplies will be accounted for and disposed of as directed by Takeda or a Takeda designee.



## 9.0 TRIAL PROCEDURES

The following sections describe the trial procedures and data to be collected as indicated in the Schedule of Trial Procedures (Section 3.0). For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. Please note that it may become necessary to perform the following procedures at unscheduled time periods, per the discretion of the investigator. For information regarding procedures that are scheduled concurrently, see Section 6.2.4.

### 9.1 Administrative Procedures

#### 9.1.1 Informed Consent Procedure

Informed consent must be obtained before the subject entering into the trial and before any protocol-directed procedures are performed. The requirements of informed consent are described in Section 13.2.

##### *9.1.1.1 Assignment of Screening and Randomization Numbers*

Parts 1 and 2:

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures. Each subject will be assigned only 1 screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will be assigned a new screening number for each screening.

Part 1:

All eligible subjects will be randomly allocated and will receive a randomization number. Once a randomization number is assigned to a subject, it can never be reassigned to another subject. A single subject cannot be assigned more than 1 randomization number.

##### *9.1.1.2 Study Drug Assignment*

On Day 1 of Part 1, subjects will be assigned a randomization number. The randomization number encodes the subject assignment to 1 of 3 active treatment arms or the placebo arm of the trial, according to the randomization schedule generated before the trial by the sponsor's Statistics Department or designee. Each participant will be dispensed blinded trial treatment throughout Part 1 of the trial.

Among subjects who complete Part 1 and are eligible to participate Part 2, approximately 6 subjects will be assigned to receive TAK-906 maleate 25 mg with and without food in an open-label 2-period crossover design. In addition, up to 12 subjects will be assigned to receive single dose metoclopramide 10 mg.

#### 9.1.2 Inclusion and Exclusion

Each subject is assessed through randomization, according to the eligibility criteria provided in Section 7.0.

### **9.1.3 Medical History, Prior and Concomitant Medications, and Demographics**

Qualified site personnel are to collect subject significant medical history (past and concurrent) per the site's standard of care and appropriate clinical judgment and subject demographics.

Qualified site personnel are to review subject prior and concomitant medication use. Medications are defined as prescription and over-the-counter drugs, vitamin supplements, nutraceuticals, and oral herbal preparations.

## **9.2 Clinical Procedures and Assessments**

### **9.2.1 Physical Examinations**

Qualified site personnel will conduct physical examinations.

### **9.2.2 Height and Weight**

Body weight and height will be obtained with the subject's shoes off and jacket or coat removed.

### **9.2.3 BMI**

BMI equals a person's weight in kilograms divided by height in meters squared ( $BMI = \text{kg}/\text{m}^2$ ).

BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

### **9.2.4 Vital Sign Measurement**

Body temperature will be measured with an oral (temperature taken at floor of the mouth) or tympanic thermometer. The same method (eg, oral or tympanic) must be used for all subsequent measurements for each individual subject and should be the same for all subjects.

Subjects should rest in a semirecumbent position for at least 5 minutes before having vital sign measurements obtained. Vital signs will include heart rate, systolic blood pressure, and diastolic blood pressure. The same method (eg, same size cuff, manual or automated) must be used for all measurements for each individual subject and should be the same for all subjects.

Subjects will need to rest in a semirecumbent position for at least 5 minutes prior to any other trial-related procedure.

### **9.2.5 12-Lead ECG**

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before lead placement. Subjects may need to be shaved to ensure proper lead placement. Women may need to remove their bra.

Subjects should be resting in a semirecumbent position for at least 5 minutes before each ECG measurement.

QTcF will be used to calculate QT intervals in this trial.

At the Screening Visit ECG, a 60-second deep inspiration and expiration must be performed to rule out autonomic neuropathy.

Before each treatment period/cohort, a predose ECG will be obtained within approximately 1 hour before dosing of TAK-906 maleate or metoclopramide. This measurement will be used as the Baseline. The principal investigator may consult a trial cardiologist as needed to review any significant ECG tracings with abnormalities.

