Original Article

EFFICACY AND SAFETY OF LINAGLIPTIN IN BLACK/AFRICAN AMERICAN PATIENTS WITH TYPE 2 DIABETES: A 6-MONTH, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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ABSTRACT

Objective: Although black/African American individuals are disproportionately affected by type 2 diabetes, there is scant clinical trial information available on antidiabetes therapies in this group. We compared linagliptin with placebo in black/African American adults who were treatment-naïve or receiving one oral antidiabetes drug.

Methods: Of 226 patients randomized to 24 weeks' linagliptin 5 mg/day or placebo, 208 had baseline and at least one on-treatment glycated hemoglobin (HbA_{1c}) measurement. Mean baseline HbA_{1c} was 8.6% in the linagliptin group (n = 98) and 8.68% in the placebo group (n = 110). The primary outcome was change in HbA_{1c} from baseline to week 24.

Results: By week 24, mean HbA_{1c} changes were –0.84% with linagliptin and –0.25% with placebo (treatment difference, –0.58%; *P*<.001), and more patients in the linagliptin group achieved HbA_{1c} <7.0% (26.8% vs. 8.3%; *P* = .001) or an HbA_{1c} reduction ≥0.5% (54.1% vs. 30.0%; *P*<.001). Mean weight loss was –1.1 kg in both groups. During the treatment period, 8 of 98 linagliptin-group patients and 17 of 110 placebo-group patients required rescue therapy (odds ratio, 0.5; *P* = .14). For postprandial glucose, values were available for few patients (11 placebo, 10 linagliptin), and thus the between-group difference was associated with wide confidence intervals (CIs) (difference, –1.97 mg/dL; 95% CI, –53.80 to 49.86; *P* = .94). In the overall study population, a similar proportion of patients in both groups had adverse events (58.5% vs. 61.7%); most events were mild or moderate and considered unrelated to study drug. Investigator-defined hypoglycemia was rare (3 linagliptin-group patients and 1 placebo-group patient), with no severe events (requiring external assistance).

Conclusion: This study confirms that linagliptin is efficacious and well tolerated in black/African American patients with type 2 diabetes. **(Endocr Pract. 2014;20: 412-420)**

Abbreviations:
AE = adverse event; **ANCOVA** = analysis of covariance; **BMI** = body mass index; **CI** = confidence interval; **DPP** = dipeptidyl peptidase; **FAS** = full analysis set; **FPG** = fasting plasma glucose; **HbA_{1c}** = glycated hemoglobin; **MI** = myocardial infarction; **MTT** = meal tolerance test; **OR** = odds ratio; **PPG** = postprandial glucose

INTRODUCTION

In the United States, black/African American individuals have a greatly increased risk of type 2 diabetes compared with whites, with a prevalence of 13.9% among non-Hispanic black adults (1). Individuals in this group are less likely to achieve glycemic control targets and are more likely to be affected by complications and comorbidities such as hypertension and renal disease (2-5). The cause of this disproportionate burden is likely multifactorial and includes socioeconomic factors, but it may also reflect differences in the pathophysiology of type 2 diabetes, with a possible increased prevalence of insulin resistance (6). Despite this increased risk, black/African Americans are underrepresented in clinical trials, with the consequence

Submitted for publication August 30, 2013
Accepted for publication November 5, 2013
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Published as a Rapid Electronic Article in Press at http://www.endocrinepractice.org on December 10, 2013. DOI:10.4158/EP13365.OR
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of a lack of high-quality clinical trial information to guide treatment decisions (7,8).

It is recognized that racial groups could have different responses to therapy, and the recent Position Statement from the American Diabetes Association/European Association for the Study of Diabetes recommended that pharmacologic agents be individualized using a patient-centered approach (9). Linagliptin is a once-daily oral antidiabetes drug of the dipeptidyl peptidase (DPP)-4 inhibitor class and has features of particular relevance for African American patients; namely, like other members of the DPP-4 inhibitor class, it does not cause weight gain, but, unlike other gliptins, linagliptin has a nonrenal route of excretion and can be used without dose adjustment, even in patients with renal impairment (10). In clinical trials to date, linagliptin demonstrated meaningful improvements in glycemia when used as monotherapy or in combination with other antidiabetes agents (11-19). However, in the four pivotal phase III trials, <1% of patients were black or African American (13-16).

How far these results can be generalized to black/African American patients is unclear. Recently, a pharmacokinetic study of linagliptin in 41 African American patients with type 2 diabetes showed no clinically meaningful differences from results in white and Asian individuals and confirmed the primarily nonrenal elimination for this population, but the study was not large enough to provide meaningful efficacy results (20). The current study was performed to elucidate the risks and benefits of glucose-lowering treatment with linagliptin 5 mg once daily in this patient population.

METHODS

This trial was registered as NCT01194830, and the detailed trial design has been published previously (21). In brief, the trial consisted of a 2-week placebo run-in, after which eligible patients were randomized to linagliptin 5 mg once daily or placebo for 24 weeks, followed by a 1-week safety follow-up. The trial was conducted in compliance with the principles laid down in the Declaration of Helsinki and in accordance with the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice. All patients provided written informed consent.

