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ORIGINAL ARTICLE

Effect of renal impairment on the pharmacokinetics of the dipeptidyl peptidase-4 inhibitor linagliptin*

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Aim: This study assessed the influence of various degrees of renal impairment on the exposure of linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor with a primarily non-renal route of excretion, in subjects with type 2 diabetes mellitus (T2DM).
Methods: Linagliptin pharmacokinetics was studied under single-dose and steady-state conditions in subjects with mild, moderate and severe renal impairment (with and without T2DM) and end-stage renal disease and compared with the pharmacokinetics in subjects with normal renal function (with and without T2DM).
Results: Renal excretion of unchanged linagliptin was <7% in all groups. Under single-dose conditions, the degree of renal impairment did not affect mean plasma linagliptin concentration–time profiles. These showed a similar decline and almost identical plasma concentrations 24 h postdosing in subjects with mild, moderate or severe renal impairment and in subjects with T2DM with and without renal impairment. Although there was a tendency towards slightly higher (20–60%) exposure in renally impaired subjects (with and without T2DM) compared with subjects with normal renal function, the steady-state AUC and C_{max} values showed a large overlap and were not affected by the degree of renal impairment. The accumulation half-life of linagliptin ranged from 14–15 h in subjects with normal renal function to 18 h in severe renal impairment. Only a weak correlation ($r^2 = 0.18$) was seen between creatinine clearance and steady-state exposure.
Conclusions: Renal impairment has only a minor effect on linagliptin pharmacokinetics. Consequently, there will be no need for adjusting the linagliptin dose in renally impaired patients with T2DM.
Keywords: DPP-4 inhibitor, end-stage renal disease, linagliptin, renal impairment, type 2 diabetes mellitus

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Introduction

Patients with type 2 diabetes mellitus (T2DM) and renal impairment have only limited treatment options. Most oral antidiabetic drugs (OADs) are either contraindicated or not recommended in T2DM patients with moderate or severe renal impairment, while the few remaining possible treatment alternatives frequently require monitoring of renal function and dose reductions as renal function declines [1]. Furthermore, the use of OADs is often limited by side effects such as fluid retention or hypoglycaemia, the latter in particular being a serious concern in patients with pronounced renal impairment [1].

Dipeptidyl peptidase-4 (DPP-4) inhibitors represent new orally available treatment options that are associated with a low risk of hypoglycaemia and a low incidence of side effects. Also, they do not cause weight gain. However, a limitation of all currently available DPP-4 inhibitors is that they undergo extensive renal clearance and therefore they either require dose adjustment or are not recommended for use in patients with a creatinine clearance (CrCl) ≤50 ml/min [2]. Thus, the development of a new DPP-4 inhibitor such as linagliptin, where renal excretion represents only a minor elimination pathway (~5% of an orally administered dose [3]), may address an important unmet medical need.

On the basis of the unique pharmacokinetic properties of linagliptin, its excretion pathways and its wide therapeutic window, we hypothesized that renal impairment would have only a minor impact on linagliptin exposure, and that linagliptin would not require dose adjustment in patients with T2DM and renal impairment.

Methods

Subjects eligible for this parallel-group, open-label study were aged 18–80 years with a body mass index (BMI) of 18–40 kg/m^2 and body mass ≥45 kg for females. Following enrolment, participants were stratified for renal impairment based on the following criteria for the degree of renal impairment: mild (CrCl >50 to ≤80 ml/min; Group 2), moderate

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(>30 to ≤50 ml/min; Group 3), severe (≤30 ml/min; Group 4) and end-stage renal disease (ESRD; ≤30 ml/min) on haemodialysis (Group 5). As far as possible, the demographic variables of Groups 2–5 were matched with respect to age (±5 years) and BMI (±10%) to healthy volunteers with normal renal function (CrCl >80 ml/min; Group 1). Estimated CrCl values were calculated using the Cockcroft–Gault formula in accordance with Food and Drug Administration guidance documents existing at the time of study initiation [4].

Due to the non-linear pharmacokinetics of linagliptin, a multiple-dose design was chosen for patients with mild or moderate renal impairment. For patients with severe renal impairment or ESRD, a single-dose design was considered more appropriate in order to limit the study duration for these severely impaired patients and steady-state pharmacokinetic parameters for these two groups were predicted using a pharmacokinetic modelling approach.

In addition, to assess the safety of linagliptin and to support dosing recommendations in renally impaired patients with T2DM, steady-state pharmacokinetics of linagliptin was investigated in patients with T2DM and CrCl ≤30 ml/min (Group 6), who were matched with respect to age (±10 years) and BMI (±15%) to a reference group of patients with T2DM and CrCl >80 ml/min (Group 7). The effect of dialysis on the pharmacokinetics of linagliptin was not specifically investigated in those patients on haemodialysis; this is in accordance with international guidance documents [4,5] for drugs with pharmacokinetic properties like linagliptin's. Owing to the large volume of distribution of unbound linagliptin and the tight binding to the target enzyme, the fraction of unbound drug is very low (≤3%) at therapeutic doses. Therefore, dialysis is not expected to contribute meaningfully to linagliptin elimination.

