16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan, Version 1.0, Date: 13 November 2019

Statistical Analysis Plan, Table, Listing, and Figure Shells, Version 1.0, Date: 13 November 2019

Statistical Analysis Plan

Protocol No. HMM0111, Version 1.3, 05 March 2019

A PHASE 1, OPEN-LABEL, SEQUENTIAL, MULTIPLE-DOSE, DRUG-DRUG INTERACTION STUDY OF DORZAGLIATIN AND SITAGLIPTIN IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS

Sponsor: Hua Medicine (Shanghai) Ltd.
No. 275 Ai Di Sheng Road
Pudong, Shanghai
P. R. China, 201203
Tel: +86 2158869997-3301

Prepared by: Frontage Clinical Services, Inc.
200 Meadowlands Parkway
Secaucus, NJ 07094, USA
Tel: (201) 678-0288
Fax: (201) 552-2597

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Signature Page

Author:	
Ruth E. Swanton, MPH Director of Biostatistics Frontage Clinical Services, Inc. 101 Carnegie Center, Suite 102 Princeton, NJ 08540	Signature: Ruth E Swanton Date: 11-13-2019
Ken Yin, PhD Director, Clinical Pharmacology Frontage Clinical Services, Inc. 200 Meadowlands Parkway Secaucus, NJ 07094	Signature: Ken Yin Date: 13- Nov -2019
Frontage Representative:	
Michelle Pluviose Project Manager Frontage Clinical Services, Inc. 200 Meadowlands Parkway Secaucus, NJ 07094	Signature: Date: 13-NOV-2019
Sponsor Representative(s):	
Shuang Ren, PhD Senior Director, Head of Clinical Pharmacology Hua Medicine (Shanghai) Ltd. No. 275 Ai Di Sheng Road Pudong, Shanghai P. R. China, 201203 Tel: +86 21 58869997-3301 Email: sren@huamedicine.com	Signature: Date: 15-Nov-2019

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Glossary and Abbreviations

Abbreviation	Term
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time Curve
AUC_{0-24h}	AUC Under the Concentration-Time Curve from 0 to 24 Hours
$AUEC_{0-4h}$	Area Under the Effect-Time Curve of Change from Baseline
BID	Twice Daily
BMI	Body Mass Index
BP	Blood Pressure
BQL	Below Quantification Limit
BUN	Blood Urea Nitrogen
CI	Confidence Interval
C_{max}	Observed Maximum Plasma Concentration
CE_{av}	Average Change from Baseline
CE_{max}	Maximum Change from Baseline
CL/F	Apparent Total Plasma Clearance of Drug after Oral Administration
CRC	Clinical Research Center
CV	Coefficient of Variation
DDI	Drug-Drug Interaction
dL	Deciliter(s)
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EOS	End of Study
FSH	Follicle Stimulating Hormone
GGT	Gamma-Glutamyl-Transferase
GK	Glucokinase
GKA	Glucokinase Activator
GLP-1	Glucagon-Like Peptide 1
GMR	Geometric Mean Ratio
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B Surface Antigen
Hct	Hematocrit
HCV	Hepatitis C Virus

Abbreviation	Term
HDL-C	High-Density Lipoprotein Cholesterol
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
h or hr	Hour (s)
ICF	Informed Consent Form
K_{el}	Elimination Rate Constant
LDH	Lactate Dehydrogenase
LDL-C	Low-Density Lipoprotein Cholesterol
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mg	Milligram(s)
mL	Milliliter(s)
N	Sample Size
NCA	Non-Compartmental Analysis
ng	Nanogram(s)
OGTT	Oral Glucose Tolerance Test
OTC	Over-The-Counter
PD	Pharmacodynamic
PE	Physical Examination
PHL	Potential Hy's Law
PK	Pharmacokinetic(s)
PR	Pulse Rate
PT	Preferred Term
QD	Once daily
RBC	Red Blood Cell
RR	Respiration Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error of the Mean
SOC	System Organ Class
T	Temperature
$T_{1/2}$	Terminal Elimination Half-Life
T2DM	Type 2 Diabetes Mellitus
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event

Abbreviation	**Term**
T_{max}	Time at which C_{max} was First Observed
ULN	Upper Limit of Normal
V_z/F	Apparent Volume of Distribution during Terminal Phase after Oral Administration
WBC	White Blood Count
WHO	World Health Organization

1. Introduction

Although the available drug interaction and pharmacokinetic (PK) data of dorzagliatin and sitagliptin detailed in **Section 3.4 of the Protocol** do not suggest a potential drug interaction, other drug transporter-mediated interactions cannot be ruled out. Furthermore, pharmacodynamic-based interaction potential needs to be evaluated. Based on the high likelihood that dorzagliatin may be co-administered with sitagliptin in Type 2 Diabetes Mellitus (T2DM) patients in a clinical setting, this study will provide clinical evidence of the Drug-Drug Interaction (DDI) potential between these two drugs.

The basis for the dosing regimen of sitagliptin is based on the recommended 100 mg once daily (QD) dosing of Januvia® for adults.[3] The 75 mg twice daily (BID) for dorzagliatin is the dose regimen proven to be safe and effective in Phase 1 and Phase 2 studies and selected for two current Phase 3 studies evaluating dorzagliatin as a mono-therapy and as an add-on treatment to metformin. In the present study, both drugs will be given for five days to ensure that steady-state is attained.

The sequential, multiple-dose study is designed to determine whether the steady-state pharmacokinetics of dorzagliatin and sitagliptin are affected, while at the same time whether there's a synergistic therapeutic effect between these two drugs when co-administered. The proposed dosing regimens with dorzagliatin and sitagliptin will allow the potential interactions to be assessed under conditions that are expected to provide maximal exposure at the doses being studied. The elimination half-lives of dorzagliatin and sitagliptin are relatively short which justifies the 24-hour interval for collecting all samples to characterize the pharmacokinetics of both drugs.

The statistical analysis follows the ICH guidance E9 and other related practices and guidance.

2. Study Objectives and Endpoints

2.1 Primary Objectives

The primary objectives of this study are:

To assess the potential pharmacokinetics interaction between dorzagliatin and sitagliptin in subjects with type 2 diabetes mellitus;

To evaluate the safety and tolerability of dorzagliatin with simultaneous administration of sitagliptin in subjects with type 2 diabetes mellitus.

2.2 Secondary Objective

The secondary objective of this study is:

To assess the pharmacodynamic responses of glucose, GLP-1, glucagon, insulin, and C-peptide following dorzagliatin, sitagliptin, or simultaneous administration of dorzagliatin and sitagliptin in subjects with type 2 diabetes mellitus.

2.3 Primary Safety Measures

Incidence of Adverse Events (AEs) and Serious Adverse Events (SAEs)

Blood glucose via glucometer readings

Laboratory abnormalities (hematology, clinical chemistry, and urinalysis)

Vital signs (blood pressure, respiratory rate, pulse rate, and oral body temperature)

12-lead electrocardiogram (ECG)

Physical Examination (PE) findings

3. Study Design and Methods

This is a Phase 1, open-label, sequential, multiple-dose, DDI study of glucokinase (GK) activator dorzagliatin and sitagliptin in subjects with T2DM. It is planned that 15 subjects will be enrolled to include at least 12 evaluable subjects. All subjects will receive treatment assignments as specified in Table 1, below.

Table 1 Treatment Assignments

Day	Sitagliptin	Dorzagliatin	PK Sample Collection
1-5	100 mg (QD) in AM for 5 days	-	Day 5: Sitagliptin alone
6-10	100 mg (QD) in AM for 5 days	75 mg (BID) for 4 days Morning dose only on Day 10	Day 10: Sitagliptin + Dorzagliatin
11-15	-	75 mg (BID) for 4 days Morning dose only on Day 15	Day 15: Dorzagliatin alone

Eligible subjects will have a minimum 12-day run-in period prior to admission to the clinical research center (CRC), during which time they will self-administer sitagliptin 100 mg QD up until and including Day -2. Sitagliptin will be dispensed by the CRC. Sitagliptin will be purchased and provided by the sponsor. Subjects will complete a diary to record sitagliptin doses taken each day and will be advised to monitor their blood glucose levels and report changes in health status to the CRC. A telephone call will be placed to all subjects at approximately Day 6 (±2 day) of the run-in period to assess general health and collect AE information.

Following completion of the run-in period, eligible subjects will be admitted to the CRC on Day -2, have a total of 18 overnight stays, and be discharged after End-of-Study procedures are completed on Day 17, or at early termination.

Blood samples for the determination of dorzagliatin and sitagliptin concentrations and corresponding PK analysis will be collected at the following time points on Days 5, 10 and 15:

- Pre-dose (within 30 minutes prior to dosing) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours post-dose.

Subjects will consume a 75-gram glucose solution 30 minutes following study drug dose administration on Days 5, 10, and 15, in lieu of a breakfast. Pharmacodynamic responses will be evaluated by measuring GLP-1 and glucagon in plasma, and glucose, insulin, and C-peptide in serum at:

- Baseline (prior to the study drug dose and within 60 minutes prior to oral glucose intake) and 0.5, 1, 1.5, 2, 2.5, 3, and 4 hours after oral glucose intake.

[The Safety measurements (laboratory analyses (chemistry, hematology, and urinalysis)) and Pharmacodynamic (PD) response measurements of glucose, insulin and C-peptide in serum will be provided by BioReference Laboratories. Pharmacodynamic (PD) response measurements of GLP-1 (Total and Active) and glucagon in plasma will be provided by Mercodia AB.]

Safety assessments will include monitoring AEs, blood glucose via glucometer readings, vital signs (blood pressure (BP), pulse rate (PR), respiratory rate (RR), and oral temperature (T)), clinical laboratory findings, resting ECGs, and physical examination (PE) findings.

Vital signs will be assessed at screening, on Day -1, on Days 1-15 within 60 minutes prior to each morning and evening dose, and on Day 17. Blood glucose will be measured using a glucometer three times each day on Days -2 (prior to first meal after admission) through Day 16, within 60 minutes before each meal and after study drug dosing when applicable.

Clinical laboratory evaluations (chemistry, hematology, urinalysis) will be performed at screening, on Days -1, 5, 10, 15 and 17. A resting 12 lead-ECG will be completed at screening, on Day -1, and 2 hours post-dose on Days 5, 10, 15 and 17.

Subjects who receive their Day 1 dose and then terminate study participation early will have Day 17 assessments performed, if possible, prior to discharge from the CRC.

All doses will be administered 60 (±5) minutes prior to a standardized meal and with approximately 240 mL (8 fluid ounces) of room temperature water. On Days 5, 10, and 15 there will be no meal offered after the morning dose and instead the oral glucose solution will be administered 30 minutes after the study drug dose. The actual time of each dose, each post-dose meal, and time of oral glucose solution administration will be recorded.

For further details of the study procedures refer to Table 2 Schedule of Procedures.

Table 2 Schedule of Procedures

Visit	**Screening**	**Run-in***	**In-patient at the CRC***									
Day	**-42 to -15**	**-14 to -3**	**-2**	**-1**	**1-4**	**5**	**6-9**	**10**	**11-14**	**15**	**16**	**17 EOS**
Informed consent	X											
Dispense/collect sitagliptin, at-home sitagliptin QD 100 mg. Tel call at Day -8±2 (Day 6 of the 12-day run-in period)*		X	X									
Admission to CRC			X									
Eligibility assessment	X			X								
Demographics	X											
Medical history	X		X									
Physical examination	X			X								X
Height (cm), Weight (kg)	X			X[1]								X[1]
Body mass index	X											
Standard 12-lead ECG[2]	X			X		X		X		X		X
Vital signs (BP, PR, RR, T)	X			X	Within 60 min prior to each study drug dose.							X
Clinical laboratory samples[3]	X			X		X		X		X		X
HIV, hepatitis B & C	X											
Urine drug /saliva alcohol	X		X									
Urine pregnancy test[4]	X		X									X
FSH and estradiol[4]	X											
OGTT/PD markers [5]						X		X		X		
C-peptide and HbA1c	X											
Dose administration[6]				Sitagliptin 100 mg QD on Day -1; Assigned treatment Days 1-15								
AE & con med reporting[7]		X	X	X	X	X	X	X	X	X	X	X
PK blood samples[8]						X	X	X	X	X	X	
Glucometer (finger stick)			Within 60 minutes before each meal and after study drug dosing when applicable									
Discharge from CRC												X

AE= adverse event; BP = blood pressure; con med = concomitant medications; CRC = clinical research center; ECG = electrocardiogram; EOS =End-of-Study; FSH: Follicle stimulating hormone; HIV = human immunodeficiency virus; PR = pulse rate; PK = pharmacokinetics; RR = respiratory rate; T = temperature.

