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

SAP Approve Date: 15 March 2018

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

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

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

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-906-1002

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

PHASE 2a

Version**:** Final

Date**:** 15 March 2018

Prepared by:

Personal Property Data

Based on:

Protocol Version: Amendment 04

Protocol Date: 14 Dec 2017

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

%CV	percent coefficient of variation
AE	adverse event
ALT	alanine aminotransferase
[redacted]	[redacted]
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{∞}	area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{τ}	area under the concentration-time curve during a dosing interval
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
C_{max}	maximum observed concentration
C_{trough}	observed concentration at the end of a dosing interval
CPK	creatine phosphokinase
CPAP	Clinical Pharmacology Analysis Plan
CRF	case report form
[redacted]	[redacted]
DG	diabetes mellitus and gastroparesis
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
GE	gastric emptying
GEBT	gastric emptying breath test
GGT	γ-glutamyl transferase
GI	gastrointestinal
GM	geometric mean
GP	gastroparesis
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IG	idiopathic gastroparesis
IVRS	Interactive Voice Response System
LDH	lactate dehydrogenase
LLN	lower limit of normal

LOCF	last observation carried forward
LS	least squares
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
OC	observed case
PD	pharmacodynamics
PK	pharmacokinetics
PO	oral administration or orally
PRO	patient-reported outcome
PT	preferred term
PTE	pretreatment events
QOL	quality-of-life
QTcF	QT interval with Fridericia correction method
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDB	standard database
SOC	system organ class
TEAE	treatment-emergent adverse event
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time of first occurrence of C_{max}
TLGs	tables, listings, and graphs
ULN	upper limit of normal
WBC	white blood cell
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of the study is:

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

4.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the prolactin pharmacokinetics (PK)/pharmacodynamics (PD) relationship in subjects with GP.
- To demonstrate the effect of TAK-906 on ^{13}C-Spirulina gastric emptying breath test (GEBT).

4.3 Exploratory Objectives

Exploratory objectives of this study are:

[redacted]

4.4 Study Design

This is a 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 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.

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 and a 1:1:1:1 ratio for 9 consecutive days, for a total of 17 doses (ie, BID Days 1 to 8 and morning dose on Day 9). Subject randomization will be stratified by the underlying condition, ie, DG versus IG. All trial drug dosing will be under fasted conditions. Gastrointestinal (GI) emptying will be evaluated following a test meal using a ^{13}C-Spirulina 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.

[redacted]

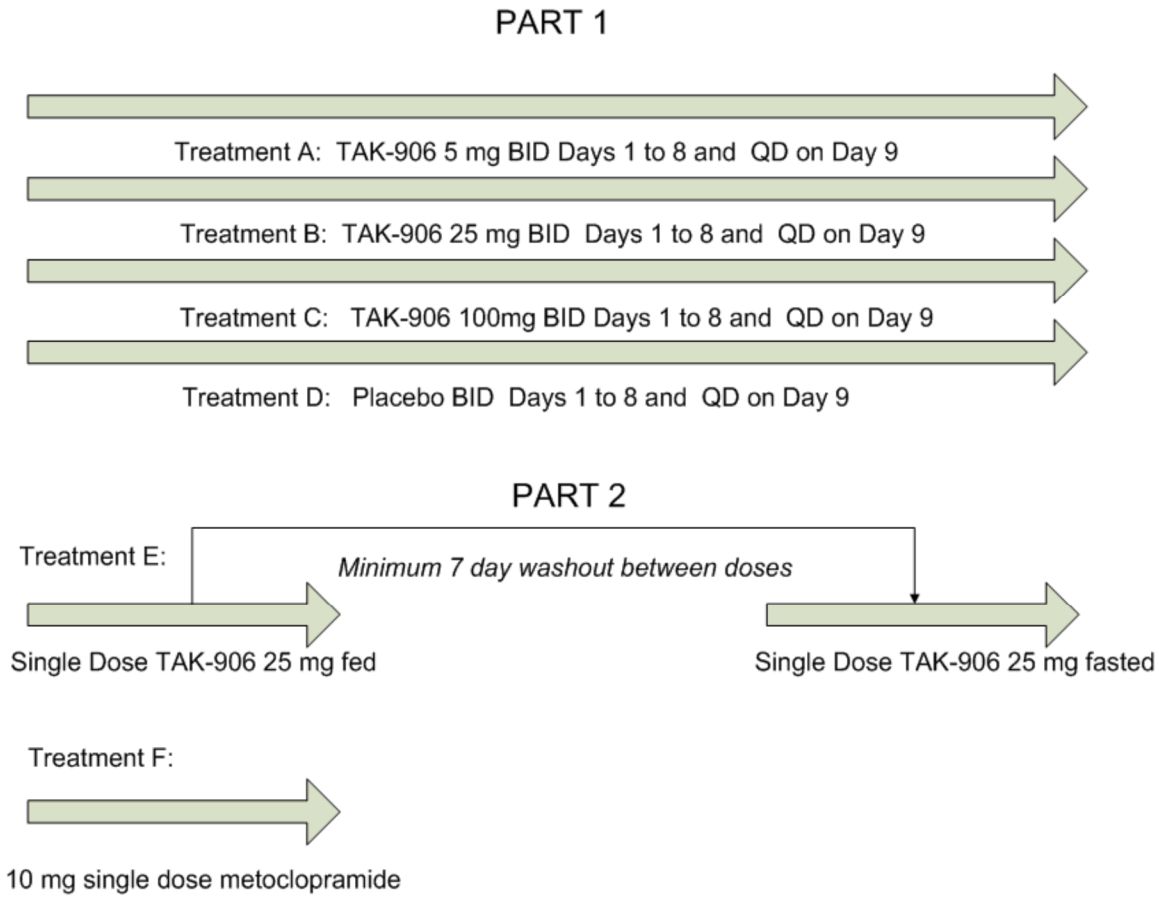
Approximately 18 subjects who completed Part 1 of the study (and following a minimum 7-day washout from the last dose in Part 1) will be enrolled into Part 2, the open-label period of the study. At the discretion of the investigator approximately 6 subjects will receive TAK-906 maleate 25 mg with and 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.

