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Efficacy and safety of linagliptin according to patient baseline characteristics: A pooled analysis of three phase 3 trials☆

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Abstract *Background and aims:* We aimed to determine if patient baseline characteristics affect responses to linagliptin and identify relevant predictors of glycated hemoglobin (HbA1c) reduction in patients with type 2 diabetes mellitus (T2DM).
Methods and results: Data were pooled from three 24-week, placebo-controlled trials of similar design (linagliptin, $n = 1651$; placebo, $n = 607$). Patients were categorized according to baseline characteristics: age, T2DM duration, gender, body mass index (BMI), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), and metabolic syndrome (MetS). Changes from baseline in HbA1c after 24 weeks were assessed with analysis of covariance (ANCOVA). The proportion of patients with baseline HbA1c >7% achieving HbA1c of ≤7% at week 24 were evaluated. Independent predictors of HbA1c response with linagliptin were analyzed in a multivariate analysis with ANCOVA. Linagliptin treatment led to significant mean (SE) placebo-corrected reductions from baseline in HbA1c across all subgroups (−0.42% [±0.11] to −0.79% [0.08]; all $p < 0.001$). Within subgroups, HbA1c reduction was more pronounced in patients without MetS (−0.74% [0.06]; treatment interaction $p = 0.0489$). The proportion of patients with baseline HbA1c >7% achieving a target HbA1c ≤7% was greater with linagliptin versus placebo (30.2% vs 11.5%; odds ratio 3.82; 95% CI 2.82 to 5.17; $p < 0.001$). Characteristics significantly predicting HbA1c reductions after 24 weeks were fasting plasma glucose and race (both $p < 0.05$).
Conclusion: This post-hoc analysis supports that linagliptin achieved clinically meaningful improvements in hyperglycemia in patients with diverse clinical characteristics. These improvements were more pronounced in patients without MetS.

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; FAS, full analysis set; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; IDF, International Diabetes Federation; MetS, metabolic syndrome; OR, odds ratio; T2DM, type 2 diabetes mellitus.

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Introduction

Recent diabetes guidelines emphasize the need for treatment individualization, and advocate selection of pharmacologic treatment for type 2 diabetes mellitus (T2DM) based on multiple parameters (e.g. efficacy, side effects, impact on body weight, and cost) [1]. In this context, prediction of response to a given treatment would be quite useful. However, the current literature does not provide clear, consistent insights regarding which non-genetic patient characteristics might influence response to treatment for T2DM [2,3]. Therefore, patients and health care providers likely would benefit if future clinical trials were to designate patient subgroups prospectively for analyses of efficacy and safety in order to further improve individualized treatment concepts in T2DM. Dipeptidyl peptidase-4 (DPP-4) inhibitors are of continuing interest in T2DM, with recent data demonstrating the efficacy of these agents in more challenging patient groups such as the elderly [4–7] and those with renal impairment [8].

The phase 3 clinical trial program of the DPP-4 inhibitor linagliptin included predefined characterizations of safety and efficacy data according to a broad range of patient attributes. The use of linagliptin as monotherapy or add-on combination therapy has been evaluated in three 24-week, placebo-controlled, phase 3 trials of >2000 patients with T2DM and results have been previously reported [9–11]. However, these 3 individual studies of linagliptin were not sufficient for determining whether some patient characteristics may affect clinical outcomes associated with linagliptin therapy. These trials had similar designs, with identical study duration, primary endpoint definition, and safety assessments, which allowed data to be pooled in an attempt to more efficiently explore potential factors predicting therapeutic response. Thus, pooled safety and efficacy data from these 3 trials were analyzed across predefined subgroups to explore to what extent baseline characteristics could be associated with variances in glucose-lowering treatment response or increased risk of side effects.

Methods

Study population

This retrospective analysis pooled data from individuals with T2DM from these 3 previously reported trials evaluating the safety and efficacy of linagliptin 5 mg once daily given as monotherapy (NCT00621140) [9], as add-on therapy in patients with T2DM inadequately controlled with metformin (NCT00601250) [11], and as add-on therapy in patients with T2DM inadequately controlled with metformin plus a sulfonylurea (NCT00602472; Supplementary Table S1) [10]. Patients were randomized to linagliptin and placebo in ratios of 2:1 (NCT00621140) [9] and 3:1 (NCT00601250, NCT00602472) [10,11]. Studies were carried out according to the Declaration of Helsinki and International Conference on Harmonisation good clinical practice principles (October 1996) and national good clinical practice regulations where applicable. The protocols, informed consent, and patient information forms were reviewed and approved by the local institutional review boards.

