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Efficacy and safety of liraglutide 3.0 mg for weight management are similar across races: subgroup analysis across the SCALE and phase II randomized trials

RESEARCH LETTER

The efficacy and safety of liraglutide 3.0 mg versus placebo, as adjunct to diet and exercise, was evaluated in racial subgroups. This *post hoc* analysis of pooled data from five double-blind randomized, placebo-controlled trials was conducted in 5325 adults with either a body mass index (BMI) ≥27 kg/m^2 plus ≥1 comorbidity or a BMI ≥30 kg/m^2. Statistical interaction tests evaluated possible treatment effect differences between racial subgroups: white (4496, 84.4%), black/African-American (550, 10.3%), Asian (168, 3.2%) and other (111, 2.1%). Effects of liraglutide 3.0 mg on weight loss, associated metabolic effects and safety profile were generally consistent across racial subgroups. All achieved statistically significant mean weight loss at end-of-treatment with liraglutide 3.0 mg versus placebo: white 7.7% versus 2.3%, black/African-American 6.3% versus 1.4%, Asian 6.3% versus 2.5%, other 7.3% versus 0.49%. Treatment effects on weight and cardiovascular risk markers generally showed no dependence on race (interaction test $p > 0.05$). Adverse events were similar across racial subgroups.

Keywords: antiobesity drug, clinical trial, glucagon-like peptide-1 analogue, liraglutide, obesity therapy, randomized trial

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Introduction

The prevalence of overweight and obesity seems to affect some racial minority groups more than others, with black individuals often having higher obesity rates than their white counterparts [1,2]. Black people and African-Americans are also most at risk of developing chronic obesity-related diseases such as diabetes and hypertension, and generally achieve lower weight loss using standard behavioural lifestyle interventions than do other racial subgroups [3].

Liraglutide 3.0 mg, as an adjunct to a reduced-calorie diet and increased physical activity, is approved in the USA, the European Union, Mexico and Canada, for chronic weight management in adults.

The present *post hoc* analysis of pooled data from five randomized, double-blind and placebo-controlled trials compares the efficacy and safety of liraglutide 3.0 mg versus placebo among different racial subgroups. Across the trials, weight loss was 5.7–9.2% with liraglutide 3.0 mg and 0.2–3.1% with placebo. Additionally, because a 5–10% weight loss is associated with improvement in obesity-related comorbidities [4], in this analysis we aimed to determine if changes in cardiovascular risk factors were different across racial subgroups.

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Methods

This was a *post hoc* analysis of pooled data from the four SCALE phase IIIa trials (3 of 56 weeks' duration, one of 32 weeks' duration) and one phase II trial at 52 weeks on racial subgroups: white; black/African-American; Asian; and other. Race was self-reported. File S1 provides details of the trials included; full methodology details have been reported previously [5–9].

Men and women either with a body mass index (BMI) of ≥27 kg/m^2 with at least one comorbidity, or with a BMI of ≥30 kg/m^2 (Table S1, Supporting Information) were included in each trial. Participants received once-daily subcutaneous injections of liraglutide or placebo, starting at a dose of 0.6 mg with weekly 0.6-mg increments to 3.0 mg. Additional liraglutide doses were investigated in the phase II dose-finding trial (1.2, 1.8 and 2.4 mg) and SCALE Diabetes (1.8 mg), but those doses were not included in this analysis, which compared liraglutide 3.0 mg and placebo. Diet and exercise guidance, provided at approximately monthly intervals [5–9], was similar across the trials.

In this pooled analysis, mean and categorical weight-related endpoints were assessed at end of treatment. Glycaemic control variables were assessed separately in participants with T2DM (from SCALE Diabetes) and in those with prediabetes or normoglycaemia. Health-related quality of life was also assessed using the Impact of Weight on Quality of Life-Lite (IWQoL-Lite) questionnaire, which was included in the phase II trial and the SCALE Obesity and Prediabetes and SCALE Diabetes trials, and the 36-item Short-Form health status survey (SF-36), which was included in the SCALE Obesity and Prediabetes and SCALE Sleep Apnoea trials.

Safety variables included pulse and overall adverse events. Events that had onset on or after the first day of treatment and no later than 14 days after the last day of treatment were reported.