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).

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.

A schematic of the study design is shown in Figure 4.a. A schedule of assessments is listed in Appendix A.

Figure 4.a Trial Schematic



5.0 ANALYSIS ENDPOINTS

5.1 Primary Safety Endpoints

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

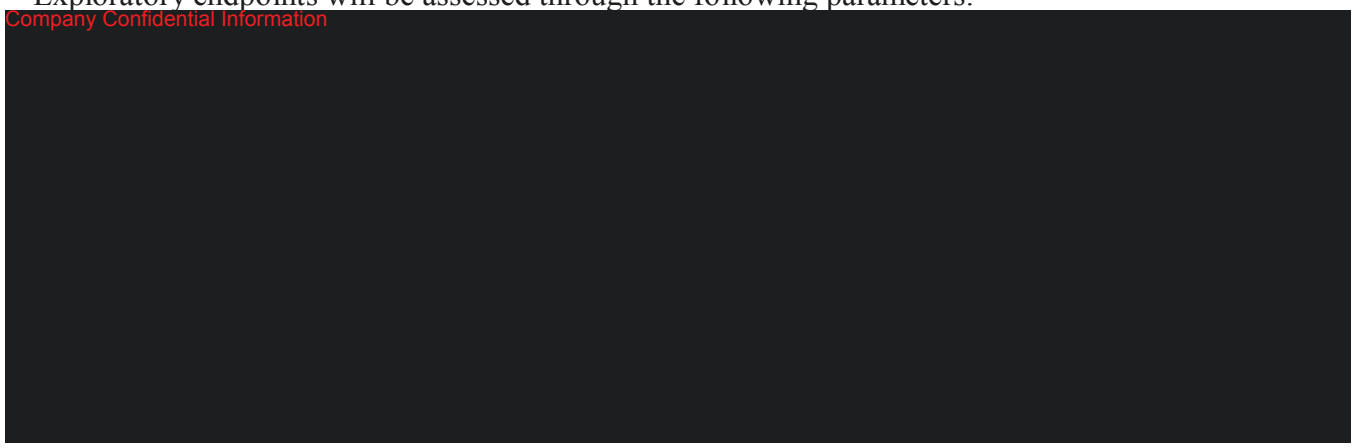
5.2 Secondary Endpoints

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}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}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 Exploratory Endpoints

Exploratory endpoints will be assessed through the following parameters:



6.0 DETERMINATION OF SAMPLE SIZE

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.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Study data will be analyzed and presented separately for Part 1, Part 2 group E (Food Effect) and Part 2 group F (metoclopramide) unless otherwise indicated. In general, Part 1 data will be analyzed by treatment, Part 2 group E data will be analyzed by regimen (fed vs fasted), and Part 2 group F data will be analyzed overall.

Categorical data will be summarized as the number and percentage of subjects in each category. Continuous data will be summarized using descriptive statistics, including the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. The coefficient of variation (%CV) and geometric mean will be included in the summary of continuous data where indicated.

Arithmetic means, geometric means, and medians will be presented to 1 more decimal place than the recorded data, and SDs will be presented to 2 more decimal places than the recorded data, where appropriate. Where applicable, confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate and p-values will be rounded to 3 decimal places prior to assessment of statistical significance.

All statistical tests and confidence intervals (CIs) will be 2-tailed at α=0.05 level for significance unless otherwise stated.

