

# Comparable pharmacodynamics, efficacy, and safety of linagliptin 5 mg among Japanese, Asian and white patients with type 2 diabetes

Akiko Sarashina<sup>1\*</sup>, Christian Friedrich<sup>2†</sup>, Susanne Crowe<sup>2</sup>, Sanjay Patel<sup>3‡</sup>, Ulrike Graefe-Mody<sup>2</sup>, Naoyuki Hayashi<sup>4</sup>, Yoshiharu Horie<sup>5</sup>

<sup>1</sup>Clinical Pharmacokinetics/Pharmacodynamics Department, Nippon Boehringer Ingelheim Co., Ltd, Hyogo, Japan, <sup>2</sup>Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany, <sup>3</sup>Boehringer Ingelheim Ltd, Bracknell, UK, <sup>4</sup>Clinical Research Department; and <sup>5</sup>Medical Data Service Department, Nippon Boehringer Ingelheim Co., Ltd, Tokyo, Japan

## Keywords

Exposure–response, Linagliptin, Race effect

## \*Correspondence

Akiko Sarashina  
Tel: +81-78-306-4532  
Fax: +81-78-302-3733  
E-mail address: akiko.sarashina@boehringer-ingenheim.com

*J Diabetes Investig* 2016; 7: 744–750

doi: 10.1111/jdi.12482

## ABSTRACT

**Aims/Introduction:** The efficacy and safety of drugs can vary between different races or ethnic populations because of differences in the relationship of dose to exposure, pharmacodynamic response or clinical efficacy and safety. In the present *post-hoc* analysis, we assessed the influence of race on the pharmacokinetics, pharmacodynamics, efficacy and safety of monotherapy with the dipeptidyl peptidase-4 inhibitor, linagliptin, in patients with type 2 diabetes enrolled in two comparable, previously reported randomized phase III trials.

**Materials and Methods:** Study 1 (with a 12-week placebo-controlled phase) recruited Japanese patients only (linagliptin,  $n = 159$ ; placebo,  $n = 80$ ); study 2 (24-week trial) enrolled Asian (non-Japanese; linagliptin,  $n = 156$ ; placebo,  $n = 76$ ) and white patients (linagliptin,  $n = 180$ ; placebo,  $n = 90$ ).

**Results:** Linagliptin trough concentrations were equivalent across study and race groups, and were higher than half-maximal inhibitory concentration, resulting in dipeptidyl peptidase-4 inhibition >80% at trough. Linagliptin inhibited plasma dipeptidyl peptidase-4 activity to a similar degree in study 1 and study 2. Linagliptin reduced fasting plasma glucose concentrations by a similar magnitude across groups, leading to clinically relevant reductions in glycated hemoglobin in all groups. Glycated hemoglobin levels decreased to a slightly greater extent in study 1 (Japanese) and in Asian (non-Japanese) patients from study 2. Linagliptin had a favorable safety profile in each race group.

**Conclusions:** Trough exposure, pharmacodynamic response, and efficacy and safety of linagliptin monotherapy were comparable among Japanese, Asian (non-Japanese) and white patients, confirming that the recommended 5-mg once-daily dose of linagliptin is appropriate for use among different race groups.

## INTRODUCTION

The clinical application of incretin-based therapies has gained worldwide use in recent years. Besides their glucose-lowering efficacy, these drug classes have shown potential pancreatic and extrapancreatic effects that might be of benefit in diabetes-related complications<sup>1</sup>. Linagliptin, a highly selective, xanthine-based, oral dipeptidyl peptidase (DPP)-4 inhibitor, is approved in more

than 80 countries including Canada, China, Europe, Japan and the USA, as a treatment (5 mg once daily) for type 2 diabetes<sup>2</sup>, either as monotherapy or in combination with other commonly prescribed antidiabetes medications. Linagliptin has a unique pharmacokinetic profile<sup>2–5</sup> because, unlike other DPP-4 inhibitors, it is excreted primarily through the enterohepatic system<sup>6</sup>, allowing it to be administered without dose adjustment in patients with renal impairment<sup>7</sup>.