Participants and Study Procedures

The study was conducted at primary care clinics and clinical research centers in the United States. At screening, men and women aged 18 to 80 years with a body mass index (BMI) ≤45 kg/m^2 were eligible if they self-reported their race as black/African American, irrespective of ethnic group (also self-reported as Hispanic or non-Hispanic), had a diagnosis of type 2 diabetes ≥3 months previously, were treatment-naïve or receiving a maximum of one oral antidiabetes drug (stable regimen for ≥10 weeks), and had a glycated hemoglobin (HbA_{1c}) level of ≥7.5% and ≤11.0%. Key clinical exclusion criteria were type 1 diabetes or a history of myocardial infarction (MI), stroke, or transient ischemic attack within 3 months before screening; detailed exclusion criteria have been described previously (21).

After screening, all patients received diet and exercise counseling and entered a 2-week placebo run-in. Patients completing the run-in were randomized in a 1:1 ratio, according to a schedule prepared using a validated pseudo-random number generator by study staff not involved in the trial conduct. The site determined treatment assignment by allocating patients the next lowest sequentially numbered medication kit. At randomization, patients were provided with home blood glucose monitoring equipment and were required to test once daily in a fasting state, as well as at any time they experienced symptoms of hyper- or hypoglycemia. Where blood glucose level was elevated, rescue therapy was initiated according to the following protocol: in weeks 1 to 12, rescue therapy was permitted for patients with a glucose level >240 mg/dL after an overnight fast or >400 mg/dL in a randomly performed measurement; and in weeks 13 to 24, rescue therapy was permitted for patients with a glucose level >200 mg/dL after an overnight fast or >400 mg/dL in a random measurement. In each case, 2 measurements, taken on different days, were required, with one or more taken at the study site after an overnight fast. Patients receiving rescue therapy continued in the trial unless fasting plasma glucose (FPG) levels remained >240 mg/dL despite initiating rescue therapy. The choice of rescue therapy was at the investigator's discretion, excluding other DPP-4 inhibitors.

A subgroup of patients participated in a meal tolerance test (MTT) substudy, with planned enrollment of the first 2 patients from each of the first 25 study sites willing to participate in the MTT substudy (total of 50 patients). The MTT was performed at baseline (before the first administration of study medication) and at week 24 (30 minutes after administration of study drug), as previously described (21).

Endpoints and Assessments

During the double-blind treatment phase, patients returned to the study site at weeks 2, 6, 12, 18, and 24, and fasting blood samples for efficacy outcomes were drawn at all visits. A central laboratory analyzed HbA_{1c} and FPG levels using validated assays. The primary outcome was change in HbA_{1c} from baseline to week 24. Prespecified secondary endpoints were reduction in HbA_{1c} over time, achievement by 24 weeks of HbA_{1c} <7.0% or <6.5%, or HbA_{1c} change ≥0.5%, change from baseline in FPG after 24 weeks, and change in 2-hour postprandial glucose (PPG) in the MTT subgroup. Exploratory outcomes were rescue therapy use, body weight, and waist circumference. Safety was measured using the incidence, intensity, and

withdrawals due to adverse events (AEs; coded using the Medical Dictionary for Regulatory Activities, version 14.1), physical examination and vital signs, 12-lead electrocardiogram, and clinical laboratory measures. Hypoglycemic episodes were classified as previously described (21), with episodes requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions defined as severe. An independent committee prospectively reviewed AEs suspected of being stroke, cardiac ischemia, and all-cause mortality to determine whether they met prespecified criteria for cardiovascular endpoints (nonfatal MI, other myocardial ischemia, nonfatal stroke, transient ischemic attack, or cardiovascular death, including fatal stroke).

Statistical Analysis

Based on an expected standard deviation of 1.1% for HbA_{1c} change from baseline at 24 weeks (15), a sample size of 103 patients per group was deemed sufficient to detect a 0.5% difference between groups with 90% power. Allowing for an estimated 5% of patients randomized but not treated or without an on-treatment HbA_{1c} value, the required sample size was 109 for both groups.

Safety evaluations were done on the treated set (all patients receiving at least one study drug dose). The primary analysis was done on the full analysis set (FAS), which included all randomized patients treated with at least one study drug dose, with a baseline HbA_{1c} measurement, and at least one on-treatment HbA_{1c} measurement. Missing values at the last visit were replaced by the last on-treatment value; missing values with subsequent present on-treatment values were imputed by interpolation (baseline values were not carried forward but could be used in interpolation). For patients receiving rescue therapy, the last HbA_{1c} value before rescue treatment was used for analysis. Sensitivity analyses were done using the per-protocol set (FAS patients treated according to essential protocol criteria) and the FAS-completers set (FAS patients completing 24 weeks of treatment and with an HbA_{1c} measurement at week 24).

The primary analysis was tested using analysis of covariance (ANCOVA), adjusting for HbA_{1c} at baseline as a linear covariate and the number of concomitant antidiabetes medications and treatment groups as fixed classification effects. The same ANCOVA model was used for the change in FPG, using continuous baseline FPG as well as continuous baseline HbA_{1c} values. The proportion of patients achieving HbA_{1c} goals was compared using logistic regression, with missing data due to discontinuation considered treatment failure. For the MTT substudy, patients with valid FPG and 2-hour PPG values at baseline and week 24 were included in the analysis, but missing values were not imputed nor were measurements after use of rescue medication included. Change in 2-hour PPG was analyzed with an ANCOVA model, with treatment, baseline HbA_{1c}, number of concomitant antidiabetes medications, and baseline 2-hour PPG as covariates. Other efficacy endpoints were analyzed using descriptive statistics. SAS software version 9.2 was used for all analyses.

