1. TITLE PAGE

Clinical Study Report

Protocol HMM0111

A Phase 1, Open-Label, Sequential, Multiple-Dose, Drug-Drug Interaction Study of Dorzagliatin and Sitagliptin in Subjects with Type 2 Diabetes Mellitus

Name of investigational product:	Dorzagliatin
Developmental phase of study:	Phase 1
Principal Investigator:	Gregory J. Tracey, MD Frontage Clinical Services, Inc. 200 Meadowlands Parkway Secaucus, New Jersey 07094 USA Email: gtracey@frontagelab.com Tel: 201-416-7745 or 201-416-7747 Fax: 201-552-2597
First subject enrolled:	21 December 2018
Last subject completed:	30 August 2019
Release date of report:	Final Version 1.0 – 17 July 2020
Sponsor:	Hua Medicine (Shanghai) Ltd. No. 275 Ai Di Sheng Road Pudong, Shanghai P.R. China, 201203

This study was conducted in accordance with the ethical principles set forth by the Declaration of Helsinki, clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56 and 312), and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. Essential study documents have been archived in accordance with applicable regulations.

2. SYNOPSIS

Title of the Study: A Phase 1, Open-Label, Sequential, Multiple-Dose, Drug-Drug Interaction Study of Dorzagliatin and Sitagliptin in Subjects with Type 2 Diabetes Mellitus

Protocol Number: HMM0111 (Protocol Version 1.0, 11 November 2018; Version 1.1, 27 December 2018; Version 1.2, 04 February 2019; Version 1.3, 05 March 2019)

Principal Investigator: Gregory J. Tracey, MD
Sub-Investigator: Alexander Prezioso, MD

Study Center: Frontage Clinical Services, Inc., Clinical Research Center, 200 Meadowlands Parkway, Secaucus, New Jersey 07094 USA

Publications (reference): None

Studied Period: 21 December 2018 to 30 August 2019 **Clinical Phase:** Phase 1

Study Objectives:

Primary:

- To assess the potential pharmacokinetic 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.

Secondary:

- 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.

Methodology:

This was a Phase 1, open-label, sequential, multiple-dose, drug-drug interaction (DDI) study of glucokinase activator (GKA) dorzagliatin and sitagliptin in subjects with type 2 diabetes mellitus (T2DM).

Study drugs were to be administered in the following treatment scheme:

Days	Sitagliptin	Dorzagliatin	PK Sample Collection
1-5	100 mg (QD) for 5 days	None	Day 5: Sitagliptin alone
6-10	100 mg (QD) for 5 days	75 mg (BID) for 4 days Morning dose only on Day 10	Day 10: Sitagliptin + Dorzagliatin
11-15	None	75 mg (BID) for 4 days Morning dose only on Day 15	Day 15: Dorzagliatin alone

Study drug was taken 60 (±5) minutes prior to meals.

Eligible subjects had to have a minimum 12-day run-in period prior to admission to the Clinical Research Center (CRC), during which time they self-administered sitagliptin 100 mg QD each morning up until and including Day -2.

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

Blood samples for the determination of dorzagliatin and sitagliptin concentrations and corresponding pharmacokinetic (PK) analysis were 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. Plasma samples were analyzed for the determination of dorzagliatin and sitagliptin using validated liquid chromatography-

tandem mass spectrometry (LC-MS/MS) methods with lower limit of quantification (LLOQ) of 1.00 ng/mL, respectively.

For oral glucose tolerance test (OGTT), subjects consumed a 75-gram glucose solution 30 minutes following study drug dose administration in the morning on Days 5, 10 and 15, in lieu of breakfast.

Pharmacodynamic (PD) responses were evaluated by measuring GLP-1 and glucagon in plasma, and glucose, insulin, and C-peptide in serum 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.

Safety assessments included monitoring of adverse events (AEs), blood glucose via glucometer readings, vital signs (blood pressure, pulse rate, respiratory rate and oral temperature), clinical laboratory findings, resting 12-lead electrocardiograms (ECGs), and physical examination (PE) findings.

Subjects who terminated study participation early were to have Day 17 assessments performed, if possible, prior to discharge from the CRC.

Number of subjects (planned and analyzed):

This study planned to enroll up to 15 eligible subjects. Subjects may have been enrolled singly or in groups. In order to have at least 12 evaluable subjects complete the study, additional subjects may have been enrolled to replace subjects who discontinued study participation prematurely. A total of 15 eligible subjects were enrolled, and 14 completed the study. All 15 subjects were included in the Safety, PK and PD population analyses, and 14 subjects were included in the Drug-Drug Interaction population analyses.