Linagliptin has been extensively evaluated in a clinical trial program comprising >8,500 patients<sup>8</sup>, including significant numbers of patients from different races or ethnic backgrounds. In the present *post-hoc* analysis, we wanted to assess whether

<sup>†</sup>Boehringer Ingelheim Pharma GmbH & Co. KG at the time of the study; now an employee of Bayer HealthCare Pharmaceuticals

<sup>‡</sup>Boehringer Ingelheim Ltd at the time of the study; now an employee of Daiichi Sankyo Development Ltd

Received 21 August 2015; revised 19 November 2015; accepted 7 January 2016

the dose–response relationship of linagliptin 5 mg was influenced by race. The varied response to any medication that is seen among patients of different races or ethnic groups can be partly attributed to the variation in the exposure (i.e., pharmacokinetics) or pharmacodynamic response of a drug<sup>9</sup>. These variations might translate into differences in efficacy and safety profiles, which could require population-specific prescribing recommendations. Therefore, a potential influence of race should first be assessed on the pharmacokinetics of linagliptin, subsequently on the relevant pharmacodynamic response marker (i.e., inhibition of the target enzyme, DPP-4), and finally on the clinical efficacy (i.e., glucose control) and safety profile of linagliptin.

The results from two previously reported, small-scale, multiple-dose, 4-week phase II studies in Japanese and white patients showed that values of maximum concentration and area-under-the-curve for linagliptin were approximately 1.4–2.4-fold higher in Japanese than white patients<sup>7,10</sup>. As a consequence of the non-linear kinetics of linagliptin, differences in trough plasma concentrations were just  $\leq 30\%$ , and no clinically relevant differences in the degree of target enzyme inhibition, the reduction of plasma glucose parameters or in the safety profile between these two race groups were observed<sup>7,10</sup>. Therefore, as a next step, we wanted to investigate whether these observations could be confirmed in large-scale phase III clinical trials. From the linagliptin clinical trials program, data were available from just two previously completed phase III studies of linagliptin monotherapy, which were broadly comparable in design and in relevant assessments of interest, and that included three different race groups: Japanese, Asian (non-Japanese) and white patients<sup>11,12</sup>. Thus, the objective of the present data analysis was to assess the exposure, the pharmacodynamic response, clinical efficacy, and safety of monotherapy with linagliptin 5 mg in Japanese, Asian (non-Japanese) and white patients with type 2 diabetes.

## MATERIALS AND METHODS

This analysis evaluated the data from two independent, randomized, double-blind, placebo-controlled phase III trials of linagliptin monotherapy in patients with type 2 diabetes and inadequate glycemic control. Pooling of the data from these trials was not possible, because the time-points of the evaluated assessments varied and, therefore, a descriptive comparison of the available data from each race group was carried out. Eligibility criteria for each of the two original trials were broadly similar<sup>11,12</sup>. Most relevant common inclusion criteria were 20–80 years-of-age (study 1) or 18–80 years-of-age (study 2), treatment naïve or treatment experienced, and body mass index (BMI) of  $\leq 40$  kg/m<sup>2</sup>. Common exclusion criteria included the following: myocardial infarction, stroke or transient ischemic attack within the previous 6 months; impaired hepatic function; and treatment with a glitazone, insulin or antiobesity drug within the previous 3 months<sup>11,12</sup>.

In study 1 (NCT00654381) by Kawamori *et al.*<sup>12</sup>, 561 Japanese patients were randomized to take linagliptin 5 mg or

10 mg, voglibose 0.6 mg or a placebo. At week 12, patients taking the placebo were randomized to linagliptin 5 mg or 10 mg and treatment continued up to week 26<sup>12</sup>. In study 2 (NCT00621140) by Del Prato *et al.*<sup>11</sup>, 503 patients (Asian 46.1%, white 53.7%) were randomized to take linagliptin 5 mg or a placebo for 24 weeks (no Japanese patients participated in that study). The efficacy and safety findings from both studies, which broadly followed the same design<sup>13</sup>, have been published previously<sup>11,12</sup>. In the primary publication of study 1, pharmacokinetics data were not reported, and the results from pharmacodynamic analyses were summarized as data not shown<sup>12</sup>. In study 2, pharmacokinetic and pharmacodynamic data were reported for the total population and not by race<sup>11</sup>.

