Clinical Study Report Synopsis

Drug Substance	Saxagliptin/Metformin XR FDC
Study Code	D1681C00004
Edition Number	1
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Bioequivalence Study of the Fixed-dose Combination of Saxagliptin/Metformin XR Tablets Relative to Saxagliptin (Onglyza™) Tablets and Australia-sourced Diabex® XR Tablets Coadministered to Healthy Subjects in the Fed State During Steady-state Administration

Study dates: First subject enrolled: 18 October 2011
Last subject last visit: 27 December 2011

Phase of development: Clinical pharmacology (I)

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

Study center(s)

The study was conducted at a single center: Quintiles Phase I Services, Overland Park, Kansas, United States.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To demonstrate the bioequivalence of saxagliptin and metformin from a 5-mg saxagliptin/1000-mg metformin extended-release fixed-dose combination tablet relative to 5-mg Onglyza™ and Australia-sourced 1000-mg Diabex® extended-release tablets administered together in the fed state during steady-state administration	Saxagliptin and metformin AUC_{ss}, $C_{max,ss}$, and $t_{max,ss}$	Pharmacokinetic
To demonstrate the bioequivalence of saxagliptin and metformin from a 5-mg saxagliptin/500-mg metformin extended-release fixed-dose combination tablet relative to 5-mg Onglyza and Australia-sourced 500-mg Diabex extended-release tablets administered together in the fed state during steady-state administration	Saxagliptin and metformin AUC_{ss}, $C_{max,ss}$, and $t_{max,ss}$	Pharmacokinetic
Secondary	**Secondary**	
To characterize the steady-state pharmacokinetics in healthy volunteers of the active metabolite of saxagliptin, 5-hydroxy-saxagliptin (BMS 510849), from the saxagliptin/metformin extended-release fixed-dose combination and from Onglyza administered together with Australia-sourced Diabex extended-release for each dose strength	5-hydroxy-saxagliptin AUC_{ss}, $C_{max,ss}$, and $t_{max,ss}$	Pharmacokinetic

AUC_{ss} area under the concentration-time curve from zero to the end of the dosing interval at steady state; $C_{max,ss}$ observed maximum concentration at steady state; $t_{max,ss}$ time of maximum concentration at steady state.

Study design

This was an open-label, randomized, 2-period, 2-treatment, 2-way crossover study to evaluate the bioequivalence of 2 different dose strengths of saxagliptin/metformin extended-release combination tablets in comparison to marketed formulations of the individual drugs in equal dose strengths in 36 healthy male and female volunteers aged 18 to 55 years of age (inclusive).

The 2 dose strengths of saxagliptin/metformin extended-release combination tablets were evaluated in 2 separate cohorts of 18 volunteers each. Enrollment into Cohort 1 was completed prior to enrollment into Cohort 2. Within each cohort, volunteers were randomized

to 1 of 2 treatment sequences (AB and BA in Cohort 1, or CD and DC in Cohort 2). All treatments were to be administered once daily for 5 days, in the morning in the fed state (within 5 minutes of completing a standardized breakfast). Breakfast on Day 5 of each treatment was high fat/high calorie.

On Day 5, serial blood samples for pharmacokinetic analysis of saxagliptin, 5-hydroxy-saxagliptin, and metformin were to be collected over a 24-hour interval following dosing in Periods 1 and 2. The washout between the last dose of Period 1 and the first dose of Period 2 was at least 5 days.

Target subject population and sample size

The target population was healthy male and female volunteers aged 18 to 55 years of age (inclusive) with a body mass index of 18 to 35 kg/m^2 (inclusive) and weighing at least 50 kg.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

All investigational product was administered orally.

Cohort 1

Treatment A: 5-mg Onglyza (saxagliptin) tablet (manufactured by Bristol-Myers Squibb/AstraZeneca, Batch Number 9K6009A), coadministered with Australia-sourced 1000-mg Diabex extended-release tablet (marketed by Alphapharm, Batch Number A202N), administered once daily for 5 days (reference).

Treatment B: 5-mg saxagliptin/1000-mg metformin extended-release fixed-dose combination tablet (manufactured by Bristol-Myers Squibb/AstraZeneca, Batch Number 1B6018A), administered once daily for 5 days (test).

Cohort 2:

Treatment C: 5-mg Onglyza (saxagliptin) tablet (manufactured by Bristol-Myers Squibb/AstraZeneca, Batch Number 9K6009A), coadministered with Australia-sourced 500-mg Diabex extended-release tablet (marketed by Alphapharm, Batch Number A265N), administered once daily for 5 days (reference).

Treatment D: 5-mg saxagliptin/500-mg metformin extended-release fixed-dose combination tablet (manufactured by Bristol-Myers Squibb/AstraZeneca, Batch Number 1A6023C), administered once daily for 5 days (test).