Diagnosis and main criteria for inclusion:

Male and/or female, nonsmoking subjects between 30 and 65 years (inclusive), who provided written informed consent and were diagnosed with T2DM at least 3 months prior to screening, and who were taking a stable dose of one of the following therapies with no change in the dose for at least 4 weeks prior to screening: a) ≥1000 mg per day of metformin, b) a dipeptidyl peptidase 4 (DPP-4) inhibitor, c) a sodium-glucose cotransporter-2 (SGLT2) inhibitor, d) metformin plus a DPP-4 inhibitor, or e) metformin plus a SGLT2 inhibitor, were eligible to participate in the study. Subjects had to agree to change their current therapy to 100 mg sitagliptin QD for at least 14 days prior to dosing on Day 1. Subjects had to have a BMI of 19 to 38 kg/m^2 (inclusive), a fasting C-peptide test results >0.3 nmol/L (>0.90 ng/mL) and an HbA1c ≥7% and ≤10.5%. Females had to be using birth control or be surgically sterile or postmenopausal.

Subjects were excluded if any of the following exclusion criteria were met, including fasting blood glucose at screening or Day -1 ≤110 or ≥270 mg/dL (one repeat screening fasting blood glucose allowed); Type 1 DM or latent autoimmune diabetes in adults; diabetic neuropathy, retinopathy or nephropathy, reported incidence of severe hypoglycemia, defined by denoting severe cognitive impairment requiring external assistance for recovery, within 3 months prior to screening and/or within 3 months prior to dosing on Day 1; known contraindications, hypersensitivity or intolerance to sitagliptin; clinically significant gastrointestinal, cardiovascular, infectious, CNS, liver or renal diseases; uncontrolled hypertriglyceridemia; hospitalization or major surgery within 90 days prior to screening; acute or chronic metabolic acidosis, including diabetic ketoacidosis; known or suspected malignancy; antidiabetic treatment with insulin, sulfonylureas, thiazolidinediones or GLP-1 agonist within 3 months prior to screening, SBP <90 or ≥160 mmHg or DBP <60 or ≥100 mmHg at screening; use of prohibited medications or herbal products; and other exclusions as specified in the protocol.
A full list of inclusion and exclusion criteria can be found in Section 9.3.1 and Section 9.3.2.

Test product, dose and mode of administration, batch number:

Dorzagliatin was provided by the Sponsor to the CRC site (research pharmacy) as film-coated tablets in 75 mg strength for oral administration. Manufactured by: Shanghai Desano Bio-Pharmaceutical Co., Ltd. Batch Number: BXE18001;

Sitagliptin was provided by the Sponsor to the CRC site (research pharmacy) as Januvia® 100 mg tablets for oral administration. Distributed by: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Batch Number: R029201.

Duration of treatment and study participation:

The total duration of participation in the study for each subject was about 59 days (including up to 28-day screening period, 12-day run-in period and 19-day in-clinic period).

Criteria and parameters for evaluation:

Safety:

Safety assessments included monitoring of AEs, blood glucose via glucometer readings, vital signs (blood pressure, pulse rate, respiratory rate and oral temperature), clinical laboratory findings, 12-lead ECGs, and PE findings.

Pharmacokinetics:

The plasma concentration-time data for dorzagliatin and sitagliptin were analyzed using non-compartmental methods to calculate PK parameters. Actual dosing and sampling times were used for analyses. The primary PK parameters of interest were: C_{max}, T_{max} and AUC_{0-24h}. Additional parameters were estimated and reported, as appropriate.

Pharmacodynamics:

Pharmacodynamic (PD) responses were evaluated by measurement of glucose, insulin and C-peptide in serum, and GLP-1 and glucagon in plasma. The PD parameters included, but were not limited to, $AUEC_{0-4h}$, CE_{max} and CE_{av}.

Statistical methods and data analysis:

All baseline, demographic, concentration and safety data were listed and summarized by descriptive statistics (n, mean, standard deviation, median, minimum and maximum) or frequency counts.

Pharmacokinetic Analysis: Summary tables were produced for plasma sitagliptin and dorzagliatin concentration data and PK parameter data with descriptive statistics. Individual subject and summary plasma concentration-time plots for plasma sitagliptin and dorzagliatin concentration data were prepared.

