Research: Treatment

Efficacy and safety of liraglutide, a once-daily human glucagon-like peptide-1 receptor agonist, in African-American people with Type 2 diabetes: a meta-analysis of sub-population data from seven phase III trials

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Abstract

Aim   To evaluate the efficacy and safety of the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide in African-American people with Type 2 diabetes.

Methods   Analyses were performed on patient-level data from individuals self-defined as African-American or non-African-American in seven phase III studies. Endpoints included change in HbA_{1c} level, fasting plasma glucose level and body weight from baseline, proportion of patients reaching HbA_{1c} target [< 53 mmol/mol (< 7.0%)], and incidence of hypoglycaemia and nausea. Analyses used data obtained after 26 weeks. Within-population comparisons of liraglutide were performed vs placebo for African-American and non-African-American patient groups. In addition, between-population comparisons with non-African-American patients were performed for each treatment.

Results   In African-American patients ($n = 225$), HbA_{1c} was significantly reduced at 26 weeks with liraglutide 1.2 and 1.8 mg (−11 and −14 mmol/mol, respectively compared with placebo; $P < 0.0001$). There were also significant reductions in fasting plasma glucose (−2.4 and −3.1 mmol/l, respectively, compared with placebo; $P < 0.0001$). Statistically significant reductions in body weight were observed with 1.8 mg liraglutide (−2.1 kg compared with placebo; $P = 0.0056$), but not with 1.2 mg liraglutide (−0.26 kg; $P = 0.7307$). The P value for interaction between treatment and race was significant for body weight ($P = 0.0355$). The incidence of non-severe hypoglycaemia with liraglutide was low (11–15% of patients), and < 25% of patients receiving liraglutide experienced nausea.

Conclusions   This meta-analysis suggests that liraglutide is well tolerated and efficacious for treatment of Type 2 diabetes in African-American patients, with an efficacy that was shown not to differ from that observed in non-African-American patients over 26 weeks.

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Introduction

The prevalence of Type 2 diabetes is higher in the US African-American population than in age-matched non-African-American people [1]. Specifically, 13.2% of the non-Hispanic African-American population aged ≥ 20 years have diabetes, compared with 7.6% of age-matched non-Hispanic white people [1]. In addition, a large proportion of African-American women (58%) and men (38%) are obese [2], a risk factor known to dramatically increase the risk of developing Type 2 diabetes [3,4]. Furthermore, certain genetic variants implicated in diabetes, such as *TCF7L2*, have been associated with increased risk of diabetes among African-American patients in particular [5–9]. Evaluation of new diabetes therapies is therefore of particular importance in this population in order to inform clinical options for personalized treatment.

What's new?

• This study is the first of its kind to assess specifically the efficacy and tolerability of a glucagon-like peptide-1 (GLP-1) receptor agonist in African-American populations.

• We showed that the GLP-1 receptor agonist liraglutide was efficacious in the treatment of African-American people with Type 2 diabetes, and had broadly similar efficacy to that seen in non-African-American people.

In patients with Type 2 diabetes, glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to improve glycaemia and reduce body weight, with a low risk of hypoglycaemia [10–12]; however, published data from race and ethnic sub-populations are limited. Since genetic differences can affect native GLP-1 concentration and influence individual response to pharmaceutical agents [13], it is important to investigate the efficacy and safety of GLP-1 agonists in a variety of populations, including African-American patients.

In this analysis, liraglutide data from all seven trials [14–20] and placebo data from four of these seven trials [16,17,19,20] were pooled and compared.

Methods

Study design and participants

Analyses were carried out using pooled patient data from seven randomized phase III trials: LEAD-1–6 and 1860-LIRA-DPP-4 (registered at ClinicalTrials.gov: NCT00395746, NCT00 614120, NCT00294723, NCT00333151, NCT00331851, NCT00518882 and NCT00700817). Trial designs and results have been published previously for all seven trials [14–20] and the race/treatment profile of patients involved in these clinical trials is shown in Table 1.