During each treatment period, if a subject demonstrates an increase in QTcF interval  $\geq 40$  msec compared with a predose baseline measurement, the ECG will be repeated within 5 minutes. The average value of the QTcF interval from the 2 ECGs will represent the value at that time point. If the average QTcF interval increase from Baseline for any postdose time point is  $\geq 40$  msec, the subject will continue to be monitored by repeat 12-lead ECGs every 60 minutes for at least 4 hours or until the QTcF is within 40 msec of the baseline value. If prolongation of the QTcF interval  $\geq 40$  msec persists, a consultation with a trial cardiologist may be appropriate and the sponsor should be notified.

If the QTcF interval is  $\geq 500$  msec, the sponsor should be notified and the ECGs should be reviewed by a cardiologist. The subject should be telemetry-monitored (until the QTcF is  $< 500$  msec) or should be considered for transfer to a location where closer monitoring is available.

If the subject has unstable hemodynamics, or has any clinically significant dysrhythmias noted on telemetry, the subject should be immediately transferred to an acute care setting for definitive therapy.

If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each subject with an ECG skin marker pen to ensure reproducible electrode placement.

The following ECG parameters will be recorded: heart rate, PR-interval, QRS-duration, QT-interval, QTcF-interval, and the interpretation of the ECG profile by the principal investigator.

### 9.2.6 Trial Drug Administration

For Part 1 of the trial subjects will be randomized on Day 1 into 1 of 3 active treatment arms (TAK-906 maleate 5, 25, or 100 mg BID) or a placebo arm to receive trial drug PO in a double-dummy manner for 9 consecutive days.

For Part 2 of the trial, approximately 6 subjects who complete Part 1 (and following a minimum 7-day washout from the last dose in Part 1) will be enrolled in Treatment Group E (food effect), and they will receive PO TAK-906 maleate 25 mg with and without food in a crossover design. A minimum 7-day washout will separate the doses in each period. An additional 12 subjects who complete Part 1 will be enrolled into Treatment Group F to receive metoclopramide 10 mg.

### 9.2.7 AE Monitoring

AE monitoring begins following signing of informed consent and continues throughout the study. A complete description of AE collection and procedures is provided in Section 10.0.

### 9.2.8 Laboratory Procedures and Assessments

Laboratory samples will be collected in accordance with acceptable laboratory procedures. Samples will be taken following a minimum 8-hour overnight fast on the days stipulated in the Schedule of Trial Procedures (Section 3.0). The local laboratory will perform laboratory tests for hematology, serum chemistries, urinalysis, in addition to other tests at time of Screening to determine eligibility (note: prolactin only at screening for inclusion/exclusion).

#### 9.2.8.1 Clinical Laboratory Tests

##### Hematology

Hematology will consist of the following tests:

Erythrocytes (red blood cells [RBCs])	Hemoglobin
Hematocrit	Platelets
Leukocytes (white blood cells [WBCs]) with absolute differential	

##### Urinalysis

Urinalysis will consist of the following tests:

Protein	Glucose
Blood	Nitrite

Urine microscopy will be performed if urinalysis is abnormal. Microscopy consists of RBC/high-power field, WBC/high-power field, and casts.

##### Chemistry

Chemistry evaluations will consist of the following standard chemistry panel:

Albumin	Alkaline phosphatase
ALT	AST
Blood urea nitrogen	Calcium
Bicarbonate	Chloride
Creatinine	Glucose
Gamma-glutamyl transferase	Sodium
Potassium	Bilirubin (total), if above ULN total bilirubin will be fractionated
Protein (total)	

#### 9.2.8.2 Diagnostic Screening

##### Serum

Serum diagnostic evaluations will include the following tests:

HIV	Hepatitis Screen (hepatitis A virus antibody, HBsAg, hepatitis C virus antibody)
β-human chorionic gonadotropin (females only)	FSH (females only)
Prolactin	

##### Alcohol Screen

Subjects will undergo an alcohol test (breathalyzer or urine, at the discretion of the investigator).

