Pharmacokinetic and pharmacodynamic evaluation of linagliptin in African American patients with type 2 diabetes mellitus

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The prevalence and severity of type 2 diabetes and its complications may be significantly greater in the African American population compared with other races. Recent literature has also suggested that this population may be characterized by pharmacogenomic differences that could influence treatment, for example with regard to drug transporters and metabolizing enzymes. Further clinical research is required to delineate clearly the pharmacology of antidiabetic agents in patients of African American race.

WHAT THIS STUDY ADDS

- This is the first pharmacologic study of the dipeptidyl peptidase-4 inhibitor linagliptin in African Americans with type 2 diabetes. This study demonstrates that relative to previous studies of this agent in populations with other genetic backgrounds, the pharmacokinetic and pharmacodynamic characteristics of linagliptin are not significantly different in African Americans.

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Keywords

dipeptidyl peptidase-4 inhibitor, linagliptin, oral antidiabetic agents, pharmacodynamic, pharmacokinetic, type 2 diabetes mellitus

Received

30 May 2012

Accepted

26 December 2012

Accepted Article Published Online

18 January 2013

AIM

This was an open label, multicentre phase I trial to study the pharmacokinetics and pharmacodynamics of the dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin in African American patients with type 2 diabetes mellitus (T2DM).

METHODS

Forty-one African American patients with T2DM were included in this study. Patients were admitted to a study clinic and administered 5 mg linagliptin once daily for 7 days, followed by 7 days of outpatient evaluation.

RESULTS

Primary endpoints were area under the plasma concentration–time curve (AUC), maximum plasma concentration (C_{max}) and plasma DPP-4 trough inhibition at steady-state. Linagliptin geometric mean AUC was 194 nmol l⁻¹ h (geometric coefficient of variation, 26%), with a C_{max} of 16.4 nmol l⁻¹ (41%). Urinary excretion was low (0.5% and 4.4% of the dose excreted over 24 h, days 1 and 7). The geometric mean DPP-4 inhibition at steady-state was 84.2% at trough and 91.9% at maximum. The exposure range and overall pharmacokinetic/pharmacodynamic profile of linagliptin in this study of African Americans with T2DM was comparable with that in other populations. Laboratory data, vital signs and physical examinations did not show any relevant findings. No safety concerns were identified.

CONCLUSIONS

The results of this study in African American patients with T2DM support the use of the standard 5 mg dose recommended in all populations.

Introduction

Linagliptin is a new dipeptidyl peptidase-4 (DPP-4) inhibitor approved by the US Food and Drug Administration (FDA) on May 2 2011 for the treatment of type 2 diabetes mellitus (T2DM) [1, 2]. Based on a xanthine scaffold, linagliptin is characterized by a high affinity for the DPP-4 enzyme (~ 1 nM 50% inhibitory concentration [IC_{50}]), >80% DPP-4 inhibition at 24 h post-dose, a low rate of hepatic metabolism and a primarily fecal route of elimination [2–4]. In a study of 12 healthy male volunteers, roughly 85% of the dose was excreted in the feces after the administration of a single ^{14}C -labelled 10 mg oral linagliptin dose. Ninety percent of the recovered radioactivity corresponded to the unchanged parent compound [3]. One main metabolite formed by CYP450 3A4 accounted for >10% of parent exposure. Linagliptin does not require dose adjustment in patients with T2DM who have renal or hepatic impairment [2]. The pharmacokinetic (PK) profile of linagliptin is non-linear, owing to high affinity but saturable binding to the DPP-4 enzyme [5–7]. As a result of this non-linearity, Retlich *et al.* [8] applied a PK modeling approach to compare linagliptin exposure after intravenous injection and oral dosing in 36 healthy male volunteers, reporting an absolute bioavailability of 30%.

