AstraZeneca

Bristol-Myers Squibb

Clinical Study Report Synopsis

Drug Substance	Saxagliptin
Study Code	D1680C00004
Date	10 June 2009

An Open-label, Pharmacokinetic Study of Single and Multiple Doses of 5 mg Saxagliptin in Healthy Chinese Subjects Living in China

Study dates:	First subject enrolled: 13 October 2008 Last subject completed: 24 October 2008
Phase of development:	Clinical pharmacology (I)

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

Study centre(s)

This was a single-site study conducted at the Drug Clinical Trial Center, Beijing, China. The first subject was enrolled on 13 October 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to assess the pharmacokinetics (PK) of saxagliptin and its pharmacologically active metabolite, BMS-510849, following single and multiple oral doses of 5 mg saxagliptin in healthy Chinese subjects.

The secondary objective was to assess the safety and tolerability of saxagliptin following single and multiple oral doses of 5 mg saxagliptin in healthy Chinese subjects.

Study design

This was a single-site, open-label, PK, single- and multiple-dose study in healthy Chinese subjects. The investigational product administration included a single 5-mg dose on Day 1, and five 5-mg once-daily doses on Days 3 through 7. Subjects were admitted to the medical unit the day prior to dosing (Day -1) and stayed until Day 9, at least 48 hours after their last dose of investigational product (which was on Day 7). Blood and urine samples were collected for PK analyses. Subjects were monitored for adverse events (AEs) throughout the study. Clinical laboratory evaluations were performed at screening, on Day -1, and on Day 9.

Target subject population and sample size

The target population included healthy Chinese subjects of either sex between 18 and 45 years old and with body mass index (BMI) between 19 and 24 kg/m^2. Approximately 16 subjects were to receive treatment with investigational product to obtain at least 12 evaluable subjects. An evaluable subject was defined as a subject completing all study procedures from the screening period to the final blood sampling for plasma levels of saxagliptin and BMS-510849.

Inclusion criteria

The inclusion criteria healthy subjects had to fulfil to enrol in the study included provision of signed written informed consent, Chinese ethnicity, age between 18 and 45 years inclusive, use of an adequate method of contraception to avoid pregnancy throughout the study and for up to 4 weeks after the study, weight of at least 50 kg and a BMI between 19 and 24 kg/m^2 inclusive, normal physical examination and laboratory values, and ability to communicate with the investigator and to understand and comply with all study requirements.

Exclusion criteria

Some major exclusion criteria from the study included hypoglycaemia, pregnancy or breastfeeding, significant acute or chronic illness, autoimmune skin disorder, gastrointestinal

disease within 3 months, major surgery within 4 weeks, any gastrointestinal surgery that could impact the absorption of investigational product, donation of blood within 3 months, blood transfusion within 4 weeks, drug or alcohol abuse, abnormal physical examination results, allergy to saxagliptin, prior exposure to saxagliptin or any other dipeptidyl peptidase 4 inhibitor, use of any other drugs including over-the-counter medications within 2 weeks, lymphocytopaenia, thrombocytopaenia, and regular smoking.

Criteria for discontinuation

Subjects could be discontinued at any time. Specific reasons for discontinuing a subject from this study included voluntary discontinuation by the subject, safety reasons, severe non-compliance to protocol, incorrect enrolment, and lost to follow-up.

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

Saxagliptin was provided in 5-mg oral tablets (batch number: H 2024-01-01-01). Saxagliptin administration included a single 5-mg dose on Day 1, and five 5-mg once-daily doses on Days 3 through 7.

Duration of treatment

The duration of each subject's participation was up to approximately 31 days, including a visit during the 21-day screening period, and 10 days on site (which included 6 days of treatment). The 48 hours between the single dose on Day 1 and the administration of investigational product in the morning of Day 3 served as the washout period between the single and multiple dosing periods. Day 3 began a 5-day regimen of once-daily doses of 5 mg saxagliptin.