##### Urine

A urine drug screen will include the following tests:

Amphetamines	3,4-methylenedioxy-methamphetamine
Barbiturates	Methadone/metabolite
Benzodiazepines	Opiates
Buprenorphine/metabolite	Oxycodone/oxymorphone
Cannabinoids	Phencyclidine
Cocaine/metabolites	

#### 9.2.9 Symptom Assessments

##### 9.2.9.1 Company Confidential Information

Company Confidential Information

##### 9.2.9.2 Company Confidential Information

Company Confidential Information

##### 9.2.9.3 Company Confidential Information

Company Confidential Information

9.2.9.4 Company Confidential  
Information  
Company Confidential Information

### 9.3 PK, PD, and Pharmacogenetic Samples

Samples for PK, PD, and or other biomarker analysis will be collected as specified in the Schedule of Trial Procedures (Section 3.0). Please refer to the Laboratory Manual for information on the collection, processing, and shipment of samples to the Central Laboratory.

The decision as to which plasma and/or serum samples collected will be assayed for evaluation of PK and PD will be determined by the sponsor (eg, samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional biomarkers.

Primary specimen collection parameters are provided in Table 9.a.

**Table 9.a Primary Specimen Collections**

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for TAK-906 PK	Plasma		PK measurements	Mandatory
Plasma sample for metoclopramide PK	Plasma		PK measurements	Mandatory
Serum sample for PD	Serum		PD measurements	Mandatory
Blood Sample for DNA PGx	Blood	DNA	PGx measurements	Mandatory

PGx=pharmacogenetic.

#### 9.3.1 PK Measurements

PK parameters will be derived using noncompartmental analysis methods and will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all PK computations involving sampling times for plasma PK parameters.

For TAK-906, the following PK parameters including, but not limited to, will be calculated as appropriate:

- Day 1: Area under the concentration-time curve during a dosing interval ( $AUC_{\tau}$ ),  $C_{max}$ ,  $t_{max}$ .
- Day 7:  $AUC_{\tau}$ ,  $C_{max}$ ,  $t_{max}$ , terminal disposition phase half-life ( $t_{1/2z}$ ), observed concentration at the end of a dosing interval ( $C_{trough}$ ).

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Additional PK parameters may be calculated as appropriate. A detailed PK analysis plan will be prepared before PK parameter computation.

#### 9.3.1.1 Plasma or Serum for PK Measurements

PK blood samples for plasma TAK-906 concentrations will be collected as specified in Parts 1 and 2 of the Schedule of Trial Procedures (See Section 3.0). The collected blood samples may be archived for additional analysis of potential metabolites.

### 9.3.2 PD Measurements

#### 9.3.2.1 Serum Samples for Pharmacodynamics

Serum prolactin levels will be measured as a PD target engagement marker using an in vitro diagnostic assay (ADVIA Centaur Prolactin assay).

#### 9.3.2.2 GEBT

The GEBT test procedure should be administered under supervision of a health care professional although no specialized facilities or specially licensed personnel are required.

#### 9.3.2.3 SmartPill Motility

SmartPill is an ingestible capsule that measures pressure, pH and temperature as it travels through the GI tract to assess GE and GI motility and will be administered under supervision of a health care professional.

### 9.3.3 PGx

#### 9.3.3.1 Blood Sample for DNA PGx

When sampling of whole blood for PGx analysis occurs, every subject must sign an informed consent/be consented to participate in the trial. PGx is a component of the trial, participation in mandatory.

PGx is the study of variations of deoxyribonucleic acid (DNA) characteristics as related to drug response. There is increasing evidence that an individual's genetic background may impact the PK (absorption, distribution, metabolism, and excretion), PD (pharmacologic effects) and/or the clinical outcome (efficacy and/or safety).

PGx research in this trial may be conducted to understand how individual genetic variation in subjects impacts their trial drug treatment response. This information may also be used, for example, to develop a better understanding of the safety and efficacy of TAK-906 and other trial drugs, to increase understanding of the disease/condition being studied and other related conditions, gain a better understanding of the drug pharmacology and for generating information needed for research, development, and regulatory approval of tests to predict response to TAK-906.

Whole blood samples for DNA isolation will be collected from each consented subject in the trial. If necessary and feasible, a second aliquot of blood may be taken at a later time point if isolation of DNA from the first sample was not successful or possible.

Since PGx is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Detailed instructions for the handling and shipping of samples are provided in the Laboratory Manual.

