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Efficacy and safety of liraglutide, a once-daily human glucagon-like peptide-1 analogue, in Latino/Hispanic patients with type 2 diabetes: *post hoc* analysis of data from four phase III trials

The aim of the present analysis was to evaluate the efficacy of the glucagon-like peptide-1 receptor agonist liraglutide in Latino/Hispanic individuals with type 2 diabetes, in addition to comparing its treatment effects with those observed in non-Latino/Hispanic individuals. Analyses were performed on patient-level data from a subset of individuals self-defined as Latino/Hispanic from four phase III studies, the LEAD-3, LEAD-4, LEAD-6 and 1860-LIRA-DPP-4 trials. Endpoints included change in glycated haemoglobin (HbA1c) and body weight from baseline. In Latino/Hispanic patients (n = 505; 323 treated with liraglutide) after 26 weeks, mean HbA1c reductions were significantly greater with both liraglutide 1.2 and 1.8 mg versus comparator or placebo in the LEAD-3 and LEAD-4 studies, and with 1.8 mg liraglutide in the 1860-LIRA-DPP-4 trial. In LEAD-3 both doses led to significant differences in body weight change among Latino/Hispanic patients versus the comparator. With 1.8 mg liraglutide, difference in weight change was significant only in the 1860-LIRA-DPP-4 trial versus sitagliptin. For both endpoints Latino/Hispanic and non-Latino/Hispanic patients responded to liraglutide similarly. In summary, liraglutide is efficacious for treatment of type 2 diabetes in Latino/Hispanic patients, with a similar efficacy to that seen in non-Latino/Hispanic patients.

Keywords: GLP-1 receptor agonist, Hispanic, Latino, liraglutide, type 2 diabetes

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Introduction

In the USA, rates of diabetes in the Latino/Hispanic population are almost double those in the non-Latino/Hispanic white population [1]. Given this context and the lack of clinical studies specifically assessing new diabetes therapies in the Latino/Hispanic population, evaluation of new diabetes therapies in Latino/Hispanic patients is crucial, and will become ever-more important in the coming years as the nature of health systems and demography changes.

In people with type 2 diabetes (T2D), glucagon-like peptide-1 (GLP-1) receptor agonists, such as liraglutide and exenatide, have been shown to improve glycaemic control and reduce body weight, and are associated with a low risk of hypoglycaemia [2–4]; however, safety and efficacy data in ethnic minority populations are very limited. Given recognized racial differences in pharmacodynamic responses and plasma GLP-1 levels [5], such data are much needed in Latino/Hispanic populations.

The main purpose of the present analysis was to compare the effects of liraglutide with a comparator drug or placebo in Latino/Hispanic individuals, in addition to comparing treatment effects versus those observed in non-Latino/Hispanic individuals. We present a *post hoc* analysis of four phase III clinical trials that compared the safety and efficacy of two doses of liraglutide (1.2 and 1.8 mg) against different comparator drugs: glimepiride [6]; placebo [7]; exenatide [8]; and sitagliptin [9], in patients with T2D.

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Methods

The present analysis was based on patient-level data from four double-blind, randomized, controlled phase III trials comparing liraglutide with a comparator therapy: LEAD-3 (NCT00294723) [6], LEAD-4 (NCT00333151) [7], LEAD-6 (NCT00518882) [8] and 1860-LIRA-DPP-4 (NCT00700817) [9]; data reported are 26-week data for all trials. The intention-to-treat and safety populations were grouped into Latino/Hispanic and non-Latino/Hispanic populations based on self-defined ethnicity.

Background study medication differed among the four trials. Trial designs and primary results have been previously reported [6–9]. Efficacy endpoints examined in this analysis at 26 weeks were change in glycated haemoglobin (HbA1c) and change in body weight.

Safety assessments included the incidence of nausea and hypoglycaemia.

Statistical Methods

All analyses were carried out separately for the four trials rather than by pooling trial data owing to the different comparator