Exclusion criteria for patients with renal impairment included moderate or severe concurrent liver function impairment (e.g. hepatorenal syndrome); significant diseases other than renal impairment as judged by the investigator (diabetic or hypertensive patients could be entered if the disease was not judged as significant); gastrointestinal surgery; central nervous system diseases; psychiatric and neurological disorders; relevant orthostatic hypotension, fainting spells or blackouts; chronic or acute infections; allergy or hypersensitivity; use of drugs that might influence the results; smoking more than 10 cigarettes, 3 cigars or 3 pipes per day; and high alcohol consumption (>60 g/day). Patients were not enrolled if they had used drugs (excluding medications for renal disease) with a half-life >24 h within the month before the start of the study or planned to use a study medication within ≤10 half-lives of administration of another medication. Patients with haemoglobin <8 g/dl (indicating severe anaemia of renal origin) were excluded. Patients using erythropoietin were eligible.

Study participants with normal renal function or mild or moderate renal impairment received single or multiple doses of 5 mg linagliptin once daily for 7 days; the treatment period was extended to 10 days in patients with T2DM and normal renal function or severe renal impairment in order to account for a potential half-life prolongation. All doses were administered under supervision after an overnight fast. Blood samples for the determination of DPP-4 concentration and plasma protein binding were drawn predosing. For individuals receiving a single dose of linagliptin, blood sampling for pharmacokinetic analysis and measurement of DPP-4 inhibition was carried out predose, at regular intervals over 24 h postdose, and for 11 days after dosing. For individuals receiving multiple doses of linagliptin, blood sampling at regular intervals was carried out throughout the first and last days of dosing, with samples drawn once daily on intervening days and for another 11 days after the last dose. Urine samples for the 24-h period after the first and, if applicable, last doses were collected for all groups.

Pharmacokinetic Analysis

Concentrations of linagliptin in plasma and urine samples were determined by mass spectrometry detection following high-performance liquid chromatography, as described previously [6,7]. Plasma DPP-4 inhibition was determined for all groups using a semiquantitative assay with fluorescence detection [7]. Plasma DPP-4 concentrations were analysed using a commercially available immunoassay (sandwich ELISA; R&D Systems, Inc., Minneapolis, MN, USA). Plasma protein binding of linagliptin was measured *in vitro* for Groups 1–5 using a radiolabelled drug assay.

Non-compartmental analysis of the linagliptin plasma/urine concentration–time data was conducted to obtain pharmacokinetic parameters using WinNonlin® software (Professional, version 5.2; Pharsight Corporation, Mountain View, CA, USA), as described previously [6].

Safety

Safety and tolerability were ascertained from adverse events, blood pressure and pulse rate, 12-lead electrocardiograms, clinical laboratory tests (haematology, clinical chemistry and urinalysis), medical examinations and investigator assessment of global tolerability. Adverse events persisting after trial completion were followed up until they had resolved or been sufficiently characterized.

Ethical Conduct

All subjects provided written informed consent. The trial was approved by the responsible Ethical Committees and complied with principles in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice and German legal requirements.

Statistical Analysis

The statistical model used for analysis of $AUC_{\tau,ss}$, $C_{max,ss}$, AUC_{0-24} and C_{max} was based on analysis of variance (ANOVA) models, separately applied to Groups 1–5 and Groups 6 and 7. Pharmacokinetic parameters were natural log-transformed before fitting the model, using renal function as the fixed effect. The difference between the expected means for log(test)–log(reference) was estimated from the difference in the corresponding least square means. The reference for Groups 2–5 was Group 1 and the reference for Group 6 was Group 7. Two-sided 90% confidence

intervals (CI) based on the *t*-distribution were computed. Results were back-transformed to derive the geometric mean (gMean) and interval estimates. For tests of the fixed effects, the denominator sum of squares was the sum of squares for error. The attainment of steady state was assessed by using linear repeated measurements on the logarithmic scale.

On the basis of the low intraindividual variability in pharmacokinetics and the close pharmacokinetic/pharmacodynamic relationship [8], a sample size of six participants per group in Groups 1–5 was considered adequate to detect the level of renal impairment at which the pharmacokinetics may be changed sufficiently to warrant dose adjustment. The sample size in Groups 6 and 7 was increased to account for a potential increase in variability among patients with T2DM and to increase the precision of the estimates in this relevant target population.