All study-related raw data for enrolled subjects, including derived data, will be presented in data listings. In addition, the actual day relative to the first dose will be presented, where applicable.

All statistical analyses will be performed using the SAS System Version 9.4.

7.1.1 Definition of Study Days, Baseline and Study Visit Windows

Study Day 1 is defined as the date of the first dose of study drug, as recorded on the electronic case report form (eCRF) study drug administration page. Other study days are defined relative to Study Day 1, with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1. Study days prior to the first dose of study drug will be calculated as: [date of assessment/event – date of first dose of study drug]. Study days on or after the first dose of study drug will be calculated as: [date of assessment/event – date of first dose of study drug + 1]. For Part 2 group E, period day will be calculated relative to the date of first dose for that treatment period.

Unless specified otherwise, for all PD, symptom assessment, and safety endpoints from Part 1, Baseline is defined as the last non-missing measurement prior to the first dose of study drug.

For PD and safety endpoints from Part 2 group F, Baseline is defined as the last non-missing measurement prior to the first dose of study drug in Part 2.

For safety endpoints from Part 2 group E, Baseline is defined as the last non-missing measurement prior to first dose of study drug for the respective treatment period in Part 2.

In Part 1, for GEBT and SmartPill, a ±1 study day window is defined for Day 7 visit. [redacted]

More than 1 result for a parameter may be obtained in a visit window. In such an event, the result with the date closest to the scheduled visit day will be used in the summary and analysis. In the event of 2 observations equidistant to the scheduled visit day, the later of the observations will be used.

7.1.2 Missing Data

There will be no imputation of incomplete or missing data unless otherwise indicated.

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero in the summarizing concentration values and deriving of PK parameters. These values will be flagged in the data listings.

7.2 Analysis Sets

- **Safety Set**: The safety set will consist of all subjects who are randomized (Part 1) or enrolled (Part 2) and receive at least 1 dose of study drug in the respective part. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.
- **PK Set**: The PK set will consist of all subjects who are randomized (Part 1) or enrolled (Part 2) and receive at least 1 dose of study drug and have at least 1 measurable plasma TAK-906 or metoclopramide 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.
- **Full Analysis Set (FAS)**: The FAS will consist of all subjects who are randomized (Part 1) or enrolled (Part 2), receive at least 1 dose of study drug, have a baseline value, and have at least 1 valid postbaseline value for assessment of at least one of the PD measurement.
- **Per-Protocol Set (PPS)**: The PPS will include all FAS subjects who had no major protocol violations. The major protocol violation criteria will be defined as part of the blinded data review prior to the unblinding of subject's treatment assignment. The categories of major protocol violations include:
  a) not meeting inclusion/exclusion criteria defined in the Protocol Amendment 04 [1],
  b) receiving an incorrect study medication that leads to a treatment change,
  c) other major protocol violations that may be identified during blinded data reviews.

For Part 1, analyses using the **Safety Set and PK Set** will be based on the actual treatment the subject received. Analyses using the **FAS** will be based on the randomized treatment the subject was assigned.

7.3 Disposition of Subjects

Study Information, including date of first subject signing Informed Consent Form (ICF), date of first/last study drug, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, Medical Dictionary for Drug Regulatory Activities (MedDRA) Version, World Health Organization Drug Dictionary (WHODrug) Version, and SAS Version, will be tabulated.

A summary of screening failures and data listing of inclusion/exclusion criteria responses for subjects with violations will be provided. Eligibility for randomization into treatment phase (Part 1) will be summarized along with the primary reasons of screen failure as recorded in eCRF.

The number and percentage of subjects randomized/enrolled will be summarized by site, and by treatment group (Part 1) or by enrollment group (Part 2). The number and percentage of subjects who comprised each analysis set will also be summarized.

Disposition of all randomized/enrolled subjects will be tabulated. Categories will include:

- Subjects who were randomized but not treated (Part 1 only).
- Subjects who completed study drug.
- Subjects who prematurely discontinued study drug.
- Primary reasons for discontinuation of study drug, as entered on the eCRF.
- Subjects who completed all study visits.
- Subjects who prematurely discontinued study visits.
- Primary reasons for discontinuation of study visits, as entered on the eCRF.

Subjects with significant protocol deviations will be summarized and listed as captured on the eCRF. For subjects enrolled in both parts, any significant protocol deviations with start date prior to Day -1 of Part 2 will be summarized in Part 1.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics, including age at informed consent, gender, ethnicity, race, height (cm), weight (kg), body mass index (kg/m^2), and underlying disease condition (DG vs IG), will be summarized by treatment (Part 1 only) and overall for all subjects in the safety set.

