The effect of age, gender, and body mass index on the pharmacokinetics and pharmacodynamics of vildagliptin in healthy volunteers

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Vildagliptin is a new, potent, and selective inhibitor of DPP-4.
- The efficacy and safety of vildagliptin in type 2 diabetes has been intensively studied in diverse subject populations.
- There has been little information published about the pharmacokinetics and pharmacodynamics of vildagliptin.

WHAT THIS STUDY ADDS

- No clinically relevant changes in pharmacokinetics or pharmacodynamics were observed between young and elderly, male and female, or high body mass index (BMI) and low BMI subjects.
- The results suggest that no dose modification is necessary for vildagliptin based on the age, gender, or BMI of a subject.

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AIMS

To evaluate the effect of age, gender, and body mass index (BMI) on the pharmacokinetics and pharmacodynamics of vildagliptin.

METHODS

Forty healthy subjects received a single oral dose of 100 mg vildagliptin to assess the effects of age, gender, and BMI on the pharmacokinetics and pharmacodynamics, reflected by the time course of inhibition of DPP-4 activity, of vildagliptin.

RESULTS

Peak concentration and exposure ($AUC_{(0-\infty)}$) of vildagliptin were 17% (90% CI 2, 35%) and 31% (90% CI 18, 45%) higher in elderly vs. young subjects. Renal clearance was reduced by 32% (90% CI 17, 45%) in elderly subjects. The pharmacokinetics of vildagliptin were not significantly influenced by gender or BMI. Inhibition of DPP-4 activity was similar regardless of age, gender, or BMI.

CONCLUSIONS

The pharmacokinetics of a single oral 100 mg dose of vildagliptin were not affected by gender and BMI. Exposure to vildagliptin was higher in elderly patients, but this was not associated with any difference in the effect of DPP-4 inhibition. Based on these results, no vildagliptin dose adjustment is necessary for age, gender, or BMI.

Introduction

Vildagliptin is an orally active, selective and potent inhibitor of dipeptidyl peptidase IV (DPP-4), a serine protease responsible for the rapid inactivation and degradation of the incretin hormone, glucagon-like peptide 1 (GLP-1) [1, 2]. The half-life of GLP-1 is typically less than 2 min. However, inhibition of DPP-4 significantly increases and prolongs concentrations of GLP-1 in response to a meal [3–7]. The glucose-dependent release of GLP-1 into the bloodstream from the L-cells in the gastrointestinal tract results in the stimulation of insulin release [8–11] and the inhibition of glucagon secretion [9, 10]. Glucagon-like peptide-1 has also been shown to delay gastric emptying [12–14] and decrease appetite [14, 15]. Preclinical studies have demonstrated that an approximately 80% inhibition of DPP-4 activity is necessary to achieve a near-maximal effect on glucose concentrations [16]. Oral doses of vildagliptin have produced significant inhibition of DPP-4 enzyme activity, leading to increased GLP-1 concentrations, reduced glucose concentrations and postprandial glucagon concentrations. However, the risk of hypoglycaemia is rare due to the glucose-dependent action of GLP-1. With long-term therapy, the net effect of these pharmacologic actions has resulted in significant reductions in HbA1c in patients with type 2 diabetes [4, 17–19], and 100 mg once daily vildagliptin dosing regimen has been shown to be effective and well tolerated.

The pharmacokinetics of vildagliptin after oral administration in healthy volunteers and patients with type 2 diabetes have been characterized by rapid absorption with peak plasma concentrations observed between 1 and 2 h after dosing. After oral administration, vildagliptin exhibited approximately dose-proportional pharmacokinetics and the mean elimination half-life was about 2 h (unpublished data, Novartis Pharmaceuticals). Vildagliptin is excreted unchanged in the urine to some extent (~23%), but is primarily hydrolyzed to the inactive metabolite LAY151 which accounts for 69% of an oral dose. Following administration of a radiolabelled oral dose of vildagliptin, approximately 85% of the dose is excreted in the urine as parent drug or metabolites (unpublished data, Novartis Pharmaceuticals).