In the present analysis, patients were grouped according to race: study 1 included Japanese patients only; study 2 included Asian (non-Japanese) and white patients. For the purposes of this report, the baseline characteristics, efficacy and safety results from study 1 were summarized for the initial 12-week treatment period only (placebo-controlled phase). Pharmacokinetic and pharmacodynamic data were summarized for the 26-week, double-blind treatment period. As mentioned, different doses of linagliptin (5 and 10 mg) were administered to patients in study 1 either at the time of randomization or as add-on to placebo after 12 weeks of treatment with the placebo. Therefore, patients had differences in their individual treatment exposure levels with linagliptin. However, the different exposure times were not relevant, because patients were already at steady state within the first week of linagliptin treatment and, therefore, all linagliptin patients could be pooled to determine the half-maximal inhibitory concentration (IC<sub>50</sub>) of linagliptin. In study 2, one patient (Native American/Alaska Native) was excluded from this analysis because of the small sample size.

Pharmacokinetic and pharmacodynamic measurements included plasma linagliptin concentrations, plasma DPP-4 inhibition and the IC<sub>50</sub> of linagliptin for DPP-4 activity, which were analyzed in each group using descriptive statistics. The IC<sub>50</sub> was calculated by race using a sigmoid  $E_{\max}$  model in the treated set (all randomized patients who received at least one dose of study medication), where  $E_{\max}$  is the maximum effect possible with the drug.

Efficacy analyses were carried out on the full analysis set, defined as all randomized patients treated with at least one dose of study medication, and who had a baseline and at least one on-treatment glycated hemoglobin (HbA1c) measurement. Analysis of covariance (ANCOVA) was used to evaluate changes in continuous efficacy end-points. In study 1, the statistical model included treatment and number of prior oral antidiabetes drugs as fixed classification effects and baseline HbA1c as the linear covariate. In study 2, the model included treatment, number of prior oral antidiabetes drugs, race, treatment  $\times$  race interaction and baseline HbA1c. A similar approach was used to analyze fasting plasma glucose (FPG) levels with the addition of baseline FPG to the model (except in study 1, where baseline HbA1c was not included as a linear

covariate in the FPG analysis). Efficacy measurements after the start of rescue medication were replaced by missing values. Missing data were imputed using a last observation carried forward approach. Safety end-points were evaluated using descriptive statistics with no formal inferential analyses. SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

## RESULTS

In study 1<sup>12</sup>, 159 Japanese patients treated with linagliptin 5 mg and 80 placebo-treated patients were available for inclusion in this analysis. In study 2<sup>11</sup>, data from 232 Asian (non-Japanese) patients (linagliptin 5 mg,  $n = 156$ ; placebo,  $n = 76$ ) and 270 white patients (linagliptin 5 mg,  $n = 180$ ; placebo,  $n = 90$ ) were available for analysis. In the Asian group, 135 patients were from India (58.2%). Demographics and clinical characteristics at baseline are shown in Table 1. As expected, there were notable differences in patient characteristics between the race groups: in study 2, BMI and body weight were higher in white patients, whereas more Asian (non-Japanese) patients were treatment-naïve and had diagnosed diabetes of shorter duration. Within each race group, however, the two treatment groups (linagliptin vs placebo) were generally similar.

Trough plasma concentrations of linagliptin remained stable in both studies from 12 weeks to the end of the study at 24 or 26 weeks of treatment with linagliptin 5 mg in the Japanese, Asian (non-Japanese) and white patients (Table 2). At the end of the study period, the geometric mean trough plasma concentrations of linagliptin were 7.12 nmol/L (26.4% geometric coefficient of variation) in study 1 (Japanese patients), and 6.63 nmol/L (67.4% geometric coefficient of variation) and

6.31 nmol/L (69.9% geometric coefficient of variation) in Asian (non-Japanese) and white patients, respectively (study 2).