Results

Patient Disposition

A total of 51 subjects were enrolled. All subjects received all scheduled doses of linagliptin, completed the study as planned and were included in the pharmacokinetic and pharmacodynamic analyses and safety evaluation. The demographic characteristics of the control groups and the different groups with renal impairment were well matched (Table 1). The patients with ESRD were slightly younger because of the practicalities of recruitment from this group.

Pharmacokinetics

For all groups, linagliptin was rapidly absorbed after single and multiple doses, reaching maximum plasma concentrations ≤3.0 h after administration (median t_{max}; Table 2). After a single dose, the gMean plasma concentration–time profiles for linagliptin were comparable, regardless of the degree of renal impairment (figure 1A). As best seen in the semi-log displays (figure 1B), the concentration–time curves declined almost in parallel and did not give any indication that even severe renal impairment would prolong the elimination of linagliptin. In fact, linagliptin plasma concentrations 24 h after a single dose (C_{24}) were almost congruent in patients with mild, moderate or severe renal impairment (Groups 2–4), as were the concentration–time profiles in the two study groups with T2DM (Groups 6 and 7). In patients receiving multiple doses of linagliptin, steady-state conditions were generally achieved after the third dose.

Steady-state exposure ($AUC_{\tau,ss}$) and maximum linagliptin concentrations ($C_{max,ss}$) were of the same magnitude in subjects with mild renal impairment as in healthy controls. Relative to the subjects with normal renal function in Group 1, the gMean ratio of the subjects with mild renal impairment in Group 2 was 1.08 for $AUC_{\tau,ss}$ (90% CI, 0.91–1.28) and 0.98 for $C_{max,ss}$ (90% CI, 0.70–1.39) (Table 3). Furthermore, relative to the subjects with normal renal function (Group 1), the exposure in patients with moderate renal impairment (Group 3) showed only a modest increase: the gMean ratio was 1.71 for $AUC_{\tau,ss}$ (90% CI, 1.34–2.18) and 1.46 for $C_{max,ss}$ (90% CI, 0.98–2.19). The individual steady-state AUC and C_{max} values in subjects with moderate renal impairment also displayed a large overlap with the values of the healthy controls (Group 1) as well as the values of the subjects with mild renal impairment (Group 2), although there was a tendency towards higher exposure.

In subjects with severe renal impairment and T2DM (Group 6), steady-state exposure was also only modestly increased compared with T2DM patients with normal renal function (Group 7). The gMean ratio was 1.42 for $AUC_{\tau,ss}$ (90% CI, 1.10–1.82) and 1.36 for $C_{max,ss}$ (90% CI, 0.97–1.90) when comparing these two groups. Overall, only a weak correlation was found between steady-state exposure and renal function across all patient groups ($r^2 = 0.18$; figure 2), indicating that for the majority of patients, regardless of renal impairment status, linagliptin exposure remained within the same range (see shaded area in figure 2).

Under single-dose conditions, the gMean ratio in patients with severe renal impairment (Group 4) was 1.41 for AUC_{0-24} (90% CI, 1.04–1.91) and 1.47 for C_{max} (90% CI, 0.83–2.61) compared with the healthy controls in Group 1 (Table 3). The corresponding values for patients with ESRD (Group 5) were 1.54 for AUC_{0-24} (90% CI, 1.18–2.00) and 1.50 for C_{max} (90% CI, 0.94–2.41). These latter values were still comparable to single-dose exposure for patients with mild or moderate renal

Table 1. Baseline and demographic characteristics.

	Group 1 (n = 6)	Group 2 (n = 6)	Group 3 (n = 6)	Group 4 (n = 6)	Group 5 (n = 6)	Group 6 (n = 10)	Group 7 (n = 11)
	Normal RF	Mild RI	Moderate RI	Severe RI	ESRD requiring haemodialysis	Severe RI + T2DM	Normal RF + T2DM
CrCl (ml/min)	>80	>50 to ≤80	>30 to ≤50	≤30	≤30 + dialysis	≤30	>80
Sex (M : F)	4:2	4:2	3:3	4:2	4:2	6:4	5:6
Age (years) Mean ± s.d.	60.2 ± 6.4	65.2 ± 4.1	60.3 ± 8.9	57.3 ± 13.2	41.7 ± 14.9	60.8 ± 7.9	60.6 ± 9.3
Height (cm) Mean ± s.d.	174.0 ± 7.9	173.2 ± 6.4	170.8 ± 5.3	176.2 ± 7.7	170.5 ± 6.0	171.7 ± 11.5	171.7 ± 12.4
Weight (kg) Mean ± s.d.	83.1 ± 5.0	74.0 ± 6.6	82.4 ± 8.3	73.7 ± 8.0	72.6 ± 14.2	81.6 ± 15.2	83.5 ± 17.0
BMI (kg/m^2) Mean ± s.d.	27.6 ± 3.3	24.7 ± 1.6	28.3 ± 3.3	23.8 ± 3.2	24.8 ± 3.7	27.7 ± 4.4	28.2 ± 3.7
Diagnosed with T2DM (yes : no)	0:6	1:5	2:4	3:3	0:6	10:0	11:0

BMI, body mass index; CrCl, creatinine clearance; ESRD, end-stage renal disease; RF, renal function; RI, renal impairment; s.d., standard deviation; T2DM, type 2 diabetes mellitus.