### 9.4 Confinement

In Parts 1 and 2 of the study, the subject will be confined for approximately the first 8 hours following the first dose of medication to allow for intensive PK sampling and close glucose monitoring. At the discretion of the investigator, subjects may be requested to remain longer in the CRU.



## 10.0 ADVERSE EVENTS

### 10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment.

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

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting 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 medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses versus 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 parameters maybe considered 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 re-test and/or continued monitoring of an abnormal value are 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:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray, etc) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication

of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). 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 condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, investigators should ensure that the AE term recorded captures the change from Baseline in the condition (eg “worsening of…”).
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, 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 the first administration of study medication or after any change in study medication, 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 severity of AEs:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study medication, the event should be captured once with the maximum severity recorded.

#### Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. 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 but should be documented in the subject’s source documents. Complications resulting from an elective surgery should be reported as AEs.

#### Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the

database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.

- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the subject should be treated symptomatically.

#### 10.1.1 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. Is 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 Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizures	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/ Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia Spontaneous abortion / stillbirth and fetal death

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.0 and 10.1.1).

## 10.2 AE Procedures

### 10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

- Mild: An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

### 10.2.2 Assigning Causality of AEs

The relationship of each AE to study medication(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 a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs 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.

### 10.2.3 Start Date

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

### 10.2.4 End Date

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

### 10.2.5 Pattern of AE (Frequency)

Episodic AEs (eg, headache) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

### 10.2.6 Action Taken With Study Treatment

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

### 10.2.7 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.

- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; 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 diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become 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.”
- Recovered/ 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 – an AE that is 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.

### **10.2.8 Collection and Reporting of AEs, SAEs, and Abnormal LFTs**

#### *10.2.8.1 Collection Period*

Collection of AEs (ie, AEs, SAEs, abnormal LFTs, and other laboratory abnormalities) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until 14 days after the last dose of investigational product. For subjects who discontinue prior to the administration of study medication, AEs will be followed until the subject discontinues study participation or lost to follow-up.

#### *10.2.8.2 Reporting AEs*

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 prior to the first exposure to investigational product 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. Nonserious AEs that begin prior to the first exposure to investigational product, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication 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:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Causality (Investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with trial drug.
- Outcome of event.
- Seriousness.

#### *10.2.8.3 Reporting SAEs*

When an SAE occurs through the AE collection period it should be reported according to the procedure outlined below:

A Takeda SAE form must be completed, in English and signed by the investigator immediately or within 24 hours of first onset or notification of the event. 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 identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section [14.1.1](#).

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

Reporting of SAEs that begin before first administration of investigational product will follow the same procedure for SAEs occurring on treatment.

#### SAE Follow-Up

If information is 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.

#### *10.2.8.4 Reporting of Abnormal LFTs*

If a subject is noted to have ALT or AST elevated  $>3 \times \text{ULN}$  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  $>3 \times \text{ULN}$  and total bilirubin  $>2 \times \text{ULN}$  for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.8.3. 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. Follow-up laboratory tests as described in Section 9.2.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

#### **10.2.9 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities**

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, 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 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 an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.



## 11.0 STATISTICAL METHODS

### 11.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

A targeted data review will be conducted before database lock. This review will assess the accuracy and completeness of the trial database, subject evaluability, or appropriateness of the planned statistical methods.

#### 11.1.1 Analysis Sets

##### *11.1.1.1 Safety Set*

The safety set will consist of all subjects who are enrolled and receive at least 1 dose of trial drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

##### *11.1.1.2 PK Set*

The PK set will consist of all subjects who are enrolled and receive at least 1 dose of trial drug and have at least 1 measurable plasma TAK-906 concentration. All subjects with valid PK parameter estimates will be included in the summaries and analyses for that parameter.

If any subject is found to be noncompliant with the dosing schedule or has incomplete data, a decision will be made on a case-by-case basis as to whether that subject should be included in the PK analyses; however, data for all subjects will be presented in the data listings.

##### *11.1.1.3 PD Set*

The PD set for each PD measurement will consist of all subjects who are enrolled, receive at least 1 dose of study drug, have a baseline value, and have at least 1 valid postbaseline value for assessment of the PD measurement.