Although clinical trials of vildagliptin have enrolled a diverse population of healthy volunteers and patients, differences in pharmacokinetic and pharmacodynamic parameters in various subpopulations have not been examined. In particular, the potential impact of increasing age, with the associated decline in renal function and renal drug elimination is relevant to antidiabetic medications as the population ages and the number of elderly patients with type 2 diabetes increases. The objective of the current study was to investigate the effect of age, gender, and BMI on the pharmacokinetics of vildagliptin and DPP-4 activity in healthy volunteers after oral administration of vildagliptin at the anticipated therapeutic dose of 100 mg once daily.

Methods

Study design

A total of 40 healthy volunteers were enrolled in this open-label, single-dose study. Twenty subjects between 18 and 40 years of age and 20 subjects ≥ 70 years of age were equally divided into two groups by gender. In addition, within each age-gender subgroup, the subjects were further stratified by BMI (≤ 25 kg m⁻² and ≥ 29 kg m⁻²). All participants had a BMI between 18.5 kg m⁻² and 40 kg m⁻² and were nonsmokers. Female participants were required to be postmenopausal, surgically sterile, or using a double barrier method of contraception. Subjects taking prescription medication within 1 month or using over-the-counter vitamins within 14 days prior to dosing were excluded from the study. Additionally, no strenuous physical exercise (7 days), alcohol (72 h), or xanthine-containing substances (e.g. caffeine, 48 h) were permitted before dosing until the end-of-study evaluation.

Following a 3 week screening period, subjects reported to the study centre on the day prior to dosing. On the treatment day, a single dose of 100 mg vildagliptin was administered with 240 ml of water between 07.00 h and 08.00 h. Subjects fasted from the prior evening (10–12 h) until 4 h after vildagliptin administration. Pharmacokinetic and pharmacodynamic assessments continued for up to 24 h postdose. Following the last pharmacokinetic sample collection, end-of-study evaluations were completed and subjects were discharged from the study site. Written informed consent was obtained from each subject and the study was conducted in full compliance with the Declaration of Helsinki following approval from the local ethics committee.

Pharmacokinetic and pharmacodynamic assessments

Blood samples for the pharmacokinetic analysis of vildagliptin and LAY151 and for the pharmacodynamic analysis of DPP-4 activity were obtained using an indwelling IV catheter inserted into a forearm vein or by direct venepuncture. Samples (2 ml each) for vildagliptin and LAY151 were collected into sodium heparin tubes prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 h postdose. Samples were then centrifuged at 4°C at 2500 rev min⁻¹ and plasma was subsequently stored at $\leq -70^\circ\text{C}$ until analysis. Urine samples were collected predose and during the first 24 h postdose, and a 5 ml aliquot was removed and frozen for later analysis. Blood samples for the determination of DPP-4 activity were collected into a tube containing potassium ethylenediaminetetraacetic acid prior to dosing and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 4, 6, 8, 10, 12, 16, and 24 h after vildagliptin administration.

The % of DPP-4 inhibition was calculated from the measured DPP-4 activity by the following equation:

$$DPP-4_{\text{inhibition}}(\%) = \left[1 - \frac{DPP-4_{\text{activity}}(t)}{DPP-4_{\text{activity}}(0)} \right] \times 100 \quad (1)$$

where DPP-4activity(*t*) is the measured DPP-4 activity at time *t*, and DPP-4activity(0) is the baseline DPP-4 activity measured before the administration of vildagliptin.