For Part 1, baseline values of PD measurements and symptom assessments (Serum Prolactin, GEBT, SmartPill, Company Confidential Information) will also be summarized by treatment group and overall based on FAS and will be compared across treatment groups using an analysis of variance (ANOVA) model with treatment, and underlying disease condition as factors.

Individual subject demographic and baseline characteristic data will be provided in the data listings. Subjects enrolled in both parts of the study will be indicated.

7.5 Medical History and Concurrent Medical Conditions

Medical history is defined as significant conditions or diseases that resolved at or prior to the time of informed consent. Concurrent medical conditions are defined as significant ongoing conditions or diseases that are present at signing of informed consent.

Medical history and concurrent medical conditions will be coded using the latest version of MedDRA available, and will be summarized by treatment and overall using System Organ Class (SOC) and MedDRA preferred term (PT). Summary table will be provided for Part 1 only. The table will include number and percentages of subjects, and will be sorted in alphabetical order by SOC. Within an SOC, PTs are sorted in decreasing frequency based on the total number of subjects. A subject will only be counted once within a particular class even if he/she has multiple conditions/symptoms. Summaries will be based on the safety set. There will be no inferential analysis of medical history and concurrent medical conditions.

All medical history and concurrent medical condition data will be presented in data listings. Subjects enrolled in both parts of the study will be indicated.

7.6 Medication History and Concomitant Medications

Medication history information includes any medication stopped at or within 30 days prior to signing of informed consent. Medications used from signing of informed consent through the end of study will be considered as concomitant medications.

Medication history and concomitant medications will be coded using the latest version of the WHO Drug Dictionary available, and summarized by giving the number and percentage of subjects by preferred term within each therapeutic class, with therapeutic class sorted in alphabetical order and preferred term sorted in decreasing frequency based on the total number of subjects. If a subject reports taking 2 drugs belonging to the same class, he/she will only be counted once within that class. Summaries of medication history and concomitant medication will be based on the safety set. There will be no inferential analysis of medication history and concomitant medications.

All medication history and concomitant medications data will be presented in data listing. Subjects enrolled in both parts of the study will be indicated.

7.7 Study Drug Exposure and Compliance

The date and time of each dose for each subject will be reported in the data listing for all subjects. Summaries and listings of TAK-906 and metoclopramide PK data will be provided. No summary statistics for the extent of exposure to study drug or compliance calculations will be performed for this study.

7.8 Efficacy Analysis

Efficacy is evaluated through symptom assessments in Part 1 but is not the primary objective of this study. The exploratory analyses and summaries for efficacy will be based on the FAS.

The symptom assessment variables for this study are presented in Table 7.a.

Table 7.a Symptom Assessment Variables

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[redacted]

7.8.1 Company Confidential Information

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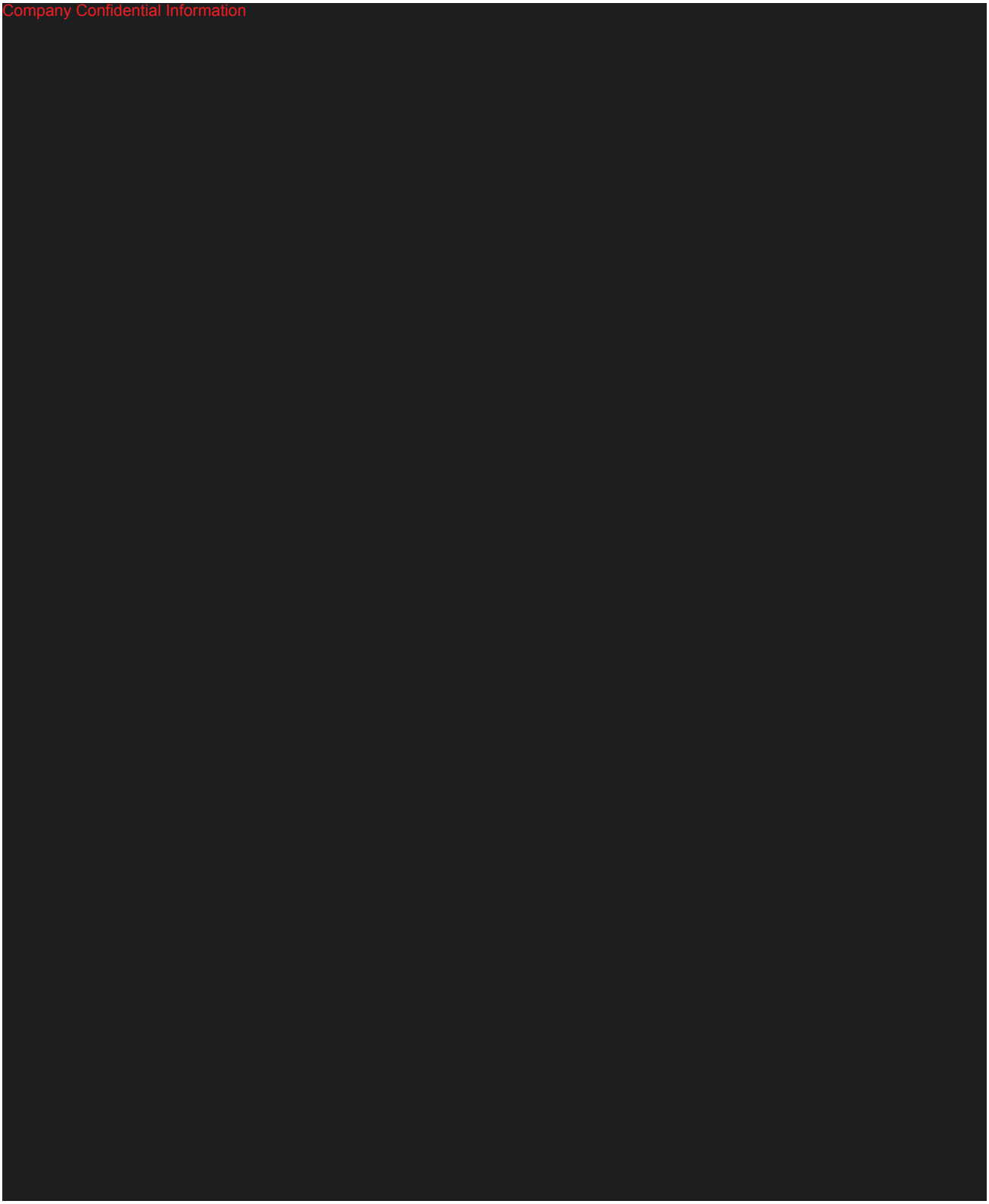
[redacted]