Background study medications were different in the seven trials: no medication (LEAD-3); metformin (LEAD-2 and 1860-LIRA-DPP-4); glimepiride (LEAD-1); metformin + rosiglitazone (LEAD-4); metformin + glimepiride (LEAD-5); and metformin, sulfonylurea or both (LEAD-6). The randomized treatment period was 26 weeks for all of the trials except for LEAD-3, in which it was 52 weeks. In addition to this, each trial contributed differing numbers of patients towards each comparison, i.e. African-American patients who took placebo ranged from one patient (LEAD-1) to 18 patients (LEAD-4), whilst LEAD-3 (64 patients) and LEAD-4 (44 patients) contributed the largest numbers of African-American patients who took liraglutide (Table 1). The data reported in the present study are 26-week data for all trials.

Outcomes and assessments

The intention-to-treat and the safety populations were grouped into African-American and non-African-American populations, based on self-defined race. Efficacy endpoints assessed in this analysis at 26 weeks were change in HbA_{1c}, proportions of patients reaching the HbA_{1c} target of < 53 mmol/mol, reductions in fasting plasma glucose (FPG) levels and reductions in body weight.

Safety assessments included incidence of nausea and hypoglycaemia, for which the safety population was used (all randomized patients who received at least one dose of study medication). Non-severe hypoglycaemia was defined as < 3.1 mmol/l (56 mg/dl) and self-treated; major hypoglycaemia was defined as requiring third-party assistance.

Data analysis

Least-squares mean changes from baseline to week 26 were estimated using an analysis of covariance model with trial, previous treatment, treatment, race, interaction between treatment and race as fixed factors, baseline value of outcome

Table 1 Race/treatment profile of intention-to-treat populations in the seven clinical trials (LEAD-1–6 and 1860-LIRA-DPP-4)

	African-American patients			Non-African-American patients		
	Liraglutide 1.2 mg, n	Liraglutide 1.8 mg, n	Placebo, n	Liraglutide 1.2 mg, n	Liraglutide 1.8 mg, n	Placebo, n
LEAD-1	7	9	1	221	225	113
LEAD-2	9	5	3	231	237	118
LEAD-3	34	30	–	217	216	–
LEAD-4	26	18	18	151	160	157
LEAD-5	–	9	5	–	221	109
LEAD-6	–	13	–	–	220	–
1860-LIRA-DPP-4	22	16	–	199	202	–

Participants enrolling in the 7 clinical trials were considered part of the sub population if they identified their race as 'African-American/Black.'

of interest as a covariate and country as a random effect. Logistic regression with trial, previous treatment, treatment, race, interaction between treatment and race as fixed factors, and baseline as a covariate, was used to estimate the proportion of patients reaching the HbA$_{1c}$ target of < 53 mmol/mol (< 7.0%). For all efficacy analyses, within-population comparisons of liraglutide were performed vs placebo; between-population comparisons were also performed for each treatment. Missing data were imputed using last observation carried forward. No statistical comparisons were performed for analysis of safety outcomes.

Results

Patients

Baseline characteristics were similar between treatment and race groups, with the exceptions of weight and HbA$_{1c}$ (higher in African-American patients; Table 2). In addition there were more women among the non-African-American patients.