Pharmacokinetic parameters of vildagliptin including the area under the plasma concentration-time curve (AUC(0–*t*), AUC(0–∞), the maximum concentration observed in plasma (*C*_{max}), the time at which the maximum concentration occurs (*t*_{max}), the elimination half-life (*t*_{1/2}), and the apparent total body clearance from plasma (CL/F) were determined by noncompartmental methods using WinNonlin Pro (Pharsight, Mountain View, CA). The elimination half-life was calculated using the equation *t*_{1/2} = ln2/λ_z, where λ_z is the terminal elimination constant which was determined by log-linear regression of the concentration–time profile. The renal clearance of drug from plasma (CL_R) was calculated by dividing the total amount of vildagliptin excreted in the urine over 24 h by the AUC(0,24 h). The following PK parameters were also determined for LAY151 in an identical manner: *C*_{max}, *t*_{max}, AUC(0,*t*), AUC(0,∞) and *t*_{1/2}.

A pharmacodynamic model was also evaluated for exploratory purposes to describe the relationship between vildagliptin plasma concentration and % DPP-4 inhibition. A simple E_{max} model was implemented in WinNonlin to provide estimates of IC₅₀ (the concentration of vildagliptin that produced 50% of the maximal response) and E_{max} (the maximum effect of vildagliptin on the % of DPP-4 inhibition).

Safety and tolerability assessments

Safety and tolerability evaluations took place at screening, baseline, and 24 h after administration of study dose. Safety and tolerability assessments included all adverse events, routine laboratory tests, ECG recordings, vital sign monitoring, and physical examinations.

Bioanalytical methods

Vildagliptin concentrations were measured by liquid chromatography tandem mass spectrometry (LC-MS/MS) for which the limit of quantification was 2 ng ml^{−1} in plasma and 5 ng ml^{−1} in urine. The concentration of LAY151 in plasma was also measured by LC-MS/MS and had a lower level of quantification of 2 ng ml^{−1}. The assays for vildagliptin and LAY151 in plasma were linear over a range of concentrations of 2 ng ml^{−1} to 1000 ng ml^{−1}. The interday precision (CV%) for the vildagliptin assay varied from 1.8% to 3.9% and the accuracy from 99.1% to 104.5% of the nominal value. For LAY151, the interday precision varied from 2.3% to 5.8% and the accuracy from 95.2% to 105.8% of the nominal value.

The DPP-4 activity was determined by Novartis Pharmaceuticals using a fluorescent substrate enzymatic assay. The H-Gly-Pro-AMC (AMC: 7-Amino-4-

Methylcoumarin) substrate is enzymatically cleaved by DPP-4 and produces fluorescent AMC. The measured concentration of AMC is then converted to DPP-4 activity. Standard concentrations of AMC were prepared over the range of 0.5–75 μM and the interday precision (CV%) varied from 1.5% to 3.1% and the accuracy from 95.6% to 103.6% of the nominal value. The lower limit of quantification for DPP-4 activity is 0.24 mU ml^{−1} × min (1 μM AMC).

Statistical analysis

To ensure 80% power of a two sample two-sided *t*-test at a 5% significance level, a sample size of 18 subjects in each stratum was needed to detect at least a 20% change in vildagliptin AUC. Twenty subjects were planned for enrolment in each stratum to address potential drop-outs.

Summary statistics for pharmacokinetic parameters are presented as median (range) or arithmetic mean (SD). An analysis of variance (ANOVA) was performed separately on log-transformed AUC and *C*_{max} data with age, gender and BMI group as ANOVA model factors. The contrast was constructed between the groups within each stratum to obtain the estimated mean difference and the 90% confidence interval (CI) for the log scale test–reference difference.

Correlations between renal function and vildagliptin clearance were explored graphically as well as with simple linear regression models. Additional correlations between renal function and LAY151 exposure were also evaluated. Creatinine clearance (CL_{CR}) was used as an indicator for glomerular filtration rate and was calculated using the formula of Cockcroft & Gault [20]. Although the Cockcroft & Gault method was developed in Caucasian subjects, this method represents a well-accepted approach that is most frequently used in clinical practice.