*Run-in period is a minimum of 12 days. If longer than 12 days, admission to CRC remains on Day -2. Sitagliptin will be dispensed by CRC to eligible subjects any day prior to start of Day -14 at-home dosing.

[1]Obtain weight only.

[2]ECG obtained in supine position after at least 5 minutes rest. On Days 5, 10 and 15 ECGs obtained 2 hours (±15 minutes) after dose administration.

[3]Clinical laboratory samples include: hematology, chemistry and urinalysis. All samples collected prior to study drug dose on days of study drug administration.

[4]For female subjects, urine pregnancy test must be negative to enroll in the study. Serum FSH and estradiol will be evaluated for postmenopausal females to confirm status.

[5]Oral glucose solution administered 30 (±5) minutes after study drug dose on Days 5, 10 and 15. PD samples to measure GLP-1 and glucagon in plasma, and glucose, insulin, and C-peptide in serum collected at baseline (prior to the study drug dose and within 60 minutes prior to oral glucose intake) and at 0.5, 1, 1.5, 2, 2.5, 3 and 4 hours after oral glucose intake. All post-glucose collection times are ±5 minutes from nominal time.

[6]All subjects will receive: sitagliptin 100 mg QD on Days 1-5 (a.m. dose); sitagliptin 100 mg QD and dorzagliatin 75 mg BID on Days 6-10 (a.m. dose only on Day 10); and dorzagliatin 75 mg BID on Days 11-15 (a.m. dose only on Day 15). Morning dosing will occur at approximately 08:00 a.m. and evening dosing will occur at approximately 06:00 p.m. All doses are 60 (±5) minutes prior to meals except for Days 5, 10 and 15 morning doses when no meals are offered following the study drug dose. Subjects are to resume their regular medication on Day 16.

[7]SAE collection starts after signing ICF.

[8]PK samples collected pre-dose (within 30 minutes prior to dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18 and 24 hours post-dose on Days 5, 10 and 15. Blood collection time windows: ±5 minutes from 0-4 hours post-dose and ±10 minutes ≥6 hours post-dose.

3.1 Randomization

There is no randomization for this study. This is an open-label, single sequence study. Subjects may be enrolled singly or in groups.

3.2 Blinding

There will be no blinding for this open-label sequential study.

3.3 Sample Size Justification

Sample size calculations based on study design and intra-subject variability were performed by the sponsor. At least 10 evaluable subjects in the sequence will be required to achieve a power of at least 0.8 for the geometric mean ratios between the two treatments (sitagliptin + dorzagliatin vs dorzagliatin alone or sitagliptin + dorzagliatin vs sitagliptin alone) for C_{max} or $AUC_{0\text{-}24h}$ with the equivalence bounds of 0.8 and 1.25, assuming a true geometric mean ratio of 1 and an intra-subject variability (coefficient of variation) of 16.1%, in an equivalence test using two one-sided tests at a significance level of 0.05. The intra-subject variability for sitagliptin C_{max} or AUC is reported to be 16.1% and 5.7%, respectively. The intra-subject variability for dorzagliatin C_{max} or $AUC_{0\text{-}24h}$ is estimated to be 14.0% and 6.2%, respectively. Therefore, to ensure a satisfactory DDI assessment, and assuming a drop-out rate of 20%, 15 eligible subjects will be enrolled in order to obtain 12 evaluable subjects for DDI assessment.

Evaluable subjects are defined as subjects included in the DDI population. Refer to the below Section 4 Study Populations.

3.4 Data Handling

Summaries for continuous variables will include the descriptive statistics for number of subjects (n), mean (arithmetic and geometric), standard deviation (SD), minimum (min), median, and maximum (max), coefficient of variation (CV%, arithmetic, and geometric). Summaries for categorical (discrete) variables will include the descriptive statistics frequency and percentage.

Conventions for presentation of numerical data:

Minimum and maximum values will be presented to the same number of decimal places as the electronic Case Report Form (eCRF) data. Means and medians will be presented to one more decimal place than the eCRF data. Standard deviations will be presented to two more decimal places than the eCRF data.

Plasma concentrations data for dorzagliatin and sitagliptin will be displayed in listings as received from the bioanalytical laboratory.

In general, individual and summary values will be displayed using 3 significant figures regardless of the decimal point position as follows:

(1) Values $\geq$ 0.0001 and < 1 will be reported to 4 decimal places (e.g., 0.0123).

(2) Values $\geq$ 1 and < 10 will be reported to 2 decimal places (e.g., 1.02).

(3) Values $\geq$ 10 and < 100 will be reported to 1 decimal places (e.g., 10.2).

(4) Values $\geq$ 100 and < 1000 will be reported to as a whole integer (e.g., 100).

(5) Values $\geq$ 1000 or equal to 0 will be reported as a whole integer (e.g., 1000).

Values for T_{max} will be reported to 2 significant figures.

Baseline

For comparison against baseline (e.g. for vital sign), baseline is considered as the last available assessment or value on or before the first treatment in the study.

For PD parameters, the baseline is defined as the last value prior to the administration of oral glucose. The baseline corrected PD parameters will be calculated by subtracting the baseline value from the values post oral glucose intake.

4. Data Analysis

4.1 Subject Disposition

Eligibility status will be listed for all subjects in the study.

Subject disposition will be summarized using number and percent of subjects who complete the study. Subject disposition and completion status will be listed for all enrolled subjects.

4.2 Protocol Deviations

Key protocol deviations will be listed by subject.

Protocol deviations will be identified prior to database lock and may include but are not limited to significant violations of inclusion/exclusion criteria, noncompliance of the trial treatment taken, use of prohibited concomitant medications and not following clinical trial protocol procedures that may affect the evaluation of the PK and PD statistical analyses. Further programmatic edit checks on the time points and allowed windows may be conducted depending on the data. A listing by subject and a summary by protocol deviation will be produced.

4.3 Analysis Populations

Safety Population

All subjects who receive study drug on Day 1.

Pharmacokinetic (PK) Population

All subjects who receive study drug, have no major protocol deviations, and who have sufficient PK data to obtain reliable estimates of the key PK variables ($AUC_{0\text{-}24h}$, C_{max}).

Pharmacodynamic (PD) Population

All subjects who receive study drug, have no major protocol deviations, and have sufficient PD data to obtain reliable estimates of at least one of key PD parameters ($AUEC_{0\text{-}4h}$, CE_{max}, and CE_{av}) for either PD marker.

Drug-Drug Interaction Population

All subjects in the PK Population who complete all treatments as defined by the protocol.

Subjects who are excluded from the populations will be listed. A summary table of the populations will be produced.

4.4 Subject Demographics/other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Safety Population. The demographic and baseline characteristics will consist of age, gender, race, ethnicity, height (cm), weight (kg), body mass index (BMI) (kg/m^2), fasting blood glucose (FBG), and HbA1c. Demographic and baseline characteristics for the Safety Population will be listed as well.

The age is a calculated parameter. Age will be calculated using the subject's date of birth and the subject's informed consent date.

Continuous variables (e.g., age, height, weight, BMI, HbA1c, FBG) will be summarized by n, mean, SD, min, median, and max. Frequencies and percentages will be used to describe categorical (discrete) variables (e.g., gender, race and ethnicity).

4.5 General Medical History and Non-Drug Therapies

The presence/absence of any current medical condition and/or other significant medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1. Any non-drug therapies that are incurred during the course of the study will also be coded using MedDRA or WHO Drug dictionary (version WHO Drug Global B3 September 2019), as appropriate. Medical history will be summarized by system organ class and preferred term and listed by subject. Non-drug therapies will be listed by subject, system organ class and preferred term.

4.6 Prior and Concomitant Medications

All prescription medications and over-the-counter (OTC) products, including herbal products, taken within 30 days prior to screening and during the study period will be documented in the subject's source documentation and the eCRF. Therapy to treat T2DM taken within 3 months prior to screening will also be documented in the subject's source documentation and the eCRF. The documented use of prescription sitagliptin during the run-in period is required in the source documentation and the eCRF.

Prior and concomitant medications will be coded using the current version of WHO Drug Dictionary, version WHO Drug Global B3 September 2019, and listed by reported term, preferred term (PT), and Anatomical Therapeutic Class (ATC) classification (level 3). Medications will be listed by treatment and subject including the start and end dates and times, whether this medication is ongoing, dose, unit, route, frequency, and indication. A summary of prior and concomitant medications by ATC class level 3 and preferred term will be produced.

5. Pharmacokinetic Analysis

Blood samples for the PK analysis for the determination of dorzagliatin and sitagliptin concentrations will be collected.

Blood samples will be collected within 30 minutes prior to dosing and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours post-dose on Days 5, 10, and 15. Deviations for these collections include the following post-dose windows: ±5 minutes from 0-4 hours post-dose, and ±10 minutes ≥6 hours post-dose.

Blood sample collection within allowable time windows will not be considered as a protocol deviation as long as the actual sampling time is recorded.

5.1 Plasma Concentrations

Plasma concentrations of dorzagliatin and sitagliptin will both be expressed in ng/mL and listed at actual and nominal timepoints by subject, and summarized by treatment at each nominal timepoint using descriptive statistics (n, mean, SD, CV%, geometric mean, geometric CV%, median, min, max). All values below the quantification limit (BQL) will be labeled as such in the concentration listings and treated as zero if BQL values occur after the first but before the last quantifiable sample for the concentration data summary statistics.

Linear and semi-log scale plots of mean concentration levels of plasma dorzagliatin and sitagliptin and individual subject concentrations versus time profiles will be presented. For the PK Population, over lay plots of mean concentration for dorzagliatin (linear and semi-log linear) versus time will be generated for dorzagliatin + sitagliptin combination and dorzagliatin alone. Also, over lay plots of mean plasma concentration for sitagliptin (linear and semi-log linear) versus time will be generated for dorzagliatin + sitagliptin combination and sitagliptin alone.

If the DDI population is different from the PK population, these same over lay plots will be generated for the DDI population in addition to the PK population.

5.2 Pharmacokinetic Parameters

All PK calculations will be performed using Phoenix WinNonlin Version 8.1 (Certara USA, Inc., Princeton, USA). Plasma PK parameters will be calculated with the non-compartmental analysis (NCA) model with actual times of blood sample collection.

For PK parameter calculations, concentrations BQL will be set to zero if they occur prior to the first or after the last quantifiable concentration, and will be set to missing for data points in between. The key PK parameters will be $AUC_{0\text{-}24h}$, C_{max}, $T_{max.}$

Additional PK parameters will be calculated as feasible including K_{el}, $T_{1/2}$, CL/F, and V_z/F. All PK parameters except T_{max} and $T_{1/2}$ will be listed by treatment and subject, and summarized by treatment with descriptive statistics (n, mean [arithmetic and geometric], SD, min, median, max, and CV% [arithmetic, and geometric]). T_{max} will be described utilizing n, min, median, and max. $T_{1/2}$ will be summarized using n, arithmetic mean and SD, CV%, min, median, and max.

$AUC_{0\text{-}24h}$ will be estimated using the linear trapezoidal method from time 0 hour to time 24 hours. The value of K_{el} will be estimated by least-squares regression of the terminal log-linear plasma concentration-time profile.

No value of K_{el}, $T_{1/2}$, V_z/F, or CL/F will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile with at least three timepoints. If the adjusted R-squared value (Rsq_adjusted) is < 0.80, the PK analyst may evaluate if other time points are more appropriate for the calculation of K_{el}, otherwise no value of K_{el}, $T_{1/2}$, V_z/F and CL/F will be reported.

5.3 Drug-Drug Interaction Evaluations

The primary PK comparison will be based on the C_{max} and $AUC_{0\text{-}24h}$ between treatments for dorzagliatin and sitagliptin. A mixed model under the sequential design will be used for analyzing the PK parameter based on natural log-transformed values, with treatment as fixed effect and subject as random effect. A point estimate and the corresponding 90% confidence interval (CI) for the difference between least squares means of the two treatments will be calculated. The point estimate and the corresponding 90% CI will then be back-transformed (natural exponentiated) to obtain a point estimate and the 90% CI for the geometric mean ratio (GMR) in the original scale. A Forest plot of the PK parameters for 90% CI will be produced.