#### 11.1.2 Analysis of Demography and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment and overall for all subjects in the safety set. Summary statistics (number of subjects, mean, SD, median, minimum, and maximum) will be presented for continuous variables (eg, age, weight, and BMI), and the number and percentage of subjects within each category will be presented for categorical variables (eg, sex, ethnicity, and race). Individual subject demographic and baseline characteristic data will be provided in the data listings.

### 11.1.3 PK Analysis

Concentrations of TAK-906 will be summarized by treatment over each scheduled sampling time. Individual plasma concentration versus time data will be presented in a data listing. Plasma PK parameters of TAK-906 will be summarized by treatment using descriptive statistics.

A more detailed analysis will be presented in the SAP. Additional analyses will be included, if appropriate.

### 11.1.4 PD Analysis

For each of the following (ie, change in prolactin, change in GEBT gastric half-emptying time, change in SmartPill GE time, Company Confidential Information endpoints), a linear model will be fit; the model will include fixed effects of stratification factor, regimen (dose level), a random effect of subject, and a covariate of baseline value. Pairwise comparisons will be performed within this linear model, with the point estimate and 95% CI derived.

If there is a significant departure from the assumptions underlying the linear model, non-parametric analyses will be performed. Pairwise comparisons will be made via Wilcoxon Rank Sum tests along with Hodges-Lehmann estimate and 95% CI.

### 11.1.5 Safety Analysis

The safety set will be used for all summaries of safety parameters. These summaries will be presented by treatment.

#### 11.1.5.1 AEs

All AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) with onset occurring within 30 days after the last dose of trial drug (onset date minus last date of dose +1 ≤ 30) will be included in the summary tables. TEAEs will be summarized by SOC and PT. The following summary tables will be included in the report: summary of TEAEs and drug-related AEs, relationship of AEs to trial drug (related vs not related), severity of AEs, and SAEs. Data listings will be provided for all AEs including TEAEs, AEs leading to trial drug discontinuation, and SAEs.

#### 11.1.5.2 Clinical Laboratory Evaluation

Baseline, postdose, and change from Baseline to postdose laboratory data will be summarized by treatment. Individual results of laboratory tests from hematology, chemistry, and urinalysis that meet Takeda's markedly abnormal criteria will be summarized. All clinical laboratory data will be provided in the data listings.

#### *11.1.5.3 Vital Signs*

Baseline, postdose, and changes from Baseline in vital sign measurements will be summarized. Individual results of vital signs that meet Takeda's markedly abnormal criteria will be summarized. All vital sign data will be provided in the data listings.

#### *11.1.5.4 Other Safety Parameters*

Baseline, postdose, and changes from Baseline in quantitative ECG parameters will be summarized by treatment. Shift tables for each will be generated to show the investigator's ECG interpretations at each postdose collection by the interpretation at Baseline. Individual results of quantitative ECG parameters from the 12-lead safety ECGs that meet Takeda's markedly abnormal criteria will be summarized.

All ECG data will be provided in the data listings.

### **11.2 Interim Analysis and Criteria for Early Termination**

No formal interim analyses will be conducted.

### **11.3 Determination of Sample Size**

Assuming an SD of 20% for the percent change from Baseline in half-emptying time, a total of approximately 48 subjects (12 per treatment group) is sufficient to achieve around 80% power to detect a difference of 25% between TAK-906 doses and placebo in the GEFT by a 2-sample t-test with a 2-sided significance level of 0.05.

## **12.0 QUALITY CONTROL AND QUALITY ASSURANCE**

### **12.1 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 study site guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or the sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, trial 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.

### **12.2 Protocol Deviations**

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial 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.

Significant 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.

### **12.3 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 Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all study documents as described in Section [12.1](#).

### 13.0 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 International Conference on Harmonisation (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 B](#). The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

#### 13.1 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 Investigator’s Brochure, 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 trial. Until the site receives drug/notification no protocol activities, including screening, may occur.

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.

### 13.2 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, subject authorization form (if applicable), and subject information sheet (if applicable) describe 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 and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is 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, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) 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, subject authorization form (if applicable), and subject information sheet (if applicable) 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, subject authorization form (if applicable), and subject information sheet (if applicable) 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, the signed subject authorization form (if applicable), and subject information sheet (if applicable) 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. The sponsor must be notified of consent withdrawal.