Table 2. Geometric mean [gCV, %] single dose and steady-state non-compartmental pharmacokinetic parameters of linagliptin after oral administration of a single dose, or multiple doses, of 5 mg linagliptin.

	Group 1 (n = 6)	Group 2 (n = 6)	Group 3 (n = 6)	Group 4 (n = 6)	Group 5 (n = 6)	Group 6 (n = 10)	Group 7 (n = 11)
	Normal RF	Mild RI	Moderate RI	Severe RI	ESRD requiring haemodialysis	Severe RI + T2DM	Normal RF + T2DM
Following a single dose of 5 mg linagliptin							
C_{max} (nmol/l)	7.32 [62.7]	9.20 [18.1]	11.5 [89.1]	10.8 [55.0]	11.0 [28.6]	12.2 [74.2]	10.0 [41.1]
AUC_{0-24} (nmol·h/l)	101 [32.6]	130 [11.0]	158 [44.3]	142 [26.3]	155 [16.8]	155 [50.3]	127 [25.3]
t_{max}* (h)	2.25 [0.500–8.00]	1.50 [0.500–3.03]	2.25 [0.750–4.00]	1.50 [0.750–3.00]	3.00 [1.00–4.00]	1.50 [0.750–4.02]	3.00 [0.500–4.00]
C_{24} (nmol/l)	3.59 [33.8]	4.66 [24.7]	4.85 [18.8]	4.61 [23.3]	5.32 [16.0]	4.88 [43.9]	4.12 [25.3]
fe_{0-24} (%)	0.232 [183]	0.332 [117]	0.368 [391]	0.308 [104]	—	0.530 [140]	0.935 [156]
$CL_{R,0-24}$ (ml/min)	4.06 [119]	4.50 [132]	4.12 [208]	3.83 [77.0]	—	6.02 [74.6]	13.0 [130]
$t_{½}$ (h)	—	—	—	133 [51.0]	129 [21.7]	—	—
Following multiple doses of 5 mg linagliptin							
$C_{max,ss}$ (nmol/l)	13.2 [38.9]	12.9 [24.5]	19.3 [41.3]	—	—	22.6 [60.8]	16.7 [32.1]
$AUC_{\tau,ss}$ (nmol·h/l)	154 [21.2]	166 [10.3]	263 [25.6]	—	—	262 [43.8]	185 [22.8]
$t_{max,ss}$* (h)	0.517 [0.500–1.50]	2.50 [0.533–3.10]	1.27 [0.750–3.00]	—	—	1.26 [0.750–2.00]	1.00 [0.500–3.00]
$C_{24,ss}$ (nmol/l)	5.13 [16.9]	5.36 [12.1]	7.91 [20.6]	—	—	7.24 [46.7]	5.70 [25.5]
$t_{½,ss}$ (h)	192 [31.4]	233 [17.6]	190 [32.5]	—	—	165 [56.6]	179 [47.2]
Accumulation $t_{½}$ (h)	15.2 [32.0]	10.1 [42.1]	15.9 [88.1]	—	—	17.7 [44.3]	13.6 [38.3]
$fe_{0-24,ss}$ (%)	4.26 [60.8]	3.71 [41.2]	4.03 [47.7]	—	—	2.68 [78.4]	6.45 [36.4]
$CL_{R,0-24,ss}$ (ml/min)	48.9 [40.3]	39.4 [38.6]	27.1 [24.2]	—	—	18.1 [43.2]	61.5 [35.6]
$R_{A,AUC_{0-24}}$	1.52 [15.6]	1.27 [14.1]	1.66 [31.9]	—	—	1.69 [22.5]	1.45 [18.3]
$R_{A,Cmax}$	1.81 [37.4]	1.40 [28.3]	1.68 [63.8]	—	—	1.85 [31.2]	1.67 [30.2]

AUC_{0-24}, area under the plasma concentration–time curve over the dosing interval; C_{24}, plasma concentration 24 h after dosing; $CL_{R,0-24}$, renal clearance over the 24-h interval after dosing; C_{max}, highest concentration observed; ESRD, end-stage renal disease; fe_{0-24}, fraction of dose excreted unchanged in urine over the 24-h interval after dosing; gCV, geometric coefficient of variation; gMean, geometric mean; $R_{A,AUC_{0-24}}$, accumulation factor based on AUC_{0-24}; $R_{A,Cmax}$, accumulation factor based on C_{max}; RF, renal function; RI, renal impairment; ss, steady-state conditions; $t_{½}$, half-life; T2DM, type 2 diabetes mellitus; t_{max}, time to maximum plasma concentration after last dosing.
*All data are presented as gMean [gCV, %] except for *t_{max} and $t_{max,ss}$ which are presented as the median and range (min–max).

impairment and did not correlate with the degree of renal dysfunction.