The effect of sitagliptin on the exposure of dorzagliatin will be determined by a PK comparison between the exposure of dorzagliatin on Day 10 vs Day 15.

The effect of dorzagliatin on the exposure of sitagliptin will be determined by a PK comparison between the exposure of sitagliptin on Day 10 vs Day 5.

6. Pharmacodynamic Evaluations

Pharmacodynamic responses will be evaluated by measurement of GLP-1 (Total and Active) and glucagon in plasma, and glucose, insulin, and C-peptide in serum. For the GLP-1, the total and active will be assayed and presented in a listing. Any GLP-1 end point (total and/or active) that is above the limit of quantification will be presented in the summary tables. Baseline corrected PD parameters will be calculated by subtracting the baseline value (last value prior to oral glucose intake) from the values post oral glucose intake for each marker. For the glucagon response, if the baseline corrected PD response has a positive value it will be set to "0", and for the negative values the absolute value will be used for estimation of the PD parameters. For the remaining PD responses, after baseline correction any negative values will be set to "0" and remaining positive values used for estimation of PD parameters. All PD responses will be listed by subject. Plots of mean value versus the scheduled time for each PD marker will be generated by treatment in linear scale and over-lay plots across treatments will be provided. Individual PD marker versus time graphs will be generated in linear scale.

Derivations and statistical analysis methods of PD parameters will include, but are not limited to $AUEC_{0\text{-}4h}$, CE_{max}, and CE_{av}. $AUEC_{0\text{-}4h}$ is defined as the area under the effect curve of change from baseline using baseline corrected values based on the specific PD response and is derived using the specific PD response from pre-dose (zero) to 4 hours. CE_{max}, and CE_{av} are derived by determining the maximum change from corrected baseline effect for the specific PD response, and the average change from baseline calculated as $AUEC_{0\text{-}4h}/4$, respectively. Summary tables will be produced for PD parameters by treatment with descriptive statistics (n, mean [arithmetic and geometric], SD, min, median, max, and CV% [arithmetic, and geometric]). In addition, homogeneity of PD parameters at pre-dose will be assessed using a t-test.

A comparison of the PD parameters will be performed using two mixed models on Day 10 versus Day 5 and on Day 10 versus Day 15, with log-transformed data for CE_{max}, CE_{av}, and $AUEC_{0\text{-}4h}$ with treatment as fixed effect and subject as random effect. The adjusted GMRs and the corresponding 90 % confidence intervals (90 % CIs) will be constructed, comparing Test (sitagliptin under co-administration with dorzagliatin) versus Reference (sitagliptin administered alone) treatments on Day 10 versus Day 5 and comparing Test (dorzagliatin under co-administration with sitagliptin) versus Reference (dorzagliatin administered alone) treatments on Day 10 versus Day 15. Additional tables and figures will be produced for these comparisons by the PD parameters for each PD response.

7. Safety Analysis

All summaries of safety data will be based on the Safety Population. Adverse events, monitoring of blood glucose via glucometer readings, resting 12-lead ECGs, vital signs (BP, respiratory rate (RR), pulse rate (PR), and body temperature (T)), and safety

laboratory (hematology, clinical chemistry, and urinalysis) data will be reviewed on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, ECG, BP, RR or PR abnormalities of potential clinical concern will be described.

Medical history and physical examination information, as applicable, collected during the study will be captured for inclusion into the study database, unless otherwise noted. Any untoward findings identified on PE conducted after the administration of the first dose of study medication will be captured as an AE, if those findings meet the definition of an AE. Data collected at Screening will be included in the study database. The assessment should include, but not be limited to, the following body systems: general appearance, skin, lymph nodes, eyes, ears, nose, and throat, neck, heart, and head, musculoskeletal/extremities, lungs, abdomen, and neurologic. The time points for PE are Screening, on Day -1, and on Day 17/End of Study. Vital Signs will be assessed at Screening, on Day -1, on Days 1-15 within 60 minutes prior to each morning and evening dose, and on Day 17/End of Study. Clinical laboratory evaluations will be performed at Screening, and on Days -1, 5, 10, 15 and 17/End of Study. Resting 12-lead ECG will be completed at Screening, on Day -1, and 2 hours post-dose on Days 5, 10, 15, and 17/End of Study. Blood glucose will be measured using a glucometer three times per day on Days -2 (prior to first meal after admission) through Day 16, within 60 minutes before each meal and after study drug dosing when applicable.

Safety evaluations will be based on the incidence, intensity (mild, moderate, or severe), and relatedness (Related, Possibly Related, Unlikely Related, or Not Related) of AEs and changes in subjects' PE findings, ECGs, vital signs, and clinical laboratory results and blood glucose. In the analysis of change from baseline for clinical laboratory parameters, 12 lead ECGs, and vital sign parameters, baseline is defined as the last value on or before the first dose of study drug.

7.1 Study Product Exposure

Exposure to study drug will be listed by subject and treatment received, indicating dose date and time. Any deviations will be documented.

For the 12 day run-in period prior to admission to the CRC, Sitagliptin 100 mg QD compliance will be defined as the actual use of Sitagliptin 100 mg QD divided by the expected use of Sitagliptin 100 mg QD multiplied by 100 (%). The actual use of Sitagliptin 100 mg QD is defined as the [number of tablets dispensed – number of tablets lost – number of tablets returned]. The expected use is defined as 1 tablet multiplied by 12 days (Sitagliptin 100 mg QD). The compliance will be listed with the run-in period data.

For the study period in the CRC the exposure to study medications will be listed.

7.2 Adverse Events

All AEs (non-serious) will be collected at the beginning of the run-in study period and until End-of-Study Visit. Adverse events reported after administration of the first dose of study drugs (Day 1) will be considered treatment-emergent. Adverse events will be considered treatment-emergent if not present prior to the initiation of the treatment with study drug on Day 1 or already present but worsens in either severity or frequency following exposure to the treatment. All reported AEs will be coded using Medical Dictionary for Regulatory Activities Version 22.0 or higher. All AEs will be graded as Mild, Moderate, or Severe. The causal relationship to study drug will be specified as Related, Possibly Related, Unlikely Related or Not Related (refer to the protocol for further information). Serious adverse events (SAE) that occur from ICF signing to the end of study (EOS) are reported, following EOS only drug related or possibly related SAEs will be reported. Should the Investigator be made aware of any SAE any time occurring after the active reporting period it must be promptly reported. Events with missing onset dates will be considered treatment-emergent. All AEs will be summarized by severity and by relationship to study drug. If a subject experiences more than 1 occurrence of the same AE (preferred term), the occurrence with the greatest severity and with association to the study drug will be used in the summary tables. Serious adverse events and AEs causing discontinuation will be tabulated. Treatment related SAEs and AEs causing discontinuation will also be summarized. All deaths during the study will be summarized and listed. All AEs will be listed by subject, System Organ Class (SOC) and Preferred Term (PT), along with information regarding onset, duration, severity, SAE (yes or not, and SAE category) and relationship to study drug, action taken with study medication, treatment of event, and outcome. (Refer to the protocol for further information.) All tabulations will be presented by treatment. All AEs will be listed by subject and by treatment.

Hypoglycemia events should be recorded on the hypoglycemia evaluation page of the eCRF. Detailed information listed below must be recorded for each occurrence of hypoglycemia: the start date and time, end date and time, whether blood glucose was tested, the type of test, blood glucose values, symptom descriptions, action taken, severe hypoglycemia or not, resolved or not, predisposing factors, causal relationship with the study drug, etc. All hypoglycemia events will be included as AEs in the summary tables. Severe hypoglycemia defined as severe cognitive impairment requiring external assistance for recovery should be reported as SAE.

7.3 Clinical Laboratory Assessments

Clinical laboratory test parameters, with associated reference ranges provided by the laboratory, will be listed for individual subjects. Summary statistics at the visit and change from baseline, including n, mean, SD, min, max, and median values, will be summarized for each quantitative laboratory parameter by treatment. Qualitative laboratory findings, normal/abnormal, will be tabulated for each parameter by treatment and visit, using shift

table from baseline to worst post-baseline visit. Refer to Table 3 Clinical Laboratory Tests below for the laboratory tests performed and refer to the Table 2 Study Procedures for the timing of the tests.

Table 3 Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hemoglobin (Hgb)	Blood urea nitrogen (BUN)	PH
Hematocrit (Hct)	Creatinine	Specific Gravity
Platelet count	Total bilirubin	Protein
Red blood cell (RBC) count	Alkaline phosphatase	Glucose
White blood cell (WBC)	Aspartate transaminase (AST)	Ketones
count with differential	Alanine transaminase (ALT)	Bilirubin
HbA1c	Gamma-glutamyl transferase (GGT)	Blood
	Lactic dehydrogenase (LDH)	Nitrites
	Glucose	Leukocytes
	Albumin	Urobilinogen
	Total protein	Microscopic urine analysis
	Bicarbonate	
	Phosphate	
	Sodium	
	Potassium	
	Chloride	
	Calcium	
	Total cholesterol	
	Triglyceride	
	HDL-C	
	LDL-C	
	Urate	

7.4 Vital Sign Assessments

Vital signs, including BP, respiratory rate, pulse rate, and oral temperature will be measured at times specified in the Study Procedures (refer to Table 2). Additional collection times will be permitted per the Investigator. All results will be listed by subject. Vital signs will be summarized using descriptive statistics including mean values and mean change from baseline values at each time point.

7.5 Physical Examinations

Refer to the Table 2 Study Procedures for the times performed. Physical examination results will be listed by subject.

7.6 Potential of Drug-Induced Liver Injury

Refer to Section 11.2.5 of the Protocol for further information and vigilance in the identification of Potential Hy's Law cases regarding liver biochemistry throughout the study. Potential Hy's Law (PHL) is defined as AST or ALT > 3x ULN and Total Bilirubin

(TBL) > 2x ULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame. Any results will be listed by treatment and subject in the AE Listing. During the study, liver function tests will be monitored regularly and recorded at discontinuation.

7.7 12-Lead ECG

To ensure safety of the subjects, a qualified individual at the investigative site will make comparisons of ECG parameters collected at various timepoints to baseline measurements. Refer to Table 2 for ECG collection timepoints. For all ECGs, details of rhythm, ventricular rhythm (VR), PR, QRS, QT, and QTc intervals and an overall evaluation will be recorded. Any ECG parameter outside of the below ranges may be considered abnormal by the Investigator:

- VR: 45-100 bpm
- PR: 120-210 msec
- QRS: ≤120 msec
- QT: <500 msec
- QTc: <450 msec

A listing of the 12-Lead ECG data will be presented by subject and treatment. Change from baseline for ECG parameters will be summarized by treatment.

QTc collected was the Fridericia's corrected parameter of QTcF.

8. Interim Analyses

No formal interim analysis will be conducted in this study.

9. Statistical Programming and Deliverables

All statistical analyses, tables, figures and listings will be generated in SAS (version 9.3 or later) with appropriate documentation and programming validation. The table of contents of all tables, listings, and figures will be presented in a Tables, Listings and Figures shell supplemental document.

10. Changes from Pre-specified Analyses

There are no changes from the pre-specified analyses for this study.

11. Changes to the Planned Analyses

Any deviation(s) of consequence from the statistical analysis plan (SAP) during the data analysis will be documented and justified in an amended SAP and/or in the final report or addressed in a separate document, as appropriate.

12. References (Numbered According to the Protocol)

3. Januvia® Package Insert, 2018, Merck and Company, Inc. Whitehouse Station, NJ 08889, USA

13. Revision History

Version	Date	Comments

Tables, Figures and Listings Shells

Protocol No. HUA HMM0111 V1.3, 05 March 2019

A PHASE 1, OPEN-LABEL, SEQUENTIAL, MULTIPLE-DOSE, DRUG-DRUG INTERACTION STUDY OF DORZAGLIATIN AND SITAGLIPTIN IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS

Sponsor: Hua Medicine (Shanghai) Ltd.
No. 275 Ai Di Sheng Road
Zhangjiang Hi-Tech Park
Pudong, Shanghai
P. R. China, 201203
Tel: +86 21 58869997-3301

Prepared by: Frontage Clinical Services, Inc.
200 Meadowlands Parkway
Secaucus, NJ 07094, USA
Tel: (201) 678-0288
Fax: (201) 552-2597

Document status: Final 1.0

Release date: 13 November 2019

TABLE OF TABLES

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Table 14.1.1
Subject Disposition by Treatment
All Enrolled Subjects

Subject Disposition	Sitagliptin 100 mg QD n (%)	Sitagliptin 100 mg QD + Dorzagliatin 75 mg BID n (%)	Dorzagliatin 75 mg BID n (%)	All Subjects n (%)
Enrolled	xx	xx	xx	xx
Completed	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Percentages are based on the number of enrolled subjects in the specified treatment group. n (%) = number and percent of subjects in the specified group.