Efficacy and safety analysis

For this pooled analysis, patients were grouped into predefined baseline categories according to age (≤50, 51 to <65, 65 to <75, ≥75 years), gender (male, female), duration of T2DM based on time elapsed since documented diagnosis (≤1, >1 to ≤5, >5 years), body mass index (BMI; <25, 25 to <30 [overweight], ≥30 [obese] kg/m^2), and the following 2 additional categories. Insulin-resistance categories were defined according to prespecified values of Homeostasis Model Assessment of Insulin Resistance (HOMA-IR): ≤4.0, >4.0 to ≤5.5, >5.5 to ≤8.5, and >8.5. Metabolic syndrome (MetS) was determined according to the International Diabetes Federation (IDF) criteria [12].

Efficacy analyses were performed on the full analysis set (FAS), which consisted of all randomized participants who were treated with ≥1 dose of study medication, who had a baseline glycated hemoglobin (HbA1c) measurement and ≥1 on-treatment HbA1c measurement. Efficacy measurements after start of rescue therapy were replaced by missing values. Missing data were imputed using a last observation carried forward approach.

The change from baseline in HbA1c after 24 weeks was compared between the linagliptin and placebo groups using analysis of covariance (ANCOVA). The general model included continuous baseline HbA1c, washout, treatment, study, subgroup, and treatment by subgroup interaction. All subgroup analyses were performed at a significance level of 5%.

The proportion of FAS patients with a baseline HbA1c >7% achieving a target HbA1c ≤7% at week 24 was evaluated overall. Logistic regression was used to model the odds ratio (OR) for achieving HbA1c ≤7% with linagliptin versus placebo treatment.

Additionally, the relationship between change from baseline in HbA1c after 24 weeks and baseline variables of interest (age, BMI, duration of T2DM, gender, fasting plasma glucose [FPG], fasting plasma insulin, MetS) was analyzed using multivariate analysis with ANCOVA. It should be noted that baseline FPG and baseline fasting plasma insulin were used in lieu of HOMA-IR and HOMA-%B. The 2 HOMA indexes are different linear transformations of the same 2 variables [13]: FPG and fasting plasma insulin, hence the 2 indexes would be associated. The fixed factors and covariates (study, treatment, washout, and baseline HbA1c) were included in all models as forced-in (core) variables independent of their p value [14]. First, the core model plus each of the baseline variables of interest were modeled separately. The values of −2 log likelihood were then obtained for each model and compared to the null model (i.e. the core model) to determine if baseline variables of interest reduced the value of this statistic (−2 log likelihood), based on the chi-squared distribution ($p < 0.05$). Second, the baseline variables deemed to be important were modeled together with the core model

(henceforth referred to as model 1) and the value of −2 log likelihood was obtained. As variables can lose importance when modeled with certain other variables, the change in −2 log likelihood was also obtained when each of the important baseline variables of interest (in model 1) was omitted. Only variables deemed important after this step were retained (henceforth referred to as model 2). Third, baseline variables of interest that were deemed not of interest in the first step may become important in the presence of the variables in model 2. These variables were then added separately to model 2 and the value of −2 log likelihood was obtained to see if the value of the statistic (−2 log likelihood) was reduced from model 2. Those baseline variables of interest deemed of importance within this step were then added to model 2 (henceforth referred to as model 3). Fourth, a check was made to ascertain if any further terms could be omitted from model 3.

Safety analyses were performed on the treated set, which consisted of all patients treated with ≥1 dose of study drug. Adverse events (AEs) were summarized using descriptive statistics, without any formal statistical testing. All AEs were coded using the Medical Dictionary for Regulatory Activities version 12.1.

