Clinical Study Report Synopsis

Drug Substance	Saxagliptin/Metformin
Study Code	D1681C00001
Edition Number	1

A Single-Center, Randomized, Open-Label, Two-Period, Cross-Over, Bioequivalence Study of the Fixed Dose Combinations of Saxagliptin/Metformin XR Relative to Co-Administration of the Individual Components in Two Cohorts of Healthy Chinese Subjects Under Fed Conditions

Study dates:	First subject enrolled: 25 February 2013 Last subject last visit: 26 April 2013
Phase of development:	Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Publications

None at the time of writing this report

Objectives and criteria for evaluation

The study objectives and variables are summarized in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	PK	To demonstrate BE of both saxagliptin and metformin from 5 mg saxagliptin/500 mg metformin XR FDC tablet compared to co-administration of a 5 mg saxagliptin tablet and a 500 mg metformin XR (Glucophage XR) tablet under fed conditions	PK parameters (C_{max}, $AUC_{[0-T]}$, and $AUC_{[INF]}$) of saxagliptin and metformin was derived from plasma concentration versus time data
	PK	To demonstrate BE of both saxagliptin and metformin from 5 mg saxagliptin/1000 mg metformin XR FDC tablet compared to co-administration of a 5 mg saxagliptin tablet and 2x500 mg metformin XR (Glucophage XR) tablets under fed conditions	PK parameters (C_{max}, $AUC_{[0-T]}$, and $AUC_{[INF]}$) of saxagliptin, and metformin was derived from plasma concentration versus time data
Secondary	PK	To assess the PK parameters of 5-hydroxy-saxagliptin, the active metabolite of saxagliptin	PK parameters (C_{max}, $AUC_{[0-T]}$, t_{max}, $AUC_{[INF]}$, MRT, $t_{1/2}$, CL/F, and Vd/F) of 5-hydroxy-saxagliptin was derived from plasma concentration versus time data
Safety	Safety	To assess and summarize the safety and tolerability of 5 mg saxagliptin co-administered with up to 1000 mg metformin XR given either separately, in tablets, or as a single FDC tablet to healthy Chinese subjects under fed conditions	AE reports; Vital sign measurements, ECGs, physical examinations, and clinical laboratory tests

$AUC_{(0-T)}$ Area under the plasma concentration-time curve from 0 to time of last quantifiable concentration; $AUC_{(INF)}$ Area under the plasma concentration versus time curve extrapolated to infinity; BE Bioequivalence; CL/F Apparent clearance of the analyte following extravascular administration; C_{max} Maximum plasma concentration; CSP Clinical study protocol; ECG Electrocardiograms; FDC Fixed dose combination; MRT Mean residence time; PK Pharmacokinetic; t1/2 Apparent terminal phase half-life; t_{max} Time to maximum concentration; Vd/F Apparent volume of distribution of the analyte following extravascular administration; XR Extended release.

Study design

This was a Phase I, single-center, randomized, open-label, 2-period, cross-over, bioequivalence (BE) study of the fixed dose combination (FDC) of saxagliptin/metformin extended release (XR) relative to co-administration of the individual components in 2 cohorts of healthy Chinese male subjects under fed conditions. The study comprised 2 visits to the clinical unit, 1 screening visit and 1 treatment visit. The 2 cohorts were independent of each other with respect to treatment and results.

Target subject population and sample size

The target population included healthy Chinese males aged ≥18 years and ≤40 years. Healthy males (2 cohorts of 32 subjects each) were randomized to receive treatment with the investigational product (IP) in order to complete at least 56 evaluable subjects (2 cohorts of 28 subjects each).

Investigational product and comparators: dosage, mode of administration, and batch numbers

The IPs was divided into 2 cohorts as follows:

Cohort 1

- Treatment A=Co-administration of a single oral dose of a 5 mg saxagliptin tablet and 500 mg metformin XR (Glucophage XR) tablet
- Treatment B=Single FDC tablet consisting of 5 mg saxagliptin and 500 mg metformin XR (Kombiglyze XR™[1]).

Cohort 2

- Treatment C=Co-administration of a single oral dose of a 5 mg saxagliptin tablet and 2x500 mg metformin XR (Glucophage XR) tablets
- Treatment D=Single FDC tablet consisting of 5 mg saxagliptin and 1000 mg metformin XR (Kombiglyze XR).

After at least a 10-hour fast, subjects had a standard low fat breakfast 30 minutes prior to administration of the study drug.