Criteria for evaluation - pharmacokinetics (main variables)

Samples were analysed to determine plasma and urine concentrations of saxagliptin and BMS-510849. PK variables were generated for samples obtained following a single dose and for samples following multiple doses (steady state). The primary PK parameters for saxagliptin and the secondary PK parameters for BMS-510849 included maximum plasma concentration, time to maximum concentration (T_{max}), terminal phase half-life, area under the curve of plasma concentration versus time from zero to time of last quantifiable concentration, area under the curve of plasma concentration versus time extrapolated to infinity, area under the curve of plasma concentration versus time during the dosing interval, and accumulation index. Secondary variables for saxagliptin included apparent volume of distribution, mean residence time, and apparent oral clearance.

The secondary variables to be assessed for saxagliptin and BMS-510849 in urine were amount excreted in urine, percentage of dose recovered in urine, and renal clearance (CLR).

Criteria for evaluation - safety (main variables)

Safety and tolerability assessments were based on medical review of AE reports and results of vital sign measurements, electrocardiograms (ECGs), physical examinations, and clinical laboratory tests (ie, clinical chemistry, haematology, and urinalysis).

Statistical methods

Summary statistics were tabulated for each of the PK parameters by study day for saxagliptin and BMS-510849. Summary statistics were also tabulated for trough plasma concentrations by study day for saxagliptin and BMS-510849. Mean trough plasma concentrations were plotted by study day. Average steady-state concentration and degree of fluctuation after multiple dosing were post-hoc analyses calculated to meet requirements of the Chinese regulatory authority. However, the degree of fluctuation was not calculated since all subjects had all trough plasma concentrations below the lower limit of quantification.

AEs were listed and summarised by system organ class, and in addition, by preferred term. Vital signs, clinical laboratory measures, and ECG assessments were summarised using descriptive statistics by protocol time.

Subject population

In total, 30 subjects were enrolled, of which 16 fulfilled the inclusion and exclusion criteria and then received treatment. They were between the ages of 21 and 33 years with BMIs between 19.5 and 23.7 kg/m^2. All were Chinese, and more than half were male (68.8%). All 16 (100%) subjects received all planned doses of investigational product and completed the study. All 16 subjects were evaluable and were included in the PK and safety data sets.

Summary of pharmacokinetic results

Saxagliptin was rapidly absorbed following oral administration in Chinese subjects with T_{max} generally observed between 0.2 to 3 hours for saxagliptin and 0.8 to 3 hours for BMS-510849. The plasma exposures of saxagliptin and BMS-510849 in healthy Chinese subjects following single-dose administration were similar to the plasma exposures of saxagliptin and BMS-510849 following once-daily dosing for 5 consecutive days. This demonstrated the absence of any time-dependent changes in saxagliptin PK, such as enzyme and/or transporter induction. In addition, these results demonstrated a lack of any meaningful plasma accumulation of either analyte with repeat once-daily dosing. The plasma exposures of BMS-510849 in Chinese subjects were generally 2- to 3-fold higher than plasma exposures of saxagliptin, which were consistent with previous assessments in the clinical development programme for saxagliptin. Renal excretion was a major route of excretion for both saxagliptin and BMS-510849. The mean CLR of saxagliptin following single and multiple doses (194 and 186 mL/min, respectively) was greater than the glomerular filtration rate (GFR) of 120 mL/min, indicating possible active tubular secretion of saxagliptin; the mean CLR of BMS-510849 following single and multiple doses (90 and 81 mL/min, respectively) was similar to GFR, indicative of passive filtration. Approximately 55% of the administered saxagliptin dose was recovered in urine as saxagliptin and BMS-510849 following single and multiple doses. PK parameters are summarised in Table S1.

Table S1 Summary statistics for saxagliptin and BMS-510849 pharmacokinetic parameters (PK-evaluable subjects)