The fraction of the total linagliptin dose that was excreted unchanged in urine over 24 h (fe_{0-24}) after a single dose was <1% for all groups. At steady state, renal excretion ($fe_{0-24,ss}$) remained low at about 4% in Groups 1–3 and 6, and <7% in Group 7. The steady-state renal clearance of linagliptin ($CL_{R0-24,ss}$) was equally low and showed a clear correlation with renal function status (Table 2).

Steady-state terminal half-life ($t_{½,ss}$), accumulation half-life and exposure accumulation factors ($R_{A,AUC_{0-24}}$ and $R_{A,Cmax}$) measured in patients with mild or moderate renal impairment were comparable to those in subjects with normal renal function (Table 2; figure 3). The accumulation half-life and accumulation factors were also similar in Groups 6 and 7, showing that total linagliptin clearance was not meaningfully altered by decreased renal function in patients with T2DM.

For patients with ESRD, single-dose exposure was determined and steady-state $AUC_{\tau,ss}$ was predicted based on AUC_{0-24} values. The prediction utilized the slope and intercept as determined by an orthogonal regression of the individual log-transformed $AUC_{\tau,ss}$ and AUC_{0-24} values from patients with T2DM and severe renal impairment (Group 6) and patients with moderate renal impairment (Group 3). Using this correlation, $AUC_{\tau,ss}$ for patients with ESRD was predicted to be increased <1.6-fold relative to patients with T2DM and normal renal function and <1.9-fold relative to subjects without T2DM with normal renal function.

Pharmacodynamic Analyses

The DPP-4 concentration at baseline showed no correlation with renal function status. Furthermore, for the T2DM subjects in Groups 6 and 7, baseline DPP-4 values were comparable, indicating that renal impairment did not relevantly influence plasma DPP-4 concentrations. The median DPP-4 inhibition exceeded 80% at trough levels of linagliptin in all groups, indicating full efficacy regardless of the degree of renal function. This pharmacokinetic/pharmacodynamic relationship was comparable for all groups and was unaffected by the degree of impairment of renal function or by the presence of T2DM. The plasma protein binding of radiolabelled linagliptin (measured in Groups 1–5 only) was concentration dependent, as previously described [9], and was not altered in patients with differing degrees of renal impairment over the concentration range investigated (0.5–200 nmol/l).

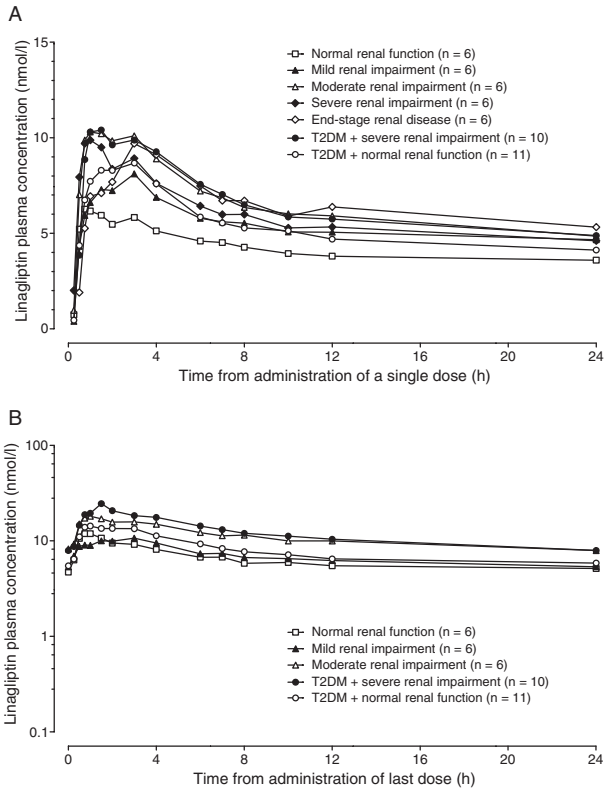


Figure 1. Effect of renal impairment on the pharmacokinetics of linagliptin. (A) Geometric mean (gMean) drug plasma concentration–time profiles of linagliptin after oral administration of a single 5 mg dose (Groups 1–7); (B) steady-state gMean drug plasma concentration–time profiles of linagliptin after oral administration of multiple 5 mg doses (Groups 1–3, 6 and 7). T2DM, type 2 diabetes mellitus.

Safety and Tolerability

No deaths and no serious or severe adverse events occurred, and no adverse events led to discontinuation of study medication. During treatment, two patients (4%) reported adverse events considered related to linagliptin by the investigator: one case of mild headache and one case of mild diarrhoea and mild fatigue. No other clinically significant adverse events were observed.