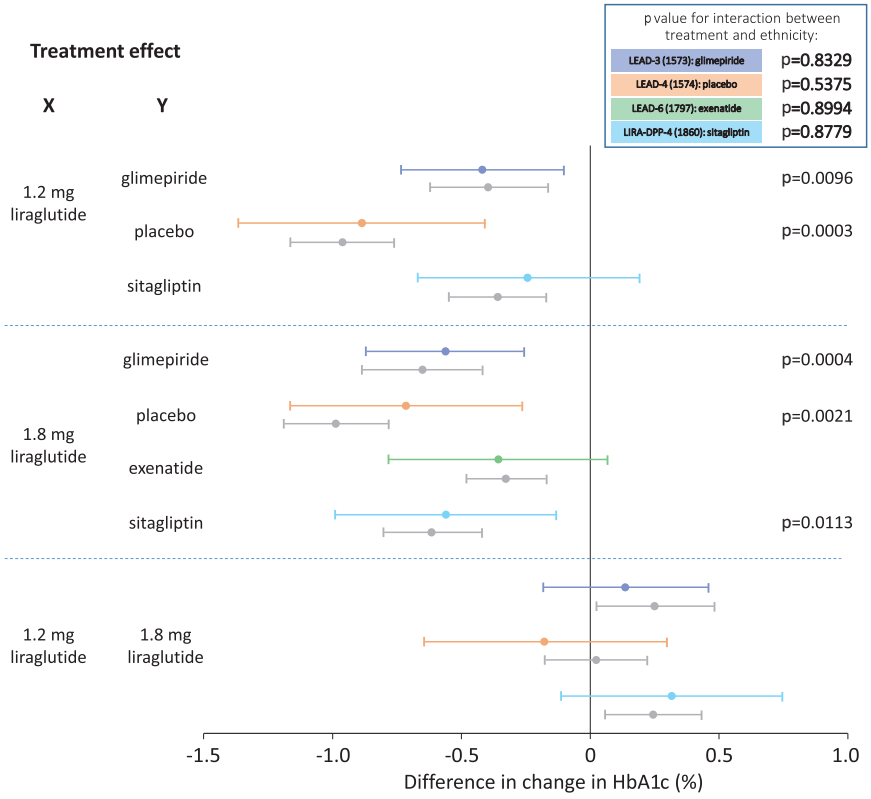

Figure 1. Forest plot of difference in change in glycated haemoglobin (HbA1c) showing treatment effects for Latino/Hispanic patients. A negative value indicates that HbA1c reductions are greater with treatment X than with treatment Y. Coloured bars represent the treatment effect for Latino/Hispanic patients and grey bars represent the effect in non-Latino/Hispanic patients. p values refer only to the treatment effect in Latino/Hispanic patients. p value for interaction between treatment and ethnicity not significant for all trials.

arms. Least-squares mean changes from baseline to week 26 were estimated using an analysis of covariance model with trial treatment, previous treatment, country, race and interaction between trial treatment and race as fixed effects and baseline value of outcome of interest as a covariate. For all efficacy analyses, within-population comparisons of liraglutide were performed versus the comparator; p values for treatment by ethnicity interaction are also presented to assess ethnicity effects between Latino/Hispanic and non-Latino/Hispanic patients.

Results

Across all four studies Latino/Hispanic patients were generally younger and had a lower body mass index (BMI) at baseline compared with non-Latino/Hispanic patients. Baseline HbA1c levels were higher among Latino/Hispanic patients. The ratio of Latino/Hispanic to non-Latino/Hispanic patients in each trial was comparatively low and ranged from 0.54 (LEAD-3) to 0.18 (LEAD-4) (Table S1, Supporting Information).

Change in Glycated Haemoglobin

In Latino/Hispanic patients, mean HbA1c reductions from baseline to week 26 were significantly greater with both liraglutide 1.2 and 1.8 mg compared with glimepiride in LEAD-3: −0.41% (−4.5 mmol/mol; p = 0.0096) and −0.56% (−6.1 mmol/mol; p = 0.0004) for liraglutide 1.2 and 1.8 mg, respectively; compared with placebo in LEAD-4: −0.88% (−9.6 mmol/mol; p = 0.0003) and −0.71% (−7.8 mmol/mol; p = 0.0021) for liraglutide 1.2 and 1.8 mg, respectively; and with 1.8 mg liraglutide compared with sitagliptin in the 1860-LIRA-DPP-4 trial: −0.56% (−6.1 mmol/mol; p = 0.0113). This was not the case for 1.8 mg liraglutide versus exenatide in the LEAD-6 trial. HbA1c reductions from baseline to week 26 in the non-Latino/Hispanic population were broadly similar, across all trials, to those seen in Latino/Hispanic patients (Figure 1). The p value for interaction between treatment and ethnicity was not significant for any trial.