### **13.3 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 study database or documentation via a unique identification 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 identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), 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 13.2).

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).

### **13.4 Publication, Disclosure, and Clinical Trial Registration Policy**

#### **13.4.1 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 clinical 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.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with

this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

#### **13.4.2 Clinical Trial Registration**

In order 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 TDC Americas 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.

#### **13.4.3 Clinical Trial Results Disclosure**

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

#### **13.5 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 for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.



## 14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

### 14.1 Administrative Information

#### 14.1.1 Study Contact Information

Contact Type / Role	Contact
SAE and pregnancy reporting	Company Confidential Information

#### 14.1.2 INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also 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 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix C).

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

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Signature of Investigator

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Date

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Investigator Name (print or type)

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Investigator's Title

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Location of Facility (City, State/Province)

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Location of Facility (Country)

### **14.1.3 Study-Related Responsibilities**

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

#### 14.1.4 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
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AST	aspartate aminotransferase
AUC <sub>∞</sub>	area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
AUC <sub>τ</sub>	area under the concentration-time curve during a dosing interval
BID	twice daily
BMI	body mass index
CI	confidence interval
C <sub>max</sub>	maximum observed concentration
CNS	central nervous system
CRU	clinical research unit
C <sub>trough</sub>	observed concentration at the end of a dosing interval
CYP	cytochrome P-450
DA	dopamine
D <sub>2</sub> /D <sub>3</sub>	dopamine receptors
DG	diabetes mellitus gastroparesis
DNA	deoxyribonucleic acid
EC <sub>50</sub>	half maximal effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GE	gastric emptying
GEBT	<sup>13</sup> C-Spirulina gastric emptying breath test
GI	gastrointestinal
GP	gastroparesis
HbA1c	glycosylated hemoglobin
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IG	idiopathic gastroparesis
IRB	institutional review board

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LFT	liver function tests
MAD	multiple-ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MTV	maximum tolerated volume
NF	National Formulary
Company Confidential Information	Company Confidential Information
PD	pharmacodynamic
PGx	pharmacogenetic
PK	pharmacokinetic
PO	oral administration or orally
PT	preferred term
QD	once daily
QTcF	QT interval with Fridericia correction method
RBC	red blood cell
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
$t_{1/2z}$	terminal disposition phase half-life
$t_{max}$	time of first occurrence of $C_{max}$
ULN	upper limit of normal
VTF	volume-to-fullness
WBC	white blood cell
WOCBP	woman of childbearing potential

## 15.0 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 conditions will be coded using MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

### 15.1 CRFs (Electronic and Paper)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. 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.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

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

After the lock of the clinical study database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principal investigator must review the data change for completeness and accuracy, and must sign and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. 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.

### 15.2 Record Retention

The investigator agrees to keep the records stipulated in Section 15.1 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 Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the Sponsor before disposing of any such documents.

## 16.0 REFERENCES

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## 17.0 APPENDICES

### Appendix A Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 04 are indicated. The corresponding text has been revised throughout the protocol.

#### **Change 1:** Changed the body mass index criteria for eligibility.

The primary change occurs in Section [7.1 Inclusion Criteria](#)

Initial Have a body mass index (BMI)  $\geq 18$  and  $\leq 35$  (kg/m<sup>2</sup>) at the Screening Visit.  
wording:

Amended or Have a body mass index (BMI)  $\geq 18$  and  $\leq 40$  (kg/m<sup>2</sup>) at the Screening Visit.  
new wording:

#### **Rationale for Change:**

To broaden the BMI range for eligibility.

## **Appendix B 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 that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. 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.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. 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.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. 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.
10. 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.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the Sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

## **Appendix C 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 that:
  - a) 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) 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 medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
  - d) Subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon 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) The subject's identity will remain confidential in the event that study results are published.
25. If applicable, woman of childbearing potential (WOCBP) (eg, nonsterilized, premenopausal women) who are sexually active must use highly effective double-barrier contraception (as defined in the informed consent) from signing the informed consent and throughout the

duration of the study, and for 90 days after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all WOCBP. 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. Men must use highly effective double-barrier contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 5 half-lives PLUS 30 days after the last dose of study drug. 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 D Investigator Consent to the 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, United States, 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 medication.
- 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 E Pregnancy and Contraception

### *Male Subjects and Their Female Partners*

From signing of informed consent, throughout the duration of the study, and for 5 half-lives PLUS 30 days after last dose of study drug, nonsterilized\*\* male subjects who are sexually active with a WOCBP\* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. WOCBP who are partners of male subjects must use additional contraception as shown in the list containing highly effective contraception below.