RESULTS

The trial was conducted between September 7, 2010 and October 3, 2011. Of 592 patients screened at 93 centers, 226 were randomized and received at least one dose of study drug (Fig. 1), and 171 patients completed 24 weeks of treatment. Mean exposure for randomized patients was 140 days for placebo and 143 days for linagliptin.

Baseline characteristics were well balanced for the 2 groups (Table 1). Use of concomitant therapies at screening was also similar for the groups, with most patients using antihypertensive drugs (65.8% placebo; 64.2% linagliptin). Hypertension was the most common concomitant diagnosis related to diabetes (72.1%), whereas other concomitant diagnoses were less common, with 5.8% of patients having a diagnosis of coronary artery disease.

In the primary analysis, treatment with linagliptin was superior to placebo for adjusted mean change in HbA_{1c} from baseline to week 24 (Table 2), with an adjusted mean difference of –0.58% (95% CI, –0.91 to –0.26%; $P<.001$). Results were confirmed by 2 sensitivity analyses. In the per-protocol set, the difference between groups in adjusted mean change in HbA_{1c} from baseline at 24 weeks was –0.54% (95% CI, –0.90 to –0.18%; $P = .003$); in the FAS completers, the difference was –0.47% (95% CI, –0.82 to –0.12%; $P = .008$). Adjusted mean HbA_{1c} values over time for the 2 treatment groups showed statistically significant differences at all timepoints (Fig. 2).

When patients were stratified by baseline HbA_{1c} level, significant reductions were seen across categories of baseline HbA_{1c}, with larger reductions in patients with higher baseline HbA_{1c} (Fig. 2). When the patients were stratified by age group or BMI, there were no significant differences among subgroup categories in change in HbA_{1c} from baseline, although the number of patients in the older age groups may have been too low to detect a difference (Fig. 2). The number of oral antidiabetes drugs at baseline had no effect on the change in HbA_{1c} from baseline (data not shown).

In the analysis of the proportion of patients achieving specified HbA_{1c} goals, patients were excluded if their baseline HbA_{1c} value was already at goal. At baseline, no patients had an HbA_{1c} value below 6.5%, whereas 2 patients (1 in each group) had an HbA_{1c} level below 7.0% and were thus not included in the analysis set. Among patients with baseline $HbA_{1c} \geq 7.0\%$, 9 of 108 patients (8.3%) in the placebo group and 26 of 97 patients (26.8%) in the linagliptin group achieved $HbA_{1c} < 7.0\%$ after 24 weeks (odds ratio [OR], 4.1; 95% CI, 1.8 to 9.4; $P = .001$). Among patients with baseline $HbA_{1c} \geq 6.5\%$, 2 of 109 patients (1.8%) in the