The high prevalence of T2DM in African Americans constitutes a significant clinical problem, with a prevalence rate nearly two-fold higher in non-Hispanic Blacks compared with Whites [9]. Unfortunately, representation of African Americans in clinical studies has historically been lower than that of other races [10–13]. In addition, some studies have suggested that there may be important racial differences in the severity and even pathophysiology of T2DM [9, 14–20], whereas other studies have indicated possible pharmacogenomic differences in African Americans compared with other races. For example, the prevalence of genetic polymorphisms in cytochrome P450 enzymes may vary significantly in African Americans compared with other races [21–24]. In particular, the prevalence of polymorphisms in ATP-binding cassette transporters such as the multidrug resistance protein-1, which may play an important role in drug PK/pharmacodynamic (PD) interindividual variability, may also be significantly different in those of African or African American descent compared with other races [25–31]. Similar to other DPP-4 inhibitors, linagliptin is a P-glycoprotein substrate [2], and thus should be evaluated in light of these epidemiologic observations. Enrolment of African Americans with T2DM in previous linagliptin phase III clinical trials was low. Therefore, the aim of this study was to evaluate the PK/PD profile of linagliptin in patients of African American origin. Results from this study were evaluated in the context of comparable studies conducted in other patient populations.

Methods

Materials

The study medication was provided by Boehringer Ingelheim Pharma GmbH & Co. (Ingelheim, Germany).

Patients

Patients of African American descent with a confirmed diagnosis of T2DM were eligible for inclusion in this study. According to the FDA guidance for collection of race and ethnicity data in clinical trials (R05-1602), the following definition was used for African American: a person having origins in any of the Black racial groups of Africa. Hispanic/Latino ethnicity refers to persons of any race who trace their origin to Mexico, Puerto Rico, Cuba, Central and South America, or other Spanish cultures. Race and ethnicity were determined by patient self-identification. Prior treatment with diet and exercise or with one oral glucose-lowering agent was permitted, excluding thiazolidinedione drugs or other DPP-4 inhibitors. Inclusion criteria were haemoglobin A_{1c} levels between 7% and 10% at screening, age 21 to 65 years and a body mass index between 18.5 and 38 kg m⁻². The primary exclusion criteria were any medical examination finding (including laboratory values, blood pressure, pulse rate or electrocardiogram [ECG] results), or conditions considered clinically relevant by the investigator, such as cardiovascular, gastrointestinal, hepatic, renal, respiratory, metabolic, neurological (except polyneuropathy), psychiatric, immunological, hormonal disorders (other than T2DM), chronic or sickle cell anaemia, chronic infections, or relevant allergies. In addition, patients were excluded for smoking (>10 cigarettes day⁻¹, >3 cigars day⁻¹ or >3 pipes day⁻¹, with inability to refrain), pregnancy/nursing or inadequate birth control, intake of drugs with a long half-life (except allowed comedications), changes in allowed comedications (antihypertensive agents, acetylsalicylic acid, statins and thyroid hormones) within the last 3 months, drug or alcohol (>60 g day⁻¹) abuse, excessive physical activity, recent blood donation or participation in another investigational drug clinical trial programme within 1 month before the treatment phase.

The study protocol was approved by a local Institutional Review Board or Independent Ethics Committee at each of the six study sites. The study was conducted and reported according to the principles of the International Committee for Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice and the Boehringer Ingelheim standard operating procedures reflecting those guidelines. Written informed consent was obtained from each patient in accordance with the guidelines.

Study design

Glucose-lowering drug treatments and known inhibitors of P-glycoprotein or CYP3A4 were discontinued 14 and 10 days prior to study drug administration, respectively. From

Figure 1

Concentration–time curves. Mean linagliptin plasma concentration after single and multiple doses of 5 mg linagliptin in 39 patients (due to the early dropout of two patients). Full pharmacokinetic profiles were taken on days 1 and 7 (144 h elapsed time); values for days 2 to 6 represent mean plasma concentration taken just prior to the administration of the morning dose (trough)

days –2 to 17, patients did not use methylxanthine-containing drinks or foods (coffee, tea, cola, energy drinks, chocolate, etc). Caffeine-free drinks were allowed on all other days except days –1, 1, and 7. Apples, oranges, grapefruit and respective fruit juices, vegetables from the mustard green family (kale, broccoli, watercress, collard greens, kohlrabi, Brussel sprouts, mustard greens), green tea or herbal products such as St John's Wort, and charbroiled meats were not allowed from day –10 until study end.

Patients were admitted to a study clinic for 7 days, followed by 7 days of outpatient evaluation. Linagliptin 5 mg was administered daily via tablet for 7 days. Pharmacokinetic samples were taken from days 1 to 15, with full PK profiles (Figure 1) and urine PK assessment on days 1 and 7. Primary endpoints included area under the plasma concentration–time curve (AUC), maximum plasma concentration (C_{max}) and plasma DPP-4 inhibition at trough, under steady-state conditions. Secondary endpoints included AUC, plasma DPP-4 inhibition and C_{max} on day 1. Safety evaluation included monitoring for adverse events (AEs), physical examination, vital signs (blood pressure, pulse rate), 12-lead ECG, laboratory tests and tolerability.