Discussion

The results of this study indicate that renal impairment does not have clinically meaningful effects on the pharmacokinetics of linagliptin. No major tendency towards increased linagliptin exposure with worsening renal impairment emerged. Increases in exposure in patients with mild, moderate and severe renal impairment were less than twofold higher relative to values observed in the control groups with normal renal function. On the basis of the available single-dose data in patients with ESRD and the established pharmacokinetic/pharmacodynamic correlation, it was also predicted that in patients with ESRD the steady-state AUC exposure levels would similarly not exceed a twofold increase over subjects with normal renal function. The effect of various degrees of renal impairment on linagliptin trough concentrations after 24–52 weeks of treatment with linagliptin 5 mg has also been assessed in a meta-analysis of phase III clinical trial data from 987 T2DM patients [10]. The results of the current pharmacokinetic study are consistent with this meta-analysis, which showed that renal impairment had only a minor effect on the long-term exposure of linagliptin.

At therapeutic concentrations, the fraction of unbound linagliptin is very low due to the tight and concentration-dependent binding of linagliptin to the target enzyme DPP-4 [8]. In fact, the average steady-state concentration of unbound linagliptin has been calculated to be about 700 pM (unpublished data), which is well below the bioanalytical limit of quantification. On the basis of the results of the current study, it has been shown that the pharmacokinetic properties of linagliptin are not altered to a clinically meaningful extent in patients with different stages of renal impairment or in patients with T2DM. As only unbound linagliptin can be removed by glomerular filtration and the concentrations of unbound linagliptin are very low, renal excretion will only be a very small contributor to the elimination of linagliptin. This is confirmed by the results of this study: the steady-state terminal half-life, accumulation half-life and exposure accumulation factors were similar in renally impaired patients and those with normal renal function, regardless of whether or not they had T2DM. This indicates that linagliptin clearance is not meaningfully altered by decreased renal function and that reduced renal clearance is unlikely to account for the mildly increased linagliptin exposure

Table 3. Geometric mean ratios (two-sided 90% confidence intervals) for linagliptin pharmacokinetic parameters of the renally impaired groups versus the corresponding normal renal function group.

	Single-dose		Steady state	
Renal impairment group	C_{max} (nmol/l)	AUC_{0-24} (nmol·h/l)	$C_{max,ss}$ (nmol/l)	$AUC_{\tau,ss}$ (nmol·h/l)
Mild*	1.26 (0.80–1.96)	1.29 (1.01–1.66)	0.98 (0.70–1.39)	1.08 (0.91–1.28)
Moderate*	1.57 (0.77–3.19)	1.56 (1.06–2.32)	1.46 (0.98–2.19)	1.71 (1.34–2.18)
Severe (+ T2DM)†	1.23 (0.82–1.84)	1.22 (0.92–1.62)	1.36 (0.97–1.90)	1.42 (1.10–1.82)
Severe	1.47 (0.83–2.61)*	1.41 (1.04–1.91)*	—	1.34†‡; 1.65*‡
ESRD	1.50 (0.94–2.41)*	1.54 (1.18–2.00)*	—	1.54†‡; 1.89*‡

AUC_{0-24}, area under the plasma concentration–time curve over the dosing interval; C_{max}, highest concentration observed; ESRD, end-stage renal disease; ss, steady-state conditions; T2DM, type 2 diabetes mellitus.
*Compared with healthy volunteers with normal renal function.
†Compared with patients with T2DM that have normal renal function.
‡Predicted values.

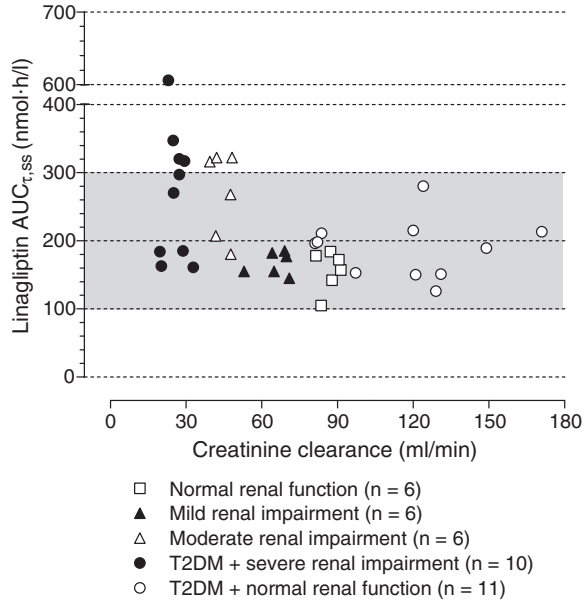


Figure 2. Scatter plot of creatinine clearance and steady-state area under the curve ($AUC_{\tau,ss}$) values for linagliptin after oral administration of multiple 5 mg doses to subjects with normal renal function and patients with various degrees of renal impairment, with or without type 2 diabetes mellitus (T2DM) (Groups 1–3, 6 and 7). For the majority of patients, regardless of renal impairment status, linagliptin exposure remained in the same range (represented by the shaded area).