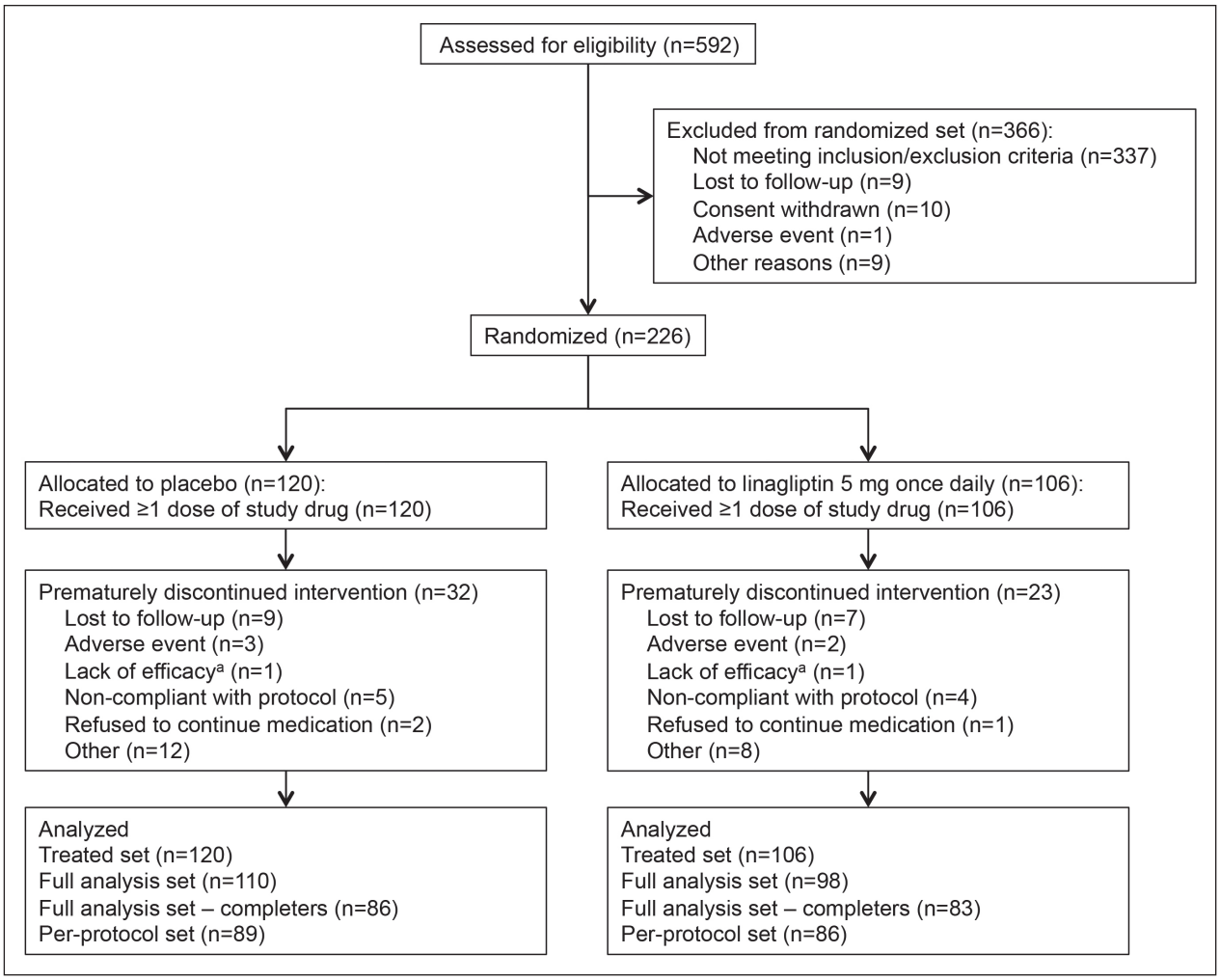

Fig. 1. Study overview. [a]Includes patients who discontinued due to hyperglycemia. The treated set included randomized patients who received at least one dose of study drug. The full analysis set included randomized patients who received at least one dose of treatment, had a baseline glycated hemoglobin (HbA_{1c}) measurement, and had at least one on-treatment HbA_{1c} measurement; patients with no on-treatment values before rescue medication use were excluded.

placebo group and 9 of 98 patients (9.2%) in the linagliptin group achieved HbA_{1c} <6.5% by week 24 (OR, 5.4; 95% CI, 1.1 to 26.3; $P = .04$). In a post hoc analysis of the recommended goal of the American Association of Clinical Endocrinologists/American College of Endocrinology, 3 of 109 patients (2.8%) in the placebo group and 15 of 98 patients (15.3%) in the linagliptin group achieved HbA_{1c} ≤6.5% (OR, 5.9; 95% CI, 1.6 to 21.3; $P = .007$). An HbA_{1c} reduction of ≥0.5% was achieved by more patients in the linagliptin group (53 of 98 [54.1%]) compared with the placebo group (33 of 110 [30.0%]) (OR, 3.0; 95% CI, 1.7 to 5.3; $P<.001$).

After 24 weeks, the mean change from baseline in FPG was larger with linagliptin than placebo but did not meet statistical significance (Table 2). In the MTT substudy, of 46 patients who participated, 21 (11 placebo, 10 linagliptin) had valid FPG and PPG values for analysis. At baseline, the mean (± standard error [SE]) PPG was 222.73 ± 20.95 mg/dL in the placebo group versus 277.40 ± 26.29 mg/dL in the linagliptin group. At week 24, adjusted mean changes were –36.77 ± 23.76 mg/dL versus –38.74 ± 22.77 mg/dL in the respective groups, giving a between-group difference of –1.97 mg/dL (95% CI, –53.80 to 49.86; $P = .94$).

Rescue therapy was required by 17 of 110 patients (15.5%) in the placebo group and 8 of 98 patients (8.2%) in the linagliptin group (OR, 0.5; 95% CI, 0.2 to 1.3; $P = .14$). There were no apparent differences between the 2 groups with respect to change from baseline in body weight (mean ± SD, placebo: –1.1 ± 7.6 kg; linagliptin: –1.1 ± 3.8 kg) or waist circumference (placebo: –2.4 ± 10.7 cm; linagliptin: –1.1 ± 20.8 cm).

The overall safety profile of linagliptin was similar to that of placebo (Table 3), and most AEs were of mild or

Table 1
Patient Characteristics at Baseline

	Placebo	Linagliptin 5 mg
Treated set, n (%)	120 (100)	106 (100)
Age, years, mean (SD)	54.1 (9.9)	53.7 (10.1)
Gender, men, n (%)	61 (50.8)	60 (56.6)
Weight, kg, mean (SD)	99.0 (20.2)	95.8 (21.0)
BMI, kg/m^2, mean (SD)	33.4 (5.4)	32.0 (6.1)
Waist circumference, cm, mean (SD)	111.4 (16.7)	103.5 (20.2)
HbA_{1c}, %, mean (SD)[a]	8.78 (1.18)	8.68 (1.05)
<8.0%, n (%)	30 (27.3)	29 (29.6)
8.0% to <9.0%, n (%)	36 (32.7)	36 (36.7)
≥9.0%, n (%)	44 (40.0)	33 (33.7)
FPG, mg/dL, mean (SD)[b]	190.9 (56.4)	177.8 (60.7)
Type 2 diabetes duration, n (%)[a]		
Up to 1 year	5 (4.5)	9 (9.2)
>1 to 5 years	38 (34.5)	37 (37.8)
>5 to ≤10 years	34 (30.9)	23 (23.5)
>10 years	33 (30.0)	29 (29.6)
Antidiabetic medication at screening, n (%)[a]		
None	11 (10.0)	14 (15.3)
Metformin	78 (78.8)	64 (77.1)
Sulfonylurea	19 (19.2)	18 (21.7)
Renal function, n (%)[c]		
Normal renal function	48 (40.0)	46 (43.4)
Mild renal impairment	52 (43.3)	46 (43.4)
Moderate renal impairment	9 (7.5)	10 (9.4)