Duration of treatment

The study consisted of 4 visits and a washout period: Visit 1 (screening) from Day -28 to Day -2; Visit 2 (first residential period) from Day -1 to Day 6; a minimum 5-day washout period occurred following Visit 2; Visit 3 (second residential period) from Day -1 to Day 6;

and Visit 4 (follow-up) which occurred 7 to 10 days after discharge from the second residential period. Total study duration was a maximum of approximately 8 weeks.

Statistical methods

Demographic, safety, and pharmacokinetic data were summarized descriptively using tables, listings, and graphs, as appropriate.

In order to evaluate bioequivalence, log-transformed AUC_{ss} and $C_{max,ss}$ values for saxagliptin and metformin (primary) and 5-hydroxy-saxagliptin (secondary) were analyzed using a mixed-effects model with sequence, period, and treatment as fixed effects, and volunteer within sequence as a random effect, separately for each cohort. From these analyses, least-squares means for each treatment, least-squares mean differences between treatments (test minus reference treatment), and 90% confidence intervals for the treatment differences on log-scale were obtained. The results were transformed back to the original scale by exponentiation to provide geometric least-squares treatment means, point estimates of the geometric least-squares mean ratios, and 90% confidence intervals for these ratios. If the 90% confidence intervals for the geometric least-squares mean ratios of AUC_{ss} and $C_{max,ss}$ (in percent) between the test treatment and the reference treatment fell within the interval (80.00%, 125.00%), then bioequivalence between the test treatment and the reference treatment was concluded. In Cohort 1, Treatment A was the reference treatment and Treatment B was the test treatment. In Cohort 2, Treatment C was the reference treatment and Treatment D was the test treatment. No adjustments were made for multiplicity.

Subject population

The volunteer population consisted of 36 study participants with 18 volunteers in each cohort. Of the 36 randomized volunteers, 32 (88.9%) completed all planned study treatment (18 [100%] in Cohort 1 and 14 [77.8%] in Cohort 2). Four volunteers (11.1%) were discontinued from the study; all were in Cohort 2 (22.2%). Two volunteers in Cohort 2 were discontinued due to severe noncompliance to the protocol [positive drug screens] and 2 were discontinued due to nonserious adverse events of vomiting [1 volunteer] and elevated alanine aminotransferase [1 volunteer]). Overall, there were 9 (25.0%) women and 27 (75.0%) men with a mean age of 33 years. All 36 volunteers were included in the safety analysis and 35 volunteers (18 in Cohort 1 and 17 in Cohort 2) were included in the pharmacokinetic analysis.

Summary of pharmacokinetic results

For bioequivalence studies, the usual practice is to assay all samples from an individual volunteer, ie, from both test and reference treatments, during a single bioanalytical run in order to minimize variability. When the plasma samples were originally analyzed for saxagliptin and 5-hydroxy-saxagliptin in this study, the samples from an individual volunteer were not assessed in this manner as different treatment periods were analyzed in separate bioanalytical runs. Therefore, in order to ensure that this study was conducted following the usual practices, the samples from all volunteers were reassayed for saxagliptin and 5-hydroxy-saxagliptin with each volunteer's samples being analyzed in the same run. The saxagliptin and 5-hydroxy-saxagliptin results described and summarized below pertain to the

reassayed data. Metformin samples were not reassayed and therefore the results below pertain to the original assay.

For each treatment, mean trough concentrations indicated that steady-state conditions were achieved by approximately Day 2 for saxagliptin, Day 5 for 5-hydroxy-saxagliptin, and Day 3 for metformin.

Pharmacokinetic parameters for saxagliptin, 5-hydroxy-saxagliptin, and metformin on Day 5 of each treatment are summarized in Table S2.

Table S2 Summary of plasma pharmacokinetic parameters for saxagliptin, 5-hydroxy-saxagliptin, and metformin on Day 5 of each treatment (Cohorts 1 and 2)