Outcomes and assessments

HbA$_{1c}$ reductions

Mean HbA$_{1c}$ reductions in African-American patients after 26 weeks were significantly greater with both liraglutide doses than with placebo: estimated placebo-adjusted treatment effect sizes were −11 and −14 mmol/mol (−1.0 and −1.3%) with liraglutide 1.2 mg and liraglutide 1.8 mg, respectively; $P < 0.0001$ for both doses (Fig. 1). HbA$_{1c}$ reductions in non-African-American patients were similar to those observed in African-American patients: estimated placebo-adjusted treatment effect sizes were −11 and −12 mmol/mol (−1.0 and −1.1%) with liraglutide 1.2 mg and liraglutide 1.8 mg, respectively; $P < 0.0001$ for
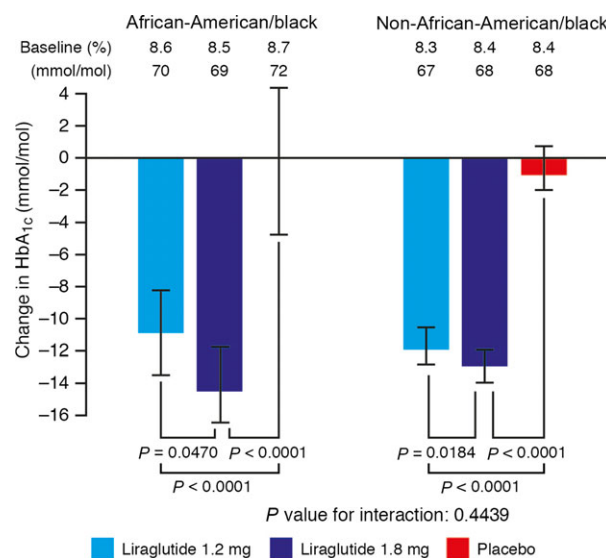

FIGURE 1 Change in HbA$_{1c}$ (mmol/mol) from baseline to week 26 of treatment. Last observation carried forward, intention-to-treat analysis set. Error bars represent 95% CIs for the estimated means. *P* values are for the estimated treatment difference relative to placebo.

both doses in non-African-American patients (Fig. 1). The HbA$_{1c}$ reductions observed with liraglutide did not significantly differ between African-American and non-African-American groups (*P* value for interaction 0.4439).

HbA$_{1c}$ target

A significantly higher proportion of African-American patients reached the American Diabetes Association-recommended HbA$_{1c}$ target of < 53 mmol/mol (< 7.0%) with liraglutide 1.2 mg (35%) and liraglutide 1.8 mg (62%) than with placebo (11%; Fig. 2). Odds ratios for achieving HbA$_{1c}$ target for liraglutide 1.2 mg and 1.8 mg relative to placebo were 4.38 (95% CI 1.29–14.8; $P = 0.0175$) and 13.73 (95% CI 4.08–46.2; $P < 0.0001$), respectively. In the non-

Table 2 Baseline characteristics of the African-American and non-African-American subgroups

|	African-American patients			Non-African-American patients		
	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Placebo	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Placebo
Number of patients	99	100	27	1024	1487	501
Mean (SD) age, years	53.7 (10.5)	52.4 (11.1)	53.7 (11.5)	56.2 (9.9)	55.7 (9.9)	55.8 (9.6)
Gender: men/women, %	36/64	34/66	22/78	52/48	54/46	57/43
Mean (SD) BMI, kg/m^2	34.1 (5.5)	33.6 (5.8)	33.2 (5.9)	31.9 (5.3)	31.9 (5.4)	32.1 (5.1)
Mean (SD) duration of diabetes, years	6.7 (5.5)	7.6 (5.6)	8.7 (6.4)	6.9 (5.4)	7.7 (5.7)	8.5 (5.9)
Mean (SD) body weight, kg,	97.1 (18.4)	95.4 (18.6)	91.5 (17.0)	89.6 (17.2)	90.1 (19.3)	91.0 (18.8)
Mean (SD) HbA$_{1c}$						
mmol/mol	70 (10.9)	69 (10.9)	72 (12.3)	67 (9.9)	68 (10.0)	68 (10.3)
%	8.6 (1.0)	8.5 (1.0)	8.7 (1.1)	8.3 (0.9)	8.4 (0.9)	8.4 (0.9)
Previous treatment, *n* (%)						
Monotherapy	53 (54)	54 (54)	7 (26)	523 (51)	604 (54)	109 (22)
Combination therapy	34 (34)	39 (39)	20 (74)	422 (41)	803 (39)	392 (78)
Diet and exercise	12 (12)	7 (7)	0*	79 (7.7)	80 (7)	0*
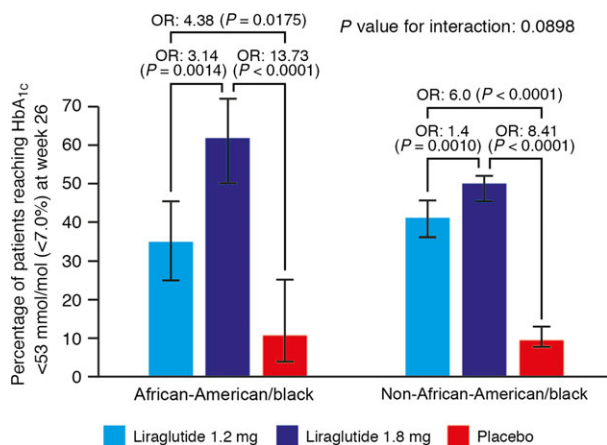
FIGURE 2 Percentage of patients achieving HbA_{1c} target < 53 mmol/mol at week 26 (estimated using logistic regression analysis, intention-to-treat analysis set, last observation carried forward). Error bars represent 95% CIs for the estimated means. *P* values are for the odds ratio (OR) of treatment relative to placebo.