Abbreviations: BMI = body mass index; FPG = fasting plasma glucose; HbA_{1c} = glycated hemoglobin.
[a] Full analysis set, placebo (n = 110), linagliptin (n = 98).
[b] Full analysis set, placebo (n = 107), linagliptin (n = 97).
[c] Renal function based on estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease equation: normal renal function, eGFR ≥90 mL/min/1.73 m^2; mild renal impairment (RI), eGFR 60 to <90 mL/min/1.73 m^2; moderate RI, eGFR 30 to <60 mL/min/1.73 m^2; severe RI eGFR <30 mL/min/1.73 m^2; no patients in the study had severe or end-stage RI; renal function data were not available for 11 patients in the placebo group (9.2%) and 4 patients in the linagliptin group (3.8%).

moderate intensity. The rate of discontinuation due to AEs was low, and no patients discontinued due to drug-related AEs. During the treatment period, there were no deaths, few serious adverse events (SAEs), and no SAEs considered to be drug related. The overall number of AEs considered drug related by the investigator was also low. As part of the wider clinical trial program for linagliptin, all suspected major vascular events were reviewed and adjudicated by a blinded independent expert committee. In this study, 1 patient, in the linagliptin group, had an adjudicated major vascular event (a nonfatal MI, not considered drug related). There were no clinically relevant changes in blood pressure, heart rate, renal function, lipid measurements, or other standard laboratory parameters.

The overall incidence of hypoglycemic events was low: 1 patient in the placebo group and 3 patients in the linagliptin group experienced an investigator-defined hypoglycemic AE. All 4 patients were on background therapy (the placebo-group patient and 2 linagliptin-group patients were receiving metformin; 1 linagliptin-group patient was receiving a sulfonylurea). All events were considered mild, only 1 episode (in the linagliptin group) was symptomatic, and no patient had a severe hypoglycemic episode.

Table 2
Change from Baseline to Week 24 in HbA_{1c} and FPG Levels

	Placebo	Linagliptin 5 mg	Difference (linagliptin – placebo)
HbA_{1c}			
n (FAS-LOCF)	105	93	
Baseline mean, % (SE)	8.68 (0.11)	8.60 (0.10)	
Change from baseline			
Mean, % (SE)	–0.28 (0.12)	–0.82 (0.13)	
Adjusted[a] mean, % (SE)	–0.25 (0.16)	–0.84 (0.15)	–0.58 (0.16); 95% CI, –0.91 to –0.26; *P*<.001
FPG			
n (FAS-LOCF)	106	95	
Baseline mean, mg/dL (SE)	191.3 (5.5)	178.4 (6.3)	
Change from baseline			
Mean (SE)	–12.2 (5.1)	–17.3 (6.8)	
Adjusted[b] mean (SE)	–11.0 (6.6)	–22.9 (6.4)	–12.0 (7.2); 95% CI, –26.1 to 2.2; *P* = .097

Abbreviations: CI = confidence interval; FAS-LOCF = full analysis set-last observation carried forward; FPG = fasting plasma glucose; HbA_{1c} = glycated hemoglobin; SE = standard error.
[a] Adjusted mean: model includes treatment, number of oral antidiabetes drugs, and baseline HbA_{1c}.
[b] Adjusted mean: model includes treatment, number of other oral antidiabetes drugs, baseline HbA_{1c}, and baseline FPG.

DISCUSSION

Despite the need for improved treatment for black/African American patients with type 2 diabetes, this group is frequently underrepresented in clinical trials of antidiabetes therapies (22,23). This study is the first randomized, controlled trial of linagliptin focused on this patient group, and, to our knowledge, this is also the only study for a DPP-4 inhibitor conducted exclusively in black/African American patients.

The reasons for the high risk of type 2 diabetes in black people in the United States are not fully understood, although there is good evidence that socioeconomic factors and genetic profiles are involved (24-27). Similarly, the reasons for the higher burden of complications compared with whites are also not defined. On average, African Americans diagnosed with type 2 diabetes have higher HbA_{1c} levels than non-Hispanic whites, yet reported differences account for only a proportion of the increased risk of complications (28), and there is evidence that African Americans are at risk of complications at lower HbA_{1c} levels (29). Indeed, the validity of using HbA_{1c} levels for comparisons between racial groups has been questioned, with evidence that African Americans have higher rates of glycation compared with whites (30). At present, this remains a controversial area, and evidence regarding racial differences in change in HbA_{1c} (as opposed to cut-points) is unclear. Therefore, while the American Diabetes Association has recommended further research, recommendations to use HbA_{1c} levels as the basis for management of hyperglycemia, for all populations, are currently unchanged (31). Hence, focus on achieving HbA_{1c} targets is central to the management of diabetes in black/African American patients, as in all racial groups (9,31,32). In our study of black/African American patients with type 2 diabetes, linagliptin 5 mg/day gave clinically meaningful reductions in HbA_{1c} levels. Significant reductions were seen at the first measurement, after 6 weeks, and were maintained throughout the trial, consistent with results observed in previous clinical trials (33).

