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Absolute Bioavailability of Sitagliptin, an Oral Dipeptidyl Peptidase-4 Inhibitor, in Healthy Volunteers

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ABSTRACT: The purpose of this study was to determine the absolute bioavailability of sitagliptin, an orally active, potent and highly selective dipeptidyl peptidase-4 inhibitor recently approved in the United States for the treatment of type 2 diabetes. The effect of a high fat meal on sitagliptin pharmacokinetics was also assessed. The study was performed in two parts. Intravenous doses (2 h infusion) of 25, 50 and 100 mg were administered double-blind to 10 (8 active, 2 placebo) subjects in a fixed-sequence manner in Part I. In Part II, 12 subjects were randomized to each of three open-label treatments: an intravenous 100 mg dose; a single oral 100 mg final market image tablet administered following a high fat meal and a single oral 100 mg final market image tablet administered fasted. Following each dose, plasma and urine were collected at pre-specified times for evaluation of sitagliptin pharmacokinetics. All doses were generally well tolerated in both parts of the study. Following rising intravenous doses of sitagliptin, $AUC_{0-\infty}$ increased dose-proportionally, indicating that plasma clearance is independent of dose over the dose range evaluated. Renal clearance of unchanged sitagliptin accounted for approximately 70% of the total plasma clearance of sitagliptin, indicating that sitagliptin is primarily cleared via renal excretion. Averaged across doses, the mean total plasma clearance was 416 ml/min. The mean absolute bioavailability of sitagliptin was 87% with a 90% CI of (81%, 93%). The $AUC_{0-\infty}$ and C_{max} geometric mean ratios (fed/fasted) and 90% CIs were 1.03 (0.97, 1.11) and 0.94 (0.86, 1.03), respectively, and were contained within the bounds of (0.80, 1.25). Additionally, the high-fat meal had no significant effect on T_{max} or apparent terminal $t_{1/2}$. Thus, food does not affect the pharmacokinetics of sitagliptin and therefore can be administered without regard to food. Copyright © 2007 John Wiley & Sons, Ltd.

Key words: sitagliptin; absolute bioavailability; pharmacokinetics

Introduction

Sitagliptin ((2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8 H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine) is an orally active, potent and highly selective inhibitor of dipeptidyl peptidase-4 (DPP-4) recently approved in the United States for the treatment of type 2 diabetes [1]. DPP-4 inhibitors represent a new therapeutic approach to the treatment of type 2 diabetes which inhibit the degradation of intact (active) incretins, particularly glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic peptide (GIP) [2,3].

The pharmacokinetics of sitagliptin has been described previously [4,5]. Briefly, sitagliptin is well absorbed after oral administration with an apparent $t_{1/2}$ of approximately 8–14 h. In initial

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studies, it was observed that the compound was predominantly renally eliminated, with the fraction of the sitagliptin dose excreted unchanged in urine averaging approximately 80% [4,5].

The primary purpose of this study was to characterize the absolute bioavailability of sitagliptin in humans. For this purpose, an intravenous formulation was developed. Since an intravenous sitagliptin formulation was used for the first time in humans, the purpose of Part I of the study was to examine the safety and tolerability and pharmacokinetics of rising single intravenous infusions of sitagliptin. Part II of this study assessed the absolute oral bioavailability of sitagliptin final market image tablets as well as the examination of the food effects on sitagliptin pharmacokinetics relative to the fasted state. Intravenous doses of sitagliptin were expected to be safe and well tolerated. The intravenous formulation (containing 10 mg/ml sitagliptin) that was employed in this study was the same as that tested in animal models and which was generally well tolerated in animals without local irritation at the site of administration.

Methods

Subjects

Twenty two healthy male ($n = 9$) and non-pregnant female ($n = 13$) volunteers were enrolled in this study. All subjects were non-smokers with a mean age of 41 years (range 23–56 years), mean body weight of 79.3 kg (range 60–94.5 kg) and were normoglycemic. Subjects were in good general health according to routine medical history, physical examination, vital signs and laboratory data. Subjects were excluded if they had any relevant history of renal, hepatic, cardiovascular, gastrointestinal, neurologic disease or diabetes or impaired glucose tolerance. Every subject gave written informed consent. The protocol was approved by Southern Institutional Review Board, Miami, Florida and the study was conducted in accordance with the guidelines on good clinical practice and with ethical standards for human experimentation established by the Declaration of Helsinki.