Results

Subjects

Forty subjects completed this study with an equal number of male and female as well as young and elderly study participants. Demographic and baseline characteristics are displayed in Table 1. Nineteen patients had a BMI ≤25 kg m^{−2} and 20 subjects had a BMI ≥29 kg m^{−2}. One subject had very low plasma concentrations of vildagliptin and LAY151 and was excluded from the pharmacokinetic and pharmacodynamic analyses. In addition, another subject had a BMI of 26.8 kg m^{−2} but was incorrectly enrolled in the ≤25 kg m^{−2} group and was therefore excluded from the pharmacokinetic and pharmacodynamic analyses based on BMI.

Pharmacokinetics

The mean concentration–time profiles for vildagliptin in the elderly and younger subjects are displayed in Figure 1a. The pharmacokinetic parameters for vildagliptin and

Table 1

Subject demographics and baseline characteristics based on age, gender, and BMI

Variable	Age Young (18–40 years) (n = 20)	Elderly (≥70 years) (n = 20)	Gender		BMI		Total (n = 40)
			Male (n = 20)	Female (n = 20)	≤25 kg m ⁻² (n = 19)	≥29 kg m ⁻² (n = 20)	
Age (years)							
Mean ± SD	32.7 ± 7.11	75.2 ± 3.38	54.5 ± 22.5	53.4 ± 22.51	51.2 ± 23.7	55.8 ± 21.3	53.9 ± 22.2
Range	19–40	70–82	22–82	19–80	19–80	27–82	19–82
Weight (kg)							
Mean ± SD	74.3 ± 12.0	70.3 ± 12.5	78.7 ± 12.0	66.0 ± 9.0	65.1 ± 8.7	78.7 ± 11.8	72.3 ± 12.3
Range	55.0–99.3	43.5–95.8	60.0–99.3	43.5–83.6	43.5–80.0	62.7–99.3	43.5–99.3
Height (cm)							
Mean ± SD	165.1 ± 10.8	161.1 ± 8.2	168.6 ± 7.3	157.6 ± 8.7	165.6 ± 7.3	160.1 ± 10.8	163.1 ± 9.7
Range	145–183	146–176	154–183	145–176	153–179	145–183	145–183
Gender							
Male	10 (50%)	10 (50%)	20 (100%)	0	9 (47%)	10 (50%)	20 (50%)
Female	10 (50%)	10 (50%)	0	20 (100%)	10 (53%)	10 (50%)	20 (50%)
Race							
Caucasian	1 (5%)	7 (35%)	4 (20%)	4 (20%)	4 (21%)	3 (15%)	8 (20%)
Black	2 (10%)	0	1 (5%)	1 (5%)	1 (5%)	1 (5%)	2 (5%)
Other*	17 (85%)	13 (65%)	15 (75%)	15 (75%)	14 (74%)	16 (80%)	30 (75%)
Creatinine clearance (ml min⁻¹ 1.73 m⁻²)							
Mean ± SD	127 ± 21.7	68.7 ± 11.6	91.2 ± 26.3	105 ± 40.2	97.1 ± 37.2	100 ± 32.2	97.9 ± 34.2
Range	85.1–162	49.3–90.2	49.3–130	49.5–162	49.3–162	58.3–154	49.3–162

*Racial origin of 'Other' was mostly of Hispanic ethnicity.

LAY151 are presented according to age, gender, and BMI in Tables 2 and 3. The median t_{max} and apparent mean elimination half-life for vildagliptin did not differ substantially between the elderly and the younger groups. Peak plasma concentrations and exposure ($AUC(0, \infty)$) of vildagliptin, however, were approximately 17% and 31% higher in elderly subjects compared with young subjects, respectively (Table 4). Renal clearance was reduced by 32% (90% CI 17, 45%) in elderly compared with younger subjects. In the elderly cohort, apparent total body clearance of vildagliptin was correlated with renal function ($r = 0.56$, $P = 0.01$), but this relationship was not observed in younger participants ($r = 0.056$, $P = 0.82$), as shown in Figure 2a.