Linagliptin acts to reduce hyperglycemia by raising levels of endogenous insulin in response to the presence of glucose in the gut. Consequently, significant reductions in PPG are expected, and these predicted reductions have been observed in previous studies of PPG with linagliptin (15,16). It is therefore unfortunate that in the PPG substudy of the current trial, very few patients had valid measurements for analysis (11 in the placebo group and 10 in the linagliptin group, of a planned sample size of 50 patients), making interpretation difficult. The confidence intervals around the mean difference between groups were very wide, and although a larger reduction in PPG was seen in the linagliptin group, the difference did not meet statistical significance. However, it is impossible to draw any

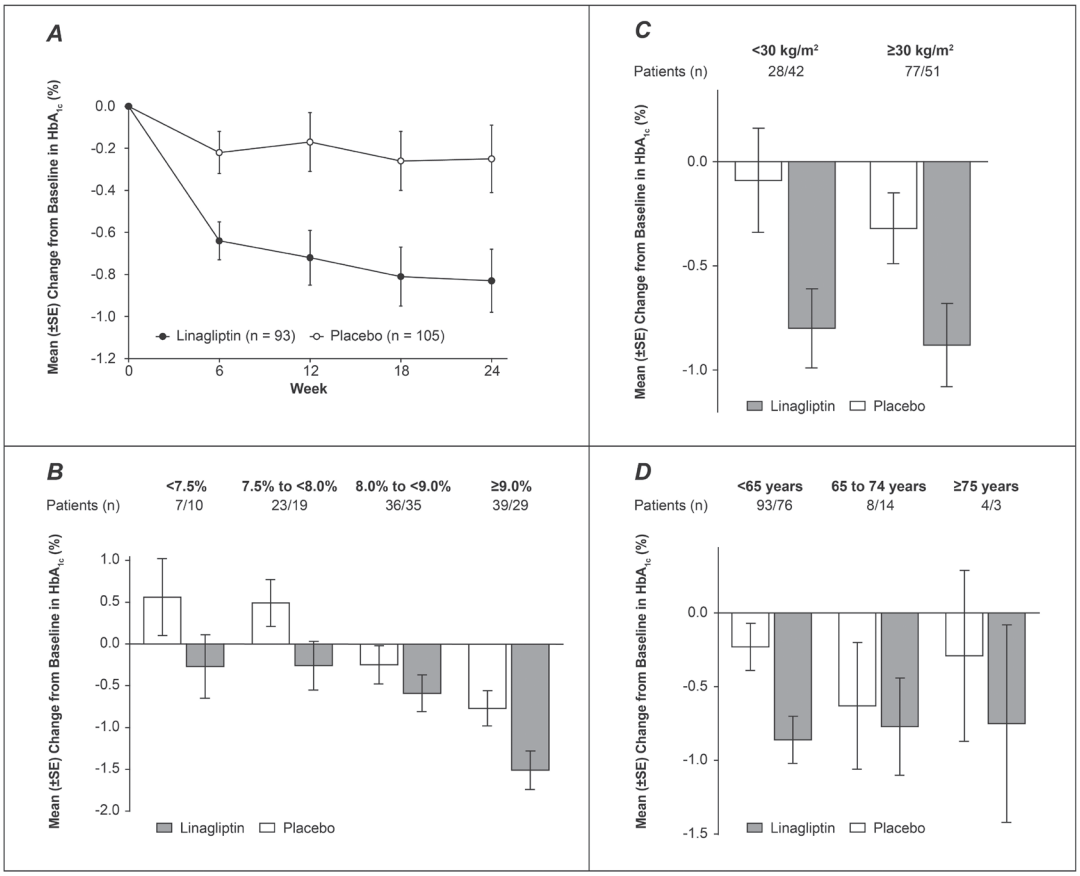

Fig. 2. Changes in mean HbA_{1c} levels from baseline through 24 weeks and for specified subgroups. *A*. Based on individual ANCOVA–FAS (LOCF), model includes treatment, baseline HbA_{1c}, and number of other oral antidiabetes drugs. Adjusted mean difference (linagliptin minus placebo) was significant at all timepoints measured: week 6, –0.42; 95% CI, –0.62 to –0.22; *P*<.0001; week 12, –0.55; 95% CI, –0.84 to –0.26; *P*<.001; week 18, –0.55; 95% CI, –0.85 to –0.26; *P*<.001; week 24, –0.58; 95% CI, –0.91 to –0.26; *P*<.001. *B*, *C*, *D*. All FAS (LOCF). *ANCOVA* = analysis of covariance; *BMI* = body mass index; *CI* = confidence interval; *HbA_{1c}* = glycated hemoglobin; *LOCF* = last observation carried forward; *SE* = standard error.

conclusion regarding potential differences in the mechanism of action of linagliptin in this patient group, and it seems more likely that the substudy was simply underpowered to detect a difference between groups.

In the current trial, linagliptin was also well tolerated, and the safety profile was consistent with that observed in previous studies, with no new safety signals seen in this population. In line with previous findings, linagliptin treatment was associated with a low rate of hypoglycemic events, and there were no severe hypoglycemic events requiring assistance (20).