Study design

This was a two-part, placebo-controlled, randomized, intravenous escalating dose and definitive absolute bioavailability and food interaction study of sitagliptin in healthy adult male and female subjects. In the double-blind fixed-sequence study (Part I), rising single intravenous doses of 25, 50 and 100 mg sitagliptin ($n = 8$) or matching placebo ($n = 2$) were given in Periods 1, 2 and 3, respectively. The same two subjects in each period received placebo. All intravenous doses of sitagliptin were given after an overnight fast. Two hundred forty (240) ml water was administered at the start of infusion. There was at least a 5 day washout between doses. Each single-dose administration was followed by collection of blood (plasma) for sitagliptin concentrations at predose, 0.25, 0.5, 1, 1.5, 2 (end of infusion), 2.25, 2.5 (following intravenous period only) 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 32, 48, 72 h in each period. All time points were relative to the start of administration of study drug ($T = 0$). Urine was collected in the following intervals for the fasting and i.v. panels only: predose, 0 to 6, 6 to 12, 12 to 24 h.

In the open label balanced crossover study (Part II), a new group of 12 subjects was randomized and received three treatments of sitagliptin in a balanced, 3-period crossover design. In treatment A, subjects received a 100 mg oral dose of sitagliptin in the fasting state. In treatment B, approximately 30 min prior to the scheduled dosing time, a standard high fat breakfast (composed of 2 eggs, 2 strips bacon, 2 pieces of toast with butter, 2–4 oz of hash brown potatoes and 250 ml of whole milk; ~57% fat content) was served and consumed in its entirety within approximately 25 min. Within 5 min of completion of the standard high fat breakfast, subjects received a single 100 mg oral dose of sitagliptin in the fed state. In treatment C, subjects received a 100 mg intravenous dose of sitagliptin infused over 2 h in the fasting state. All doses of study drug (i.v. and oral) were administered with 240 ml of water given orally. There was at least a 5 day washout between each period. Each single-dose administration was followed by collection of blood (plasma) for sitagliptin concentrations at predose, 0.25, 0.5, 1,

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1.5, 2 (end of infusion), 2.25, 2.5 (following intravenous period only) 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 32, 48, 72 h. All time points were relative to the start of administration of study drug ($T = 0$). Urine was collected in the following intervals for the fasting oral and intravenous treatment periods only: predose, 0–6, 6–12, 12–24 h. Urine was kept on ice during collection, the volume recorded to the nearest 5 ml and a 4 ml aliquot was saved for analysis. Since $AUC_{0-24\,h}$ represents approximately 80% of the plasma $AUC_{0-\infty}$, 24 h of urine collection was deemed sufficient to compute renal clearance and urinary excretion of sitagliptin. Plasma and urine samples were stored at –70°C until assayed.

Safety

Physical examinations, vital signs, 12-lead electrocardiograms, and safety laboratory measurements, and urinalysis were performed prestudy, at various time points post dosing and at poststudy. Adverse experiences were monitored throughout the study. An investigator evaluated all clinical adverse experiences in terms of intensity (mild, moderate or severe), duration, severity, outcome and relationship to study drug.

Bioanalytical methods

Plasma and urine samples were analysed for sitagliptin concentrations using an assay method that has been published [6]. Briefly, samples were injected direct onto a Cohesive Technologies high turbulent liquid chromatography system (HTLC). Analyte and internal standard were detected by tandem mass spectrometry (MS/MS) using selected reaction monitoring (SRM) with turbo-ionspray interface in the positive ion mode. The lower limit of quantitation (LLOQ) for the plasma assay was 0.5 ng/ml and the linear calibration range was 0.5–1000 ng/ml. The LLOQ for the urine assay was 0.1 μg/ml and the linear calibration range was 0.1–50 μg/ml.