In both studies, inhibition of DPP-4 by linagliptin was similar in the Japanese, Asian (non-Japanese) and white patients (Table 2). Median DPP-4 inhibition remained unchanged from week 12 to the end of the study at 24 or 26 weeks, and was 81.0% (week 26), 82.6% (week 24) and 84.8% (week 24) in Japanese, Asian (non-Japanese) and white patients, respectively. In both studies, linagliptin showed similarly high potency in Japanese, Asian (non-Japanese) and white patients, with IC<sub>50</sub> values in the low nanomolar range (Table 2).

Treatment with linagliptin 5 mg showed statistically significant reductions from baseline in HbA1c and FPG in study 1 (Japanese) and study 2 (Asian [non-Japanese], white; Table 3). As previously reported<sup>12</sup>, the placebo-corrected adjusted mean  $\pm$  standard error change from baseline in HbA1c at week 12 was  $-0.87 \pm 0.09\%$  in study 1 (Japanese;  $P < 0.0001$ ). In study 2, the placebo-corrected adjusted mean  $\pm$  standard error changes from baseline at week 24 were  $-0.91 \pm 0.12\%$  and  $-0.52 \pm 0.11\%$  for Asian (non-Japanese) and white patients, respectively ( $P < 0.0001$  for both). A significant interaction with treatment was shown for race ( $P = 0.0190$ ) in study 2. The mean change from baseline in HbA1c at 24 weeks in study 2 was calculated by race for several baseline variables (Table S1). The placebo-corrected adjusted mean  $\pm$  standard error changes from baseline in FPG were  $-19.7 \pm 2.9$  mg/dL at week 12 in study 1 (Japanese)<sup>12</sup>, and  $-23.7 \pm 5.1$  mg/dL and  $-23.3 \pm 4.9$  mg/dL at week 24 in study 2 for Asian (non-Japanese) and white patients, respectively ( $P < 0.0001$  for all).

The frequency of adverse events (AEs) in both studies (study 1: Japanese; study 2: Asian [non-Japanese], white) is

**Table 1** | Demographics and clinical characteristics at baseline (treated set)

	Study 1		Study 2			
	Japanese*		Asian		White	
	Linagliptin $n = 159$	Placebo $n = 80$	Linagliptin $n = 156$	Placebo $n = 76$	Linagliptin $n = 180$	Placebo $n = 90$
Male, $n$ (%)	111 (69.8)	57 (71.3)	84 (53.8)	36 (47.4)	80 (44.4)	42 (46.7)
Mean age, years (SD)	60.3 (9.4)	59.7 (8.9)	52.7 (10.0)	50.3 (9.9)	59.5 (9.2)	57.8 (9.3)
Mean BMI, kg/m <sup>2</sup> (SD)	24.6 (4.0)	24.3 (3.4)	26.6 (4.3)	26.5 (4.0)	31.2 (4.1)	31.3 (4.4)
Mean bodyweight, kg (SD)	64.6 (12.0)	65.3 (11.6)	68.1 (12.3)	68.4 (11.0)	87.6 (14.7)	88.5 (13.6)
Mean HbA1c, % (SD)	8.07 (0.66)	7.95 (0.67)	8.02 (0.91)	8.02 (0.88)	7.98 (0.83)	7.98 (0.86)
Mean FPG, mg/dL (SD)	163.3 (31.8)	161.7 (30.6)	157.3 (38.4)	156.2 (35.1)	171.4 (43.7)	179.0 (40.6)
No. prior antidiabetes drugs, $n$ (%)						
No therapy	87 (54.7)	43 (53.8)	97 (62.2)	47 (61.8)	92 (51.1)	48 (53.3)
One therapy	58 (36.5)	29 (36.3)	59 (37.8)	29 (38.2)	88 (48.9)	41 (45.6)
Two or more therapies	14 (8.8)	8 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Duration of diabetes, $n$ (%)						
Up to 1 year	19 (11.9)	7 (8.8)	85 (54.5)	42 (55.3)	35 (19.4)	20 (22.2)
1–5 years	61 (38.4)	36 (45.0)	48 (30.8)	22 (28.9)	81 (45.0)	40 (44.4)
>5 years	79 (49.7)	37 (46.3)	23 (14.7)	12 (15.8)	64 (35.6)	30 (33.3)

\*Previously reported by Kawamori *et al.*<sup>12</sup>. BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; SD, standard deviation.