Results

Patient population

In total, 2258 patients with T2DM (linagliptin, $n = 1651$; placebo, $n = 607$) were randomized and received ≥1 dose of study drug (treated set). The efficacy population (FAS) comprised 2224 patients (linagliptin, $n = 1624$; placebo, $n = 600$). Baseline demographic and clinical characteristics for the FAS were similar between the 2 treatment groups (Table 1). Gender was evenly distributed. Overall, 58% of study participants were white and the remainder predominantly Asian (42%). More than one-third (38%) of participants were obese (mean BMI ± SD, 29.0 ± 4.8 kg/m^2). Most (63%) patients met the IDF criteria for MetS, 57% had T2DM duration >5 years, and 10% had HOMA-IR >8.5 mU/L·mmol/L. Mean fasting C-peptide levels were comparable between the treatment groups, and more than half of participants were taking ≥2 oral glucose-lowering medications.

When baseline characteristics were stratified according to age, duration of T2DM, BMI, HOMA-IR, presence of MetS, or gender, notable differences were seen across subgroups (Supplementary Tables S2–7). As expected, a greater proportion of older patients had duration of diabetes >5 years and used ≥2 glucose-lowering drugs. Additionally, most patients aged >50 years were white, whereas most patients ≤50 years were Asian. Most patients with a duration of diabetes ≤1 year were Asian, whereas those with a longer duration of diabetes were more often white. Mean HOMA-IR values were lowest in patients with duration of diabetes >5 years. Mean (±SD) fasting plasma insulin levels were lower in patients with duration of diabetes >5 years (9.9 ± 10.3 mU/L) than in those with duration of diabetes <1 year (13.0 ± 12.4 mU/L). These findings suggest that reduced mean HOMA-IR values in patients with long-standing diabetes may be a result of low residual β-cell function. Among the BMI subgroups, the mean value for HOMA-IR and the proportion of white patients were higher in the BMI ≥30 kg/m^2 subgroup than in the BMI <25 kg/m^2 subgroup. In the MetS subgroups, a greater percentage of patients without MetS had mean HOMA-IR of ≤4.0 mU/L·mmol/L, were Asian, and had lower BMI. In the gender subgroups, a greater proportion of females than males had MetS and used ≥2 glucose-lowering drugs.

Table 1 Patient demographics and baseline characteristics (FAS).

	Linagliptin ($n = 1624$)	Placebo ($n = 600$)
Age (years)	57.4 (10.0)	56.5 (10.2)
Male (%)	49.2	50.5
Race (%)		
White	57.6	57.2
Asian	41.7	42.1
Black	0.7	0.7
BMI (kg/m^2)	29.0 (4.9)	29.0 (4.8)
BMI category (%)		
<25 kg/m^2	22.2	22.5
25 to <30 kg/m^2	40.1	40.3
≥30 kg/m^2	37.6	37.2
HbA1c (%)	8.1 (0.8)	8.1 (0.9)
Presence of MetS (%)[a]	63.3	62.3
Duration of T2DM (%)		
≤1 year	12.2	14.3
1–5 years	30.0	31.2
>5 years	57.8	54.5
HOMA-IR, mean (SD) (mU/L·mmol/L)[b]	4.7 (5.7)	4.4 (4.0)
HOMA-IR (%)[b]		
≤4.0 mU/L·mmol/L	59.8	59.2
>4.0 to ≤5.5 mU/L·mmol/L	15.3	15.4
>5.5 to ≤8.5 mU/L·mmol/L	13.1	14.6
>8.5 mU/L·mmol/L	11.8	10.8
Fasting C-peptide (nmol/L)[c]	0.948 (0.481)	0.994 (0.529)
Previous OAD (%)		
None	11.5	15.5
1	30.7	31.8
≥2	57.9	52.7

BMI: body mass index; FAS: full analysis set; HbA1c: glycated hemoglobin; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; MetS: metabolic syndrome; OAD: oral antidiabetes drug; T2DM: type 2 diabetes mellitus.
Data are mean (SD) or % of patients.
[a] According to the International Diabetes Federation definition.
[b] Values are based on patients from the FAS with nonmissing HOMA-IR values. Values were missing for 261 and 93 patients in the linagliptin and placebo groups, respectively.
[c] Linagliptin n = 263, placebo = 106.