Pharmacokinetic methods

Apparent terminal rate constant (λ) was estimated by regression of the terminal log-linear portion of the plasma concentration-time profile; $t_{1/2}$ was calculated as the quotient of ln (2) and λ. *AUC* to the last time point was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations [7]. $AUC_{0-\infty}$ was estimated as the sum of *AUC* to the last measured concentration and the extrapolated area given by the quotient of the last measured concentration and λ. Following oral doses only, C_{max} and T_{max} were obtained by inspection of the plasma concentration data. Nominal plasma sampling times were used to determine T_{max}. Following intravenous doses, C_{eoi} was taken as the observed concentration at 2 h postdose since all infusions in this study were 2 h in duration. Bioavailability for each subject participating in Part II of this study was determined by the ratio of the $AUC_{0-\infty}$ values for the 100 mg fasted oral dose and the 100 mg fasted intravenous dose. Following intravenous doses, the area under the plasma concentration moment curve extrapolated to infinity ($AUMC_{0-\infty}$) was calculated as follows:

$$AUMC_{0-\infty} = AUMC_{last} + \frac{C_{last} \bullet T_{last}}{\lambda} + \frac{C_{last}}{\lambda^2}$$

where $AUMC_{last}$ is *AUMC* to the last time point (computed using linear trapezoidal method for increasing values and the log trapezoidal method for descending values), C_{last} is the last observed concentration greater than the assay limit of quantitation and T_{last} is the corresponding time after the onset of dose.

Total plasma clearance (Cl_P) following intravenous doses was computed by dose/$AUC_{0-\infty}$. The mean residence time (MRT) following intravenous doses was computed as follows:

$$MRT = \left[\frac{AUMC_{0-\infty}}{AUC_{0-\infty}} - \frac{\tau}{2}\right]$$

where τ is the duration of infusion (2 h). The volume of distribution at steady state ($V_{d,ss}$) was determined as the product of MRT and Cl_P.

The amount of sitagliptin excreted unchanged in urine in each collection interval was determined by the product of the urine concentration and the urine volume. The fraction of the sitagliptin dose that was excreted unchanged in urine over the dosing intervals ($f_{e,0-24\,h}$) was determined by the quotient of the sum of sitagliptin collected over all dosing intervals

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and the dose administered. The total fraction of the sitagliptin dose that was excreted unchanged in urine ($f_{e,0-\infty}$) was determined as the product of $f_{e,0-24\,h}$ and the $AUC_{0-\infty}/AUC_{0-24\,h}$ ratio. Renal clearance (Cl_R) was determined as the quotient of $f_{e,0-24\,h}$•dose and $AUC_{0-24\,h}$.

Since intravenous doses administered deviated from nominal values by up to 11%, pharmacokinetic parameters were potency-adjusted prior to statistical analysis.

Statistical methods

Prior to the following statistical analysis, log-transformation was applied to the data of $AUC_{0-\infty}$, C_{eoi}, C_{max}, Cl_P, Cl_R and the ratio of Cl_R/Cl_P, inverse-transformation was applied to the data of apparent terminal $t_{1/2}$, and rank-transformation was applied to the data of T_{max}.

In Part I, summary statistics are reported for the pharmacokinetic parameters $AUC_{0-\infty}$, C_{eoi}, $C_{24\,h}$, $V_{d,ss}$, apparent terminal $t_{1/2}$, Cl_P, Cl_R, Cl_R/Cl_P, $f_{e,0-\infty}$ and *MRT* after the administration of 25, 50, 100 mg i.v. doses of sitagliptin. To assess the dose proportionality of sitagliptin $AUC_{0-\infty}$, C_{eoi} and $C_{24\,h}$ following three increasing i.v. doses, a linear mixed-effect model was fitted separately to log-transformed $AUC_{0-\infty}$, C_{eoi} and $C_{24\,h}$ with log-transformed dose as a covariate and subject as a random effect. Estimation of the slope from the model and its 95% CI were obtained for $AUC_{0-\infty}$, C_{eoi} and $C_{24\,h}$, respectively. A slope equal to 1.00 indicates perfect dose proportionality for a pharmacokinetic parameter, a slope greater than 1.00 indicates greater than dose-proportional increases and a slope less than 1.00 indicates less than dose-proportional increases in the parameter. A plot with the fitted regression line, the corresponding 95% Scheffe's confidence band, and the observed geometric mean at each of the three doses was provided separately for $AUC_{0-\infty}$, C_{eoi} and $C_{24\,h}$. To supplement the analysis on dose proportionality, summary statistics on dose-adjusted (to 100 mg) $AUC_{0-\infty}$, C_{eoi} and $C_{24\,h}$ and an overall test on the equivalence of these dose-adjusted values across the three doses were also provided for each of the three pharmacokinetic parameters. Trend tests were performed via a linear mixed-effect model respectively for $V_{d,ss}$, terminal $t_{1/2}$, Cl_P, Cl_R, Cl_R/Cl_P, $f_{e,0-\infty}$ and *MRT* to evaluate their changes with doses on each of the listed PK parameters. The models contained dose as a fixed effect and subject as a random effect. The result of the *F*-test to compare the three i.v. doses on the Cl_R/Cl_P ratio from the model was examined. If no statistically significant difference among the three i.v. doses was detected, the data of the Cl_R/Cl_P ratio were pooled across all doses from Part I and from the 100 mg i.v. dose from Part II to calculate the overall geometric mean on Cl_R/Cl_P.