African-American population, the proportion of patients reaching the HbA_{1c} target with liraglutide 1.2 mg (41%) and liraglutide 1.8 mg (50%) was significantly higher than that with placebo (10%): odds ratios 6.0 (95% CI 4.33–8.33) and 8.41 (95% CI 6.14–11.53) for liraglutide 1.2 mg and 1.8 mg, respectively; *P* < 0.0001 for both doses of liraglutide. No significant differences in the HbA_{1c}-lowering effect of liraglutide attributable to race were observed. The *P* value for test of interaction between treatment and race (African-American and non-African-American) was 0.0898.

Fasting plasma glucose reductions
Significant reductions in mean FPG level were seen with both doses of liraglutide compared with placebo. In the African-American population, the estimated treatment effect sizes

were −2.4 and −3.1 mmol/l for liraglutide 1.2 mg and 1.8 mg, respectively (*P* < 0.0001 compared with placebo for both comparisons; Fig. 3). In the non-African-American population, FPG reduction treatment effect estimates were −2.0 and −2.2 mmol/l for liraglutide 1.2 and 1.8 mg, respectively, compared with placebo (*P* < 0.0001 for both comparisons; Fig. 3).

The FPG reductions observed with liraglutide did not significantly differ between African-American and non-African-American groups (*P* value for interaction 0.1027).

Change in body weight
Significant reductions in mean body weight were observed with 1.8 mg liraglutide compared with placebo in both African-American and non-African-American individuals after 26 weeks of treatment.

In the African-American population, the estimated treatment effect size with liraglutide 1.8 mg was −2.1 kg (*P* = 0.0056); however, the estimated treatment effect size with liraglutide 1.2 mg (−0.3 kg) was not statistically significant relative to placebo in the African-American subgroup (*P* = 0.7307).

In the non-African-American population, significant reductions in body weight were observed with both doses of liraglutide compared with placebo: treatment effect estimates were −0.9 and −1.4 kg for liraglutide 1.2 mg and 1.8 mg, respectively, compared with placebo (*P* < 0.0001 for both comparisons; Fig. 4).