Efficacy

In the pooled analysis of efficacy, linagliptin showed significant ($p \leq 0.0013$) mean placebo-adjusted reductions in HbA1c levels across all subgroups studied (Fig. 1). Mean (±SE) placebo-corrected reductions from baseline in HbA1c ranged from −0.42% (±0.11) to −0.79% (±0.08) across all subgroups. The effect of linagliptin was similar

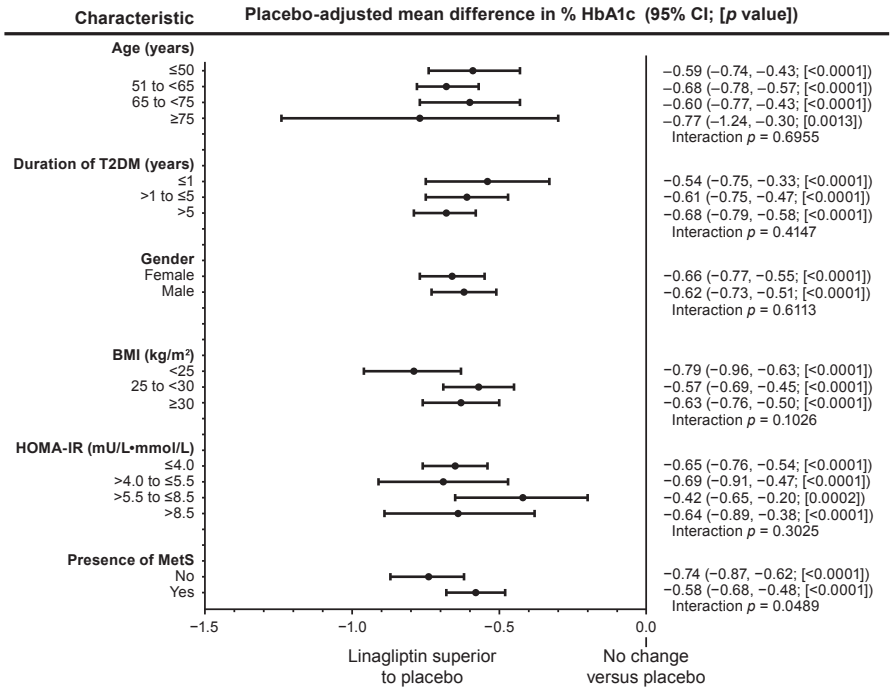

Figure 1 Placebo-corrected adjusted mean HbA1c (%) reduction from baseline after 24 weeks by subgroup (full analysis set [last observation carried forward]). BMI: body mass index; CI: confidence interval; HbA1c: glycated hemoglobin; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; MetS: metabolic syndrome; T2DM: type 2 diabetes mellitus.

across the subgroups defined by age, gender, duration of T2DM, BMI, and HOMA-IR (treatment interaction, $p > 0.1$).

Within the BMI subgroup, the treatment difference measured by mean change in HbA1c favored linagliptin in all subcategories; however, the magnitude of effect was greatest, though not statistically significant, for patients with BMI <25 kg/m^2 (treatment interaction, $p = 0.1026$). Similarly, when data were stratified based on presence or absence of MetS, linagliptin was superior to placebo in reducing mean HbA1c in both strata; however, the effect of linagliptin was greater in patients without MetS (treatment interaction, $p = 0.0489$). These subgroups included a higher percentage of Asian patients than those of other races; in patients with BMI <25 kg/m^2, 80% were Asian (Supplementary Table S4) and in patients without MetS, 53% were Asian (Supplementary Table S6).

In addition, more patients with baseline HbA1c >7% treated with linagliptin (30.2% [$n/N = 450/1491$]) achieved an HbA1c ≤7% versus those treated with placebo (11.5% [$n/N = 62/538$]; OR 3.82; 95% CI 2.82 to 5.17; $p < 0.0001$).