In Part II, summary statistics are reported for the pharmacokinetic parameters $AUC_{0-\infty}$ and apparent terminal $t_{1/2}$, after the administration of 100 mg IV dose (fasting) and 100 mg oral tablet doses (fed and fasting) of sitagliptin. Summary statistics for Cl_R, $f_{e,0-\infty}$ were also determined for the 100 mg i.v. and oral fasting sitagliptin treatments only; summary statistics for C_{eoi}, $V_{d,ss}$, Cl_P and *MRT* were determined for the 100 mg i.v. dose only; summary statistics for C_{max} and T_{max} were determined following the oral doses. To estimate the absolute bioavailability (fasting) of the tablet formulation of sitagliptin, the potency-adjusted $AUC_{0-\infty}$ data (the $AUC_{0-\infty}$ data with the i.v. dosing were corrected for total amount of drug delivered for each subject prior to analysis) were analysed with a linear mixed-effect model appropriate for a 3-period crossover study. The model included fixed effects for period and treatment and a random effect for subject. The absolute bioavailability (fasting) of sitagliptin was estimated by calculating the corresponding $AUC_{0-\infty}$ GMR of [tablet/i.v.] and its 90% CI from the model. Apparent terminal $t_{1/2}$, Cl_R and $f_{e,0-\infty}$ were also compared between i.v. and oral tablet dosing of sitagliptin (fasting) using the same model as above. The $AUC_{0-\infty}$ GMR of [fed/fasted] following the oral administration of 100 mg sitagliptin tablet and its 90% CI were obtained via a similar linear mixed-effect model fitted to the $AUC_{0-\infty}$ data as above. This 90% CI was compared with the prespecified bounds of (0.80, 1.25) to evaluate the food effect on sitagliptin $AUC_{0-\infty}$ with the oral tablet formulation. The C_{max} GMR of [fed/fasted] following the oral administration of the 100 mg sitagliptin tablet and its 90% CI were obtained via a similar linear mixed-effect model that was fitted to the

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C_{max} data. This CI was compared with the prespecified bounds of (0.70, 1.43) to evaluate the food effect on sitagliptin C_{max} with the tablet formulation. T_{max} and apparent terminal $t_{1/2}$ were compared separately between the oral tablet dosing of sitagliptin (fed versus fasted) using similar models as above.

If no statistically significant difference among the three i.v. doses was detected, the data of the Cl_R/Cl_P ratio were pooled across all doses from Part I and from the 100 mg i.v. dose from Part II to calculate the overall geometric mean for Cl_R/Cl_P.

Results

Safety

Administration of sitagliptin doses by either route was generally well tolerated. No serious clinical adverse experiences were reported and there were no discontinuations due to an adverse experience. There were no laboratory adverse experiences reported during the study. Four of the 22 subjects reported a total of six non-serious clinical adverse experiences, all of which were considered by the investigator to be mild and transient. These included increased hunger, drowsiness, dizziness, nausea, menstrual spotting and headache. There were no consistent treatment-related changes in laboratory, vital signs or ECG parameters during any of the study treatments.

Pharmacokinetics

Intravenous dosing. Mean sitagliptin plasma concentration versus time profiles following 25, 50 or 100 mg intravenous doses of sitagliptin to healthy subjects are depicted in Figure 1.

Dose proportionality. Dose proportionality of sitagliptin $AUC_{0-\infty}$ across the range of intravenous doses evaluated in this study (25, 50 and 100 mg) is summarized in Table 1. Since the fraction of extrapolated AUC in the determination of $AUC_{0-\infty}$ was negligible (<10%), $AUC_{0-\infty}$ was