Company Confidential Information

Company Confidential Information

Company Confidential Information

7.8.2 Company Confidential Information

Company Confidential Information

7.8.3 Company Confidential Information

Company Confidential Information

7.8.4 Company Confidential Information

Company Confidential Information

[redacted]

7.8.5 Company Confidential Information

Company Confidential Information

[redacted]

7.8.6 Non-Parametric Analysis

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

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

The schedule of blood samples for PK analysis of TAK-906 and metoclopramide is specified in Appendix A.

The plasma concentration of TAK-906 and any measured metabolites will be summarized by treatment group (Part 1) or by regimen (Part 2 group E) over each scheduled sampling time point using descriptive statistics (N, arithmetic mean, SD, SE, %CV, median, minimum and maximum). For Part 1, the plasma concentration of TAK-906 will be summarized in overall population and by underlying disease condition (DG and IG). For Part 2 group F, plasma concentration of metoclopramide will be summarized over each scheduled sampling time point using descriptive statistics. Individual plasma concentration data versus time will be presented together with the descriptive statistics as well as in separate data listing.

The figures for mean plasma concentrations of TAK-906 (both Part 1 and Part 2 group E) and metoclopramide (Part 2 group F) versus time (linear and semi-log scale) will be generated. For Part 1, mean concentration-time curves will be generated separately for Day 1, Day 7, and Day 1 - Day 9. The mean concentration versus time curves in Part 1 and Part 2 group F will be presented in overall population and by underlying disease condition (DG and IG).

The figures for individual plasma concentrations of TAK-906 (both Part 1 [Day 1- Day 9] and Part 2 group E) and metoclopramide (Part 2 group F) versus time (semi-log scale) will be generated.

Plasma PK parameters will be calculated from the concentration-time data for TAK-906, any measured metabolites of TAK-906, and metoclopramide using non-compartmental analysis. The key PK parameters are listed below:

Part 1- TAK-906

- AUC_{τ}: Area under the concentration-time curve during a dosing interval (Day 1 and 7).
- C_{max}: Maximum observed concentration (Day 1 and 7).
- C_{trough}: Observed concentration at the end of a dosing interval (Day 2- Day 9).
- t_{max}: Time of first occurrence of C_{max} (Day 1 and 7).

Plasma PK parameters of TAK-906, any measured metabolites of TAK-906, and metoclopramide will be summarized using descriptive statistics (N, arithmetic mean, SD, SE, %CV, median, minimum and maximum). In addition, geometric mean and geometric mean %CV will be computed. Individual plasma PK parameters will be presented in data listings. For Part 1,

the PK parameters of TAK-906 will be summarized by treatment and day, in overall population and by underlying disease condition (DG and IG).

For Part 1, individual plots for AUC_{τ} and C_{max} will be generated by treatment (dose) and day, in overall population and by underlying disease condition (DG and IG). For Part 2 group E, scatter plots for AUC_{∞} and C_{max} will be generated by regimen. For Part 2 group F, scatter plots for AUC_{∞} and C_{max} will be generated overall and by underlying disease condition, if applicable.