**Table 2** | Pharmacokinetic and pharmacodynamic parameters of linagliptin

	Study 1		Study 2			
	Japanese		Asian		White	
Trough plasma concentration of linagliptin (nmol/L)*	n	gMean (gCV%)	n	gMean (gCV%)	n	gMean (gCV%)
Week 12	153	7.15 (30.5)	144	6.71 (55.4)	149	6.07 (70.3)
End of study <sup>†</sup>	147	7.12 (26.4)	124	6.63 (67.4)	124	6.31 (69.9)
DPP-4 inhibition at trough (%) <sup>‡</sup>	n	Median (range)	n	Median (range)	n	Median (range)
Week 12	159	81.5 (26.6–95.4)	144	84.5 (14.9–96.1)	167	83.9 (–35.2–99.2)
End of study <sup>†</sup>	159	81.0 (55.7–93.0)	134	82.6 (–21.2–95.0)	155	84.8 (–309.2–95.2)
IC <sub>50</sub> between DPP-4 inhibition and plasma concentration of linagliptin <sup>§</sup>	Estimate (approximate SE)		Estimate (approximate SE)		Estimate (approximate SE)	
E <sub>max</sub> (%)	96.8 (4.0)		93.8 (2.1)		90.7 (3.0)	
Gamma	1.1 (0.2)		1.7 (0.2)		2.2 (0.4)	
IC <sub>50</sub> (nmol/L)	1.6 (0.2)		2.2 (0.1)		2.3 (0.2)	

\*Study 1: analysis based on the pharmacokinetic set (only after administration of linagliptin); study 2: analysis based on full analysis set (FAS; observed results [OR]). <sup>†</sup>End of study: study 1, at 26 weeks in the analysis of Japanese patients; study 2, at 24 weeks in the analysis of Asian and white patients. <sup>‡</sup>Study 1: analysis based on FAS (last observation carried forward [LOCF]); study 2: analysis based on FAS (OR). <sup>§</sup>All analyses based on the treated set of patients. Study 1: based on pooled linagliptin (5 and 10 mg). DPP-4, dipeptidyl peptidase-4; E<sub>max</sub>, maximum effect possible with the drug; gCV, geometric coefficient of variation; gMean, geometric mean; IC<sub>50</sub>, half-maximal inhibitory concentration; SE, standard error.

summarized in Table 4. Overall, the proportion of patients in both treatment groups reporting any AE was similar in each race group. The rates of drug-related AEs were similar between the linagliptin and placebo groups in study 1 (Japanese) and for Asian (non-Japanese) patients in study 2. In white patients (study 2), 5.6% and 2.2% of the linagliptin and placebo groups

had drug-related AEs, respectively. Serious AEs and AEs leading to drug discontinuation tended to be lower with linagliptin than the placebo in each race group. Overall, the AE profile by race in study 2 showed a similar trend between treatment groups to that seen in the original parent trial<sup>11</sup>. Nasopharyngitis was the most frequently reported AE in study 1;

**Table 3** | Measures of glycemic control in the linagliptin and placebo groups at 12 weeks in Japanese patients, and 24 weeks in Asian (non-Japanese) and white patients (full analysis set; last observation carried forward)

	Study 1		Study 2			
	Japanese* 12 weeks		Asian 24 weeks		White 24 weeks	
	Linagliptin	Placebo	Linagliptin	Placebo	Linagliptin	Placebo
HbA1c (%)						
Patients (n)	159	80	155	72	178	90
Change from baseline <sup>†</sup> (adjusted mean ± SE)	–0.24 ± 0.06	0.63 ± 0.08	–0.45 ± 0.07	0.46 ± 0.10	–0.42 ± 0.06	0.10 ± 0.09
Difference vs placebo <sup>‡</sup> (adjusted mean ± SE)	–0.87 ± 0.09		–0.91 ± 0.12		–0.52 ± 0.11	
P-value	<0.0001		<0.0001		<0.0001	
FPG (mg/dL)						
Patients (n)	159	80	155	70	163	78
Change from baseline <sup>†</sup> (adjusted mean ± SE)	–12.3 ± 1.9	7.4 ± 2.5	–10.9 ± 12.1	12.8 ± 12.5	7.5 ± 12.1	30.8 ± 12.0
Difference vs placebo <sup>‡</sup> (adjusted mean ± SE)	–19.7 ± 2.9		–23.7 ± 5.1		–23.3 ± 4.9	
P-value	<0.0001		<0.0001		<0.0001	