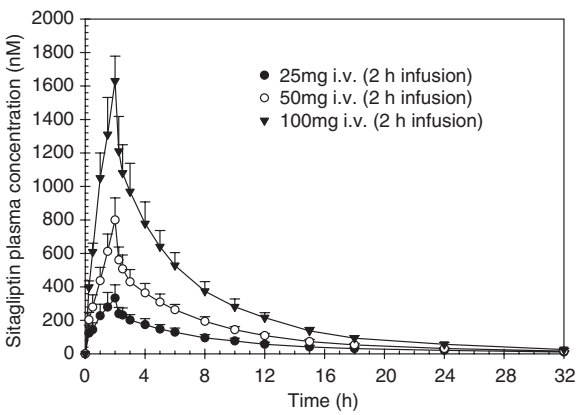

Figure 1. Mean (SD) sitagliptin plasma concentrations following single intravenous doses of sitagliptin administered as a 2 h constant-rate infusion to healthy male and female subjects

Table 1. Mean sitagliptin (SD) pharmacokinetic parameters following administration of 25, 50 and 100 mg intravenous doses of sitagliptin to healthy adult male and female subjects ($n = 8$)

Parameter	Mean[a] (Between-subject SD[b])		
	25 mg	50 mg	100 mg
$AUC_{0-\infty}$ (μM●h)	2.47 (0.52)	4.85 (0.58)	9.88 (1.33)
C_{eoi} (nM)	342 (91)	830 (140)	1741 (184)
$C_{24\,h}$ (nM)	20.5 (6.2)	32.8 (5.0)	60.3 (11.1)
Cl_R (ml/min)	249 (168)	340 (124)	279 (126)
Cl_P (ml/min)	414 (88)	421 (50)	413 (56)
Cl_R/Cl_P	0.60 (0.33)	0.81 (0.21)	0.67 (0.22)
$V_{d,ss}$ (l)	262 (44)	234 (28)	198 (30)
MRT (h)	10.39 (0.82)	9.20 (0.33)	7.92 (0.55)
Apparent terminal $t_{1/2}$ (h)	11.7 (1.5)	12.3 (0.7)	10.9 (1.0)
$f_{e,0-\infty}$	0.654 (0.265)	0.828 (0.172)	0.700 (0.193)

[a] Mean = geometric mean for $AUC_{(0-\infty)}$, C_{eoi}, $C_{24\,h}$, Cl_R, Cl_P and Cl_R/Cl_P, harmonic mean for apparent terminal $t_{1/2}$ and arithmetic mean for $V_{d,ss}$, MRT and $f_{e,0-\infty}$.

[b] SD = Standard deviation; back-transformed from log scale for $AUC_{(0-\infty)}$, C_{eoi}, Cl_R, Cl_P and Cl_R/Cl_P, jackknife SD for apparent terminal $t_{1/2}$.

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used in the calculations. The plot of observed geometric mean $AUC_{0-\infty}$ versus dose along with the fitted regression line and its 95% Scheffe's confidence band is provided in Figure 2. The estimated slope (95% CI) from the model to assess dose proportionality of $AUC_{0-\infty}$ was 1.00 (0.96, 1.04). There was no statistically significant increasing or decreasing trend in sitagliptin Cl_P, Cl_R, Cl_R/Cl_P, $f_{e,0-\infty}$ (all p>0.200) or apparent terminal $t_{1/2}$ across the dose range ($p = 0.133$). However, C_{eoi} increased in an apparently greater than dose proportional manner, $C_{24\,h}$ increased in an apparently less than dose proportional manner, and $V_{d,ss}$ and MRT (both $p < 0.001$) tended to decrease with increasing dose.

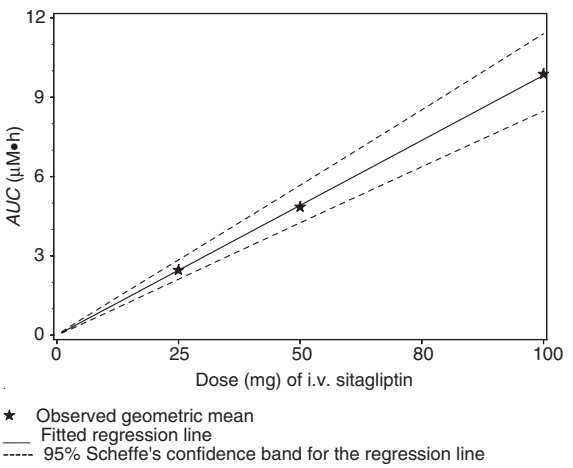

Figure 2. Observed geometric mean and regression line from dose proportionality assessment of sitagliptin $AUC_{(0-\infty)}$ following single intravenous doses of sitagliptin administered as a 2 h constant-rate infusion to healthy male and female subjects