Table 14.1.2
Summary of Analysis Populations by Treatment
All Enrolled Subjects

Population	Sitagliptin 100 mg QD (N=xx) n (%)	Sitagliptin 100 mg QD + Dorzagliatin 75 mg BID (N=xx) n (%)	Dorzagliatin 75 mg BID (N=xx) n (%)	All Subjects (N=xx) n (%)
Safety Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PK Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PD Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
DDI Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Percentages are based on the number of enrolled subjects in the specified treatment. n (%) = number and percent of subjects in the specified group; N = number of subjects in the specified study population. Safety Population: All subjects who receive study drug on Day 1. PK Population: All subjects who receive study drug, have no major protocol deviations, and who have sufficient PK data to obtain reliable estimates of the key PK variables ($AUC_{0\text{-}24h}$, C_{max}). PD Population: All subjects who receive study drug, have no major protocol deviations, and have sufficient PD data to obtain reliable estimates of key PD parameters ($AUEC_{0\text{-}4h}$, CE_{max}, and CE_{av}) for either PD marker. Drug-Drug-Interaction (DDI) Population: All subjects in the PK Population who complete all treatments as defined by the protocol.

Table 14.1.3
Protocol Deviations
All Enrolled Subjects

Deviation Type	All Subjects (N=xx) n (%)
Inclusion/Exclusion	xx (xx.x)
Restricted Concomitant Medications	xx (xx.x)
Study Drug Non-compliance	xx (xx.x)
Non-compliance with study procedures	xx (xx.x)

Percentages are based on the total number of enrolled subjects. n (%) = number and percent of subjects in the specified group; N = number of subjects in the specified study population.

Programming note: Use all categories as specified in the CRF.

Table 14.1.4
Demographics and Baseline Characteristics
Safety Population

Parameter	All Subjects (N=xx)
Age (years)	
n	xx
Mean	xx.x
SD	xx.x
Median	xx.x
Min, Max	xx, xx
Gender, n (%)	
Male	xx (xx.x)
Female	xx (xx.x)
Race, n (%)	
White	xx (xx.x)
Black or African American	xx (xx.x)
Asian	xx (xx.x)
American Indian or Alaskan Native	xx (xx.x)
Native Hawaiian or Other Pacific Islander	xx (xx.x)
Other	xx (xx.x)
Ethnicity, n (%)	
Hispanic or Latino	xx (xx.x)
Not Hispanic or Latino	xx (xx.x)
Not Reported	xx (xx.x)
Weight (kg)	
n	xx
Mean	xx.x
SD	xx.x
Median	xx.x
Min, Max	xx, xx
Height (cm)	
n	xx

Parameter	All Subjects (N=xx)
Mean	xx.x
SD	xx.x
Median	xx.x
Min, Max	xx, xx
BMI (kg/m^2)	
n	xx
Mean	xx.x
SD	xx.x
Median	xx.x
Min, Max	xx, xx
HbA1c (%)	
n	xx
Mean	xx.x
SD	xx.x
Median	xx.x
Min, Max	xx, xx
FBG (mg/dL)	
n	xx
Mean	xx.x
SD	xx.x
Median	xx.x
Min, Max	xx, xx

BMI = body mass index; Min = minimum; Max = maximum; n (%) = number and percent of subjects in the specified group; N = number of subjects in the specified study population; SD = standard deviation. FBG = fasting blood glucose. HbA1c = hemoglobin A1c.

Programming note: please follow Frontage convention for number of decimal places to display, unless otherwise specified by the sponsor. For the BMI, derive the BMI and use the decimal places instead of the dataset from the database which does not retain the zero decimals on export.

Table 14.1.5
Medical History
All Enrolled Subjects

System Organ Class Preferred Term	All Subjects (N=xx) n (%)
Subjects with any Medical History	xx (xx.x)
System Organ Class 1	xx (xx.x)
Preferred Term 1	xx (xx.x)
Preferred Term 2	xx (xx.x)
Preferred Term 3	xx (xx.x)
System Organ Class 2	xx (xx.x)
Preferred Term 1	xx (xx.x)
Preferred Term 2	xx (xx.x)
Preferred Term 3	xx (xx.x)
Etc.	

Percentages are based on the total number of enrolled subjects. N = number of subjects in the specified study population; n (%) = number and percent of subjects in the specified group. Subjects are counted once for each system organ class and once for each preferred term. MedDRA version 22.1 was used to code the Medical History.

Table 14.1.6
Prior and Concomitant Medications
Safety Population

ATC Class Preferred Term	All Subjects (N=xx) n (%)
Subjects with any Prior or Concomitant Medications	xx (xx.x)
ATC Class 1	xx (xx.x)
Preferred Term 1	xx (xx.x)
Preferred Term 2	xx (xx.x)
Preferred Term 3	xx (xx.x)
ATC Class 2	xx (xx.x)
Preferred Term 1	xx (xx.x)
Preferred Term 2	xx (xx.x)
Preferred Term 3	xx (xx.x)
Etc.	

Percentages are based on the total number of enrolled subjects. N = number of subjects in the specified study population; n (%) = number and percent of subjects in the specified group. Subjects are counted once for treatment, ATC Class, and once for each preferred term. Drug Enhanced Dictionary, version WHO Drug Global B3 September 2019 was used to code the Prior Medications. ATC = Anatomical/Therapeutic/Chemical (ATC) Level 3.

Table 14.2.1.1
Summary of Dorzagliatin Plasma Concentrations (unit)
PK Population

Scheduled Time Point	Statistic	Dorzagliatin 75 mg BID (N=xx)	Sitagliptin 100 mg QD + Dorzagliatin 75 mg BID (N=xx)
Pre-Dose	n	xx	xx
	Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
	CV%	xxx.x	xxx.x
	Geometric Mean	xx.x	xx.x
	Geometric CV%	xxx.x	xxx.x
	Median	xxx.x	xxx.x
	Min, Max	xxx, xxx	xxx, xxx
0.25 hours Post-Dose	n	xx	xx
	Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
	CV%	xxx.x	xxx.x
	Geometric Mean	xx.x	xx.x
	Geometric CV%	xxx.x	xxx.x
	Median	xxx.x	xxx.x
	Min, Max	xxx, xxx	xxx, xxx
Etc.			

CV = coefficient of variation; Min = minimum; Max = maximum; Mean = arithmetic mean; n = number of subjects in the specified group; N = number of subjects in the specified study population under each treatment; SD = standard deviation.

Programming Note**:** Include all applicable time points per the SAP. Refer to the SAP for the data handling of decimal places for each descriptive statistic.

Repeat:

.

Table 14.2.1.2
Summary of Sitagliptin Plasma Concentrations (unit)
PK Population

Programming Note: this is the same as 14.2.1.1 except using Sitagliptin concentrations alone instead of Dorzagliatin.

Table 14.2.2.1
Summary of Dorzagliatin Pharmacokinetic Parameters
PK Population

Parameter (unit)	Statistic	Dorzagliatin 75 mg BID (N=xx)	Sitagliptin 100 mg QD + Dorzagliatin 75 mg BID (N=xx)
AUC_{0-24h} (unit)	n	xx	xx
	Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
	CV%	xxx.x	xxx.x
	Geometric Mean	xxx.x	xxx.x
	Geometric CV%	xxx.x	xxx.x
	Median	xxx.x	xxx.x
	Min, Max	xxx, xxx	xxx, xxx
C_{max} (unit)	n	xx	xx
	Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
	CV%	xxx.x	xxx.x
	Geometric Mean	xxx.x	xxx.x
	Geometric CV%	xxx.x	xxx.x
	Median	xxx.x	xxx.x
	Min, Max	xxx, xxx	xxx, xxx
$T_{1/2}$ (unit)	n	xx	xx
	Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
	CV%	xxx.x	xxx.x
	Median	xxx.x	xxx.x
	Min, Max	xxx, xxx	xxx, xxx
T_{max} (unit)	n	xx	xx
	Min	xxx	xxx
	Median	xxx.x	xxx.x
	Max	xxx	xxx
Etc.			

CV = coefficient of variation; Min = minimum; Max = maximum; Mean = arithmetic mean; n = number of subjects in the specified group; N = number of subjects in the specified study population under each treatment; SD = standard deviation.

Programming Note:

- The order for PK parameters in the table is: C_{max}, AUC_{0-24h}, T_{max}, $T_{1/2}$, K_{el}, CL/F, V_z/F.
- Summarize PK parameters.
- Please follow Frontage convention for number of decimal places to display, unless otherwise specified by the Sponsor.
- All PK parameters except T_{max}, and $T_{1/2}$ will be summarized by treatment using descriptive statistics (n, mean, median, SD, CV%, min, and max). In addition, geometric mean and geometric CV% will be calculated for AUC_{0-24h}, C_{max}, K_{el}, V_z/F and CL/F. T_{max} will be described utilizing n, minimum, median, and maximum. The $T_{1/2,}$ will be summarized using n, arithmetic mean and SD, CV%, min, median, and max.

Table 14.2.2.2
Summary of Sitagliptin Pharmacokinetic Parameters
PK Population

Programming Note: for this use template for 14.2.2.1 and change the Dorzagliatin 75 mg BID alone to Sitagliptin 100mg QD.

Table 14.2.2.3
In-Text Table for Summary of Dorzagliatin Pharmacokinetic Parameters
PK Population

PK Parameter	Statistic	Dorzagliatin 75 mg BID (N=xx)	Sitagliptin 100 mg QD + Dorzagliatin 75 mg BID (N=xx)
C_{max} (units)	n Mean (SD)		
AUC_{0-24h} (units)	n Mean (SD)		
T_{max} (h)	n Median (Min-Max)		
$T_{1/2}$ (h)	n Mean (SD)		
K_{el} (1/h)	n Mean (SD)		
V_z/F (L)	n Mean (SD)		
CL/F (L/h)	n Mean (SD)		

N = number of subjects in the specified study population under each treatment; Mean = arithmetic mean; SD = standard deviation; Min = minimum; Max = maximum; n = number of subjects in the specified group.

Programming Note:
The order for PK parameters in the table is: C_{max}, AUC_{0-24h}, T_{max}, $T_{1/2}$, K_{el}, CL/F. V_z/F. (same as 14.2.2.1)
This in-text table is summarized from Tables 14.2.2.1 and directly used for Clinical Study Report (CSR).