Pharmacokinetic and pharmacodynamic assessments

Plasma and urine concentrations of linagliptin were analyzed by a validated method (see Tables 1 and 2) using high performance liquid chromatography (HPLC) coupled with tandem mass spectrometry (HPLC-MS/MS) in the Department of Bioanalytical Services of Covance Laboratories Ltd. (Harrogate, UK). Plasma and urine concentra-

tions of linagliptin were quantified using $^{13}C_3$ linagliptin as an internal standard. The assay utilized sample purification by solid phase extraction in the 96-well plate format. Chromatography was performed on an analytical Phenyl-Hexyl reversed-phase HPLC column with gradient elution. The analyte was detected and quantified by HPLC-MS/MS.

Plasma linagliptin concentration was determined from day –1 to 15. On days 1 and 7, blood samples were taken at –0.5, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h time points. On days 2 to 6, blood samples were taken before the morning dose. Urine samples were taken at pre-dose and at 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h post-dose on days 1 and 7.

DPP-4 activity in ethylenediaminetetraacetic acid (EDTA) plasma was analyzed by a validated method at the Institut für Klinische Forschung und Entwicklung GmbH (Mainz, Germany), using a quasi-quantitative enzyme activity assay with fluorescence detection. The enzyme DPP-IV present in human plasma samples reacts with the added substrate H-Ala-Pro-AFC (H-Alanin-Prolin-7-amido-4-trifluoro-methylcoumarin).

The following descriptive statistics were calculated for analyte concentrations as well as for all PK and PD parameters: n , # subjects; arithmetic mean; gMean, geometric mean; and gCV, geometric coefficient of variation. Pharmacokinetic parameters were calculated using WinNonlin 5.2 (Pharsight Corporation, Cary, North Carolina, USA). The areas under the plasma concentration curve spanning various time intervals after a single dose and at steady-state were calculated using the linear up/log down algorithm. Individual maximum plasma concentration at steady-state ($C_{max,ss}$) values were directly determined from the plasma concentration–time profiles of each patient.

Terminal half-life was calculated according to: $t_{1/2,ss} = \ln 2 / \lambda_{Z,ss}$, where $\lambda_{Z,ss}$ is the apparent terminal rate constant, calculated via regression of $\ln(C)$ vs. time over the terminal log-linear disposition portion of the concentration–time profiles. Accumulation half-life was calculated according to: $\tau \cdot \ln 2 / \ln (RA_{AUC} / [RA_{AUC} - 1])$, where τ corresponds to the dosing interval and RA_{AUC} is the steady-state accumulation ratio $AUC_{\tau,ss} : AUC_{0-24day1}$. Renal clearance over 24 h at steady-state was calculated as the quantity of the analyte excreted in urine divided by the AUC within the same time interval.

The statistical model to explore the attainment of steady-state using the trough concentrations of linagliptin between days 2 and 7 and the concentrations taken directly at the end of the last dosing interval ($C_{\tau,7}$) was a repeated measures linear model on the logarithmic scale including ‘subject’ as a fixed effect and ‘time’ as a repeated effect. Adjusted least square means and two-sided 95% confidence intervals (CIs) were calculated and back transformed by exponentiation, followed by pairwise comparisons of the log-transformed differences between all subsequent time points ($\log(C_{pre,i} / C_{pre,j}) = \log(C_{pre,i}) - \log(C_{pre,j})$ where $j > i$). Comparisons that generated small P values were inspected to determine if the differences between time points resulted from not yet attaining steady state. Based on visual inspection of gMean trough concentrations, steady-state was reached after three to five doses.