There will be no inferential analysis of PK parameters.

7.9.2 Pharmacodynamic Analysis

The analyses and summaries for PD will be based on the FAS.

7.9.2.1 Analysis of Serum Prolactin

Summary and analysis of serum prolactin will be performed in Part 1 only. Serum prolactin concentrations will be listed. Baseline, postbaseline and ratio of postbaseline relative to baseline in serum prolactin concentrations will be summarized at each scheduled time point by treatment group, in overall population and by underlying disease condition (DG and IG). Figures for mean serum prolactin concentrations (linear and semi-log scale) and ratio of postbaseline serum prolactin concentration relative to baseline versus time will be generated, in overall population and by underlying disease condition (DG and IG).

Baseline is defined as the predose concentration on Day 1 and Day 7.

PD parameters, including AUC (using exact method) and C_{max}, for Day 1 and Day 7 will be derived. PD parameters will be summarized by treatment and day, in overall population and by underlying disease condition (DG and IG). The change in serum prolactin from Baseline to Day 1 at time of first occurrence of C_{max} (t_{max}) will be quantified by a ratio of C_{max} relative to baseline concentration, and will be assessed using pairwise comparison from an ANCOVA model, in overall population and by underlying disease condition (DG and IG) if applicable. The model will include treatment and underlying disease condition (for analysis in overall population) as fixed factors, natural logarithm of baseline as covariate, and natural logarithm of ratio between C_{max} and baseline as the response. The appropriate estimates for the differences and the associated CIs will be exponentiated to evaluate the ratios under the original scale. Geometric mean and geometric mean %CV will be included in the summary of PD parameters. AUC will be analyzed in a similar manner with natural logarithm of the AUC as the response. A sensitivity analysis based on the PPS will be performed on PD parameters.

7.9.2.2 Analysis of GEBT

For both Part 1 [redacted], baseline and postbaseline GEBT gastric half-emptying time will be summarized and listed.

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In addition, Change from Baseline and Percent Change from Baseline in GEBT gastric half-emptying time at Day 1 and Day 7 in Part 1 will be analyzed using ANCOVA models, with treatment and underlying disease condition (for analysis in overall population) as fixed factors,

and baseline as covariate, in overall population and by underlying disease condition (DG and IG) if applicable. In case there is a significant departure from the assumptions underlying the linear model, non-parametric analysis method described in Section 7.8.6 will be applied.

For Part 1, figure of mean change from baseline in GEBT gastric half-emptying time over time (study day) will be generated by treatment.

Another GEBT metric, the percent dose excreted at time t multiplied by 1000 (*k*PCD) [4], will be summarized at each scheduled time point by treatment group for both Part 1 [redacted]. For Part 1, figure of mean change from baseline in *k*PCD over time (minutes) will be generated by treatment for both Day 1 and Day 7.

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Change from day 1 to day 7 in gastric half-emptying time and *k*PCD will be summarized.

Primary analysis of GEBT parameters will be based on FAS and will exclude subjects who is non-compliant to the test meal or test procedure, which is defined as consuming < 90% of the test meal (for both gastric half-emptying time and *k*PCD) or having any incomplete breath sample post 30 minutes and not equals 60 minutes (for gastric half-emptying time).

Two sensitivity analyses will be performed on GEBT parameters:

1. Analysis based on the PPS excluding subjects who is non-compliant to the test meal or test procedure as described in the primary analysis.
2. Analysis including all subjects in the FAS regardless whether they are fully compliant to the test meal/procedure, unless the parameters are not evaluable.

7.9.2.3 Analysis of SmartPill Motility

SmartPill will be administered in Part 1 only to assess GE and GI motility. Baseline and postbaseline GE time (Gastric Transit Time), Small Bowel Transit Time, and Colonic Transit Time measured by SmartPill will be summarized and listed. Percent Change from Baseline to Day 7 of these parameters will be analyzed in a manner similar to GEBT, in overall population and by underlying disease condition (DG and IG) if applicable. A sensitivity analysis based on the PPS will be performed.

In addition, exposure-response relationships may be investigated. A separate analysis plan will be prepared prior to the analysis, should it be necessary.

7.10 Other Outcomes

Meal data will be presented in data listing.

7.11 Safety Analysis

Safety analyses include adverse events (AEs), clinical laboratory parameters, vital sign parameters, 12-lead electrocardiogram (ECG) results.

All summaries of safety data are based on subjects in the Safety Set. For Part 1, safety data of the three TAK-906 dose groups will be summarized separately and pooled (excluding subject mapping tables).

7.11.1 Adverse Events

All AE verbatim terms will be coded by SOC and PT using the latest version of MedDRA dictionary.