The mean C_{max} was increased for vildagliptin (10%) in females compared with males. However, these findings were not statistically significant (Table 4). Furthermore, there were no substantial gender differences in vildagliptin exposure, or apparent plasma and renal clearance. The mean plasma vildagliptin concentration–time profiles for each gender are provided in Figure 1b. All pharmacokinetic parameters were comparable between subjects with BMI ≤ 25 kg m⁻² and ≥ 29 kg m⁻² (Table 2). The mean plasma concentration–time profiles for vildagliptin in the two BMI groups are displayed in Figure 1c.

The mean time to peak concentration of LAY151, the inactive metabolite of vildagliptin, was 8.0 h in all groups (Table 3). Peak concentration and exposure ($AUC(0, \infty)$) to LAY151 was approximately 61% and 77% higher,

respectively, in the elderly compared with the younger subjects (Table 4). A clear correlation between renal function and exposure (Figure 2b) was evident, with the highest exposure observed in elderly subjects with the lowest calculated creatinine clearance ($r = 0.76$ for all subjects). Females had 20% higher peak concentrations of LAY151 compared with males, consistent with the higher peak concentration of vildagliptin observed in females. However, this difference was not statistically significant. Exposure to LAY151 was also higher in females than males ($AUC(0, \infty)$, 7% higher), but again the difference was not statistically significant (Table 4). The pharmacokinetics of LAY151 were comparable between subjects with BMI ≤ 25 kg m⁻² and ≥ 29 kg m⁻² (Tables 3 and 4).

The 90% confidence intervals for the ratio of the geometric mean for C_{max} , $AUC(0, t)$, and $AUC(0, \infty)$ in elderly vs. younger subjects were outside the generally acceptable bioequivalence limits of 0.8–1.25 for both vildagliptin and LAY151. The pharmacokinetics of vildagliptin and LAY151 were similar in males and females and the 90% confidence intervals for both $AUC(0, t)$ and $AUC(0, \infty)$ were within limits for bioequivalence. Although the lower limit of the 90% confidence interval for C_{max} (0.76) was marginally out of the accepted equivalence range, this was not statistically significant. Confidence intervals for comparisons of the two BMI groups were all within bioequivalence limits, indicating that BMI has no significant effect on the pharmacokinetics of vildagliptin or LAY151.

Figure 1

Plasma concentration–time profiles of vildagliptin after a single 100 mg oral dose according to (a) age (18–40 years, (○); ≥70 years, (▲)), (b) gender (Males, (○); Females, (▲)) and (c) BMI (mean ± SD) (BMI < 25 kg/m², (○); BMI ≥ 29 kg/m², (▲))

Pharmacodynamics

A 100 mg dose of vildagliptin achieved a greater than 90% inhibition of DPP-4 activity within 0.5 h of administration. The mean % DPP-4 inhibition over time stratified by age, gender, and BMI is displayed in Figure 3. Inhibition of DPP-4 remained above 90% until 12 h after the administration of

vildagliptin and recovered to approximately 50% at 24 h after the dose in all groups. The relationship between the vildagliptin plasma concentrations and the % of DPP-4 inhibition was explored and no hysteresis was identified, suggesting that the plasma DPP-4 activity directly reflected the effect compartment. An $E_{\max}$ model was applied to estimate the maximum inhibition of DPP-4 activity achieved and the potency (IC_{50}) of vildagliptin in DPP-4 inhibition in healthy volunteers. It was recognized that the estimation could be highly data dependent due to the fact that the majority of the data collected for DPP-4 inhibition was above 50%. Nonetheless, the estimated $E_{\max}$ was approximately complete DPP-4 inhibition (>97%) and estimated IC_{50} was approximately 1 ng ml⁻¹ (3 nM), which were both independent of age, gender and BMI. Overall, there were no differences in the inhibition of DPP-4 activity, reflected by the pharmacodynamic parameters such as $E_{\max}$ or IC_{50} of vildagliptin, based on age, gender, or BMI.