		Day 1 (single dose), n=16	Day 7 (steady state), n=16
Parameter	**Summary statistics**	**Results**	**Results**
Saxagliptin			
C_{max} (ng/mL)	Geometric mean (%CV)	34.36 (31)	34.15 (22)
C_{ss_av} (ng*h/mL)	Geometric mean (%CV)	NA	4.57 (18)
T_{max} (h)	Median (range)	0.5 (0.2 to 1.5)	1.0 (0.2 to 3.0)
$AUC_{(0-T)}$ (ng*h/mL)	Geometric mean (%CV)	95.49 (14)	NC
$AUC_{(INF)}$ (ng*h/mL)	Geometric mean (%CV)	100.96 (13)	NC
$AUC_{(TAU)}$ (ng*h/mL)	Geometric mean (%CV)	NC	109.69 (18)
T-HALF (h)	Mean (SD)	3.07 (1.02)	3.08 (0.73)
Vd/F or V_{ss}/F (L)	Mean (SD)	221.76 (85.48)	202.86 (50.98)
MRT (h)	Mean (SD)	3.99 (0.97)	4.12 (0.70)
CL/F (mL/min)	Mean (SD)	833.70 (128.10)	767.22 (135.15)
AI	Geometric mean (%CV)	NC	1.10 (14)
Ae[a] (mg)	Mean (SD)	1.20 (0.26)	1.22 (0.35)
%UR (%)	Mean (SD)	24.07 (5.13)	24.38 (7.07)
CLR (mL/min)	Geometric mean (%CV)	194.23 (17)	185.94 (27)
BMS-510849			
C_{max} (ng/mL)	Geometric mean (%CV)	57.79 (29)	58.04 (25)
C_{ss_av} (ng*h/mL)	Geometric mean (%CV)	NA	11.80 (19)
T_{max} (h)	Median (range)	1.03 (0.80 to 2.00)	1.50 (1.00 to 3.00)
$AUC_{(0-T)}$ (ng*h/mL)	Geometric mean (%CV)	262.73 (20)	NC
$AUC_{(INF)}$ (ng*h/mL)	Geometric mean (%CV)	277.23 (19)	NC
$AUC_{(TAU)}$ (ng*h/mL)	Geometric mean (%CV)	NC	283.31 (19)
T-HALF (h)	Mean (SD)	3.80 (0.88)	4.09 (1.12)
AI	Geometric mean (%CV)	NC	1.04 (17)
Ae[a] (mg)	Mean (SD)	1.52 (0.27)	1.41 (0.48)
%UR (%)	Mean (SD)	30.41 (5.49)	28.22 (9.52)
CLR (mL/min)	Geometric mean (%CV)	89.86 (16)	80.91 (34)

[a] Ae is also known as total urinary recovery (URT)

Day 1 results follow administration of saxagliptin 5 mg as a single dose; Day 7 results follow 5 once-daily doses of saxagliptin 5 mg (Day 3 to Day 7).

C_{ss_av} and degree of fluctuation were post-hoc analyses. The degree of fluctuation was not calculated since all subjects had all trough plasma concentrations less than the lower limit of quantification.

%UR Percentage of dose recovered in urine; Ae Amount excreted in urine; AI Accumulation index; $AUC_{(0-T)}$ Area under the curve of plasma concentration versus time from zero to time of last quantifiable concentration; $AUC_{(INF)}$ Area under the curve of plasma concentration versus time extrapolated to infinity; $AUC_{(TAU)}$ Area under the curve of plasma concentration versus time during the dosing interval; C_{max} Maximum plasma concentration; C_{ss_av} Average steady-state concentration; CL/F Apparent oral clearance; CLR Renal clearance; CV Coefficient of variation; MRT Mean residence

time; n Number of evaluable subjects; NA Not applicable; NC Not calculated; PK Pharmacokinetic; SD Standard deviation; T_{max} Time to maximum concentration; T-HALF Terminal phase half-life; Vd/F Apparent volume of distribution; V_{ss}/F Apparent volume of distribution at steady state.

Summary of safety results

Saxagliptin 5 mg (single dose and once-daily doses for 5 days) was generally well tolerated in healthy Chinese subjects. There were no deaths or serious AEs during this study. No subjects discontinued the study due to an AE. Of the 16 subjects, 6 (37.5%) experienced an AE. All AEs were of mild intensity and were judged by the investigator as not related to the investigational product. Alanine aminotransferase increased was the only AE that occurred in more than a single subject (2 subjects). There was a single subject with a mild-intensity AE of mouth ulceration which lasted less than 2 days, and was resolved without treatment before the multiple dose portion of the study.

No new clinically meaningful findings were observed in mean changes for the group or in the occurrence of abnormal results for individual subjects from haematology, clinical chemistry, urinalysis, vital sign, ECG, or physical examination results.