Clinical predictors of HbA1c reduction after 24 weeks

Selected baseline variables (age, BMI, gender, duration of T2DM, continuous FPG, continuous fasting plasma insulin, MetS) were modeled in an ANCOVA along with the forced-in (i.e. core) variables known to affect treatment response (treatment, study, washout, continuous baseline HbA1c) using the statistical approach outlined earlier to assess the potential predictive determinants of change from baseline in HbA1c after 24 weeks. After applying this method, 2 clinical parameters were kept in the final model; baseline FPG and race (in addition to the core variables).

Safety

Table 2 summarizes AE data across the subgroups. The incidence of overall AEs, AEs leading to discontinuation, or serious AEs was similar in patients who received linagliptin versus placebo when analyzed according to BMI, T2DM duration, HOMA-IR, MetS, gender, and age (except ≥75 years). Among those aged ≥75 years, the overall incidence of AEs was numerically higher with placebo than with linagliptin (93% [$n/N = 14/15$] vs 70% [$n/N = 42/60$]); however, this subgroup was small. The incidence of serious AEs ranged from 2.2 to 4.3% with linagliptin versus 2.2 to 6.7% for placebo for patients across all categories in all subgroups.

The overall incidence of investigator-defined hypoglycemia AEs was 11.6% for linagliptin versus 7.9% for placebo. However, the incidence was <1% in linagliptin-treated patients in the monotherapy (NCT00621140) and add-on to metformin (NCT00601250) studies, whereas an increased frequency of hypoglycemia with linagliptin only occurred in those with a background of sulfonylurea (NCT00602472; 23.7%, linagliptin vs 16.0%, placebo). The incidence of confirmed hypoglycemia AEs across subgroup categories ranged from 0.5 to 26.7% for linagliptin versus rates of 0 to 20% for placebo. In the overall pooled analysis, incidence of confirmed hypoglycemia AEs (investigator-defined hypoglycemia AEs confirmed with plasma

Table 2 Adverse events in patients by selected baseline subgroups (TS).

Characteristic (n = linagliptin/placebo)	Any AE (%)		AEs leading to discontinuation (%)		Serious AEs (%)	
	Linagliptin	Placebo	Linagliptin	Placebo	Linagliptin	Placebo
Age						
≤50 years (n = 398/164)	55.0	54.3	1.5	1.8	2.5	3.7
51 to <65 years (n = 845/304)	58.3	58.2	1.9	1.6	3.1	2.6
65 to <75 years (n = 348/124)	64.1	58.9	2.9	3.2	4.3	4.8
≥75 years (n = 60/15)	70.0	93.3	5.0	0	3.3	6.7
Time since diagnosis						
≤1 years (n = 203/89)	48.3	51.7	2.5	2.2	3.0	3.4
1–5 years (n = 495/188)	56.4	58.5	2.4	1.6	2.8	3.7
>5 years (n = 953/330)	65.3	62.7	2.3	2.7	3.5	4.2
Gender (%)						
Male (n = 813/307)	56.0	59.6	1.7	2.0	3.0	3.3
Female (n = 838/300)	62.3	56.7	2.5	2.0	3.5	3.7
BMI						
<25 kg/m^2 (n = 366/136)	58.2	64.7	1.9	4.4	4.1	5.1
25 to <30 kg/m^2 (n = 662/248)	58.0	54.8	2.6	1.2	3.0	3.6
≥30 kg/m^2 (n = 623/223)	61.0	57.8	1.8	1.3	2.9	2.2
HOMA-IR (mU/L·mmol/L)[a]						
≤4.0 (n = 828/304)	60.5	61.5	1.9	1.6	3.9	3.9
>4.0 to ≤5.5 (n = 214/79)	61.2	62.0	4.7	1.3	2.3	3.8
>5.5 to ≤8.5 (n = 181/74)	61.9	56.8	1.7	1.4	2.2	5.4
>8.5 (n = 165/55)	60.0	58.2	1.8	5.5	3.0	5.5
Presence of MetS						
No (n = 603/230)	56.6	59.6	2.7	3.9	4.0	3.0
Yes (n = 1047/377)	62.8	59.9	2.2	1.3	2.8	4.5

AE: adverse event; BMI: body mass index; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; MetS: metabolic syndrome; TS: treated set.

[a] Does not include AEs for patients missing HOMA-IR.

glucose ≤ 70 mg/dL or where assistance was required) was 9.6% for linagliptin versus 6.4% for placebo. Very few events occurred among patients with T2DM duration of ≤1 year (Table 3).