Duration of treatment

Single dose of Treatment A or Treatment B in Cohort 1 and Treatment C or Treatment D in Cohort 2 with a washout period of at least 7 days between doses.

Statistical methods

The summary and analyses were conducted separately for each cohort (Cohort 1 and Cohort 2). To demonstrate the BE of FDC tablet versus co-administration of a saxagliptin tablet and a metformin XR tablet in the fed state, point estimates and 90% CI for C_{max}, $AUC_{(0-T)}$, and $AUC_{(INF)}$ were calculated. For Treatment B to Treatment A and Treatment D to Treatment C, ratios of geometric least square (LS) means of saxagliptin and metformin were reported by using a linear mixed effects model. PROC MIXED procedure was used to perform linear mixed effects model.

[1] Kombiglyze XR™ (saxagliptin/metformin hydrochloride extended release) is a trademark of Bristol-Myers Squibb Company and AstraZeneca Pharmaceuticals LP.

Summary statistics were tabulated by treatment for each PK parameter (C_{max}, $AUC_{[0-T]}$, t_{max}, $AUC_{[INF]}$, MRT, $t_{1/2}$, CL/F, and Vd/F) of saxagliptin, 5-hydroxy-saxagliptin, and metformin. Concentration and PK parameter data are presented in data listings and summarized.

All recorded AEs are listed and tabulated by system organ class (SOC), preferred term (PT), and formulation. Vital signs and clinical laboratory test results are listed and summarized by formulation. Any significant physical examination findings, ECG results, and clinical laboratory results are all listed. AEs of special interest and confirmed clinically significant hypoglycemia were also recorded.

Subject population

A total of 93 subjects were enrolled at a single center in China. The first and last subjects were enrolled on 25 February 2013 and 9 April 2013, respectively, and the last subject completed the study on 26 April 2013. Twenty-nine subjects were enrolled but not randomized due to eligibility criteria not fulfilled (26 subjects) and subjects' decision (3 subjects).

Of the 64 randomized subjects, 32 subjects were randomized within Cohort 1 (16 subjects each in TS1[2] and TS2[3]) and 32 subjects were randomized within Cohort 2 (16 subjects each in TS1 and TS2). All randomized subjects received the IP and completed the study. The study population consisted of healthy, Chinese males (32 [100%] subjects in each Cohort) between 23 years and 32 years of age. The demography, baseline characteristics, weight, and body mass index of the subjects were balanced between the treatment sequences in both cohorts. Only 1 subject (E1301056) in Cohort 2 received second-generation cephalosporins on Day 6, as concomitant medication for acute tonsillitis; this medication was confirmed by the study physician as not a restricted medication. There were no concerns regarding concomitant medications or prior medical conditions. All 64 (100%) subjects completed the treatment and the study. There was no important protocol deviation observed during the study.

Summary of efficacy results

Not applicable.

Summary of pharmacokinetic results

With respect to $AUC_{(INF)}$, $AUC_{(0-T)}$, and C_{max} for both saxagliptin and metformin, the geometric least squares (LS) mean ratio 90% CI were entirely contained within the 80.00% to

2 Treatment Sequence (TS) 1: Cohort 1=Treatment A followed by Treatment B after washout.

Cohort 2=Treatment C followed by Treatment D after washout.

3 TS2: Cohort 1=Treatment B followed by Treatment A after washout.

Cohort 2=Treatment D followed by Treatment C after washout.

125.00% BE limits for AUC parameters and within the 70.00% to 143.00% BE limits for C_{max}. The geometric mean and 90% CI for ratio is presented in Table S2.

Table S2 Geometric mean and 90% CIs for ratio (PK analysis set)