Oral bioavailability. The observed fasting oral bioavailability ($AUC_{0-\infty}$ following a 100 mg fasting oral dose/$AUC_{0-\infty}$ following a 100 mg fasting i.v. dose) of sitagliptin was 87% with a corresponding 90% CI of (81%, 93%) (Table 2). No statistically significant differences were observed in sitagliptin Cl_R between oral and i.v. doses. Consistent with an oral bioavailability of 87%, $f_{e,0-\infty}$ was slightly numerically higher following the i.v. dose compared with the oral dose, although this difference did not reach statistical significance ($p = 0.163$). A small but statistically significant difference ($p = 0.026$) in apparent terminal $t_{1/2}$ was observed between oral and i.v. doses.

Food effect. Mean sitagliptin plasma concentration versus time profiles following fasting 100 mg intravenous doses, fasting 100 mg oral doses and 100 mg oral doses following a high fat meal are depicted in Figure 3. The 90% CI for the $AUC_{0-\infty}$ GMR (0.97, 1.11) fell within the prespecified bounds of (0.80, 1.25), demonstrating an absence of a food effect on sitagliptin bioavailability (Table 2). The 90% CI for the C_{max} GMR (0.86, 1.03) also fell within the prespecified bounds of (0.70, 1.43), as well as (0.80, 1.25). Administration

Table 2. Mean sitagliptin (SD) pharmacokinetic parameters following administration of 100 mg intravenous doses (fasted) and food effect on $AUC_{0-\infty}$ (μM●h) and C_{max} (nM) following 100 mg oral dosing (fasted and fed) of sitagliptin to healthy adult male and female subjects ($n = 12$)

Parameter	Mean[a] (Between-subject SD[b])			
	100 mg i.v. fasted	100 mg oral fasted	100 mg oral fed	GMR[c] (90% CI[d]) (fed/fasted oral)
$AUC_{0-\infty}$ (μM●h)	9.08 (1.24)	7.90 (1.22)	8.17 (0.97)	1.03 (0.97, 1.11)
C_{max} (nM)	NA	817 (250)	772 (180)	0.94 (0.86, 1.03)
T_{max} (h)	NA	3.0 (NA)	3.0 (NA)	NA
Apparent terminal $t_{1/2}$ (h)	10.6 (2.0)	11.7 (2.0)	11.8 (2.0)	NA
Cl_R (ml/min)	249 (168)	340 (124)	NA	NA
$f_{e,0-\infty}$	0.731 (0.159)	0.651 (0.149)	NA	NA

NA = not available. [a]Mean = geometric mean for $AUC_{(0-\infty)}$, C_{max}, Cl_R, harmonic mean for apparent terminal $t_{1/2}$ and arithmetic mean for $f_{e,0-\infty}$, and median for T_{max}.
[b]SD = Standard deviation; Back-transformed from log scale for $AUC_{(0-\infty)}$, C_{max}, Cl_R and jackknife SD for apparent terminal $t_{1/2}$.
[c]GMR = geometric mean ratio (fed/fasted oral).
[d]CI = confidence interval.

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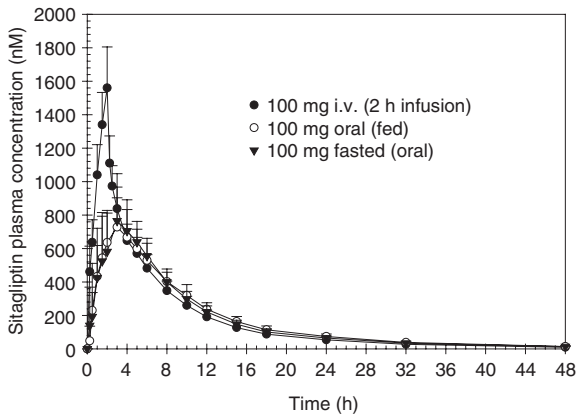

Figure 3. Mean (SD) sitagliptin plasma concentrations following single oral (fasted or following a high-fat meal) or intravenous doses of sitagliptin administered to healthy male and female subjects

of a high fat meal prior to dosing also had no statistically significant effect on T_{max} or apparent terminal $t_{1/2}$ compared with the fasting state.

Cl_R/Cl_P ratio. No significant difference was detected among the three i.v. doses of sitagliptin on the Cl_R/Cl_P ratio ($p = 0.172$) in Part I. The geometric mean (standard error) of Cl_R/Cl_P was 0.69 (0.04) based on the pooled i.v. data from Parts I and II ($n = 36$).