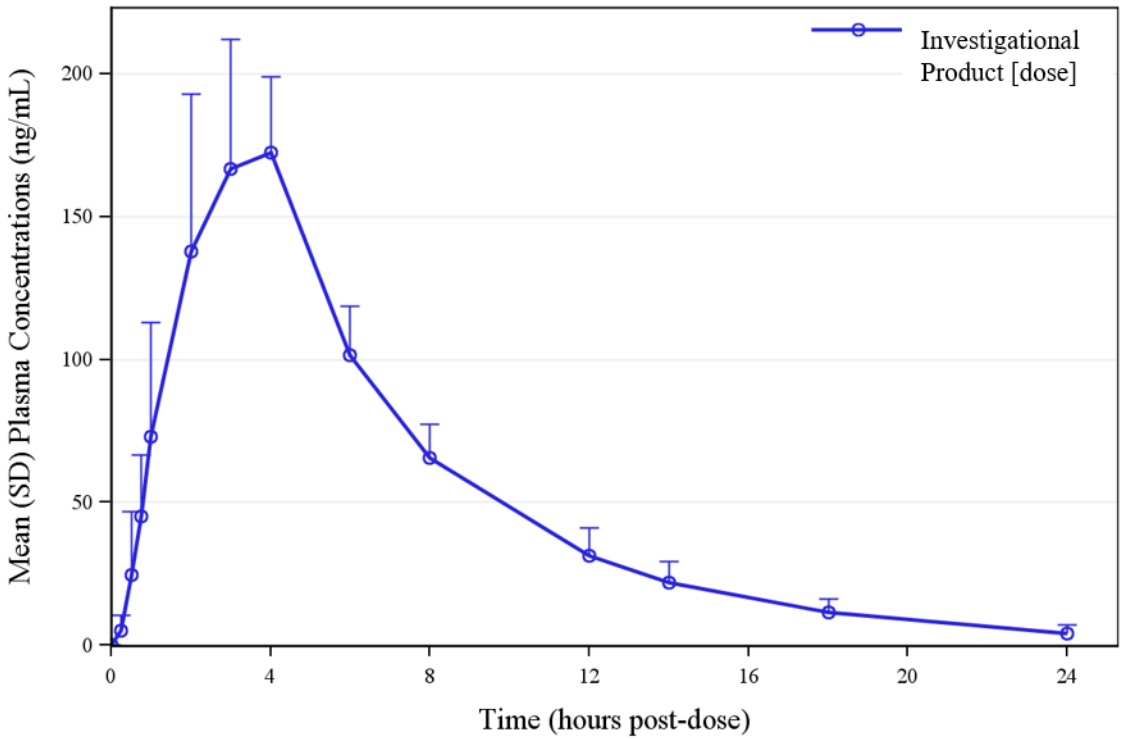
Table 14.2.2.4
In-Text Table for Summary of Sitagliptin Pharmacokinetic Parameters
PK Population

PK Parameter	Statistic	Sitagliptin 100 mg QD (N=xx)	Sitagliptin 100 mg QD + Dorzagliatin 75 mg BID (N=xx)
C_{max} (units)	n Mean (SD)		
AUC_{0-24h} (units)	n Mean (SD)		
T_{max} (h)	n Median (Min-Max)		
$T_{1/2}$ (h)	n Mean (SD)		
Kel (1/h)	n Mean (SD)		
V_z/F (L)	n Mean (SD)		
CL/F (L/h)	n Mean (SD)		

N = number of subjects in the specified study population under each treatment; Mean = arithmetic mean;
SD = standard deviation; Min = minimum; Max = maximum; n = number of subjects in the specified group.

Programming Note:
The order for PK parameters in the table is: C_{max}, AUC_{0-24h}, T_{max}, $T_{1/2}$, AUC_{0-4h}, Kel, CL/F. Vz/F. (same as 14.2.2.2)
This in-text table is summarized from Tables 14.2.2.1 and directly used for Clinical Study Report (CSR).

Figure 14.2.1.1
Mean (SD) Dorzagliatin Plasma Concentrations versus Time by Treatment (Linear Scale)
(Dorzagliatin + Sitagliptin and Dorzagliatin alone)
PK Population



Programming Note:

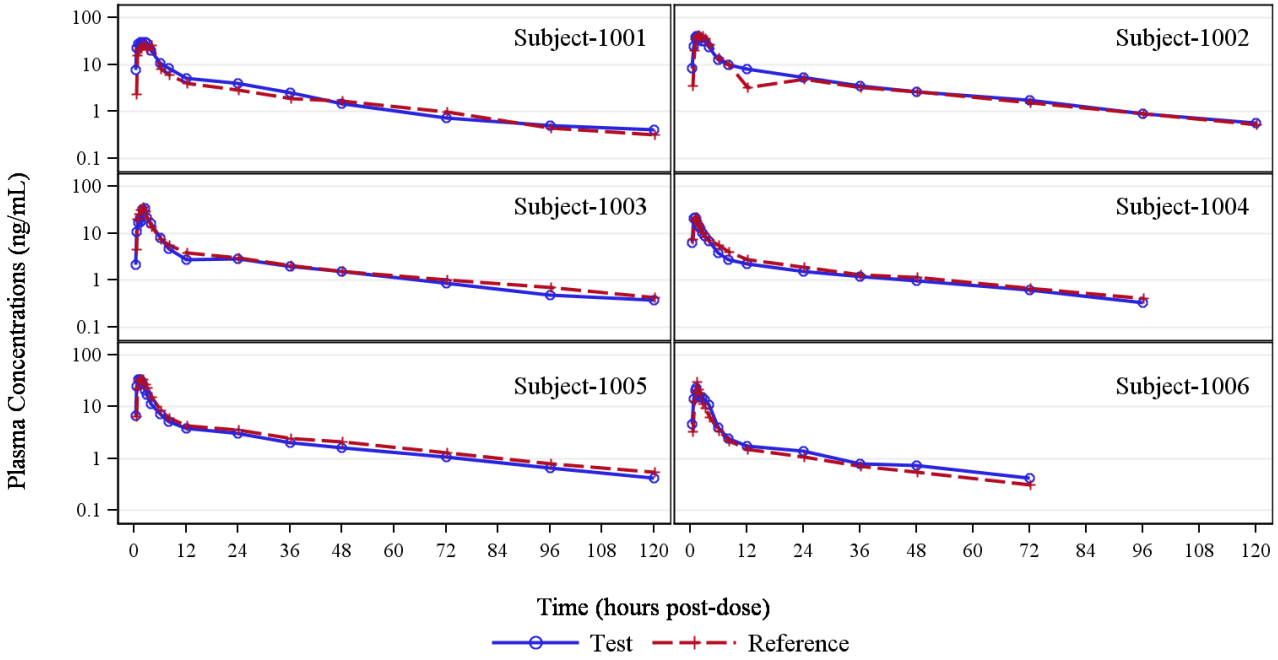
- Include 2 treatments on one plot. Replace Investigational Product with 2 treatments of Dorzagliatin + Sitagliptin, Dorzagliatin
- Include all timepoints and adjust the X axis time points as needed.
- If the DDI population is different from the PK Population, generate Figure 14.2.1.1a for the PK Population and Figure 14.2.1.1b for the DDI Population. If the PK and DDI are not different then only generate Figure 14.2.1.1 above.

Repeat:

Figure 14.2.1.2
Mean (SD) Dorzagliatin Plasma Concentrations versus Time (Semi-Log Scale)
(Dorzagliatin + Sitagliptin and Dorzagliatin alone)
PK Population

Programming Note:
Refer to notes for 14.2.1.1 except this is semi-log scale

Figure 14.2.1.3
Individual Dorzagliatin Plasma Concentrations versus Time (Linear Scale)
(Dorzagliatin + Sitagliptin and Dorzagliatin alone)
PK Population



Programming Note:

- Create a page containing 6 plots on each page corresponding to 6 subjects 2 treatments of Dorzagliatin + Sitagliptin, Dorzagliatin
- Include timepoints from 0 to 24 hours post dose by x hours as each tick unit.
- If necessary, modify the range of the x, y axis.

Repeat:

Figure 14.2.1.4
Individual Dorzagliatin Plasma Concentrations versus Time (Semi-Log Scale)
(Dorzagliatin + Sitagliptin and Dorzagliatin alone)
PK Population

Programming Note:

- Create a page containing 6 plots on each page corresponding to 6 subjects. Refer to notes for 14.2.1.3
- Change the legend to reflect the treatment.
- If necessary, modify the range of the x, y axis.

Figure 14.2.2.1
Mean (SD) Sitagliptin Plasma Concentrations versus Time by Treatment (Linear Scale)
(Dorzagliatin + Sitagliptin and Sitagliptin alone)
PK Population

Programming Note:

- Include 2 treatments on one plot. Replace Investigational Product with 2 treatments of Dorzagliatin + Sitagliptin, Sitagliptin
- Include all timepoints and adjust the X axis time points as needed.
- If the DDI population is different from the PK Population, generate Figure 14.2.2.1a for the PK Population and Figure 14.2.2.1b for the DDI Population. If the PK and DDI are not different then only generate Figure 14.2.2.1 above.
- This same note applies to the semi-log scare version (s) except for the Figure number (s).

Repeat:

Figure 14.2.2.2
Mean (SD) Sitagliptin Plasma Concentrations versus Time by Treatment (Semi-Log Scale)
(Dorzagliatin + Sitagliptin and Sitagliptin alone)
PK Population

Figure 14.2.2.3
Individual Sitagliptin Plasma Concentrations versus Time (Linear Scale)
(Dorzagliatin + Sitagliptin and Sitagliptin alone)
PK Population

Programming Note:

- Create a page containing 6 plots on each page corresponding to 6 subjects.
- Change the legend to reflect the treatment.
- If necessary, modify the range of the x, y axis.

Repeat:

Figure 14.2.2.4
Individual Sitagliptin Plasma Concentrations versus Time (Semi-Log Scale)
(Dorzagliatin + Sitagliptin and Sitagliptin alone)
PK Population

Figure 14.2.3.1
Mean (SD) Glucose Serum Concentrations versus Time by Treatment (Linear Scale)
PD Population

Programming Note: Use above template for Figure 14.2.1.1 and change the y-axis to 'Mean (SD) Glucose (unit) Concentrations', change the x-axis to 'Time (hr) Post-Oral Glucose Intake' and include 3 treatments: Sitagliptin, Dorzagliatin + Sitagliptin, Dorzagliatin

Figure 14.2.3.2
Individual Glucose Serum Concentrations versus Time (Linear Scale)
PD Population

Programming Note: Use above Figure 14.2.1.3 template and change the y-axis to 'Mean (SD) Glucose (unit) Concentrations', change the x-axis to 'Time (hr) Post-Oral Glucose Intake' and include 3 treatments: Sitagliptin, Dorzagliatin + Sitagliptin, Dorzagliatin
Each set of glucose times is based on pre-dose to 4 hours

Figure 14.2.3.3
Mean (SD) Insulin Serum Concentrations versus Time by Treatment (Linear Scale)
PD Population

Programming Note: Use above Figure 14.2.1.1 template and change the y-axis to 'Mean (SD) Insulin (unit) Concentrations', change the x-axis to 'Time (hr) Post-Oral Glucose Intake' and include 3 treatments: Sitagliptin, Dorzagliatin + Sitagliptin, Dorzagliatin

Figure 14.2.3.4
Individual Insulin Serum Concentrations versus Time (Linear Scale)
PD Population

Programming Note: Use above Figure 14.2.1.3 template and change the y-axis to 'Mean (SD) Insulin (unit) Concentrations', change the x-axis to 'Time (hr) Post-Oral Glucose Intake' and include 3 treatments: Sitagliptin, Dorzagliatin + Sitagliptin, Dorzagliatin
Each set of glucose times is based on pre-dose to 4 hours

Figure 14.2.3.5
Mean (SD) C-Peptide Serum Concentrations versus Time by Treatment (Linear Scale)
PD Population

Programming Note: Use above Figure 14.2.1.1 template and change the y-axis to 'Mean (SD) C-Peptide (unit) Concentrations', change the x-axis to 'Time (hr) Post-Oral Glucose Intake' and include 3 treatments: Sitagliptin, Dorzagliatin + Sitagliptin, Dorzagliatin

Figure 14.2.3.6
Individual C-Peptide Serum Concentrations versus Time (Linear Scale)
PD Population

Programming Note: Use above Figure 14.2.1.3 template and change the y-axis to 'Mean (SD) C-Peptide (unit) Concentrations', change the x-axis to 'Time (hr) Post-Oral Glucose Intake' and include 3 treatments: Sitagliptin, Dorzagliatin + Sitagliptin, Dorzagliatin
Each set of glucose times is based on pre-dose to 4 hours

Figure 14.2.3.7a
Mean (SD) GLP-1 Total Plasma Concentrations versus Time by Treatment (Linear Scale)
PD Population

Programming Note: Use above Figure 14.2.1.1 template and change the y-axis to 'Mean (SD) GLP-1 <Total or Active> (unit) Concentrations' , change the x-axis to 'Time (hr) Post-Oral Glucose Intake' and include 3 treatments: Sitagliptin, Dorzagliatin + Sitagliptin, Dorzagliatin. If GLP-1 active is above the limit of quantification then renumber the Figure 14.2.3.7a for the GLP-1 Total and 14.2.3.7b for GLP-1 Active, add either Total or Active in the Title .

Figure 14.2.3.8a
Individual GLP-1 Total Plasma Concentrations versus Time (Linear Scale)
PD Population

Programming Note: Use above Figure 14.2.1.3 template and change the y-axis to 'Mean (SD) GLP-1 (unit) Concentrations' , change the x-axis to 'Time (hr) Post-Oral Glucose Intake' and include 3 treatments: Sitagliptin, Dorzagliatin + Sitagliptin, Dorzagliatin. If GLP-1 active is above the limit of quantification then renumber the Figure 14.2.3.8a for the GLP-1 Total and 14.2.3.8b for GLP-1 Active.

Each set of glucose times is based on pre-dose to 4 hours.