							Comparison		

Cohort	**Analyte**	**Parameter (Unit)**	**Treatment**	**N**	**Geometric LS Means**	**95% CI**	**Pair**	**Ratio (%)**	**90% CI**
1	Metformin	AUC(0-T) (hr.ng/mL)	A	32	5499.15	(5071.35,5963.04)	B/A	97.96	(92.89,103.31)
			B	32	5387.04	(4967.96,5841.47)			
		AUC(INF) (hr.ng/mL)	A	30	5635.31	(5191.05,6117.60)	B/A	97.32	(91.75,103.24)
			B	30	5484.46	(5051.53,5954.49)			
		CMAX (ng/mL)	A	32	603.15	(560.17,649.44)	B/A	101.41	(96.96,106.06)
			B	32	611.65	(568.06,658.59)			
	Saxagliptin	AUC(0-T) (hr.ng/mL)	A	32	111.54	(102.61,121.25)	B/A	94.90	(90.12,99.92)
			B	32	105.85	(97.37,115.06)			
		AUC(INF) (hr.ng/mL)	A	32	112.69	(103.69,122.47)	B/A	94.96	(90.21,99.95)
			B	32	107.01	(98.46,116.30)			
		CMAX (ng/mL)	A	32	27.41	(25.17,29.86)	B/A	94.57	(87.52,102.18)
			B	32	25.92	(23.80,28.24)			
2	Metformin	AUC(0-T) (hr.ng/mL)	C	32	9678.79	(8910.12,10513.77)	D/C	97.01	(90.63,103.85)
			D	32	9389.75	(8644.03,10199.79)			
		AUC(INF) (hr.ng/mL)	C	29	9888.38	(9065.07,10786.46)	D/C	96.44	(89.39,104.05)
			D	27	9536.40	(8723.87,10424.61)			
		CMAX (ng/mL)	C	32	1069.98	(989.02,1157.58)	D/C	103.99	(98.41,109.88)
			D	32	1112.64	(1028.45,1203.72)			
	Saxagliptin	AUC(0-T) (hr.ng/mL)	C	32	116.01	(110.22,122.10)	D/C	104.16	(100.81,107.62)
			D	32	120.83	(114.81,127.18)			
		AUC(INF) (hr.ng/mL)	C	32	117.63	(111.80,123.76)	D/C	104.08	(100.70,107.58)
			D	32	122.43	(116.36,128.82)			
		CMAX (ng/mL)	C	32	32.29	(29.75,35.06)	D/C	97.91	(91.86,104.36)
			D	32	31.62	(29.13,34.32)			

The statistical model is ANCOVA on the log transformed pharmacokinetic variable ($AUC_{(0-T)}$, $AUC_{(INF)}$, and C_{max}) by fitting treatment, sequence, and period as fixed effects, and subject within sequence as random effects.

N Number of subjects in treatment group.
Treatment A=Co-administration of a single oral dose of a 5 mg Saxagliptin tablet and a 500 mg Metformin XR (Glucophage XR) tablet.
Treatment B=Single FDC tablet consisting of 5 mg Saxagliptin and 500 mg Metformin XR (Kombiglyze XR).
Treatment C=Co-administration of a single oral dose of a 5 mg Saxagliptin tablet and two (2) 500 mg Metformin XR (Glucophage XR) tablets.
Treatment D=Single FDC tablet consisting of 5 mg Saxagliptin and 1000 mg Metformin XR (Kombiglyze XR).
ANCOVA Analysis of covariance; $AUC_{(0-T)}$ Area under the plasma concentration-time curve from 0 to time of last quantifiable concentration; AUC(INF) Area under the plasma concentration versus time curve extrapolated to infinity; CI Confidence interval; Cmax Maximum plasma concentration; FDC Fixed dose combination; PK Pharmacokinetic; XR Extended release.
Medical Dictionary for Regulatory Activities (MedDRA) version 16.0.

Following a 5 mg dose of saxagliptin administered either as saxagliptin/metformin XR FDC or as saxagliptin concurrently with metformin XR (both dose strengths), geometric mean $AUC_{(INF)}$ for 5-hydroxy-saxagliptin ranged from 227.7 to 256.5 hr.ng/mL and C_{max} from 38.5 to 44.1 ng/mL across treatments. Median t_{max} occurred at 2 to 3 hours post-dose across treatments.

Summary of safety results

All 64 subjects (32 each from Cohort 1 and Cohort 2) received a single dose of the IP in each treatment period with a washout period of at least 7 days between the treatment periods.

A total of 6 (18.8%) subjects from Cohort 1 and 2 (6.3%) subjects in Cohort 2 experienced at least 1 AE:

- 3 (9.4%) subjects from Treatment A group
- 3 (9.4%) subjects from Treatment B group
- 2 (6.3%) subjects from Treatment C group
- No AEs were reported in Treatment D group.

The AEs reported in Cohort 1 were upper respiratory tract infection, alanine aminotransferase increased, aspartate aminotransferase increased, limb injury, and toothache and the AEs reported in Cohort 2 were acute tonsillitis, fatigue, and pain in extremity.

There were no deaths, serious AEs, discontinuations due to IP, other significant AEs, and/or AEs of special interest during this study. The treatment groups were balanced with respect to the number of subjects who experienced at least 1 AE.

Overall, there were few treatment-emergent changes in clinical laboratory evaluation, vital signs, ECGs, and physical examination, and there were no abnormalities of major clinical importance.