Safety and tolerability

All subjects were assessed for safety and tolerability. However, no adverse events were reported during this study when vildagliptin was given as a single dose at 100 mg. In addition, there were also no reports of clinically significant abnormalities in ECG recordings, routine laboratory tests, or vital signs.

Discussion

The results of this study demonstrate that the pharmacokinetics and pharmacodynamics of vildagliptin were unaffected by differences in gender or BMI. Vildagliptin exposure was approximately 30% higher in elderly subjects compared with younger subjects. However, the pharmacodynamic endpoint reflected by the extent of DPP-4 inhibition was unaltered. Therefore, no dose adjustments are necessary in elderly patients.

Although hydrolysis is the primary route of elimination for vildagliptin, about 23% of the vildagliptin is excreted as unchanged in the urine after oral administration. Renal function represents an important consideration because approximately 85% of the total vildagliptin dose is recovered in the urine as parent drug or metabolites (unpublished data, Novartis Pharmaceuticals). Physiological changes in renal function associated with advanced age are well recognized, in addition, decreased glomerular filtration, renal tubular secretion, and renal perfusion in the elderly population have been reported [21, 22]. In this study, the difference in total plasma clearance (CL/F) between young and elderly subjects is approximately 10 l h⁻¹, a value that is greater than the glomerular filtration rate. In addition, both CL_R and CL/F of vildagliptin were correlated with creatinine clearance in elderly subjects, but no such correlation was found in younger subjects. Interestingly, there appears to be a creatinine clearance thresh-

Table 2

Pharmacokinetic parameters of vildagliptin following administration of a single 100 mg dose to healthy volunteers

Variable	n	t_{max} (h) median (min, max)	C_{max} (ng ml ⁻¹) mean $\pm$ SD* (CV%)	AUC(0,t) (ng ml ⁻¹ h) mean $\pm$ SD* (CV%)	AUC(0, ∞) (ng ml ⁻¹ h) mean $\pm$ SD* (CV%)	$t_{1/2}$ (h) mean $\pm$ SD* (CV%)	CL/F (l h ⁻¹) mean $\pm$ SD* (CV%)	CL _R (l h ⁻¹) mean $\pm$ SD* (CV%)
Age								
18–40 years	19	2.00 (0.50, 5.00)	488 $\pm$ 113 (23)	2318 $\pm$ 355 (15)	2329 $\pm$ 354 (15)	2.17 $\pm$ 0.62 (28)	43.92 $\pm$ 7.09 (16)	8.45 $\pm$ 2.91 (34)
≥ 70 years	20	1.50 (0.50, 6.00)	578 $\pm$ 179 (31)	3056 $\pm$ 696 (23)	3076 $\pm$ 698 (23)	2.47 $\pm$ 0.94 (38)	34.05 $\pm$ 7.47 (22)	5.81 $\pm$ 2.16 (37)
P value		0.546†	0.077†	0.0003†	0.0003†	0.232†	0.0001‡	0.003‡
Gender								
Male	19	1.50 (0.50, 6.00)	501 $\pm$ 107 (21)	2596 $\pm$ 645 (25)	2615 $\pm$ 650 (25)	2.56 $\pm$ 1.01 (39)	40.02 $\pm$ 7.92 (20)	7.32 $\pm$ 2.42 (33)
Female	20	1.75 (0.50, 5.00)	565 $\pm$ 189 (33)	2792 $\pm$ 685 (25)	2804 $\pm$ 687 (25)	2.10 $\pm$ 0.47 (23)	37.75 $\pm$ 9.56 (25)	6.88 $\pm$ 3.26 (47)
P value		0.526†	0.399†	0.232†	0.232†	0.103†	0.424‡	0.635‡
Body mass index								
≤ 25 kg m ⁻²	19	1.00 (0.50, 6.00)	551 $\pm$ 189 (34)	2831 $\pm$ 735 (26)	2850 $\pm$ 738 (26)	2.50 $\pm$ 0.98 (39)	36.95 $\pm$ 7.84 (21)	6.74 $\pm$ 2.59 (38)
≥ 29 kg m ⁻²	19	2.00 (0.50, 5.00)	522 $\pm$ 120 (23)	2574 $\pm$ 595 (23)	2587 $\pm$ 597 (23)	2.13 $\pm$ 0.57 (27)	40.68 $\pm$ 6.94 (24)	7.46 $\pm$ 3.19 (43)
P value		0.056†	0.884†	0.365†	0.350†	0.199†	0.200‡	0.454‡