A treatment-emergent adverse event (TEAE) will be defined as an AE or serious adverse event (SAE) that started or worsened after first study drug administration and within 30 days of last dose of study drug (onset date – date of last dose + 1 ≤30). For subjects enrolled in both parts, any TEAEs with onset date prior to the date of first dose in Part 2 will be summarized in Part 1. AEs with missing onset dates will be summarized with TEAEs regardless of severity and relationship to study medication.

TEAEs will be summarized by giving the number and percentage (N [%]) of subjects reporting any event for each term. The following is a list of TEAE summary tables to be generated.

- Overview of TEAEs (at both subject and event level).
- TEAEs by SOC and PT (at both subject and event level).
- Subject Mappings for TEAEs.
- TEAEs by SOC and PT by underlying disease condition (DG and IG).
- TEAEs by PT.
- Relationship of TEAEs to Study Drug by SOC and PT.
- Drug-Related TEAEs by SOC and PT.
- Intensity of TEAEs by SOC and PT.
- TEAEs leading to study discontinuation by SOC and PT (Part 1 only).
- Treatment-emergent SAEs by SOC and PT (Part 1 only).
- Most Frequent (>=5%) Non-serious TEAEs by SOC and PT (at both subject and event level, Part 1 only).

SOCs will be sorted by alphabetical order. Within a SOC, PTs will be sorted in descending order based on the total number of subjects with AEs. For each category and overall, subjects reporting more than 1 occurrence for a term (SOC or PT) being summarized will be counted only once using the most extreme incident (most severe for the intensity tables and related for the relationship to study drug tables).

Data listings will be provided for all TEAEs, TEAEs that led to study drug discontinuation, TEAEs that led to abnormal liver functions, SAEs, AEs that resulted in death, pretreatment events (PTEs), and AEs occurring more than 30 days after the last dose of study medication.

7.11.2 Clinical Laboratory Evaluations

Clinical safety laboratory tests include chemistry, hematology, urinalysis, and diagnostic screening. Refer to Appendix A for scheduled clinical laboratory test measurements and to Appendix B for the list of all clinical laboratory tests.

For Part 1, descriptive statistics (N, mean, median, SD, minimum and maximum) of clinical safety laboratory variables will be summarized for baseline, postbaseline values, and change from baseline by treatment group and overall at each visit. Only the scheduled measurements will be included in the summary. No inferential analysis will be performed.

Individual results for hematology and chemistry laboratory tests in Part 1 will be evaluated against the Takeda predefined laboratory markedly abnormal value (MAV) criteria (Appendix C). All subjects that meet the MAV criteria will be presented in a data listing. If a subject has a MAV for a particular laboratory test, all visits for that subject and for that parameter will be listed. The number and percentage of subjects with at least 1 postbaseline markedly abnormal laboratory test result will be presented by treatment group and overall. All postbaseline clinical lab results within 7 days of the last dose, including scheduled and unscheduled measurements will be included in the MAV summaries. The mapping of the subjects with postbaseline results which meet the MAV criteria will be listed as a table.

All clinical laboratory data will be presented in both SI in the data listings. Laboratory data outside of the normal reference range will be flagged on the listing.

In addition, shift in serum prolactin from baseline to postbaseline will be summarized using the criteria defined in Appendix D.

7.11.3 Vital Signs and Weight

Vital sign measurements include body temperature, heart rate, respiratory rate, and blood pressure. Refer to Appendix A for scheduled vital signs and weight measurement visits.

Descriptive statistics (N, mean, median, SD, minimum and maximum) of vital signs parameters and weight will be summarized for baseline, postbaseline, and change from baseline at each scheduled time point. Only the vital signs and weight collected at the scheduled visits or time points will be included in the summary. No inferential analysis will be performed.

All individual vital signs that meet Takeda's predefined criteria for markedly abnormal values (Appendix E) will be listed. If a subject has a MAV for a particular vital sign parameter, all visits for that subject and for that parameter will be listed. The number and percentage of subjects with at least 1 postbaseline markedly abnormal vital sign measurement will be summarized. All postbaseline vital signs within 7 days of the last dose, including both scheduled and unscheduled measurements, will be included in the MAV summaries. The mapping of the subjects with postbaseline results which meet the MAV criteria will be listed as a table.

All vital sign data will be presented in the listings. Vital sign MAVs will be flagged in the listings.

7.11.4 12-Lead ECGs

The scheduled 12-lead ECG data will be collected according to Appendix A. The ECG parameters include heart rate, PR interval, QRS duration, QT interval, and QT interval with Fredericia's corrections (QTcF).