Interestingly, a significant difference in body weight change between African-American and non-African-American groups with liraglutide was observed. The *P* value for test of interaction between treatment and race (African-American and non-African-American) was 0.0355.
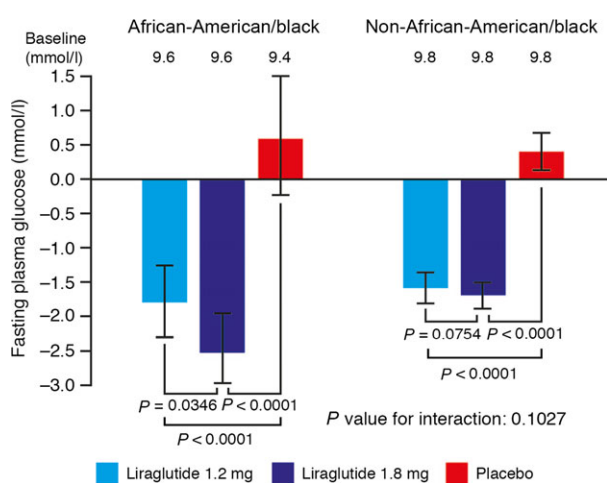

FIGURE 3 Change in fasting plasma glucose (mmol/l) from baseline to week 26 of treatment. Last observation carried forward, intention-to-treat analysis set. Error bars represent 95% CIs for the estimated means. *P* values are for the estimated treatment difference relative to placebo.
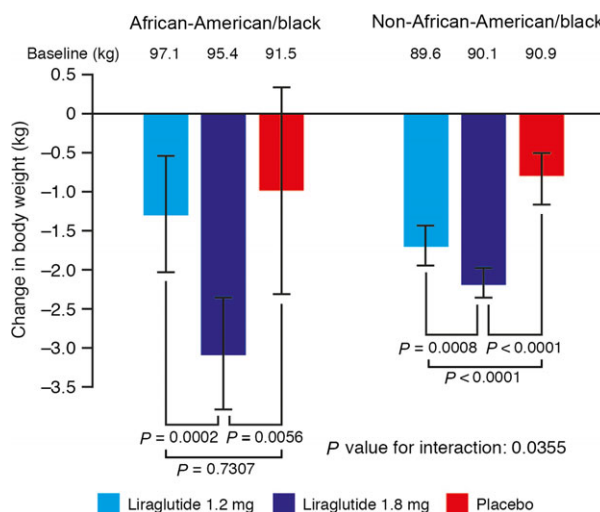

FIGURE 4 Change in body weight (kg) from baseline to week 26 of treatment. Last observation carried forward, intention-to-treat analysis set. Error bars represent 95% CIs for the estimated means. *P* values are for the estimated treatment difference relative to placebo.

Safety endpoints

After 26 weeks, among the African-American population, non-severe hypoglycaemia occurred in 11.2% of patients with liraglutide 1.2 mg, 15.0% with liraglutide 1.8 mg and 7.4% with placebo. One major hypoglycaemic episode occurred in a patient receiving liraglutide 1.2 mg in combination with metformin, and one major hypoglycaemic episode occurred in a patient receiving liraglutide 1.8 mg in combination with metformin and glimepiride. Among the non-African-American population, 5.7% of patients experienced non-severe hypoglycaemia with liraglutide 1.2 mg, 11.7% with liraglutide 1.8 mg, and 6.4% with placebo.

Within the African-American population after 26 weeks, the proportion of patients experiencing gastrointestinal adverse events was higher with liraglutide 1.2 mg (43.9%) and 1.8 mg (41.0%) than with placebo (18.5%; no statistical comparisons conducted). These proportions appeared similar to those in the non-African-American population: 39.9, 43.0 and 17.7% with liraglutide 1.2 mg, liraglutide 1.8 mg and placebo, respectively. Nausea was the most common gastrointestinal event among African-American patients (experienced by 22.4, 21.0 and 11.1% of patients with liraglutide 1.2 mg, liraglutide 1.8 mg and placebo, respectively). The proportions of non-African-American patients experiencing nausea were 20.1, 22.0 and 4.4% with liraglutide 1.2 mg, liraglutide 1.8 mg and placebo, respectively. Nausea was primarily experienced at initiation, and was mild and transient in nature.