In addition to controlling hyperglycemia, weight and obesity are recognized as particularly important in the management of black/African American patients with type 2 diabetes (34). It is therefore noteworthy that linagliptin was weight-neutral in this trial, with no change in waist circumference, confirming findings in other ethnic groups. About two-thirds of patients in the trial were classified as obese, and reductions in HbA_{1c} with linagliptin treatment were similar for obese and nonobese subgroups. Of further potential relevance for black/African American patients, who have higher rates of chronic kidney disease and end-stage renal disease, is the fact that linagliptin has a predominantly nonrenal route of excretion and can be used without dose adjustment in patients with any level of renal impairment (35).

CONCLUSION

In conclusion, among black/African American patients with type 2 diabetes, linagliptin 5 mg once daily provides clinically meaningful improvements in glycemic control, consistent with results seen in other populations. Furthermore, linagliptin has a good safety profile, with a low rate of hypoglycemic events and no change in weight. Linagliptin therefore appears to be an effective treatment option for black/African American patients with type 2 diabetes.

Table 3
Summary of Adverse Events[a]

	Placebo	Linagliptin 5 mg
Treated set, n (%)	120 (100)	106 (100)
Any AE	74 (61.7)	62 (58.5)
Drug-related AEs	11 (9.2)	4 (3.8)
SAEs[b]	2 (1.7)	1 (0.9)
Of which considered drug-related	0	0
AEs leading to discontinuation[c]	3 (2.5)	2 (1.9)
Deaths	0	0
Most common AE (>5% in any treatment group), by preferred term		
Nasopharyngitis	6 (5.0)	4 (3.8)
Urinary tract infection	4 (3.3)	7 (6.6)
Hyperglycemia	11 (9.2)	3 (2.8)
Prespecified AEs of special interest[d]		
Renal AEs	0 (0.0)	1 (0.9)
Hypersensitivity reactions	3 (2.5)	2 (1.9)
Hepatic AEs	2 (1.7)	2 (1.9)
Pancreatitis	0	0

Abbreviations: AE = adverse event; SAE = serious adverse event.
[a] Patients with at least one adverse event.
[b] SAEs in the placebo group were food allergy, pneumonia, and angioedema in 1 patient and musculoskeletal chest pain in 1 patient. The 1 patient with a SAE in the linagliptin group had nonfatal myocardial infarction and bronchitis. During the posttreatment period, a SAE was reported for 1 additional patient in the linagliptin group (large intestine perforation and septic shock).
[c] AEs that led to premature discontinuation of study medication in the placebo group were reported as diabetes mellitus in 1 patient, type 2 diabetes mellitus in 1 patient, and urticaria in 1 patient; in the linagliptin group, they were nausea and vomiting in 1 patient and urticaria in 1 patient.
[d] Two of the events of special interest were considered drug-related by the investigator; one hypersensitivity reaction (urticaria) in the placebo group and one hepatic AE (hyperbilirubinemia), also in the placebo group.

ACKNOWLEDGMENT

Results of this study were presented in brief at the American Association of Clinical Endocrinologists (AACE) 21st Annual Meeting and Clinical Congress in Philadelphia, Pennsylvania, May 23-27, 2012.

This study was funded by Boehringer Ingelheim Pharmaceuticals Inc. (BIPI). 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. All authors approved the final version of the manuscript. The authors received no compensation related to the development of the manuscript.

We thank Stephen Koval and Zhenchao Guo for statistical analysis support. Writing and editorial support was provided by Geraldine Thompson of Envision Scientific Solutions, which was contracted and compensated by BIPI for these services.

DISCLOSURE

Dr. James Thrasher has received research grant funding and speaker bureau support from BIPI. Kristen Daniels and Dr. Jacqueline Whetteckey are employed by BIPI. Dr. Sanjay Patel is employed by Boehringer Ingelheim, Ltd. Dr. Hans-Juergen Woerle is employed by Boehringer Ingelheim GmbH & Co. KG.

REFERENCES

1. **Cowie CC, Rust KF, Ford ES, et al.** Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006. *Diabetes Care*. 2009;32:287-294.