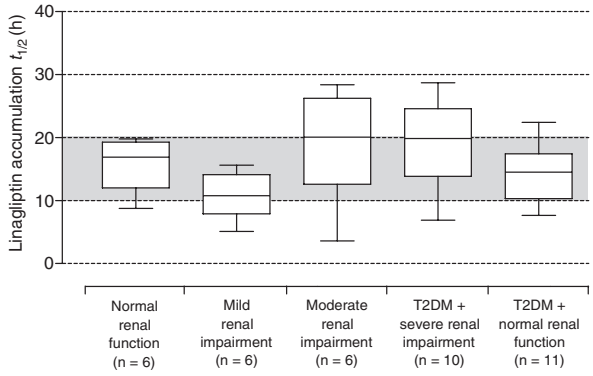


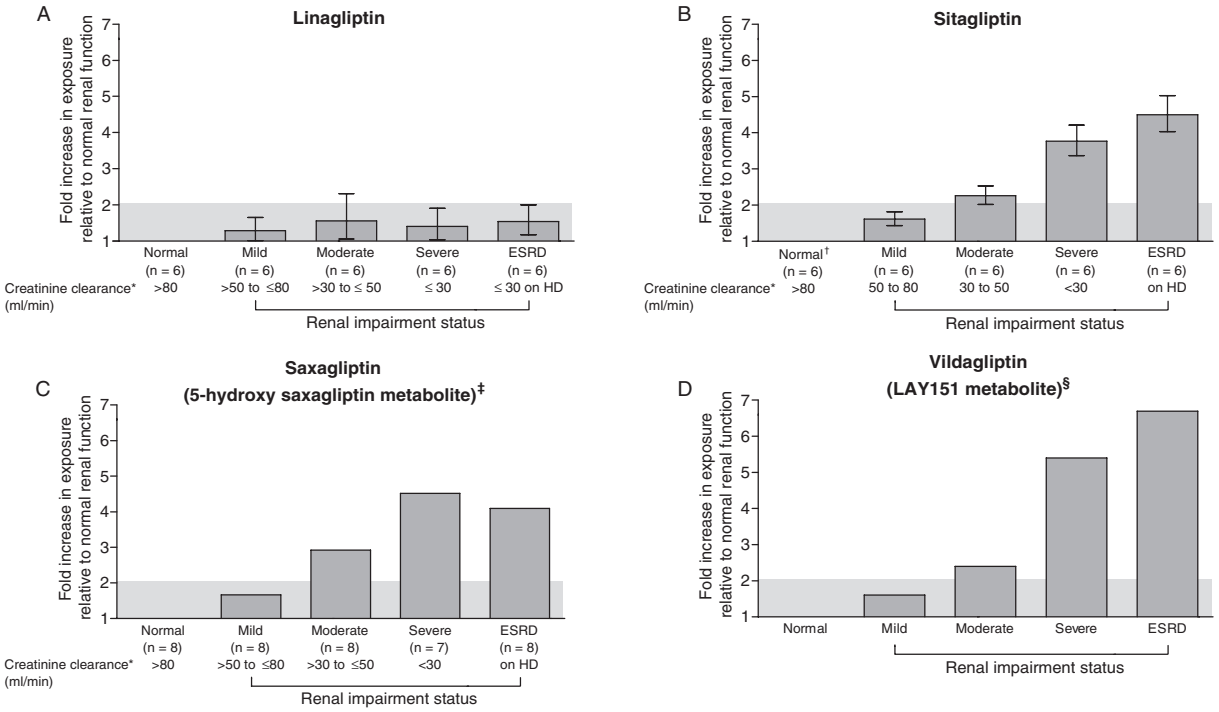
Figure 3. Box and whisker plot (median; lower and upper quartiles; minimum and maximum value) of accumulation half-life ($t_{1/2}$) of linagliptin at steady state after oral administration of multiple 5 mg doses to subjects with normal renal function and patients with various degrees of renal impairment, with or without type 2 diabetes mellitus (T2DM) (Groups 1–3, 6 and 7). For the majority of patients, regardless of renal impairment status, linagliptin accumulation $t_{1/2}$ remained in the same range (represented by the shaded area).

observed in renally impaired patients. Similarly, haemodialysis cannot be expected to effectively remove linagliptin from the systemic circulation. In a similar study in subjects with impaired hepatic function, linagliptin exposure was also not affected by mild, moderate or severe hepatic impairment [11]. Thus, the specific pharmacokinetic properties may make linagliptin a suitable option for patients with reduced clearance, regardless of the cause.