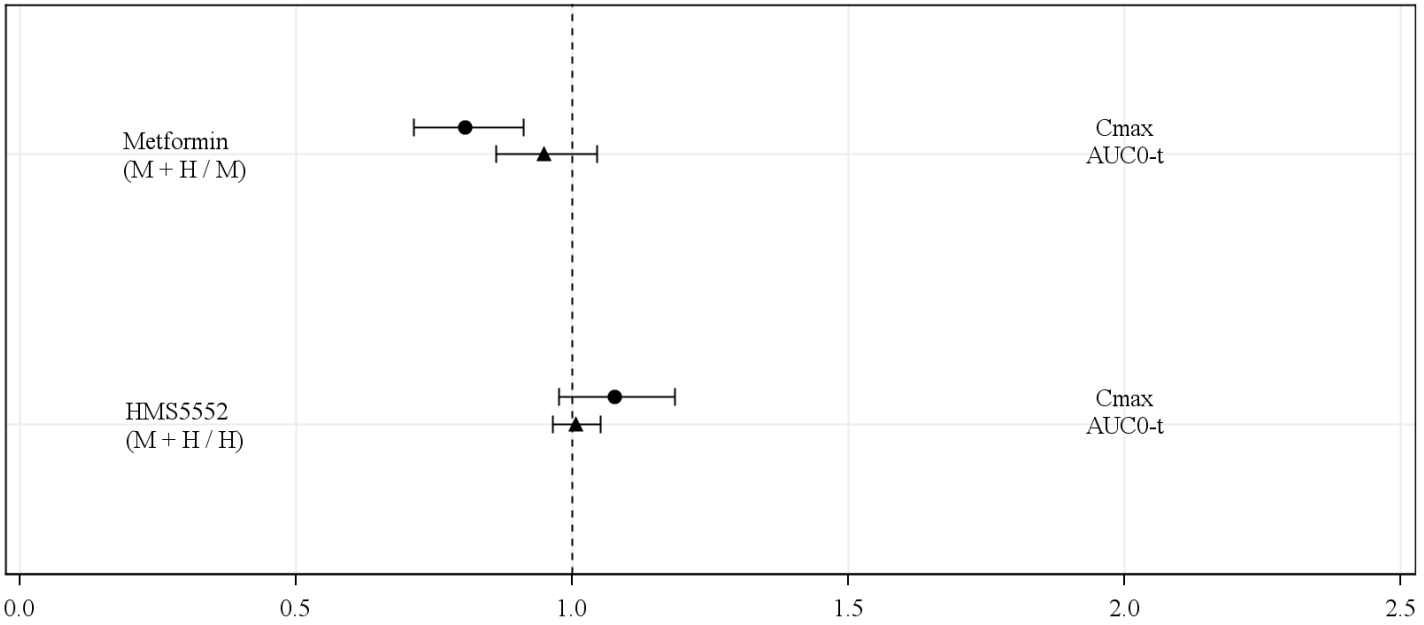
Figure 14.2.3.9
Mean (SD) Glucagon Plasma Concentrations versus Time by Treatment (Linear Scale)
PD Population

Programming Note: Use above Figure 14.2.1.1 template and change the y-axis to 'Mean (SD) Glucagon (unit) Concentrations', change the x-axis to 'Time (hr) Post-Oral Glucose Intake' and include 3 treatments: Sitagliptin, Dorzagliatin + Sitagliptin, Dorzagliatin.

Figure 14.2.3.10
Individual Glucagon Plasma Concentrations versus Time (Linear Scale)
PD Population

Programming Note: Use above Figure 14.2.1.3 template and change the y-axis to 'Mean (SD) Glucagon (unit) Concentrations', change the x-axis to 'Time (hr) Post-Oral Glucose Intake' and include 3 treatments: Sitagliptin, Dorzagliatin + Sitagliptin, Dorzagliatin
Each set of glucose times is based on pre-dose to 4 hours.

Figure 14.2.4
Dorzagliatin and Sitagliptin Drug-Drug Interaction Assessment Geometric Mean Ratio of PK Parameters and 90% Confidence Interval
DDI Population



Note: DDI Population: All subjects in PK population who complete all treatments. Dorzagliatin alone and Dorzagliatin + Sitagliptin and Sitagliptin alone. D + S/S = (Dorzagliatin 75 mg + Sitagliptin 100 mg/Sitagliptin 100 mg). D + S/D = (Dorzagliatin 75 mg + Sitagliptin 100 mg/Dorzagliatin 75 mg).

Programming Note: (The source program is from Hua HMM0104) Add 2 reference vertical dash lines for lower and upper bounds of 0.8 and 1.25, respectively.

Figure 14.2.5.1
Dorzagliatin and Sitagliptin Drug-Drug Interaction Assessment Geometric Mean Ratio of Glucose (mg/dL) PD Parameters and 90% Confidence Interval PD Population

Figure 14.2.5.2
Dorzagliatin and Sitagliptin Drug-Drug Interaction Assessment Geometric Mean Ratio of Insulin (uIU/mL) PD Parameters and 90% Confidence Interval PD Population

Figure 14.2.5.3
Dorzagliatin and Sitagliptin Drug-Drug Interaction Assessment Geometric Mean Ratio of C-Peptide (ng/mL) PD Parameters and 90% Confidence Interval PD Population

Figure 14.2.5.4a
Dorzagliatin and Sitagliptin Drug-Drug Interaction Assessment Geometric Mean Ratio of GLP-1 Total (unit) PD Parameters and 90% Confidence Interval PD Population

Programming Note: If GLP-1 active is above the limit of quantification then renumber the Figure 14.2.5.4a for the GLP-1 Total and 14.2.5.4b for GLP-1 Active.

Figure 14.2.5.5
Dorzagliatin and Sitagliptin Drug-Drug Interaction Assessment Geometric Mean Ratio of Glucagon (unit) PD Parameters and 90% Confidence Interval PD Population

Table 14.2.3.1
Summary of Drug-Drug-Interaction Assessment (effect of Sitagliptin on exposure of Dorzagliatin)
DDI Population

PK Parameter (unit)	Least Squares Geometric Means				Ratio of Geometric Means	Ratio of Geometric Means 90% CI	
	n	Dorzagliatin 75mg BID +Sitagliptin 100mg QD	n	Dorzagliatin 75mg BID	Dorzagliatin 75mg BID + Sitagliptin 100mg QD/Dorzagliatin 75mg BID	Dorzagliatin 75mg BID + Sitagliptin 100mg QD/Dorzagliatin 75mg BID	Intra-Subject CV%
C_{max} (ng/mL)	x	xxx.x	x	xxx.x	xxx.xx	(xxx.xx – xxx.xx)	xx.xx
AUC_{0-24h} (ng*hr/mL)	x	xxx.x	x	xxx.x	xxx.xx	(xxx.xx – xxx.xx)	xx.xx

CI = confidence interval; CV% = percent of coefficient of variation; Drug-Drug-Interaction (DDI) Population: All subjects in the PK Population who complete all treatments as defined by the protocol. Geometric mean is the mean back transformed from the mean of logarithmic values to the original scale. Least squares means are derived from a mixed model with terms for Treatment as a fixed effect and Subject as a random effect. The intra-subject CV% is the coefficient of variation based on the model defined as the sqrt(e^sigma2 - 1) * 100, sigma2 is the within-subject variance of log-scale data. N is the number of subjects with the corresponding non-missing PK parameters in both treatments.

Table 14.2.3.2
Summary of Drug-Drug-Interaction Assessment (effect of Dorzagliatin on exposure of Sitagliptin)
DDI Population

	Least Squares Geometric Means				Ratio of Geometric Means	Ratio of Geometric Means 90% CI	
PK Parameter (unit)	n	Dorzagliatin 75mg BID +Sitagliptin 100mg QD	n	Sitagliptin 100mg QD	Dorzagliatin 75mg BID + Sitagliptin 100mg QD/Sitagliptin 100mg QD	Dorzagliatin 75mg BID + Sitagliptin 100mg QD/ Sitagliptin 100mg QD	Intra-Subject CV%
C_{max} (ng/mL)	x	xxx.x	x	xxx.x	xxx.xx	(xxx.xx – xxx.xx)	xx.xx
AUC_{0-24h} (ng*hr/mL)	x	xxx.x	x	xxx.x	xxx.xx	(xxx.xx – xxx.xx)	xx.xx

CI = confidence interval; CV% = percent of coefficient of variation; Drug-Drug-Interaction (DDI) Population: All subjects in the PK Population who complete all treatments as defined by the protocol. Geometric mean is the mean back transformed from the mean of logarithmic values to the original scale. Least squares means are derived from a mixed model with terms for Treatment as a fixed effect and Subject as a random effect. The intra-subject CV% is the coefficient of variation based on the model defined as the sqrt(e^sigma2 - 1) * 100, sigma2 is the within-subject variance of log-scale data. n is the number of subjects with the corresponding non-missing PK parameters in both treatments.

Table 14.2.4.1
Summary of Pharmacodynamic Results: Glucose (mg/dL), Insulin (uIU/mL), C-Peptide (ng/mL), GLP-1, and Glucagon by Treatment
PD Population

Parameter (unit)	Timepoint	Statistic	Sitagliptin 100 mg QD (N=xx)	Sitagliptin 100 mg QD + Dorzagliatin 75 mg BID (N=xx)	Dorzagliatin 75 mg BID (N=xx)
Glucose (unit)	0 hr	n	xx	xx	xx
		Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
		Median	xxx.x	xxx.x	xxx.x
		Min, Max	xxx, xxx	xxx, xxx	xxx, xxx
		p-value (a)	0.xx	0.xx	0.xx
	0.5 hr	n	xx	xx	xx
		Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
		Median	xxx.x	xxx.x	xxx.x
		Min, Max	xxx, xxx	xxx, xxx	xxx, xxx
	1.0 hr	n	xx	xx	xx
		Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
		Median	xxx.x	xxx.x	xxx.x
		Min, Max	xxx, xxx	xxx, xxx	xxx, xxx
Etc.					

N = number of subjects in the specified study group; n (%) = number and percent of subjects in the specified group; Mean = arithmetic mean; SD = standard deviation; Min = minimum; and Max = maximum. (a) P-value is for t-test for homogeneity of the pre-dose original value.

Programming Note: include a t-test for homogeneity of pre-dose and a column for p-value. GLP-1 Active and Total should be included if above limit of quantification.

Table 14.2.4.2
Summary of Pharmacodynamic Parameters: Glucose (mg/dL) by Treatment
PD Population

Parameter (unit)	Statistic	Sitagliptin 100 mg QD (N=xx)	Sitagliptin 100 mg QD + Dorzagliatin 75 mg BID (N=xx)	Dorzagliatin 75 mg BID (N=xx)
$AUEC_{0-4hr}$ (unit)	n	xx	xx	xx
	Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
	CV%	xxx.x	xxx.x	xxx.x
	Geometric Mean	xxx.x	xxx.x	xxx.x
	Geometric CV%	xxx.x	xxx.x	xxx.x
	Median	xxx.x	xxx.x	xxx.x
	Min, Max	xxx, xxx	xxx, xxx	xxx, xxx
CE_{max} (unit)	n	xx	xx	xx
	Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
	CV%	xxx.x	xxx.x	xxx.x
	Geometric Mean	xxx.x	xxx.x	xxx.x
	Geometric CV%	xxx.x	xxx.x	xxx.x
	Median	xxx.x	xxx.x	xxx.x
	Min, Max	xxx, xxx	xxx, xxx	xxx, xxx
CE_{av} (unit)	n	xx	xx	xx
	Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
	CV%	xxx.x	xxx.x	xxx.x
	Geometric Mean	xxx.x	xxx.x	xxx.x
	Geometric CV%	xxx.x	xxx.x	xxx.x
	Median	xxx.x	xxx.x	xxx.x
	Min, Max	xxx, xxx	xxx, xxx	xxx, xxx

Note: PD parameters are estimated using baseline correction. CV = coefficient of variation; Min = minimum; Max = maximum; n = number of subjects in the specified group; N = number of subjects in the specified study population under each treatment; SD = standard deviation

Programming note: (Source program in HHM0104) include Day 5, Day 10, Day 15. Include Timepoints 0 hr, 0.5 hr, 1.0 hr, 1.5 hr, 2.0 hr, 2.5 hr, 3.0 hr, 4.0 hr.