Weight Change

In LEAD-3, both doses of liraglutide led to significant differences in body weight change among Latino/Hispanic patients, compared with glimepiride (−2.82 and −3.60 kg with liraglutide 1.2 and 1.8 mg; p < 0.0001 for both). In the 1860-LIRA-DPP-4 trial, the difference in body weight change was significant only for 1.8 mg liraglutide versus sitagliptin (−1.85 kg; p = 0.0440). In LEAD-4 and LEAD-6 no difference was found between liraglutide and the comparator. Among non-Latino/Hispanic patients, weight reductions were broadly similar to those observed in Latino/Hispanic patients, although reductions were numerically slightly greater among non-Latino/Hispanic patients in the LEAD-4 and LEAD-6

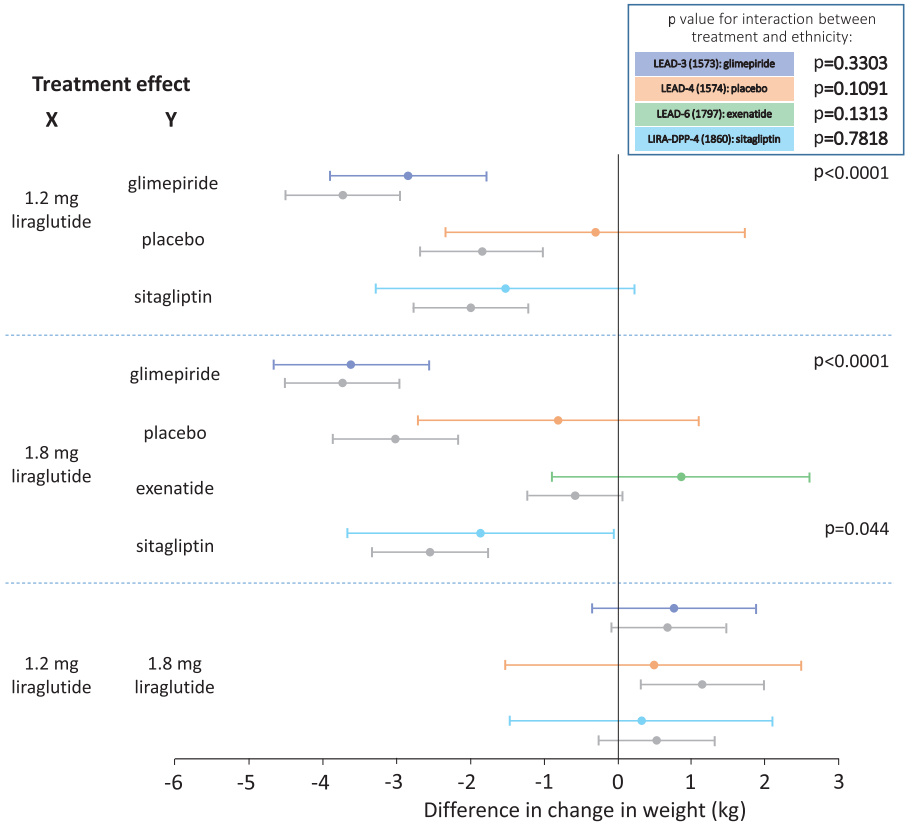

Figure 2. Forest plot of difference in change in weight showing treatment effects for Latino/Hispanic patients. A negative value indicates that weight reductions are greater with treatment X than with treatment Y. Coloured bars represent the treatment effect for Latino/Hispanic patients and grey bars represent the effect in non-Latino/Hispanic patients. p values refer only to the treatment effect in Latino/Hispanic patients. p value for interaction between treatment and ethnicity not significant for all trials.

trials (Figure 2). Nonetheless the p value for interaction between treatment and ethnicity for change in body weight was not significant in any trial.

Adverse Events and Safety Assessments

The most common adverse events across the studies for both ethnicity groups were diarrhoea and nausea (Tables S2–S5, Supporting Information). Nausea, a known side effect of GLP-1 receptor agonists, was reported with liraglutide at similar rates among Latino/Hispanic patients (lowest: 13% in LEAD-4, highest: 32% in 1860-LIRA-DPP-4) and non-Latino/Hispanic patients (lowest: 22% in 1860-LIRA-DPP-4, highest: 42% in LEAD-4). In LEAD-3, among patients of both ethnicity groups taking liraglutide, minor hypoglycaemia occurred in <10% of patients at both doses; however, in the other trials minor hypoglycaemia occurred more frequently (and at a similar rate in both ethnicity groups). Symptomatic hypoglycaemia occurred almost as frequently as minor hypoglycaemia and with a similar pattern of frequency (Tables S2–S5, Supporting Information).

Only three patients in the four trials, all non-Latino/Hispanic, experienced major hypoglycaemia: two taking exenatide in LEAD-6 and one taking liraglutide 1.2 mg in the 1860-LIRA-DPP-4 trial.

Discussion

Data on the effects of incretin-based therapies in Latino/Hispanic populations are scarce. The present *post hoc* analysis is, to the best of our knowledge, the first study specifically examining the effect of GLP-1 receptor agonists in Latino/Hispanic populations. The results reported in the present paper show that liraglutide is effective and generally well tolerated in Latino/Hispanic patients with T2D. The reductions in HbA1c observed were similar to those reported for the overall populations of the LEAD trials and the 1860-LIRA-DPP-4 trial [6–9].