Linagliptin has a large safety margin. In a previous study in healthy male volunteers, daily exposures of up to and including 600 mg (120 times the expected therapeutic dose) were well tolerated [7]. Similarly, in another study following the ICH E14 guideline recommendations on assessment of the potential of a drug to delay cardiac repolarization, the effect of linagliptin on the cardiac QT interval was examined in healthy volunteers [12]. This study demonstrated that even 20-fold supratherapeutic doses of linagliptin (100 mg) produced no relevant changes in heart rate or other electrocardiographic parameters. The safety of linagliptin was assessed as 'good' by the investigator at this supratherapeutic 100 mg dose, which produced maximum plasma concentrations that were about 38-fold higher than after a therapeutic dose of 5 mg. The relatively modest increases in linagliptin exposure observed in patients with renal impairment in this study are, therefore, not considered clinically relevant. Furthermore, linagliptin exhibited a low accumulation potential in the current study and the total clearance was not meaningfully altered by the decreased renal function.

All the other available DPP-4 inhibitors are predominantly eliminated via the kidneys. Following the administration of a single dose, approximately 87% of sitagliptin [13], 75% of saxagliptin [14] and 85% of vildagliptin (not currently approved in the United States) [15,16] are excreted in the urine. Pharmacokinetic studies have shown clinically meaningful differences in exposure between subjects with and without renal impairment with these drugs (figure 4). Plasma sitagliptin exposure was increased in patients with moderate and severe renal impairment and in those with ESRD relative to controls with normal renal function (increases in $AUC_{0-\infty}$ of 2.3-, 3.8- and 4.5-fold, respectively) [17]. Similarly, plasma exposure to saxagliptin and its active metabolite (5-hydroxy saxagliptin) was higher in patients with moderate renal impairment (increases in $AUC_{0-\infty}$ of 1.4- and 2.9-fold, respectively) and severe renal impairment (increases in $AUC_{0-\infty}$ of 2.1- and 4.5-fold, respectively) than in subjects with normal renal function [18]. Systemic exposure to vildagliptin was also 32–134% (AUC) higher in subjects with mild, moderate or severe renal impairment [15,16]. On the basis of these findings, dose adjustments are recommended with sitagliptin and saxagliptin in patients with moderate or severe renal impairment and in those with ESRD requiring dialysis [19,20]. A recent study has shown that a 2.5 mg dose of saxagliptin reduces HbA1c levels and is well tolerated in patients with T2DM and different degrees of renal impairment [21]. Vildagliptin should not be used in these patient groups [15]. Assessment of renal function is also recommended before, and regularly after, the initiation of sitagliptin or saxagliptin treatment.

In conclusion, declining renal function had only a minor and clinically insignificant influence on the pharmacokinetics of linagliptin in patients with T2DM. Given its large safety window, the observed changes in exposure indicate that no dose adjustment of linagliptin will be necessary in T2DM patients with any degree of renal impairment, suggesting that linagliptin could provide a valuable treatment option for all T2DM patients irrespective of their renal function status.



ESRD, end-stage renal disease; HD, haemodialysis.
*Estimated creatinine clearance values were calculated using the Cockcroft–Gault formula.
†The sitagliptin pharmacokinetic study reported by Bergman et al [17] involved six subjects with normal renal function; data from these subjects were then combined with data from 145 more subjects with normal renal function from 11 other studies whose $AUC_{0-\infty}$ had been adjusted based on a 50 mg dose to derive the reference value (i.e. from a total n = 151).
‡Geometric mean ratios for saxagliptin were calculated from the geometric mean data reported by Boulton et al [18]; 90% confidence intervals are not available from that publication.
§Numbers of patients, 90% confidence intervals and definitions of renal impairment status according to creatinine clearance are not available for the vildagliptin study.

Figure 4. Geometric mean ratios (with 90% confidence intervals, where available) for single-dose exposure of renally excreted unchanged compound (or major metabolite) for (A) linagliptin (data from current study), (B) sitagliptin [17], (C) saxagliptin [18] and (D) vildagliptin [16] in study participants with normal renal function versus patients with the degree of renal impairment indicated. Exposure in patients with renal impairment is shown relative to exposure in subjects with normal renal function, which is set to 1. The shaded area represents up to a twofold increase in exposure relative to values observed in the control group with normal renal function.

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Conflict of Interest

U. G.-M., C. F., A. P., S. R. and H.-J. W. are employees of Boehringer Ingelheim. A. R. was an employee of Boehringer Ingelheim at the time of planning and reporting the study. T. H. and A. H. conducted the study under contract from Boehringer Ingelheim. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). All authors contributed to the study design, analysis of data and the writing or revision of the manuscript. All authors saw and approved the final version of the manuscript.

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