Drug-Drug Interaction Analysis: The primary PK comparison was based on the C_{max} and AUC_{0-24h} between treatments for dorzagliatin and sitagliptin based on a mixed model analysis. Least square geometric means and point estimates and 90% CI for the geometric mean ratio (GMR) for C_{max} and AUC_{0-24h} were calculated to assess the effect of sitagliptin on the exposure of dorzagliatin and to assess the effect of dorzagliatin on the exposure of sitagliptin. A forest plot of the PK parameters for 90% CI was produced.

Pharmacodynamic Analysis: Summary tables were produced for PD responses and PD parameter data with descriptive statistics. Individual subject and summary PD responses-time plots for each PD marker were prepared by treatment in linear scale. Pharmacodynamic comparisons for $AUEC_{0-4h}$, CE_{max}, and CE_{av} were computed based on a mixed model analysis.

Safety Analysis: Adverse events were summarized by treatment; tabulations were prepared for all AEs and all AEs by relationship and intensity. Adverse events resulting in termination and AEs meeting regulatory criteria for seriousness were tabulated separately.

Four analysis populations were used to summarize the results from this study.

Safety Population: All subjects who received study drug on Day 1.

Pharmacokinetic Population: All subjects who received study drug, had no major protocol deviations, and who had sufficient PK data to obtain reliable estimates of the key PK variables (AUC_{0-24h} and C_{max}).

Pharmacodynamic Population: All subjects who received study drug, had no major protocol deviations, and had sufficient PD data to obtain reliable estimates of at least one of key PD parameters ($AUEC_{0-4h}$, CE_{max}, and CE_{av}).

Drug-Drug Interaction Population: All subjects in the PK Population who completed all treatments as defined by the protocol.

SUMMARY AND CONCLUSIONS

Study Completion:

A total of fifteen (15) T2DM subjects were confirmed eligible on Day -2 and were enrolled in the study, and fourteen subjects (93.3%) completed the study. One subject (6.7%) discontinued from the study early due to an adverse event of erythematous rash; the AE was assessed as being moderate in severity and possibly related to dorzagliatin and sitagliptin, and resolved within 15 days after early termination.

Demographics:

Subjects were representative of subjects with T2DM, including adult male (n=4, 26.7%) and female (n=11, 73.3%) population ranging from 40 to 64 years of age. Overall mean (SD) age was 56.7 (5.39) years and mean (SD) BMI was 32.06 (3.571) kg/m^2. Three of 15 subjects (20.0%) were Black or African American, and 12 subjects (80.0%) were White. Fourteen of 15 subjects (93.3%) were Hispanic or Latino and one subject (6.7%) was not Hispanic or Latino.

Study Medication Exposure Results:

A total of 15 eligible subjects received sitagliptin in the run-in period, then received sitagliptin 100 mg daily in-house on Days -1 through 5, then received sitagliptin 100 mg daily with dorzagliatin 75 mg twice daily on Days 6 through 10 (morning dose of dorzagliatin only on Day 10), then received dorzagliatin 75 mg twice daily on Days 11 through 15 (morning dose of dorzagliatin only on Day 15). One subject (Subject 1001) early discontinued from the study after the Day 11 morning dose.

Pharmacokinetic Results:

A summary of the PK parameters for dorzagliatin is displayed in Table 2-1. Mean dorzagliatin C_{max} and AUC_{0-24h} and median T_{max} appeared similar when dorzagliatin was administered with or without sitagliptin.

Table 2-1: Summary of Dorzagliatin PK Parameters by Treatment – PK Population

PK Parameter	Statistic	Sitagliptin + Dorzagliatin (N=15)		Dorzagliatin Alone (N=15)	
		n		n	
C_{max} (ng/mL)	Mean (SD)	15	923 (338)	14	861 (340)
AUC_{0-24h} (h*ng/mL)	Mean (SD)	15	6930 (1780)	14	6720 (1420)
T_{max} (h)	Median (Min-Max)	15	3.0 (0.5-6.0)	14	3.5 (1.0-6.0)

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.

Source: Table 14.2.2.3

A summary of the PK parameters for sitagliptin is displayed in Table 2-2. Mean sitagliptin C_{max} and AUC_{0-24h} and median T_{max} appeared similar when sitagliptin was administered with or without dorzagliatin.