*Arithmetic mean. †Wilcoxon rank-sum test. ‡t-test.

Table 3

Pharmacokinetic parameters of LAY151 following administration of a single 100-mg dose of vildagliptin in healthy volunteers

Variable	n	t_{max} (h) median (min, max)	C_{max} (ng ml ⁻¹) mean $\pm$ SD* (CV%)	AUC(0,t) (ng ml ⁻¹ h) mean $\pm$ SD* (CV%)	AUC(0, ∞) (ng ml ⁻¹ h) mean $\pm$ SD* (CV%)	$t_{1/2}$ (h) mean $\pm$ SD* (CV%)
Age group						
18–40 years	19	8.00 (5.00, 8.00)	317 $\pm$ 75 (24)	4370 $\pm$ 898 (21)	5129 $\pm$ 1049 (20)	7.22 $\pm$ 1.14 (16)
≥ 70 years	20	8.00 (5.00, 12.00)	514 $\pm$ 150 (29)	7503 $\pm$ 1944 (26)	9216 $\pm$ 2586 (28)	7.82 $\pm$ 1.87 (24)
Gender						
Male	19	8.00 (5.00, 12.00)	379 $\pm$ 83 (22)	5598 $\pm$ 1277 (23)	6906 $\pm$ 1941 (28)	7.98 $\pm$ 1.40 (18)
Female	20	8.00 (5.00, 10.00)	456 $\pm$ 196 (43)	6336 $\pm$ 2785 (44)	7528 $\pm$ 3539 (47)	7.09 $\pm$ 1.62 (23)
Body mass index						
≤ 25 kg m ⁻²	19	8.00 (5.00, 12.00)	421 $\pm$ 183 (43)	5996 $\pm$ 2536 (42)	7365 $\pm$ 3285 (45)	7.93 $\pm$ 1.39 (18)
≥ 29 kg m ⁻²	19	8.00 (5.00, 10.00)	415 $\pm$ 131 (32)	5898 $\pm$ 1897 (32)	7001 $\pm$ 2488 (36)	7.08 $\pm$ 1.67 (24)

*Arithmetic mean.

old of approximately 100 ml min⁻¹ 1.73 m⁻² above which a correlation is no longer discernable (i.e. no effect on CL/F or CL_R if CL_{CR} >100 ml min⁻¹ 1.73 m⁻²). In elderly subjects, the correlation between clearance of vildagliptin and renal function was stronger with CL/F compared with CL_R. This phenomenon is not well understood but may suggest that reduced renal clearance is responsible only for some of the observed increase in vildagliptin exposure in elderly patients as other factors such as the rate or capacity of vildagliptin hydrolysis appear to also be important.