Descriptive statistics (N, mean, median, SD, minimum and maximum) of quantitative ECG data will be summarized for baseline, postbaseline, and change from baseline at each scheduled time point. Only the ECGs collected at the scheduled visits or time points will be included in the summary. No inferential analysis will be performed for the observed ECGs.

For ECG interpretation data, shift tables will be provided as the number of subjects to assess interpretation status change from baseline to each scheduled postbaseline measurement.

All individual ECGs that meet Takeda's predefined criteria for markedly abnormal values (Appendix F) will be listed. If a subject has a MAV for a particular ECG parameter, all visits for that subject and for that parameter will be listed. The number and percentage of subjects with at least one markedly abnormal ECG measurement will be summarized. All post dose ECGs within 7 days of the last dose, including both scheduled and unscheduled measurements, will be included in the MAV summaries. The mapping of the subjects who meet the MAV criteria will be listed as a table.

All ECG data will be presented in the listings. ECG MAVs will be flagged in the listings.

7.11.5 Other Observations Related to Safety

Reproductive System Findings and Pregnancy Test data of female subjects will be presented in data listings. Fingerstick Glucose data of subjects with diabetes mellitus will also be listed.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

None.

8.0 REFERENCES

1. 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, Millennium Pharmaceuticals, Inc. (Takeda Global Research and Development –United States), Protocol No. TAK-906-1002, dated 14 December, 2017.

Appendix A Schedule of Trial Procedures

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)
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											

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----------X											
PD evaluations															
Serum samples for PD (n)	X	X		X----------X						X--------X					
Other															
Company Confidential Information															
Test meal (p)	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.

(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 [redacted].
(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 [redacted]
(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 ^{13}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**										
	-1	**Predose**	**0**	**0.5**	**1**	**1.5**	**2**	**4**	**8**	**24**	**48**	**Early Termination**	**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

Company Confidential Information [redacted]

(g Company Confidential Information [redacted]

(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.

Appendix B Clinical Laboratory Tests and Screening

Chemistry

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)	

Hematology

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

Urinalysis

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.

Urine Drug Screen

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

Alcohol Screen

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

Screening - Serum

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

Appendix C Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	<0.8 × LLN	>1.2 × ULN
Hematocrit	Both	<0.8 × LLN	>1.2 × ULN
RBC count	Both	<0.8 × LLN	>1.2 × ULN
WBC count	Both	<0.5 x LLN	>1.5 x ULN
Platelet count	Conventional SI	<75 x 10^3/μL <75 x 10^9/L	>600 x 10^3/μL >600 x 10^9/L

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3x ULN
AST	Both	--	>3x ULN
GGT	Both	--	>3x ULN
Alkaline phosphatase	Both	--	>3x ULN
Total bilirubin	Conventional SI	-- --	>2.0 mg/dL >34.2 μmol/L
Albumin	Conventional SI	<2.5 g/dL <25 g/L	-- --
Total protein	Both	<0.8x LLN	>1.2x ULN
Creatinine	Conventional SI	--	>2.0 mg/dL >177 μmol/L
Blood urea nitrogen	Conventional SI		>30 mg/dL >10.7 mmol/L
Sodium	Conventional SI	<130 mEq/L <130 mmol/L	>150 mEq/L >150 mmol/L
Potassium	Conventional SI	<3.0 mEq/L <3.0 mmol/L	>6.0 mEq/L >6.0 mmol/L
Glucose	Conventional SI	<50 mg/dL <2.8 mmol/L	>350 mg/dL >19.4 mmol/L
Chloride	Conventional SI	<75 mEq/L <75 mmol/L	>126 mEq/L >126 mmol/L
Calcium	Conventional SI	<7.0 mg/dL <1.75 mmol/L	>11.5 mg/dL >2.88 mmol/L
Bicarbonate	Conventional SI	<8.0 mEq/L <8.0 mmol/L	

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix D Criteria for Abnormal Values for Serum Prolactin

Unit	Gender	Normal	Markedly Abnormal Value
ng/mL	Female	≤29.2	>5x ULN
	Male	≤17.7	>5x ULN

Appendix E Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Heart Rate	bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	^{o}C	<35.6	>37.7
	^{o}F	<96.1	>99.9

Appendix F Criteria for Markedly Abnormal Values for the 12-Lead ECG Parameters

Parameter	Lower Criteria	Upper Criteria
Heart rate	<50 beats per minute	>120 beats per minute
PR	≤120 milliseconds	≥200 milliseconds
QT Interval	≤300 milliseconds	≥460 milliseconds
QTcF Interval	≤300 milliseconds	≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QRS	≤60 milliseconds	≥120 milliseconds

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Personal Protected Data	Statistical Approval	21-Mar-2018 14:02 UTC
	Statistical Approval	21-Mar-2018 14:02 UTC
	Clinical Approval	21-Mar-2018 14:05 UTC