Table 2-2: Summary of Sitagliptin PK Parameters by Treatment – PK Population

PK Parameter	Statistic	Sitagliptin Alone (N=15)		Sitagliptin + Dorzagliatin (N=15)	
		n		n	
C_{max} (ng/mL)	Mean (SD)	15	425 (112)	15	436 (170)
AUC_{0-24h} (h*ng/mL)	Mean (SD)	15	3020 (541)	15	2860 (741)
T_{max} (h)	Median (Min-Max)	15	1.0 (1.0-3.0)	15	1.0 (0.5-4.0)

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.

Source: Table 14.2.2.4

Drug-Drug Interaction Results:

Fourteen of 15 subjects (93.3%) in the PK population were included in the DDI population. Subject 1001 discontinued on Day 11 and was excluded from the DDI population.

Effect of Sitagliptin on Exposure of Dorzagliatin:

In the analysis of the effect of sitagliptin on the PK of dorzagliatin, the percentage of estimated GMR for dorzagliatin C_{max} and AUC_{0-24h} was 102.34 (90% CI: 86.92, 120.50), and 100.34 (90% CI: 96.08, 104.79), respectively.

The 90% CIs for C_{max} and AUC_{0-24h} fell within the 80 to 125% boundaries (a commonly accepted criteria for declaring equivalence), suggesting that co-administration of sitagliptin and dorzagliatin treatment did not significantly change the pharmacokinetics of dorzagliatin.

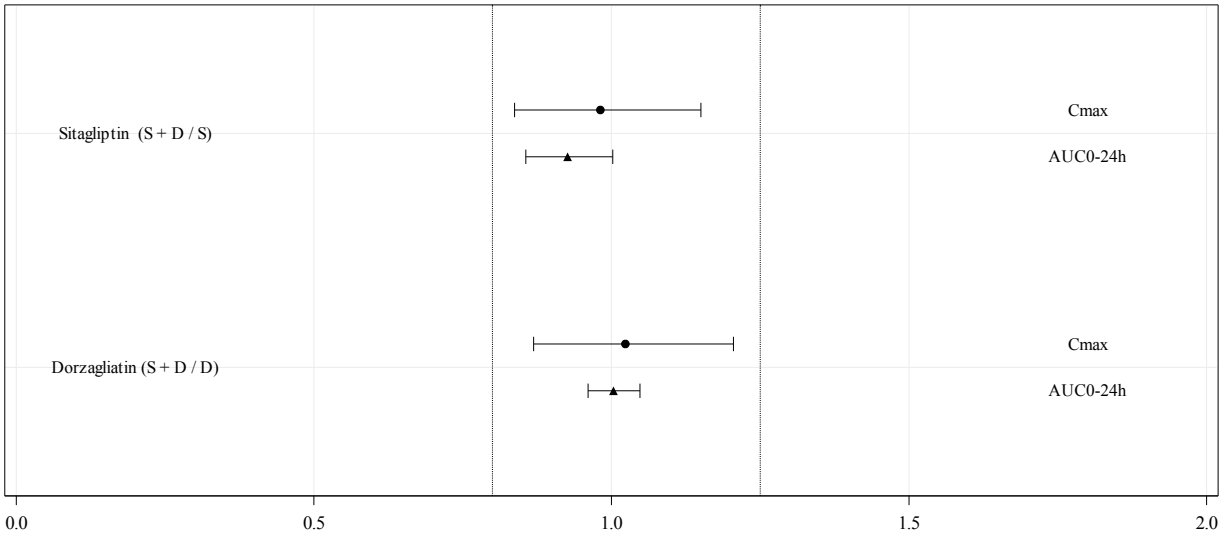
Effect of Dorzagliatin on Exposure of Sitagliptin:

In the analysis of the effect of dorzagliatin on the PK of sitagliptin, the percentage of estimated GMR for sitagliptin C_{max} and AUC_{0-24h} was 98.14 (90% CI: 83.73, 115.03) and 92.63 (90% CI: 85.61, 100.22), respectively.

The 90% CIs for C_{max} and AUC_{0-24h} fell within the 80 to 125% boundaries (a commonly accepted criteria for declaring equivalence), suggesting that co-administration of dorzagliatin and sitagliptin treatment did not significantly change the pharmacokinetics of sitagliptin.