			Geometric Mean (CV%)		Median (Min, Max)
Cohort	**Treatment**	**N**	**AUC_{ss} (ng*h/mL)**	**$C_{max,ss}$ (ng/mL)**	**$t_{max,ss}$ (h)**
			Saxagliptin (reassayed data)		
1	A	18	96.9 (17.1)[a]	24.6 (40.9)	1.25 (0.48, 4.00)
	B	18	91.4 (21.8)	27.3 (44.9)	0.88 (0.25, 4.00)
2	C	16	102 (21.3)	27.6 (41.5)	1.00 (0.48, 4.00)
	D	15	95.8 (26.5)	27.7 (52.5)	1.00 (0.25, 3.00)
			5-Hydroxy-saxagliptin (reassayed data)		
1	A	18	284 (33.5)	48.5 (34.4)	2.50 (0.98, 4.00)
	B	18	286 (34.8)	51.4 (37.2)	2.00 (0.75, 5.00)
2	C	16	268 (31.5)	44.5 (37.4)	1.75 (1.50, 5.00)
	D	15	254 (34.6)	44.1 (40.8)	2.00 (1.00, 4.00)
			Metformin		
1	A	18	12700 (22.8)	1080 (17.1)	6.00 (5.00, 10.00)
	B	18	12500 (21.3)	1100 (20.1)	6.00 (5.00, 10.00)
2	C	16	6450 (16.1)	572 (16.0)	5.03 (4.00, 10.00)
	D	15	6340 (19.7)	552 (17.4)	5.02 (4.00, 10.00)

[a] n = 17.

CV% geometric coefficient of variation in percent; FDC fixed-dose combination; Max maximum; Min minimum; N number of volunteers included in pharmacokinetic analysis for that treatment and analyte; n number of values (observations); XR extended release.

Volunteers in Cohort 1 received Treatments A and B and volunteers in Cohort 2 received Treatments C and D. Each treatment was administered orally once daily for 5 days: A: 5-mg Onglyza tablet + Australia-sourced 1000-mg Diabex XR tablet (reference); B: 5-mg saxagliptin/1000-mg metformin XR FDC tablet (test); C: 5-mg Onglyza tablet + Australia-sourced 500-mg Diabex XR tablet (reference); D: 5-mg saxagliptin/500-mg metformin XR FDC tablet (test).

In Cohort 1, Treatment B (test) was found to be bioequivalent to Treatment A (reference) with respect to AUC_{ss} and $C_{max,ss}$ for metformin and with respect to AUC_{ss} for saxagliptin (90% confidence intervals on the geometric least-squares mean ratios were within 80.00 to 125.00%), but was not bioequivalent with respect to $C_{max,ss}$ for saxagliptin (ratio of 111.12% and 90% CI of 95.86 to 128.81%). Median saxagliptin $t_{max,ss}$ values were similar between Treatments A and B. Treatment B was also bioequivalent to Treatment A with respect to AUC_{ss} and $C_{max,ss}$ for 5-hydroxy-saxagliptin.

In Cohort 2, Treatment D (test) was found to be bioequivalent to Treatment C (reference) with respect to AUC_{ss} and $C_{max,ss}$ for metformin and with respect to AUC_{ss} for saxagliptin (90% confidence intervals on the geometric least-squares mean ratios were within 80.00 to 125.00%), but was not bioequivalent with respect to $C_{max,ss}$ for saxagliptin (ratio of 106.42% and 90% CI of 88.05 to 128.62%). Median saxagliptin $t_{max,ss}$ values were similar between Treatments C and D. Treatment D was also bioequivalent to Treatment C with respect to AUC_{ss} and $C_{max,ss}$ for 5-hydroxy-saxagliptin.

Summary of safety results

There were no deaths or serious adverse events reported. Two volunteers in Cohort 2 were discontinued from the study due to mild adverse events of vomiting (1 volunteer) and elevated alanine aminotransferase (1 volunteer).

Adverse events were reported for 15 (41.7%) volunteers. Adverse events were reported for 9 (50.0%) volunteers during Treatment A, 4 (22.2%) volunteers during Treatment B, 5 (29.4%) volunteers during Treatment C, and 2 (13.3%) volunteers during Treatment D. The most frequently reported adverse events overall were headache (8/36 volunteers, 22.2%), nausea (3/36, 8.3%), and decreased appetite (3/36 volunteers, 8.3%).

Twelve (33.3%) of the 36 volunteers reported adverse events assessed by the Investigator as related to investigational product: 7 (38.9%) volunteers during Treatment A, 2 (11.1%) volunteers during Treatment B, 4 (23.5%) volunteers during Treatment C, and 1 (6.7%) volunteers during Treatment D. The most frequently reported related adverse events overall were headache (5/36 volunteers, 13.9%) and decreased appetite (3/36 volunteers, 8.3%).

Three female volunteers in Cohort 1 who received 5-mg/1000-mg treatments (Treatments A or B) experienced adverse events of decreased appetite, nausea, or retching considered notable by the Investigator. Decreased appetite was sustained and significant and lasted from approximately 15.5 hours to 7 days. The Investigator assessed all the events as mild in severity and related to investigational product.

One moderate adverse event of nausea was reported (Cohort 2, Treatment C); all other adverse events were mild in severity.

Overall, there were no trends or clinically relevant changes noted in mean clinical laboratory, vital sign, physical examination, or electrocardiogram data following dosing.