Discussion

The demographics of the future population of patients with T2DM will be characterized by a shift toward a higher prevalence of obesity and associated risk constellations alongside longer disease duration. As a result, patient heterogeneity is expected to further increase, with higher proportions of patients presenting with dyslipidemia, hypertension, insulin resistance, declining β-cell function, and overall diabetes-related complications. All of these factors may influence individualized treatment choices relating to achievement of glycemic targets [1].

The aim of this post-hoc analysis of three phase 3 trials from the linagliptin program was to explore whether treatment response and overall safety of the DPP-4 inhibitor linagliptin may vary based on clinically relevant patient characteristics, such as age, disease duration, obesity, insulin resistance, and prevalence of MetS. Linagliptin therapy led to significant improvements of hyperglycemia in all predefined subgroups and was well tolerated. Overall, the mean placebo-corrected HbA1c reductions with linagliptin reported in this analysis (−0.42 to −0.79%) were generally consistent with the placebo-corrected reductions reported in the individual study populations in primary phase 3 studies, which were mainly composed of patients on stable glucose-lowering background treatment (−0.62 to −0.69%) [9–11].

Improvements in HbA1c from baseline at week 24 favored linagliptin in all subgroups studied; however, heterogeneous treatment response was observed in the MetS category. Despite numerically small differences among subgroups, linagliptin reduced HbA1c to a greater extent in patients without versus with MetS, and showed a trend for a greater reduction in patients with normal body weight compared with those who were overweight or obese. Although our analyses cannot provide evidence for any underlying causality between the observed different treatment responses in those subgroups, one likely explanation may be the well-known close relationship between features of peripheral tissue and liver insulin resistance with other clinical parameters, such as presence of MetS or increased BMI. The DPP-4 inhibitors predominantly increase glucose-dependent insulin secretion from pancreatic β-cells and this mode of action may lead to more pronounced treatment responses in conditions of preserved peripheral tissue insulin sensitivity. Baseline characteristics deemed significant in the predictive analysis of HbA1c reduction after 24 weeks were FPG and race.

Differences in BMI across ethnic groups have been shown to mediate the efficacy of DPP-4 inhibitors according to some studies [15–17]. For example, among Korean T2DM subjects, those with low BMI were more likely to respond to sitagliptin add-on therapy [16]. A

Table 3 Overall incidence of confirmed[a] hypoglycemia adverse events by selected baseline subgroups (TS).

Characteristic[a] (n = linagliptin/placebo)	Linagliptin (%)	Placebo (%)
Age		
≤50 years (n = 398/164)	7.0	3.7
51 to <65 years (n = 845/304)	9.1	6.6
65 to <75 years (n = 348/124)	10.9	8.1
≥75 (n = 60/15)	26.7	20.0
Time since diagnosis		
≤1 year (n = 203/89)	0.5	0
>1 to ≤5 years (n = 495/188)	6.9	5.3
>5 years (n = 953/330)	13.0	8.8
Gender		
Male (n = 813/307)	8.4	6.2
Female (n = 838/300)	10.9	6.7
BMI		
<25 kg/m^2 (n = 366/136)	10.1	7.4
25 to <30 kg/m^2 (n = 662/248)	9.8	6.5
≥30 kg/m^2 (n = 623/223)	9.1	5.8
HOMA-IR (mU/L·mmol/L)[b]		
≤4.0 (n = 828/304)	12.2	8.6
>4.0 to ≤5.5 (n = 214/79)	6.1	3.8
>5.5 to ≤8.5 (n = 181/74)	6.1	5.4
>8.5 (n = 165/55)	7.3	3.6
Presence of MetS[c]		
No (n = 603/230)	7.1	4.8
Yes (n = 1047/377)	11.1	7.4

BMI: body mass index; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; MetS: metabolic syndrome; TS: treated set.
[a] A confirmed hypoglycemia adverse event is defined as any investigator-defined hypoglycemia adverse event confirmed with a plasma glucose ≤70 mg/dL or where assistance is required.
[b] Does not include incidence of hypoglycemia for patients missing HOMA-IR.
[c] According to the International Diabetes Federation definition.