Discussion

The safety, tolerability and pharmacokinetics of the sitagliptin were evaluated using the intravenous formulation at escalating doses of 25, 50 and 100 mg. Further, the absolute bioavailability of sitagliptin as the final market formulation and the effect of food (high-fat meal) on the pharmacokinetics of sitagliptin were also evaluated. Sitagliptin was found to be well tolerated regardless of the dose or route of administration. A dose of 100 mg sitagliptin was selected as the anticipated oral clinical dose. Assuming the oral bioavailability of sitagliptin to be at least ~80%, given the fractional excretion of intact drug into urine was ~80% [4], it was considered likely that intravenous doses of 80–100 mg would provide similar exposures to those obtained following administration of a 100 mg oral tablet dose of sitagliptin. Since fractional excretion into urine of sitagliptin does not appear to vary with dose, *AUC* is approximately dose-proportional [4] and final market formulations of sitagliptin are weight multiples (including 25 mg and 50 mg tablets), it was considered that the information obtained by studying the bioavailability and food effect at the 100 mg dose can be extrapolated to other doses.

The plasma $AUC_{0-\infty}$ of sitagliptin was found to be dose proportional over the range of intravenous doses studied (25–100 mg). Consistent with this observation, total plasma clearance of sitagliptin did not change in a statistically significant manner with dose. Similarly, renal clearance, $f_{e,0-\infty}$ and apparent terminal $t_{1/2}$ also did not change in a statistically significant manner with dose. These results suggest that both the total plasma and renal clearance of sitagliptin are independent of dose over the range of doses studied. These results corroborate data from previous studies which showed that sitagliptin *AUC*, a clinically relevant pharmacokinetic parameter, increased approximately dose proportionally with increasing dose following both single oral doses and multiple oral doses [4,5]. There appeared to be modest differences in pharmacokinetics in males and females, although the study was not designed to assess the impact of gender on sitagliptin pharmacokinetics. Since clearance does not appear to change with dose, these differences in C_{eoi}, $C_{24\,h}$, V_{dss} and *MRT* following intravenous doses are likely due to minor changes in the distributional pharmacokinetics of sitagliptin with increasing dose. Since the target site of action is well equilibrated with blood, changes in distribution are not expected to alter efficacy of sitagliptin meaningfully. This is corroborated in excellent dose-related inhibition of DPP-4 activity by sitagliptin after single and multiple doses [4,5]. The absolute oral bioavailability of the final market image formulation of sitagliptin was estimated to be 87% with a 90% CI of (81%, 93%). This result is consistent with results of previous studies where up to 80% of the oral dose was excreted unchanged in urine [4,5], suggesting that sitagliptin oral bioavailability was at least 80%. Renal clearance of sitagliptin accounted for approximately 69% of

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the total plasma clearance of sitagliptin, indicating that sitagliptin is primarily renally eliminated, also consistent with previous results [4,5]. Given that approximately 69% of the sitagliptin clearance is via renal excretion, inhibition of enzymes involved in drug metabolism are not expected to have a meaningful effect on the pharmacokinetics of sitagliptin. A high-fat meal administered prior to sitagliptin dosing had a negligible effect on the plasma pharmacokinetic profile of sitagliptin. The $AUC_{0-\infty}$ and C_{max} GMRs and 90% CIs were 1.03 (0.97, 1.11) and 0.94 (0.86, 1.03), respectively, which met the protocol pre-specified similarity bounds. Additionally, there were no statistically significant differences in $AUC_{0-\infty}$, C_{max} or T_{max} between the fed and fasted groups, indicating that food has no effect on sitagliptin pharmacokinetics. These results demonstrate an absence of an effect of food on the pharmacokinetic profile of sitagliptin and sitagliptin can therefore be dosed without respect to food, consistent with the findings of a preliminary assessment [4].

Conclusions

Following intravenous doses, sitagliptin $AUC_{0-\infty}$ was approximately dose proportional, indicating that the clearance of sitagliptin is independent of dose. Renal clearance accounts for approximately 69% of the total plasma clearance of sitagliptin, confirming that sitagliptin is primarily cleared through renal elimination. The absolute bioavailability of sitagliptin final market image tablets is approximately 87%, with no effect of food intake on sitagliptin pharmacokinetics. Sitagliptin is generally well tolerated when administered orally or intravenously.

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