Latino/Hispanic patients treated with both liraglutide doses (1.2 and 1.8 mg) achieved significant HbA1c reductions versus the comparator in LEAD-3 and LEAD-4 (glimepiride and placebo, respectively). The treatment effect varied in magnitude but was generally greater in LEAD-4, which is unsurprising given the placebo comparator. This effect did not manifest itself in the comparison of 1.8 mg liraglutide versus exenatide in the LEAD-6 trial, but did versus sitagliptin in the 1860-LIRA-DPP-4 trial.

In the LEAD-3 trial both doses of liraglutide caused a significant reduction in weight compared with glimepiride; however, this could be partly attributable to the small weight gain with the comparator drug. Only with 1.8 mg liraglutide in the

1860-LIRA-DPP-4 trial were significant reductions in weight observed.

Based on the four trials, the efficacy of liraglutide did not indicate a different treatment effect in Latino/Hispanic and non-Latino/Hispanic patients. This is reflected by the similar effect sizes between Latino/Hispanic and non-Latino/Hispanic patients, for the two endpoints, and that the p value for interaction between treatment and ethnicity was not significant for either of these clinical endpoints in any of the trials; however, in LEAD-4, non-Latino/Hispanic patients taking 1.8 mg liraglutide achieved greater numerical reductions in weight compared with Latino/Hispanic patients, a finding that was repeated in LEAD-6.

This analysis is unique in analysing individual patient subgroup data from four individual trials, but is limited by not being a *bona fide* meta-analysis. If comparator arms had been sufficiently similar it may have been possible to produce an overall effect size and odds ratio, although this would probably also have been limited by the relatively low number of Latino/Hispanic patients. Another factor worth considering is the differences in pretreatment between the various studies, which may be a source of variation in the results.

The main side effects were gastrointestinal in nature, are well known, and are typical of GLP-1 receptor agonists.

Overall the data did not indicate a different treatment effect between Latino/Hispanic and non-Latino/Hispanic patients with liraglutide, suggesting that liraglutide could be considered as part of individualization of therapy equally in both of these populations.

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Conflict of Interest

J. A. D. discloses the following relationships: honoraria for advisory board participation from Amgen, Aspire Bariatrics, AstraZeneca, Eli Lilly, Janssen, Merck, Novo Nordisk and REMD Bio; speaker fees from AstraZeneca, Janssen, Novo Nordisk and Takeda. D. D. Ø. is an employee and stock owner at Novo Nordisk. Carlos Campos is a member of the NNI Speaker Bureau and serves on NNI Advisory Boards.

J. A. D., D. D. Ø. and C. C. all designed and carried out the analysis, contributed to the writing of the manuscript, and approved the final draft for submission.

Supporting Information

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

Table S1. Baseline characteristics in the various subgroups of LEAD-3, LEAD-4, LEAD-6 and 1860-LIRA-DPP-4 for Latino/Hispanic and non-Latino/Hispanic patients.

Table S2. LEAD-3 adverse events.

Table S3. LEAD-4 adverse events.

Table S4. LEAD-6 adverse events.

Table S5. 1860-LIRA-DPP-4 adverse events.

References

1. American Diabetes Association. Por tu familia. 2014. Available URL from: http://www.diabetes.org/in-my-community/awareness-programs/latino-programs/por-tu-familia.html. Accessed 10 November 2015.
2. Barnett AH. New treatments in type 2 diabetes: a focus on the incretin-based therapies. Clin Endocrinol (Oxf) 2009; **70**: 343–353.
3. Drab SR. Incretin-based therapies for type 2 diabetes mellitus: current status and future prospects. Pharmacotherapy 2010; **30**: 609–624.
4. Russell S. Incretin-based therapies for type 2 diabetes mellitus: a review of direct comparisons of efficacy, safety and patient satisfaction. Int J Clin Pharm 2013; **35**: 159–172.
5. Velásquez-Mieyer PA, Cowan PA, Pérez-Faustinelli S et al. Racial disparity in glucagon-like peptide 1 and inflammation markers among severely obese adolescents. Diabetes Care 2008; **31**: 770–775.
6. Garber A, Henry R, Ratner R et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009; **373**: 473–481.
7. Zinman B, Gerich J, Buse JB et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met + TZD). Diabetes Care 2009; **32**: 1224–1230.
8. Buse JB, Rosenstock J, Sesti G et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009; **374**: 39–47.
9. Pratley RE, Nauck M, Bailey T et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet 2010; **375**: 1447–1456.