A population pharmacokinetic/pharmacodynamic analysis was performed to characterize the relationship between plasma linagliptin concentration and plasma DPP-4 inhibition. The analysis was conducted using the non-linear mixed-effects modelling software NONMEM Version VI (Icon Development Solutions, Ellicott City, Maryland, USA). The first order conditional estimation algorithm with the interaction option was used as the estimation method. A simple I_{max} model and a sigmoid I_{max} model were tested. These models are described in equations 1 and 2. In these equations, the maximum inhibition parameter I_{max} represents the maximum DPP-4 inhibition. Linagliptin plasma concentration is depicted by C . The IC_{50} value is the linagliptin concentration that leads to half-maximum DPP-4 inhibition. In the sigmoid I_{max} model the sigmoid character of the curve is determined by the Hill coefficient n .

$$\text{DPP-4 inhibition} = \frac{I_{max} \times C}{C + IC_{50}} \quad (1)$$

$$\text{DPP-4 inhibition} = \frac{I_{max} \times C^n}{C^n + IC_{50}^n} \quad (2)$$

Interindividual variability was investigated for all typical parameters, and modelled using exponential random

effect models, assuming lognormally distributed individual model parameters. The residual variability was modelled using a combined (proportional plus additive) residual variability model. Model discrimination was based on the following criteria: objective function values (for nested models), graphical goodness of fit analyses, the precision of parameter estimates as reported by the relative standard error (RSE) obtained from NONMEM and the plausibility of the parameter estimates. The appropriateness of the model was evaluated using a visual predictive check (VPC). The VPC of data from day 1, day 7, and the complete study (see Supplementary materials) clearly show that the predicted median accurately describes the population pharmacodynamics, showing close alignment with the true median and with the vast majority of patient values falling within the 10th and 90th percentiles

Blood glucose monitoring

Patients were provided with home blood glucose monitoring (HBGM) equipment and instructed to check blood glucose using the HBGM if they felt symptoms of hypoglycaemia or hyperglycaemia. Blood glucose values were recorded in a patient’s log. If the results of a HBGM test (or a laboratory test) revealed blood glucose of $>270 \text{ mg dl}^{-1}$ (15 mmol l^{-1}) after an overnight fast or a randomly determined blood glucose $>400 \text{ mg dl}^{-1}$ (22.2 mmol l^{-1}) the patient was instructed to contact the study site. Elevated blood glucose concentrations were confirmed with a second measurement performed on a separate day after an overnight fast at the investigational site. If the results were confirmed the patient was discontinued from the trial.

Safety evaluation

Vital signs, 12-lead ECG, physical examination, urinalysis, laboratory haematological parameters and clinical chemistry panels were evaluated over the 7 day course of treatment. Safety endpoints included the following: incidence and intensity of AEs, withdrawal from study because of AEs, clinically relevant new or worsening findings in physical examination reported as AEs, clinically relevant changes from baseline in vital signs (blood pressure and pulse), clinically relevant new or worsening findings in a 12-lead ECG reported as AEs or clinically relevant changes from baseline in clinical laboratory assessments. The Medical Dictionary for Drug Regulatory Affairs was used to code AEs.

Results

Forty-one (22 men, 19 women) African American patients with T2DM entered the study and 39 completed it. Owing to the early dropout of two patients, steady-state PK comprises data from 39 patients. One patient had elevated blood glucose after the single dose and one patient

Table 1

Accuracy and precision data of quality control samples for [¹³C₃] linagliptin in human plasma

Standard concentration [nmol l ⁻¹]	n	Deviation (%)	Coefficient of variation (%)
0.250	45	0.4	6.6
1.00	45	2.0	5.1
15.0	45	1.3	3.6

Table 2

Accuracy and precision data of quality control samples for linagliptin in acidified human urine

Standard concentration [nmol l ⁻¹]	n	Deviation (%)	Coefficient of variation (%)
2.50	14	4.4	8.5
50.0	13	3.8	2.8
800	14	-4.0	4.3

Table 3

Patient demographics and baseline characteristics

	Linagliptin 5 mg
Number of patients	41
Gender, n (%)	
Male	22 (53.7)
Female	19 (46.3)
Hispanic/Latino, n (%)	19 (46.3)
Age, mean years (SD)	51 (10)
Any concomitant therapy at screening,* n (%)	38 (92.7)
Metformin	32 (78.0)
Lisinopril	7 (17.1)
Acetylsalicylic acid	6 (14.6)

*With the exception of allowed comedications (antihypertensives, acetylsalicylic acid, statins, and thyroid hormones), concomitant therapies were discontinued during the 14-day washout period before treatment.