### *Female Subjects and Their Male Partners*

From signing of informed consent, throughout the duration of the study, and for 5 half-lives PLUS 30 days after last dose of study drug, a WOCBP\* who are sexually active with a nonsterilized male partner\*\* must use a highly effective method of contraception (from the list below). As there is a lack of adequate reproductive toxicity data, female subjects should be instructed to use 2 highly effective double-barrier methods of contraception/1 highly effective (from the list below) and 1 effective method (eg, condom with or without spermicidal cream or jelly).

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

### *Definitions and Procedures for Contraception and Pregnancy Avoidance*

#### The following definitions apply for contraception and pregnancy avoidance procedures.

\* A female subject is considered a WOCBP, ie, fertile, following menarche and until becoming post-menopausal 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 FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 years of age) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

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

#### 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 excluded, the only acceptable highly effective methods of contraception are:
  - Nonhormonal Methods:
    - Intrauterine device.
    - Bilateral tubal occlusion.



- Vasectomized partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success.
- True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 5 half-lives PLUS 30 days after last dose.

Note: Hormonal contraception may be susceptible to interaction with the investigative compound, comparator, concomitant medications, which may reduce the efficacy of the contraception method. Because the drug-drug interaction of TAK-906 with hormonal contraceptives has not been evaluated, hormonal methods of contraception are not an acceptable contraception method.

2. Effective method of contraception (ie, there may be a higher than 1% failure rate), to be used in conjunction with a highly effective method of contraception above, is defined as:
  - Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams PLUS male condom).
3. Unacceptable methods of contraception are:
  - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation 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.
4. Subjects will be provided with information on highly effective double-barrier 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 course of the study.
5. During the course of the study, regular serum/urine hCG pregnancy tests will be performed only for WOCBP and all subjects (men and women) 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:
  - a) Contraceptive requirements of the study.
  - b) Reasons for use of barrier methods (ie, condom) in males with partners of childbearing potential.

- c) Assessment of subject compliance through questions such as
  - i. Have you used the contraception consistently and correctly since the last visit?
  - ii. Have you forgotten to use contraception since the last visit?
  - iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is “yes”)
  - iv. Is there a chance you could be pregnant?
- 6. In addition to a negative serum/urine hCG pregnancy test at Screening, WOCBP must also have confirmed menses in the month before first dosing (no delayed menses). Subjects must also have a negative serum/urine hCG pregnancy test within 24 hours prior to receiving first dose of investigational drug, ie, as close as possible and prior to first dose of investigational drug, preferably on the same day.

*General Guidance With Respect to the Avoidance of Pregnancy*

Such guidance should include a reminder of the following:

- Contraceptive requirements of the study.
- Reasons for use of barrier methods (ie, condom) in males 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?
  - Is 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?

**Pregnancy**

WOCBP will be included in this study.

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug (TAK-906) should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 5 half-lives PLUS 30 days after the last dose, should also be recorded following authorization from the subject’s partner.

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.

If the pregnancy occurs during administration of active study drug, eg, after Day 1 of the study or within 5 half-lives PLUS 30 days of the last dose of active study drug, the pregnancy should be reported immediately to the contact listed in Section 14.1.1, using a pregnancy notification form.

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 woman/female partner of the male 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 (including comparator, if applicable) 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.

Amendment 4 A 2-Part, Randomized, Double-Blind and Open-Label, Placebo and Active-Comparator Controlled Trial to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics for TAK-906 in Subjects With Diabetes Mellitus and Gastroparesis or With Idiopathic Gastroparesis

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Personal Protected Data	Statistical Approval	14-Dec-2017 14:52 UTC
	Clinical Pharmacology Approval	14-Dec-2017 16:51 UTC
	Clinical VP Approval	14-Dec-2017 21:40 UTC