Repeat for Insulin, C-peptide, Glucagon, and GLP-1(active and total if above limit of quantification):

Table 14.2.4.3 Summary of Pharmacodynamic Parameters: Insulin (uIU/mL) by Treatment, PD Population

Table 14.2.4.4 Summary of Pharmacodynamic Parameters: C-Peptide (ng/mL) by Treatment, PD Population

Table 14.2.4.5a Summary of Pharmacodynamic Parameters: GLP-1 Total (unit) by Treatment, PD Population

Programming Note: if GLP-1 active is above limit of quantification then renumber Table 14.2.4.5a GLP-1 Total, and Table 14.2.4.5b for GLP-1 Active.

Table 14.2.4.6 Summary of Pharmacodynamic Parameters: Glucagon (unit) by Treatment, PD Population

Table 14.2.4.7.1 Analysis of Glucose (mg/dL) PD Parameters (combination of Sitagliptin and Dorzagliatin versus Sitagliptin alone), PD Population

Table 14.2.4.7.2 Analysis of Glucose (mg/dL) PD Parameters (combination of Sitagliptin and Dorzagliatin versus Dorzagliatin), PD Population

Table 14.2.4.8.1 Analysis of Insulin (uIU/mL) PD Parameters (combination of Sitagliptin and Dorzagliatin versus Sitagliptin alone),PD Population

Table 14.2.4.8.2 Analysis of Insulin (uIU/mL) PD Parameters (combination of Sitagliptin and Dorzagliatin versus Dorzagliatin alone), PD Population

Table 14.2.4.9.1 Analysis of C-Peptide (ng/mL) PD Parameters (combination of Sitagliptin and Dorzagliatin versus Sitagliptin alone), PD Population

Table 14.2.4.9.2 Analysis of C-Peptide (ng/mL) PD Parameters (combination of Sitagliptin and Dorzagliatin versus Dorzagliatin alone), PD Population

Table 14.2.4.10.1a Analysis of GLP-1 Total (unit) PD Parameters (combination of Sitagliptin and Dorzagliatin versus Sitagliptin alone), PD Population

Table 14.2.4.10.2a Analysis of GLP-1 Total (unit) PD Parameters (combination of Sitagliptin and Dorzagliatin versus Dorzagliatin alone), PD Population

Programming Note: if GLP-1 active is above limit of quantification then renumber Table 14.2.4.10.1a for GLP-1 Total, and Table 14.2.4.10.1b for GLP-1 Active and Table 14.2.4.10.2a for GLP-1 Total, and Table 14.2.4.10.2b for GLP-1 Active.

Table 14.2.4.11.1 Analysis of Glucagon (unit) PD Parameters (combination of Sitagliptin and Dorzagliatin versus Sitagliptin alone), PD Population

Table 14.2.4.11.2 Analysis of Glucagon (unit) PD Parameters (combination of Sitagliptin and Dorzagliatin versus Dorzagliatin alone), PD Population

Programming Note: use the Table 14.2.3.1 and 14.2.3.2 as templates for the PD parameter comparisons.

Table 14.3.1.1
Summary of Adverse Events by Treatments
Safety Population

Category	Sitagliptin 100 mg QD (N=xx) n (%)	Sitagliptin 100 mg QD + Dorzagliatin 75 mg BID (N=xx) n (%)	Dorzagliatin 75 mg BID (N=xx) n (%)	All Subjects (N=xx) n (%)
Number of Adverse Events (AE)	xx	xx	xx	xx
Subjects with Any AE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of TEAE	xx	xx	xx	xx
Subjects with Any TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with Severe TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with Serious AE (SAE)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with Serious TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with Treatment Related AE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with Treatment Related SAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects Discontinued Due to AE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects Discontinued Due to SAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with AEs Resulting in Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

All AEs collected from first study drug dose to end of study visit or premature withdrawal are included. Adverse events will be considered treatment-emergent if not present prior to the initiation of the treatment with study drug on Day 1 or already present but worsens in either severity or frequency following exposure to the treatment. All SAEs collected from ICF signing to end of study visit or premature withdrawal are included. N = number of subjects in the specified study population; n (%) = number and percent of subjects in the specified group; AE = adverse event; TEAE = treatment emergent adverse event; SAE = serious adverse event.
MedDRA Version 22.1 was used to code adverse events

Table 14.3.1.2
Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Treatment
Safety Population

System Organ Class Preferred Term	Sitagliptin 100 mg QD (N=xx) n (%)	Sitagliptin 100 mg QD + Dorzagliatin 75 mg BID (N=xx) n (%)	Dorzagliatin 75 mg BID (N=xx) n (%)	Total (N=xx) n (%)
Subjects with at least one TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.				

Note: n (%) = number and percent of subjects in the specified group; N = number of subjects in the specified study population. Subjects are counted once for each system organ class and once for each preferred term at the highest intensity reported. Adverse events will be considered treatment-emergent if not present prior to initiation of the treatment with study drug on Day 1 or already present but worsens in either severity or frequency following exposure to the treatment.
MedDRA Version 22.1 was used to code adverse events

Table 14.3.1.3
Treatment Emergent Adverse Events by Intensity, System Organ Class, Preferred Term and Treatment
Safety Population

System Organ Class Preferred Term	Intensity	Sitagliptin 100 mg QD (N=xx) n (%)	Sitagliptin 100 mg QD + Dorzagliatin 75 mg BID (N=xx) n (%)	Dorzagliatin 75 mg BID (N=xx) n (%)	Total (N=xx) n (%)
Subjects with at least one TEAE	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 1					
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1					
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2					
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: n (%) = number and percent of subjects in the specified group; N = number of subjects in the specified study population. Subjects are counted once for each system organ class and once for each preferred term at the relationship reported at the most severe intensity. All AEs that occur after first study drug dose date (treatment emergent adverse event = TEAE) to end of study visit or premature withdrawal are included. Adverse events will be considered treatment-emergent if not present prior to initiation of the treatment with study drug or already present but worsens in severity or frequency following exposure to the treatment.
MedDRA Version 22.1 was used to code adverse events.

Table 14.3.1.4
Treatment Emergent Adverse Events by Relationship to Study Drug, System Organ Class, Preferred Term and Treatment
Safety Population

System Organ Class Preferred Term	Relationship	Sitagliptin 100 mg QD (N=xx) n (%)	Sitagliptin 100 mg QD + Dorzagliatin 75 mg BID (N=xx) n (%)	Dorzagliatin 75 mg BID (N=xx) n (%)	Total (N=xx) n (%)
Subjects with at least one TEAE	Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Possibly Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Unlikely Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Not Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 1					
	Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Possibly Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Unlikely Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Not Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1					
	Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Possibly Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Unlikely Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Not Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2					
	Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Possibly Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.					

Note: n (%) = number and percent of subjects in the specified group; N = number of subjects in the specified study population. Subjects are counted once for each system organ class and once for each preferred term at the relationship reported. All AEs that occur after first study drug dose date (treatment emergent adverse event = TEAE) to end of study visit or premature withdrawal are included. Adverse events will be considered treatment-emergent if not present prior to initiation of the treatment with study drug on Day 1 or already present but

worsens in either severity or frequency following exposure to the treatment. MedDRA Version 22.1 was used to code adverse events.

Table 14.3.1.5
Adverse Events Leading to Discontinuation by System Organ Class,
Preferred Term and Treatment
Safety Population

Table 14.3.1.6
Summary of Death by Treatment
Safety Population

Programming Note: Table 14.3.1.6 may not need to be produced depending on the data.

Table 14.3.2
All Serious Adverse Events, Including Deaths
Safety Population

Treatment: Subject Number: xxxx

System Organ Class/ Preferred Term/ Reported Term	Study Drug Admin Date/Time	AE Start Date/Time (Study Day)/ End Date/Time (Study Day)	SAE Category	Intensity	Relationship to Study Medication	Outcome	Death Date

Programming Note: Please create single sheet for each subject. Sort by AE Start Date/Time, AE End Date/Time. All SAEs collected from ICF signing to End of Study Visit or premature discontinuation are included. If possible, add treatment and subject number as columns and include all subjects on one page.

Table 14.3.4.1
Summary of Clinical Laboratory Parameters: Hematology and Change from Baseline
Safety Population

Laboratory Test (Unit)	Treatment (N=xx)	Visit	Statistic	Result	Change from Baseline
Lab Test (unit)	NA	Day -1 (Baseline)	n	xx	---
			Mean (SD)	xx.x (xx.xx)	
			Median	xx.xx	
			Min, Max	xx.x, xx.x	
	Sitagliptin 100mg (N=xx)	Day 5	n	xx	xx
			Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.x	xx.x
			Min, Max	xx.x, xx.x	xx.x, xx.x
	Sitagliptin 100mg + Dorzagliatin 75mg (N=xx)	Day 10	n	xx	xx
			Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.xx	xx.xx
			Min, Max	xx.x, xx.x	xx.x, xx.x
	Dorzagliatin 75mg (N=xx)	Day 15	n	xx	xx
			Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.xx	xx.xx
			Min, Max	xx.x, xx.x	xx.x, xx.x
	NA	Day 17 (EOS)	n	xx	xx
			Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
			Median	xx.xx	xx.xx
			Min, Max	xx.x, xx.x	xx.x, xx.x

Note: Baseline is defined as the last available assessment or value before or at start of the first treatment.
N = number of subjects in the specified study population under each treatment; Mean = Arithmetic mean; SD = standard deviation;
Max = maximum; Min = minimum; n = number of subjects in the specified group. NA = Not Applicable, EOS = End of Study.

Programming note: Template is for sequence of study drugs present in order of administration, present all the hematology parameters as specified in the SAP. Include all visits. (Source code from HMM0104 is Program Source:T_14_3_3_1.sas Data source Listing: 16.2.8.1)

Table 14.3.4.2
Summary of Clinical Laboratory Parameters: Chemistry and Change from Baseline
Safety Population

Programming note: This table will not include the screening tests. *Use same template as Table 14.3.4.1*
Present all the applicable chemistry parameters. Baseline is defined as the last available assessment or value before or at start of the first treatment
Include all visits.

Table 14.3.4.3
Summary of Clinical Laboratory Parameters: Urinalysis and Change from Baseline
Safety Population

Programming note: This table will not include the screening tests. Baseline is defined as the last available assessment or value before or at start of the first treatment *Use same template as Table 14.3.4.1* Present all the applicable urinalysis parameters. Include all visits.

Table 14.3.4.4
Clinical Laboratory Parameters: Hematology Shift from Baseline to Post Baseline Results
Safety Population

Laboratory Test Parameter (unit)	Treatment (N=xx)	Visit		All Subjects (N=xx) Baseline	
				Normal n (%)	Abnormal n (%)
Hct (unit)	Sitagliptin 100mg (N=xx)	Post-Baseline Day x	Normal	xx (xx.x)	xx (xx.x)
			Abnormal	xx (xx.x)	xx (xx.x)
	Sitagliptin 100mg + Dorzagliatin 75mg (N=xx)	Post-Baseline Day x	Normal	xx (xx.x)	xx (xx.x)
			Abnormal	xx (xx.x)	xx (xx.x)
	Dorzagliatin 75mg (N=xx)	Post-Baseline Day x	Normal	xx (xx.x)	xx (xx.x)
			Abnormal	xx (xx.x)	xx (xx.x)
Etc					

n (%) = number and percent of subjects in the specified group; N = number of subjects in the specified study population under each group. Abnormal includes either low or high.

Programming Note: The scheme above is Normal (N), and Abnormal is defined as either Low (L) or High (H) for the shift from baseline to post-baseline Visit. Include all post-baseline visits.

Table 14.3.4.5
Clinical Laboratory Parameters: Chemistry Shift from Baseline to Post Baseline Results
Safety Population

Programming Note: use the same template as 14.3.4.4 include only Chemistry parameters.

Table 14.3.4.6
Clinical Laboratory Parameters: Urinalysis Shift from Baseline to Post Baseline Results
Safety Population

Programming Note: use the same template as 14.3.4.4 include only Urinalysis parameters.

Table 14.3.4.7
Vital Signs: Summary and Change from Baseline
Safety Population

Programming Note: Present all the following vital signs parameters: Systolic Blood Pressure, Diastolic Blood Pressure, Pulse Rate, Temperature and Respiratory Rate. Include all visits. Baseline is defined as the last available assessment or value before or at start of the first treatment. *Use same template as Table 14.3.4.1*

Table 14.3.4.8
12-Lead ECG Parameters: Summary and Change from Baseline
Safety Population

Programming Note: Present all the numeric ECG parameters per the SAP. Include all visits. Baseline is defined as the last available assessment or value before or at start of the first treatment. *Use same template as Table 14.3.4.1*

Listing 16.2.1.1
Subject Disposition and Completion Status
All Enrolled Subjects

Subject Number	Informed Consent Date	Completed Study? (Y/N)	Completion/ Early Withdrawal Date	Reason for Early Withdrawal	If Reason is Early Withdrawal Other, Specify	Death Date

Y = Yes; N = No.