discontinued as the result of an undisclosed patient-provider decision. The subject who discontinued due to high blood glucose showed exposure and DPP-4 inhibition values within the range of the other patients. Mean age was 51 ± 10 years (Table 3) and mean body mass index was 30.9 ± 3.9 kg m⁻². Thirty-two (78%) of the 41 participants were taking metformin at screening. The use of metformin or other glucose-lowering therapy was discontinued 14 days before the first dose of linagliptin was administered. Following a single oral dose of 5 mg linagliptin, the gMean AUC over 24 h post-dose (AUC₀₋₂₄) was 137 nmol l⁻¹ h (gCV 32.4%; Table 4). The cor-

Table 4

Geometric mean (gMean) non-compartmental pharmacokinetic parameters of linagliptin after single and multiple oral administration of 5 mg linagliptin to African American patients with T2DM

	Single dose gMean (% gCV)	Steady-state gMean (% gCV)
AUC (nmol l ⁻¹ h)	137 (32.4)	194 (25.8)
C _{max} (nmol l ⁻¹)	10.9 (57.6)	16.4 (40.9)
t _{max} (h)	1.5 (1.00–8.00)	1.5 (0.50–4.00)
t _{1/2} (h)	–	119 (22.4)
CL _R (ml min ⁻¹)	6.45 (151)	40.3 (33.7)
fe(0,24 h) (%)	0.504 (214)	4.42 (45.2)
V ₂ /F (l)	–	9400 (36)
CL/F (ml min ⁻¹)	–	911 (25.8)
RA, AUC ₀₋₂₄	–	1.4 (22.8)
RA, C _{max}	–	1.49 (52.8)
Accumulation t _{1/2} (h)	–	13.1 (44)

gCV, geometric coefficient of variation; AUC, area under the concentration-time curve over a uniform dosing interval (AUC₀₋₂₄ for single dose exposure, and AUC_{τ,ss} for steady-state exposure); C_{max}, maximum measured concentration of linagliptin in plasma; t_{max}, time to the maximum measured concentration of the analyte in plasma; t_{1/2}, terminal half-life; CL_R, renal clearance over a 24 h period; fe(0,24 h), fraction excreted in urine over a 24 h period; V₂/F, apparent volume of distribution; CL/F_{ss}, apparent plasma clearance at steady-state; RA, AUC₀₋₂₄, accumulation ratio based on area under the concentration-time curve; RA, C_{max}, accumulation ratio based on C_{max}; accumulation t_{1/2}, accumulation based half-life.

responding C_{max} of 10.9 nmol l⁻¹ (gCV 57.6%) was reached after a median time of 1.50 h (range 1.00–8.00 h; Figure 1).

The gMean extent of exposure at steady-state (AUC_{τ,ss}) was 194 nmol l⁻¹ h (gCV 25.8%). The corresponding gMean C_{max,ss} was 16.4 nmol l⁻¹ (gCV 40.9%), which was reached after a median time of 1.50 h (range 0.50–4.00 h). gMean concentrations at 24 h after the first dose and at steady-state trough were 4.35 nmol l⁻¹ and 5.94 nmol l⁻¹, respectively. Following multiple doses, a large apparent volume of distribution (gMean 9400 l; gCV 36.0%) and a moderate apparent clearance (gMean 911 ml min⁻¹; gCV 25.8%) were observed. However, values for apparent clearance and volume of distribution after the first dose and at steady-state should be interpreted with caution since linagliptin pharmacokinetics are non-linear [5, 6, 8] and the absolute bioavailability is not known from this study. At steady-state, plasma DPP-4 activity was inhibited over 24 h by >80% (Figure 2), with a gMean trough inhibition of 84.2% (maximum 94.2%).

The relationship between linagliptin plasma concentrations and plasma DPP-4 inhibition was best described by a sigmoid E_{max} model, with a typical I_{max} value of 96.8%, a typical IC₅₀ value of 2.48 nM, and a typical Hill coefficient of 2.10 (Table 5). Interindividual variability could be accounted for by variability in the parameters IC₅₀ and Hill coefficient. The concentration that led to 80% DPP-4 inhibition (IC₈₀) was 5.21 nmol l⁻¹.