univariate meta-regression analysis of comparative monotherapy or combination therapy showed greater HbA1c-lowering efficacy of DPP-4 inhibitor therapy in Asian-dominant studies (>50% Asian participants) compared with non-Asian dominant studies [15]. However, the relationship between the percentage of Asian participants and HbA1c-lowering efficacy was no longer significant after adjusting for BMI. In a study of linagliptin monotherapy in Asian patients, the effectiveness of linagliptin versus placebo was not influenced by BMI [18]. In the current post-hoc analysis, the imbalance in Asian patients across BMI subgroups may be contributing to the differences in HbA1c reduction and contributing to the significant association between race and efficacy of linagliptin. Moreover, the interpretation of our results is limited by the nature of this post-hoc analysis of studies of short duration. The relationship between HbA1c-lowering and other factors closely related to BMI, including insulin sensitivity among different racial/ethnic groups, warrants further evaluation.

Based on our exploratory predictive analyses, we also confirmed that baseline FPG, in combination with the core model consisting of baseline HbA1c, was a significant predictor of linagliptin efficacy. Our results are supported by a recent meta-regression analysis of 98 randomized controlled trials of DPP-4 inhibitors versus placebo or any comparator drug with a follow-up duration longer than 12 weeks [19]. In their meta-analysis, baseline HbA1c and FPG were predictive of HbA1c response to individual DPP-4 inhibitors; FPG improved the predictive value of HbA1c, but alone FPG was not significant. In a separate meta-analysis, the placebo-corrected effect of DPP-4 inhibitors on HbA1c was greater in patients with a lower baseline FPG and HbA1c [20].

Our findings differ from those of other studies that have investigated the relationship between age and HbA1c response to DPP-4 inhibition. Although other studies have shown greater efficacy of DPP-4 inhibitors among older patients versus younger patients [20], age was not found to be a significant predictor of linagliptin efficacy in this pooled analysis. A wider range of placebo-adjusted mean changes in HbA1c among those aged ≥75 years was likely due to small subgroup size compared with the sample size of the other age subgroups. In a separate study of patients ≥70 years of age, linagliptin treatment for 24 weeks significantly lowered HbA1c [4].

In our analysis, the rates of serious AEs and AEs leading to discontinuation were comparable for linagliptin versus placebo across all patient subgroups. Linagliptin retained an acceptable safety profile across all different categories, which supports it as a treatment option for a broad range of patients with T2DM. The rates of hypoglycemia and other AEs in patients treated with linagliptin were generally comparable with placebo when assessed within subgroups. Therefore, these findings are consistent with the recent results of 2 studies evaluating long-term therapy with linagliptin, demonstrating favorable safety and efficacy through 2 years of treatment with linagliptin [21,22]. Linagliptin was well tolerated with no particular clinical patient parameter predicting an increased risk for developing AEs, including hypoglycemia.

In summary, this post-hoc analysis in predefined subgroups from three phase 3 studies showed that no MetS, Asian ethnicity, and baseline FPG influenced the pharmacologic response to linagliptin. Leaner individuals appeared to have relatively greater reductions in HbA1c, whereas heavier individuals and those with MetS experienced a still meaningful but numerically slightly lower response. This finding could suggest that a leaner patient who may be more insulin deficient than insulin resistant, as it is believed to be the case for most Asian patients with diabetes, has a better response to an insulin secretagogue than a patient with a higher BMI and greater insulin resistance. However, the association between BMI and efficacy may be confounded by race/ethnicity, thus conclusions about this potential effect cannot be drawn.

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critical revision of the manuscript, the decision to submit the manuscript for publication, and take responsibility for the content of the manuscript.

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Competing interests

SDP has served on advisory panels and speakers' bureaus and received research support from Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi-Aventis.

SP was an employee of Boehringer Ingelheim Ltd. UK at the time of the study, and is now an employee of Daiichi Sankyo Development, Ltd. UK.

MvE is an employee of Boehringer Ingelheim Pharma GmbH & Co. KG.

SC was an employee of Boehringer Ingelheim Pharma GmbH & Co. KG at the time of the study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.numecd.2016.06.015.

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