\*Previously reported by Kawamori *et al.*<sup>12</sup> <sup>†</sup>In study 1, the model includes treatment, baseline glycated hemoglobin (HbA1c) and number of prior oral antidiabetes drugs (OADs); in study 2, the model includes baseline HbA1c, number of prior OADs, race, treatment group and treatment × race interaction. <sup>‡</sup>In study 1, the model includes treatment, baseline fasting plasma glucose (FPG) and number of prior OADs; in study 2, the model includes baseline HbA1c, baseline FPG, number of prior OADs, race, treatment group and treatment × race interaction. SE, standard error.

**Table 4** | Summary of adverse events (treated set)

	Study 1		Study 2			
	Japanese* 12 weeks		Asian 24 weeks		White 24 weeks	
	Linagliptin <i>n</i> = 159	Placebo <i>n</i> = 80	Linagliptin <i>n</i> = 156	Placebo <i>n</i> = 76	Linagliptin <i>n</i> = 180	Placebo <i>n</i> = 90
Any AE, <i>n</i> (%)	89 (56.0)	45 (56.3)	89 (57.1)	43 (56.6)	95 (52.8)	55 (61.1)
Drug-related AEs, <i>n</i> (%)	15 (9.4)	8 (10.0)	10 (6.4)	5 (6.6)	10 (5.6)	2 (2.2)
AEs leading to discontinuation of trial medication, <i>n</i> (%)	3 (1.9)	7 (8.8)	1 (0.6)	2 (2.6)	4 (2.2)	3 (3.3)
Serious AEs, <i>n</i> (%)	1 (0.6)	1 (1.3)	3 (1.9)	3 (3.9)	7 (3.9)	5 (5.6)
AEs occurring in >5% of patients <sup>†</sup> , <i>n</i> (%)						
Constipation	9 (5.7)	5 (6.3)	4 (2.6)	1 (1.3)	0	0
Dyslipidemia	–	–	5 (3.2)	4 (5.3)	1 (0.6)	1 (1.1)
Upper respiratory tract infection	2 (1.3)	0	9 (5.8)	7 (9.2)	0	0
Nasopharyngitis	26 (16.4)	10 (12.5)	3 (1.9)	0	10 (5.6)	7 (7.8)
Hyperglycemia	1 (0.6)	3 (3.8)	10 (6.4)	9 (11.8)	23 (12.8)	29 (32.2)

Study 1: Medical Dictionary for Regulatory Activities (MedDRA) version 12.1<sup>12</sup>; study 2: MedDRA version 14.0<sup>11</sup>. \*Previously reported by Kawamori *et al.*<sup>12</sup>

<sup>†</sup>A frequency cut-off of >5% in either treatment group at the preferred term level. AE, adverse event.

hyperglycemia was the most frequently reported AE occurring in Asian and white patients (study 2). Investigator-reported hypoglycemia occurred in two white patients (one in each treatment group).

## DISCUSSION

Linagliptin has a unique pharmacokinetic and pharmacodynamic profile that is characterized by target-mediated non-linear pharmacokinetics and a large safety window (>100-fold the recommended daily dose)<sup>5,14</sup>. Linagliptin has shown clinically meaningful glucose-lowering efficacy and good tolerability as monotherapy or add-on to existing antidiabetes therapy across several race groups enrolled in phase III trials<sup>11,12,15–20</sup>. Studies dedicated to assessing the use of linagliptin in Japanese patients were included early in the clinical trial program in order to confirm the pharmacokinetic, pharmacodynamic, efficacy and safety profiles<sup>7,10</sup>.