Renal excretion of linagliptin was low after single dosing and at steady-state, accounting for 0.5% of the

Figure 2

Arithmetic mean dipeptidyl peptidase-4 (DPP-4) inhibition vs. time profiles after single (○, $n = 39$) and multiple oral administration (●, $n = 37$) of 5 mg linagliptin (A) and correlation of plasma DPP-4 inhibition and linagliptin plasma concentrations after single and multiple oral doses (B)

administered dose within 24 h following the first dose and 4.4% during the dosing interval at steady state. The gMean renal clearance following a single dose was 6.45 ml min⁻¹ and 40.3 ml min⁻¹ at steady state. Interindividual variability for the single dose and steady-state PK parameters was generally low to moderate, ranging from 20.3% to 57.6% (gCV). Urinary parameters after the first dose were an exception, where a high interindividual variability was observed (151–214% [gCV]) owing to the negligible amounts excreted. Linagliptin had a long terminal elimination phase ($t_{1/2} = 119$ h) with still measurable plasma concentrations in all patients 192 h after the last administered dose. From 24 to 192 h after the last dose, gMean concentrations decreased by about 75%. Based on the accumulation factors of 1.40 ($AUC_{\tau,ss}/AUC_{0-24}$) and 1.49 ($C_{max,ss}/C_{max}$) observed over the course of this study, the accumulation

potential for linagliptin is low. The accumulation half-life was calculated to be 13.1 h (gCV 44%).

Safety

Laboratory data, vital signs and physical examinations did not demonstrate any clinically significant findings. AEs occurred in 16 of 41 patients (39%) during the treatment phase, compared with four of 41 (10%) during the screening phase. All but three AEs were mild in intensity and each of these AEs were moderate: one incident of hypoglycaemia, one of increased blood glucose, and one of diarrhoea (all patients recovered). No AEs were serious, only one led to study or medication withdrawal (increased blood glucose), and only seven were deemed related to study drug by the investigators. Only headache and

Table 5

Parameter estimates describing the relationship between plasma linagliptin concentration and plasma DPP-4 inhibition (sigmoid maximum inhibition model)

	Estimate	RSE [%]
Typical parameter		
$I_{\max}$ (%)	96.8	0.64
IC_{50} (nmol L ⁻¹)*	2.48	4.15
Hill coefficient**	2.10	3.67
Interindividual variability		
$\omega_{IC_{50}}$ (%)	25.1	21.8
ω_{Hill} coefficient (%)	16.0	31.9
Residual variability		
σ_{prop} (%)	7.21	24.4
σ_{add} (nmol L ⁻¹)	0.0001 fixed	–

RSE: Relative standard error. *ETA shrinkage: 0%. **ETA shrinkage: 5%.

dyspepsia occurred in more than one patient ($n = 5$ and $n = 2$, respectively).

Discussion

The PK/PD profile of linagliptin in African American patients with T2DM is characterized by rapid absorption, low urinary excretion and >80% inhibition of the DPP-4 enzyme over the full 24 h period at steady-state. An apparent high plasma clearance and long terminal half-life were observed, with low accumulation factors. These results are consistent with previous linagliptin PK evaluations. Based on preclinical studies, Retlich *et al.* [7] demonstrated that linagliptin is rapidly cleared from DPP-4-deficient rat models whereas the terminal half-life in wildtype rats with DPP-4 is significantly longer. Taken together, these results suggest that the high apparent clearance at steady-state is the result of (a) the almost complete saturation of DPP-4 over the whole dosing interval at steady-state (with high clearance of linagliptin not bound to DPP-4) and (b) the incomplete (30%) bioavailability of linagliptin [2]. The long terminal half-life and shorter accumulation half-life can most likely be explained by high affinity but saturable binding of linagliptin to DPP-4 at the therapeutic dose, whereby bound linagliptin dissociates slowly from DPP-4 and unbound linagliptin is rapidly eliminated.

The pharmacokinetic profile of linagliptin in this study of African Americans with T2DM was comparable with that in other populations. The observed steady-state $AUC_{\tau,ss}$ of 194 nmol L⁻¹ h (gCV 26%) was within the exposure range previously observed in White, Japanese and Chinese healthy subjects [3, 6, 32–34]. For example, Sarashina *et al.* [34] evaluated 12 days of treatment with 5 mg daily linagliptin in six Japanese healthy male volunteers, with a reported mean steady-state $AUC_{\tau,ss}$ of 193 nmol L⁻¹ h (gCV 16.2%). Friedrich *et al.* recently

reported a pharmacokinetic evaluation of linagliptin in healthy Chinese volunteers [35]. Twelve healthy subjects were treated with 5 mg daily linagliptin for 6 consecutive days, resulting in a mean steady-state $AUC_{\tau,ss}$ of 204 nmol L⁻¹ h (gCV 24.5%). Lastly, Heise *et al.* [33] reported a mean steady-state $AUC_{\tau,ss}$ of 158 nmol L⁻¹ h (gCV 10.1%) after 12 days of 5 mg daily linagliptin in eight White males with T2DM.