2. **Lopes AA.** End-stage renal disease due to diabetes in racial/ethnic minorities and disadvantaged populations. *Ethn Dis*. 2009;19(1 suppl 1):47-51.
3. **Campbell JA, Walker RJ, Smalls BL, Egede LE.** Glucose control in diabetes: the impact of racial differences on monitoring and outcomes. *Endocrine*. 2012;42:471-482.
4. **Goldberg JB, Goodney PP, Cronenwett JL, Baker F.** The effect of risk and race on lower extremity amputations among Medicare diabetic patients. *J Vasc Surg*. 2012;56: 1663-1668.
5. **Kountz D.** Special considerations of care and risk management for African American patients with type 2 diabetes mellitus. *J Natl Med Assoc*. 2012;104:265-273.
6. **Dagogo-Jack S.** Ethnic disparities in type 2 diabetes: pathophysiology and implications for prevention and management. *J Natl Med Assoc*. 2003;95:774,779-789.
7. **Mount DL, Davis C, Kennedy B, et al.** Factors influencing enrollment of African Americans in the Look AHEAD trial. *Clin Trials*. 2012;9:80-89.
8. **Corbie-Smith G, St George DM, Moody-Ayers S, Ransohoff DF.** Adequacy of reporting race/ethnicity in clinical trials in areas of health disparities. *J Clin Epidemiol* 2003;56:416-420.
9. **Inzucchi SE, Bergenstal RM, Buse JB, et al.** Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35: 1364-1379.
10. **Graefe-Mody U, Friedrich C, Port A, et al.** Effect of renal impairment on the pharmacokinetics of the dipeptidyl peptidase-4 inhibitor linagliptin. *Diabetes Obes Metab*. 2011;13:939-946.
11. **Gallwitz B, Rosenstock J, Rauch T, et al.** 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. *Lancet*. 2012;380:475-483.
12. **Haak T, Meinicke T, Jones R, Weber S, von Eynatten M, Woerle HJ.** Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab*. 2012;14:565-574.
13. **Owens DR, Swallow R, Dugi KA, Woerle HJ.** Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study. *Diabet Med*. 2011;28:1352-1361.
14. **Gomis R, Espadero RM, Jones R, Woerle HJ, Dugi KA.** Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab*. 2011;13: 653-661.
15. **Del Prato S, Barnett AH, Huisman H, et al.** Effect of linagliptin monotherapy on glycaemic control and markers of β-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. *Diabetes Obes Metab*. 2011;13:258-267.
16. **Taskinen MR, Rosenstock J, Tamminen I, et al.** Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab*. 2011;13:65-74.
17. **Barnett AH, Huisman H, Jones R, von Eynatten M, Patel S, Woerle HJ.** Linagliptin for patients aged 70 years or older with type 2 diabetes inadequately controlled with common antidiabetes treatments: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2013;382: 1413-1423.
18. **Yki-Järvinen H, Rosenstock J, Durán-Garcia S, et al.** Effects of adding linagliptin to basal insulin regimen for inadequately controlled type 2 diabetes: a ≥52-week randomized, double-blind study. *Diabetes Care*. 2013;36: 3875-3881.
19. **Groop PH, Cooper ME, Perkovic V, Emser A, Woerle HJ, von Eynatten M.** Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. *Diabetes Care*. 2013;36:3460-3468.
20. **Friedrich C, Glund S, Lionetti D, et al.** Pharmacokinetic and pharmacodynamic evaluation of linagliptin in African American patients with type 2 diabetes mellitus. *Br J Clin Pharmacol*. 2013;76:445-454.
21. **Thrasher J, Daniels K, Patel S, Whetteckey J.** Black/African American patients with type 2 diabetes mellitus: study design and baseline patient characteristics from a randomized clinical trial of linagliptin. *Expert Opin Pharmacother*. 2012;13:2443-2452.
22. **Ard JD, Durant RW, Edwards LC, Svetkey LP.** Perceptions of African-American culture and implications for clinical trial design. *Ethn Dis*. 2005;15:292-299.
23. **Powell JH, Fleming Y, Walker-McGill CL, Lenoir M.** The project IMPACT experience to date: increasing minority participation and awareness of clinical trials. *J Natl Med Assoc*. 2008;100:178-187.
24. **Palmer ND, McDonough CW, Hicks PJ, et al.** A genome-wide association search for type 2 diabetes genes in African Americans. *PLoS One*. 2012;7:e29202.
25. **Maty SC, James SA, Kaplan GA.** Life-course socioeconomic position and incidence of diabetes mellitus among blacks and whites: the Alameda County Study, 1965-1999. *Am J Public Health*. 2010;100:137-145.
26. **Signorello LB, Schlundt DG, Cohen SS, et al.** Comparing diabetes prevalence between African Americans and Whites of similar socioeconomic status. *Am J Public Health*. 2007; 97:2260-2267.
27. **Cheng CY, Reich D, Haiman CA, et al.** African ancestry and its correlation to type 2 diabetes in African Americans: a genetic admixture analysis in three U.S. population cohorts. *PLoS One*. 2012;7:e32840.
28. **Kirk JK, D'Agostino RB Jr, Bell RA, et al.** Disparities in HbA1c levels between African-American and non-Hispanic white adults with diabetes: a meta-analysis. *Diabetes Care*. 2006;29:2130-2136.
29. **Tsugawa Y, Mukamal KJ, Davis RB, Taylor WC, Wee CC.** Should the hemoglobin A(1c) diagnostic cutoff differ between blacks and whites? A cross-sectional study. *Ann Intern Med*. 2012;157:153-159.
30. **Herman WH, Ma Y, Uwaifo G, et al.** Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. *Diabetes Care*. 2007;30:2453-2457.
31. **American Diabetes Association.** Standards of medical care in diabetes--2013. *Diabetes Care*. 2013;36(suppl 1): S11-S66.
32. **Garber AJ, Abrahamson MJ, Barzilay JI, et al.** AACE comprehensive diabetes management algorithm 2013. *Endocr Pract*. 2013;19:327-336.
33. **Schernthaner G, Barnett AH, Emser A, et al.** Safety and tolerability of linagliptin: a pooled analysis of data from randomized controlled trials in 3572 patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2012;14:470-478.
34. Diabetes in the African American Community. Available at: http://www.nmadiabetesnet.org/images/uploads/NMA_diabetes_final6.pdf. Accessed October 16, 2013.
35. **Heise T, Graefe-Mody EU, Hüttner S, Ring A, Trommeshauser D, Dugi KA.** Pharmacokinetics, pharmacodynamics and tolerability of multiple oral doses of linagliptin, a dipeptidyl peptidase-4 inhibitor in male type 2 diabetes patients. *Diabetes Obes Metab*. 2009;11:786-794.