Listing 16.2.1.2
Eligibility Status
All Enrolled Subjects

Subject Number	Did the Subject Meet All Eligibility Criteria?	Date	If no, Record Details: Inclusion/Exclusion criteria not met	Inclusion/Exclusion Criteria Comment

Programming Notes: Treatment Sequence is S/S+D/D (Program Source:L_16_2_1_2.sas)

Listing 16.2.2.1
Protocol Deviations
All Enrolled Subjects

Treatment	Subject Number	Any Deviation? (Yes/No)	Date of Deviation	Protocol Deviation Type	Protocol Deviation Term

Note: S/S+D/D = Sitagliptin 100mg QD/Sitagliptin 100mg QD + Dorzagliatin 75mg BID/Dorzagliatin 75mg BID

Listing 16.2.3.1
Subjects in Analysis Populations
All Enrolled Subjects

Treatment	Subject Number	Population	Reason(s) for Exclusion
	xxx-xxx	Safety Population PK Population PD Population DDI Population	

Note: S/S+D/D = Sitagliptin 100mg QD/Sitagliptin 100mg QD + Dorzagliatin 75mg BID/Dorzagliatin 75mg BID

Safety Population: All subjects who receive study drug on Day1. Pharmacokinetic (PK) Population: All subjects who receive study drug, have no major protocol deviations, and who have sufficient PK data to obtain reliable estimates of the key PK variables ($AUC_{0\text{-}24h}$, C_{max}). Pharmacodynamic (PD) Population: All subjects who receive study drug, have no major protocol deviations, and have sufficient PD data to obtain reliable estimates of at least one of key PD parameters($AUEC_{0\text{-}4h}$, CE_{max}, and CE_{av}) for either PD marker. Drug-Drug-Interaction (DDI) Population: All subjects in the PK Population who complete all treatments as defined by the protocol.

Listing 16.2.4.1
Demographics and Baseline Characteristics
Safety Population

Subject Number	Age (yr)	Gender	Race	Ethni-city	Height (cm)	Weight (kg)	Derived BMI (kg/m²)	FBG	HbA1c	Date of Diagnosis of T2DM	Date of Reproduc-tive Status Assessment	Reproduc-tive Status	Current Method of Contracep-tion, if Childbearing Potential

FBG is defined as fasting blood glucose (mg/dL). T2DM = type 2 diabetes mellitus.

Listing 16.2.4.2
Medical/Surgical History
Safety Population

Subject Number	Any Past and/or Concomitant Diseases/Surgery? (Y/N)	System Organ Class/ Preferred Term/ Reported Term	Start Date	End Date	Continuing?

Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 was used. Y = yes; N = No.

Listing 16.2.5.1.1
Study Drug Exposure During Run-In
Safety Population

Subject Number	Date Sitagliptin 100mg and Diary Dispensed For at-home Administration	Number of Sitagliptin 100mg Tablets Dispensed	Date of Day -8 Telephone Contact	Did the subject have any new AE/SAE during Run-in from study drug administer-ation?	Did the subject take any concomitant medications for Run-in?	Date Tablets Returned and Diary Reviewed	Number of Tablets Returned	Number of Tablets Lost	Compli-ance (%)
Etc.									

Compliance is defined as the actual use of Sitagliptin 100mg QD used over the 12 day run-in divided by the expected for the 12 days (1 tablet per day X 12 days) multiplied by 100 (%). Actual use of Sitagliptin 100mg is defined as the number of tablets dispensed minus the number of tablets lost minus the number of tablets returned. AE = adverse event; SAE = serious adverse event.

Listing 16.2.5.1.2
Study Drug Exposure
Safety Population

Subject Number	Treatment	Completion Status	Study Day	Date and Time of Administration

Listing 16.2.5.2
Prior and Concomitant Medications
Safety Population

Treatment	Subject Number	Prior or Concomi-tant	ATC Class/ Preferred Term /Reported Term	Study Drug Start Date/Time	Indication	Dose (Unit)	Freq	Route	Start Date/ End Date	Ongoing?

Freq = Frequency, 1X=one time only, QD=once a day, BID=twice a day, QID=4 times a day. ATC = Anatomical/Therapeutic/Chemical (ATC) Level 3. WHO Drug Enhanced Dictionary, version WHO Drug Global B3 September 2019 was used.

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Listing 16.2.5.3
Procedures/Non-Drug Therapies
Safety Population

Treatment	Subject Number	Any Procedures/ Non-Drug Therapies (Y/N)	System Organ Class/ Preferred Term/ Reported Term	Indication	Start Date	End Date	Continuing?

Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 or WHO Drug version WHO Drug Global B3 September 2019 was used. Y = yes; N = no.

Listing 16.2.5.4
Dorzagliatin Plasma Concentrations
Safety Population

Subject Number	Treatment	Date and Time (Study Day)	Nominal Time (h)	Actual Collection Time (h)	Time Difference	Concentration (unit)
		2014-08-08T00:00 (xx)				

Any value below the lower quantification limit (LLOQ, XX unit) was reported as BQL.

Programming Note: This listing will include all plasma concentrations for the study.

Listing 16.2.5.5
Sitagliptin Plasma Concentrations
Safety Population

Programming Note: Refer to Listing 16.2.5.4.

Listing 16.2.5.6
Pharmacodynamic Responses by Actual Time Point
Safety Population

Subject Number	Treatment	Start Date/Time of Oral Glucose 75g	End Date/ Time of Oral Glucose 75g	Date and Time (Study Day)	Nominal Time	Actual Collection Time	Time Difference	PD Response Type	Response (unit)	Baseline Corrected Response (unit)
				2014-08-08T00:00 (xx)						

Note: Baseline corrected PD responses is defined as subtracting the baseline from the post oral glucose intake value. PD = pharmacodynamic.

Programming Note: This includes all PD responses over time, refer to the SAP (Glucose, GLP-1 (Active and Total), glucagon, insulin, and C-peptide). For the GLP-1 use GLP-1 Total, GLP-1 Active for these in the PD Response Type.

Listing 16.2.5.7
Meal Status and Blood Glucose via Glucometer by Treatment
All Enrolled Subjects

Subject Number	Treatment	Completion Status	Study Day	Blood Glucose Date and Time of Assessment	Meal	Meal Start Date/Time	Meal End Date/Time	Nominal Time point	Blood Glucose Result (mg/dL)
				2014-08-08T12:00	Breakfast Lunch Dinner Snack			Within 60 min before Breakfast	

Programming Note: This includes all responses over time, refer to the SAP

Listing 16.2.6.1
Dorzagliatin Pharmacokinetic Parameters
PK Population

Subject Number	Treatment	C_{max} (unit)	AUC_{0-24h} (unit)	T_{max} (unit)	$T_{1/2}$ (unit)	K_{el} (unit)	CL/F (unit)	V_z/F (unit)

Programming Note: Include all PK parameters specified in the SAP.

Listing 16.2.6.2
Sitagliptin Pharmacokinetic Parameters
PK Population

Programming Note: use the 16.2.6.1 template.

Listing 16.2.6.3
Pharmacodynamic Parameters
PD Population

Subject Number	Treatment	PD Response (marker) Type	$AUEC_{0-4h}$ (unit)	CE_{max} (unit)	CE_{av} (unit)
		Insulin			
		Glucagon			
		Glucose			
		GLP-1 Active			
		GLP-1 Total			
		C-peptide			

The PD parameters are estimated using baseline correction. PD = pharmacodynamic. For glucagon after baseline correction, the positive values are set to zero and the absolute of the negative values is used for PD parameter estimation. For the other PD responses after baseline correction, any negative values are set to zero and the positive values are used for PD parameter estimation.

Programming Note: Include all PD parameters specified in the SAP.

Listing 16.2.7.1
All Adverse Events
Safety Population

Treatment: Subject Number:

System Organ Class/ Preferred Term/ Reported Term	Study Drug Admin Date/ Time	Start Date/ Time / End Date/ Time	SAE (Y/N)	SAE Cate-gory	Rela-tion-ship to Study Medica-tion	Outcome	Possibly Related to Study Drug (S, D, S+D)	Most Possible Reason for AE if Unlikely/ Not Related to Study Drug	Intensity	Action Taken With Regard to Study Treatment	AE Caused Subject's Termi-nation from Study?	Concomi-tant Medica-tion or Other Treat-ment Given	Date of Death	Autopsy Date And Specifica-tion

TE = Treatment Emergent. All AEs (adverse event) collected between first study drug dose and end of study visit are included. Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 was used. SAE (serious adverse event) are defined as any serious AE collected from ICF to end of study and the category is defined as D = Death, L = Life-threatening, H = Requires or prolongs inpatient hospitalization, S = Persistent or significant disability/incapacity, C = Congenital anomaly/birth defect, O = Other medical intervention. Y = yes; N = no.

Programming Note: Additional variables for Hospital Admission Date and Discharge Date will be on a 2nd page of this listing along with other variables that don't fit on the first page.

Listing 16.2.7.2
Adverse Events Leading to Study Discontinuation
Safety Population

Subject Number	Treat-ment	TEAE	System Organ Class/ Preferred Term/ Reported Term	Start Date Time/ End Date Time	Ong oing	Intensity	Relation -ship to Study Medica-tion	Outcome	Action Taken with Regard	SAE (Y/N)	Study D/C Date
				2014-08-08 Txx:xx/ 2014-08-09 Txx:xx							

Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 was used.
D/C = Discontinuation; SAE = Serious Adverse Event; TEAE = Treatment emergent adverse event; Y/N = Yes or No. All AEs leading to discontinuation of study drug within 28 days of the discontinuation of study drug are included.

Listing 16.2.7.3
All Adverse Events Related to Study Drug
Safety Population

Programming Note: Use the same template for 16.2.7.1 for all AEs with relationship of (Related and Possibly Related).

Listing 16.2.7.4
Hypoglycemic Events
Safety Population

Programming Note: Use the same template for 16.2.7.1 with some variations in the variables based on eCRF pg154.

Listing 16.2.8.1
Laboratory Data: Hematology
Safety Population

Treatment	Subject Number	Visit	Date/Time	Did Subject Fast for at least 10 hr?	Lab Test Name (unit)	Result	Reference Range	Reference Flag	Clinically Significant

Flag L: Below the lower limit of normal; H: Above the upper limit of normal.

Programming Notes: If there are no 'Clinically Significant' lab results based on the reference range then this column can be deleted. Include all lab tests as specified in the SAP and Protocol.

Repeat:

Listing 16.2.8.2
Laboratory Data: Serum Chemistry
Safety Population

Programming Notes: If there are no 'Clinically Significant' lab results based on the reference range then this column can be deleted. Include all lab tests as specified in the SAP and Protocol.

Repeat:

Listing 16.2.8.3
Laboratory Data: Urinalysis
Safety Population

Repeat:

Listing 16.2.8.4
Laboratory Data: Serology, Saliva Alcohol, Drug Screen, Pregnancy Tests,
and FSH and Estradiol Test All Enrolled Subjects

Listing 16.2.8.5
Vital Signs Data
Safety Population

Treatment	Subject Number	Visit	Date/Time of Vitals	Time-point	Weight (kg)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Respiratory Rate (breaths/ minute)	Pulse Rate (bpm)	Oral Temperature (ºC)

BPM: beats per minute.

Programming Note: Add all time points as specified in the SAP.

Listing 16.2.8.6
12-Lead Electrocardiogram Results
Safety Population

Treatment	Subject Number	Visit	Date/ Time	PR (msec)	QRS (msec)	QT (msec)	QTcF (msec)	Ventri-cular Rate (bpm)	Inter-preta-tion	Abnormal-ity	Clin. Signi.?

Note: eCRF specifies QTc, this was collected as the Fridericia's correction, QTcF.

Listing 16.2.8.7
Physical Examination Results
Safety Population

Treatment	Subject Number	Visit	Physical Exam Date	Physical Exam Body System	Exam Finding (Abnormal/Normal/ Not Done)	Other Body System (Specify)	If Abnormal Specify	Clinically Significant?

Revision history

Version	Date	Comments