In the present analysis of two independent phase III studies, linagliptin monotherapy was shown to have a similar dose–exposure–response relationship in Japanese, Asian (non-Japanese) and white patients. Consistent with the results from the 4-week phase II studies<sup>7,10</sup>, trough concentrations of linagliptin were comparable in Japanese, Asian (non-Japanese) and white patients, and were higher than IC<sub>50</sub>, resulting in a >80% inhibition of plasma DPP-4 activity at trough. This degree of inhibition was previously shown to result in maximum reductions in plasma glucose<sup>21</sup>. FPG levels were decreased relative to the placebo by a similar magnitude across the three race groups. Clinically relevant reductions in HbA1c levels were also seen among all race groups, with a greater effect observed in Japanese and Asian (non-Japanese) patients. This finding is consistent with previously published evidence suggesting the glucose-lowering efficacy of DPP-4 inhibitors is greater in Asian

patients than in non-Asian or Caucasian patients<sup>22,23</sup>. It has been suggested that differences in BMIs between ethnic groups might contribute to the variation in the efficacy response to DPP-4 inhibitors<sup>22</sup>, although other physiological or pathophysiological factors related to race or ethnicity could also account for the variation in efficacy, including differences in genetic factors, insulin sensitivity and insulin response, and the levels of incretin hormones<sup>24,25</sup>. In the present study, the BMIs of the Japanese and Asian (non-Japanese) patients were lower than those of their white counterparts; however, previous research has shown that BMI/bodyweight had no clinically meaningful effect on the pharmacokinetics/pharmacodynamics of linagliptin<sup>8,26</sup>. In addition, a pooled analysis of three pivotal phase III trials of linagliptin showed that there were no statistically significant effects of BMI on treatment efficacy or BMI–treatment interactions<sup>27</sup>. Other obvious study-specific differences in patient characteristics at baseline between the race groups (for example, the duration of diabetes) might account for the variations in efficacy outcomes. Furthermore, the short duration of the washout period in these studies might have confounded the efficacy outcomes<sup>11,12</sup>.

Linagliptin appeared to be well tolerated in both studies (study 1: Japanese; study 2: Asian [non-Japanese], white), with no new or unexpected specific risks observed. Importantly, few patients experienced symptomatic hypoglycemia. This finding is consistent with the glucose-dependent action of glucagon-like peptide-1 and, therefore, DPP-4 inhibitors are inherently less likely to cause hypoglycemia compared with insulin, sulfonylureas or meglitinides.

The present study was limited by its *post-hoc* nature, and by the fact that the analysis was undertaken separately on study 1 and study 2. Different protocol-defined time-points for the evaluation of the end-points did not allow for pooling of the

two studies. Therefore, the findings should be regarded as exploratory.

In summary, the present analysis shows that the dose–exposure–response relationship of linagliptin is similar in Japanese, Asian (non-Japanese) and white patients. Linagliptin treatment resulted in clinically relevant improvements in glycemic control in all groups, although the effect on HbA1c is more pronounced in Japanese and Asian (non-Japanese) patients. Overall, linagliptin 5 mg is a safe and effective treatment option in patients with type 2 diabetes regardless of race or ethnic backgrounds.

## ACKNOWLEDGMENTS

This study was supported by the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development and have approved the final version. Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Paul MacCallum PhD of Envision Scientific Solutions during the preparation of this manuscript.

## DISCLOSURE

AS, SC, UG-M, NH and YH are all employees of Boehringer Ingelheim, the manufacturer of linagliptin. CF was an employee of Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany, at the time of the study, and is now an employee of Bayer HealthCare Pharmaceuticals, Berlin, Germany. SP was an employee of Boehringer Ingelheim Ltd, Bracknell, UK, at the time of the study, and is now an employee of Daiichi Sankyo Development Ltd, Gerrards Cross, UK.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Table S1** | Mean change from baseline in glycated hemoglobin in the linagliptin and placebo groups at 24 weeks in Asian (non-Japanese) and white patients by various subgroups.