A forest plot of the dorzagliatin and sitagliptin drug-drug interaction assessment of GMR of C_{max} and AUC_{0-24h} PK parameters and associated 90% CI is presented in Figure 2-1 (N=14) and illustrates that the C_{max} and AUC_{0-24h} GMRs and associated 90% CIs for the effect of dorzagliatin on sitagliptin (top portion) and for the effect of sitagliptin on dorzagliatin (lower portion) were contained within the 0.80 to 1.25 (80 to 125%) boundaries.

Figure 2-1: Dorzagliatin and Sitagliptin Drug-Drug Interaction Assessment of the GMR of PK Parameters and 90% Confidence Interval – DDI Population



Source: Figure 14.2.4

Pharmacodynamic (PD) Results:

Serum Glucose:

Baseline corrected $AUEC_{0-4h}$ (253 hr*mg/dL) was significantly lower after combination treatment of sitagliptin and dorzagliatin than administration of dorzagliatin (339 hr*mg/dL, p<.05) or sitagliptin (378 hr*mg/dL, p<.05) alone. The result suggested that combination treatment of sitagliptin and dorzagliatin achieved a better glucose reduction effect than either sitagliptin or dorzagliatin treatment alone, and resulted in improved glycemic control in the studied T2DM patients.

Serum Insulin and C-peptide:

Mean baseline corrected insulin and C-peptide levels following co-administration of sitagliptin and dorzagliatin were significantly higher than dorzagliatin monotherapy (p<.05), and numerically higher than sitagliptin monotherapy. The results suggested that combination treatment of sitagliptin and dorzagliatin increased insulin secretion more than the sitagliptin or dorzagliatin treatment did alone.

Plasma total and active GLP-1:

Mean baseline corrected plasma total GLP-1 levels following co-administration of sitagliptin and dorzagliatin were significantly lower than dorzagliatin monotherapy (p<.05), and were slightly lower than sitagliptin monotherapy.

Mean baseline corrected plasma active GLP-1 levels were numerically higher after co-administration of sitagliptin and dorzagliatin than administration of either sitagliptin or dorzagliatin alone.

Plasma Glucagon:

Mean baseline corrected plasma glucagon levels were slightly lower after combination treatment of sitagliptin and dorzagliatin than either sitagliptin or dorzagliatin treatment alone.

Safety Results:

Overall, dorzagliatin was well tolerated when given alone and when given together with sitagliptin. No serious TEAEs were reported during the study.

A total of eighteen (18) treatment-emergent AEs (TEAEs) were reported in 7 (46.7%) subjects. No serious adverse events were reported. No deaths occurred. One (1) subject was early discontinued from the study due to the adverse event of erythematous rash.

Six TEAEs in 5 subjects (33.3%) were considered possibly related to treatment, including rash in 2 subjects, erythematous rash in 1 subject, and hunger in 1 subject possibly related to both dorzagliatin and sitagliptin treatments, and headache in 1 subject possibly related to sitagliptin treatment alone.

Hypoglycemia was reported in 1 subject, beginning at 3 hours post-dose on Day 10 during combination treatment with dorzagliatin and sitagliptin and resolving within 1.5 hours without intervention. The AE of hypoglycemia was considered possibly related to treatment (dorzagliatin and sitagliptin) and was mild in intensity.

No clinically significant findings or overall changes were detected in clinical chemistry, hematology and urinary analysis.

No clinically significant findings or overall changes in vital signs, ECG and physical examination were observed.

Conclusions:

Pharmacokinetic and drug-drug interaction conclusions:

With respect to the effect of sitagliptin on the PK of dorzagliatin, study results showed that sitagliptin did not change the pharmacokinetics of dorzagliatin as measured by C_{max} and $AUC_{0\text{-}24h}$.

With respect to the effect of dorzagliatin on the PK of sitagliptin, the results suggested that dorzagliatin did not have a significant effect on sitagliptin as measured by C_{max} and $AUC_{0\text{-}24h}$.

The study results demonstrated that there was no drug-drug interaction potential on the pharmacokinetics between dorzagliatin and sitagliptin when they are co-administered in this study.

Pharmacodynamic Conclusions:

Combination treatment of sitagliptin and dorzagliatin further improved glycemic control as compared to administration of either sitagliptin or dorzagliatin alone in the T2DM study population.

Safety Conclusions:

The study results demonstrated that the multiple doses of dorzagliatin (75 mg, BID) alone or in combination with sitagliptin (100 mg QD) were safe and well-tolerated by T2DM subjects in this study.

Date of Report

17 July 2020, Version 1.0 (Final)