In addition, the pharmacodynamic profile of linagliptin was consistent with previous studies. The parameter estimates of the sigmoid maximum effect model used here ($I_{\max}$ 96.8%, IC_{50} and IC_{80} values of 2.48 and 5.21 nM, and Hill coefficient 2.10) were similar to those found in studies of linagliptin in other populations. For example, in a study of healthy Caucasian volunteers Retlich *et al.* reported an $I_{\max}$ of 94.2%, an IC_{50} and IC_{80} of 2.82 and 5.61 nM, and a Hill coefficient of 2.51 [8]. Likewise, IC_{50} values ranging from 2.26 to 3.15 were observed following single and multiple doses in Japanese individuals (healthy or with T2DM) [34, 36].

No safety concerns were identified in this study. Only seven AEs were determined by investigators to be related to treatment with linagliptin. These were mild, with a frequency similar to or less than that previously reported in other PK studies. For instance, Heise *et al.* [33] observed AEs in 54% of white male patients with T2DM randomized to linagliptin for 12 days ($n = 35$), compared with 75% of those assigned placebo ($n = 12$). In this study, three AEs were moderate and the remainder were of mild intensity. In a study administering linagliptin doses up to 10 mg daily to Japanese patients with T2DM, fewer AEs were observed in the treatment group ($n = 55$) compared with placebo (20% vs. 35%, respectively) over the 28 day treatment period [36].

Multiple dosing of 5 mg linagliptin led to >80% inhibition of the DPP-4 enzyme in African American patients with T2DM, with trough inhibition values of 84.2% (gCV 5%). These results are comparable to trough values reported in Japanese healthy subjects (80%–90%) and White T2DM patients ($84.8\% \pm 3.2\%$ SD) [33, 34]. Thus, no meaningful differences in the PK/PD properties of linagliptin in African American patients were observed in this study, compared with those properties previously observed in White and Asian patients. The primarily non-renal route of elimination previously observed in other patient populations was confirmed in this study of African American patients with T2DM. No safety concerns were identified. These findings support the use of linagliptin 5 mg once daily in African American patients with T2DM.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf

(available on request from the corresponding author) and declare all authors are employed (CF, SG, DL, JR, SP, UGM, SR, HJW) or contracted by (CJK) Boehringer Ingelheim. There were no other relationships or activities that could appear to have influenced the submitted work.

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE) and were fully responsible for all content and editorial decisions, and were involved at all stages of manuscript development. The authors received no compensation related to the development of the manuscript. This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). Writing, editorial support and formatting assistance was provided by Michael P. Bennett of the UBC-Envision Group, which was contracted and compensated by BIPI for these services.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1

Observed vs. individual prediction. Values are indicated by open circles. The line of identity (dashed black) is included as a reference

Figure S2

Observed vs. population prediction. Values are indicated by open circles. The line of identity (dashed black) is included as a reference

Figure S3

Observed vs. individual prediction, in log scale. Values are indicated by open circles. The line of identity (dashed black) is included as a reference

Figure S4

Observed vs. population prediction, in log scale. Values are indicated by open circles. The line of identity (dashed black) is included as a reference.

Figure S5

Weighted residuals vs. Time. Values are indicated by open circles. A dashed line at $y = 0$ is included as a reference. One data point with a weighted residual of 68 excluded

Figure S6

Visual predictive check – complete study. Observed values are indicated by open circles, the observed median as red

line. The predicted median is shown as solid black line and the 10th and 90th percentile as dashed black lines

Figure S7

Visual predictive check – study day 1. Observed values are indicated by open circles, the observed median as red line. The predicted median is shown as solid black line and the 10th and 90th percentile as dashed black lines

Figure S8

Visual predictive check – study day 7. Observed values are indicated by open circles, the observed median as red line. The predicted median is shown as solid black line and the 10th and 90th percentile as dashed black lines

Table S1

Model code