Discussion

The present study was a meta-analysis of a sub-population, and so the findings should be interpreted with caution because of possible biases; however, some interesting and clinically relevant insights were obtained. In this analysis, African-American patients treated with either liraglutide 1.2 mg or liraglutide 1.8 mg achieved significant HbA_{1c} and FPG reductions compared with placebo. Additionally, with 1.8 mg liraglutide, body weight reductions were also significant compared with placebo. This shows that liraglutide was efficacious in the present African-American population. Furthermore, there was no overall difference in effect of glycaemic control between African-American and non-African-American patients.

Among African-American patients, significant reductions in HbA_{1c} compared with placebo were observed with both 1.2 mg and 1.8 mg liraglutide. These reductions were also apparent in the significantly greater proportions of patients reaching the American Diabetes Association-recommended HbA_{1c} target of < 53 mmol/mol with both doses of liraglutide. Similarly, both doses of liraglutide were associated with significantly greater FPG reductions compared with placebo, and significant differences in weight change compared with placebo were observed with 1.8 mg liraglutide.

The improvements in glycaemia observed in African-American patients treated with liraglutide were accompanied by a low risk of hypoglycaemia. Additionally, nausea—a known side effect of GLP-1 receptor agonists—was reported by < 25% of African-American patients, a similar proportion to non-African-American patients.

In this secondary analysis, the first of its kind to assess the efficacy and tolerability of GLP-1 receptor agonists in an African-American population, liraglutide was shown to have broadly similar safety and efficacy in African-American and non-African-American patients.

In terms of differences between African-American and non-African-American patients, the *P*-value for interaction (African-American and non-African-American) between treatment and race was significant for weight change, implying greater weight loss with liraglutide attributable to race ($P = 0.0355$), but not for any other endpoint evaluated. This finding should be interpreted with caution, however, given that baseline weight and BMI was originally greater among the African-American patients compared with the non-African-American patients.

When compared with non-African-American patients, there appears to be a more pronounced difference in the dose response between the 1.2 mg and 1.8 mg treatment doses for African-American patients; however, based on the present analysis, it cannot be concluded that this is illustrative of a real dose–response effect, as potential mechanisms for an altered dose response are not clear. There have been suggestions that genetic differences may confer increased responsiveness to GLP-1-based therapies in some populations [21]. African-American individuals generally carry a significantly higher burden of risk alleles compared with European-American people [6]. Most notably there are variants of the gene *TCF7L2*, which have been shown to negatively modify the effects of incretins on insulin secretion [22–24], raising the possibility of an effect on the efficacy of GLP-1 receptor agonists [25]. Further studies will be required to determine the effect of these variants on treatment with GLP-1 receptor agonists.

Overall, personalized medicine and race-based prescription are viewed by African-American individuals as positive advances [26]; however, these are also associated with a degree of mistrust towards the medical community, with concerns about prescription of inferior medicines and inequity of access to treatment [26]. These factors need to be taken into account when considering treatment of different racial sub-populations.

A limitation of this analysis is that comparison with all separate individual race groups was not possible, and it may be the case that unique responses are observed in other sub-populations; however, a sensitivity analysis comparing all clinical efficacy outcomes for African-American patients versus white patients (the largest constituent racial group within the non-African-American category) supports the findings of the main analysis of this study (Table S1).

Another limitation was that a significant proportion of African-American patients included were from trials in which there was no placebo arm, and a large proportion of these African-American subjects came from LEAD-3, a monotherapy trial, in which subjects were likely to be healthier than those on multiple therapies.

In summary, the reductions in HbA_{1c} levels, FPG levels and body weight observed in the present study were similar to those reported for the overall populations of the LEAD trials and the 1860-LIRA-DPP-4 trial. This, allied to the similar safety profile between race groups, shows that liraglutide is efficacious for the treatment of African-American patients with Type 2 diabetes, and has similar efficacy to that seen in non-African-American patients over 26 weeks. This work supports the use of liraglutide in African-American populations.

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Supporting Information

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

Table S1. Baseline values and outcome measures for all clinical endpoints presented as a sensitivity analysis comparing African-American patients versus white patients.