The pharmacologically inactive metabolite, LAY151, displayed significant increases in peak plasma concentration and total exposure in the elderly group compared with the

group with younger subjects. Since LAY151 primarily undergoes renal excretion, impaired renal function would be expected to increase the C_{max} and AUC of LAY151. In addition, because renal clearance of vildagliptin is reduced, metabolism may account for a larger percentage of overall elimination, therefore further contributing to increased concentrations of the LAY151 metabolite. The estimated elimination half-life of LAY151 remained unchanged (7–8 h) irrespective of the increased exposure. However, caution should be exercised when explaining these findings because plasma concentrations of LAY151 were only measured for up to two half-lives after reaching C_{max} . Another plausible explanation is that formation of LAY151

Table 4

Ratio of geometric mean pharmacokinetic parameters and 90% confidence intervals (ANOVA) based on age, gender, and BMI

Pharmacokinetic parameter	Ratio Age (Elderly vs. young)	Gender (Male vs. female)	BMI (≤25 kg m ⁻² vs. ≥29 kg m ⁻²)
Vildagliptin			
C _{max}	1.17 (1.02, 1.35)	0.90 (0.78, 1.04)	0.96 (0.83, 1.11)
AUC(0,t)	1.31 (1.18, 1.45)	0.93 (0.84, 1.03)	0.90 (0.81, 0.99)
AUC(0, ∞)	1.31 (1.18, 1.45)	0.93 (0.84, 1.03)	0.90 (0.81, 0.99)
LAY151			
C _{max}	1.61 (1.41, 1.84)	0.87 (0.76, 1.00)	0.99 (0.86, 1.13)
AUC(0,t)	1.70 (1.51, 1.92)	0.93 (0.82, 1.05)	0.98 (0.86, 1.11)
AUC(0, ∞)	1.77 (1.56, 2.02)	0.97 (0.85, 1.10)	0.95 (0.83, 1.08)

Figure 2

Creatinine clearance vs. (a) plasma clearance of vildagliptin, (18–40 years, (◆); ≥70 years, (◇)) and (b) LAY151 exposure (18–40 years, (◆); ≥70 years, (◇))

might be a rate limiting step instead of the elimination half-life. Higher concentrations of LAY151 in the elderly population are not expected to be clinically important because LAY151 is a pharmacologically inactive compound that has displayed no toxic effects in preclinical studies in rats and dogs (unpublished data, Novartis Pharmaceuticals).

The pharmacodynamics of vildagliptin were not altered by age, gender, or BMI. In this study in healthy volunteers and in a previous study [4] of type 2 diabetics, nearly complete inhibition of DPP-4 activity, that is greater than 90% inhibition of DPP-4, occurs between 15 and 45 min following oral administration of vildagliptin at various doses. In addition, there were no clinically relevant differences in E_{max} or IC₅₀ between the groups in each stratum. The range of the mean IC₅₀ estimates in the various strata (0.75–1 ng ml⁻¹) was similar to the K_i (concentration at which 50% of the enzyme is inactivated) value of approximately 1.5 ng ml⁻¹ (5 nM) obtained from *in vitro* studies, and the IC₅₀ of 1.5 ng ml⁻¹ obtained from patients in type 2 diabetes [23].

No adverse events were observed or reported in this study following a single oral dose administration of 100 mg vildagliptin. Specifically, no subject experienced hypoglycaemia, which further verifies the glucose-dependent mode of action of vildagliptin [4, 18].

In conclusion, the pharmacokinetics and pharmacodynamics of a single oral 100 mg dose of vildagliptin are unaffected by gender and BMI, and the increased exposure to vildagliptin observed in elderly subjects is not expected to be clinically important based on available safety and tolerability data as well as the lack of affect of age on DPP-4 inhibition. Thus, no dose adjustments are required in elderly patients receiving vildagliptin.

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Figure 3

DPP-4 inhibition (%; mean $\pm$ SD) over 24 h following a single oral dose of 100 mg vildagliptin according to (a) age (18–40 years, (○); ≥ 70 years, (▲)), (b) gender (Males, (○); Females, (▲)) and (c) BMI (BMI < 25 kg/m², (○); BMI ≥ 29 kg/m², (▲))

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