Statistical Analysis

The power calculations for the individual trials have been published previously [5–9]. In the present efficacy analysis, data were pooled from all randomized individuals who received at least one treatment dose of either liraglutide 3.0 mg or placebo and had at least one post-baseline efficacy assessment. Missing values at end of treatment were replaced using last observation carried forward imputation. Estimated changes from baseline were calculated using an analysis of covariance (ANCOVA), with treatment, race, interaction between treatment and race, country, sex, trial and baseline diabetes status as fixed factors, and the baseline value of the variable as a covariate. Categorical weight loss was analysed using logistic regression, using the same fixed factors and covariates as used in the respective ANCOVA. A test for interaction between race and treatment was performed for each analysis, to investigate possible differential effects of treatment in the various racial subgroups. All statistical tests were two-sided at a 5% significance level and were performed using the SAS software package (version 9.3; SAS Institute, Cary, NC, USA).

All randomized individuals receiving at least one treatment dose were included in the safety analyses.

Results

A total of 5325 randomized and exposed participants were included in this pooled analysis. There were notable differences in the numbers of individuals in the different racial subgroups, with white participants outnumbering non-white participants. Baseline characteristics were generally similar across racial subgroups (Table S2, Supporting Information). Most participants were female. Mean BMI and body weight at baseline was lowest in Asian participants and highest in black/African-American participants.

Efficacy

In each racial subgroup, greater mean relative (Figure 1A) and absolute (Table 1) weight loss from baseline to end of treatment was achieved with liraglutide 3.0 mg than with placebo. Significantly more individuals lost ≥5%, >10% and >15% of their baseline body weight in the liraglutide 3.0 mg group than in the placebo group across racial subgroups (Figure 1B). The mean and categorical weight loss effects did not show any dependence on racial subgroup, as each race–treatment interaction test p value was >0.05; moreover, the estimated treatment differences were similar across races.

Greater mean reductions in cardiovascular risk markers were generally seen with liraglutide 3.0 mg versus placebo in each racial subgroup (Table 1). Importantly, none of the treatment effects showed any dependence on racial subgroup ($p > 0.05$), except for glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG) in individuals with prediabetes, where the race–treatment interaction test p value was statistically significant (Table 1).

In general, health-related quality of life improved with liraglutide treatment, and the beneficial treatment effects of liraglutide 3.0 mg on health-related quality of life were similar across racial subgroups. The race–treatment interaction test was non-significant for the total score ($p = 0.13$) and physical function score ($p = 0.56$) of the IWQoL-Lite, as well as for the physical component summary ($p = 0.36$), mental component summary ($p = 0.98$) and physical function ($p = 0.34$) scores of the SF-36.

Safety

The proportion of individuals reporting overall adverse events, serious adverse events and events leading to discontinuation was similar for white, black/African-American, Asian and other racial groups (Figure S1A, Supporting Information). In each racial subgroup the most frequently reported events were gastrointestinal disorders, which were reported more frequently with liraglutide 3.0 mg than placebo (Figure S1B, Supporting Information). The proportion of individuals on liraglutide 3.0 mg discontinuing because of side effects (mostly gastrointestinal disorders) was greater than that in the placebo group across racial subgroups (Figure S1A, Supporting Information).

A mean increase in resting pulse was observed with liraglutide 3.0 mg compared with placebo in each racial subgroup (the increase ranged from 0.6 to 3.2 beats/min across subgroups), and the treatment effects did not show any dependence on racial subgroup (Table 1).

Discussion

The results of this pooled analysis showed that the effects of liraglutide 3.0 mg on weight, cardiovascular risk markers, and side effects were consistent across racial subgroups. In contrast to our findings, studies of other weight loss interventions of up to 1 year in duration have reported lower weight reductions in black and African-American subgroups than in their white counterparts [3,10,11]. In two of the studies, mean weight losses were similar over the longer term for black/African-American subjects [3,11], suggesting that initial weight loss may be slower for this group, but less weight regain is experienced with longer follow-up periods.

The consistent treatment effects that we observed across racial subgroups on cardiovascular risk markers have also been seen in other studies; thus, despite the lower weight loss among black/African-American subjects compared with white subgroups in trials of behavioural lifestyle interventions for weight loss [3], changes in risk factors were similar across racial subgroups. Similarly, in a study of exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, in adults with T2DM, significant improvements were seen in body weight, HbA1c, FPG and systolic blood pressure across racial subgroups [12].

Overall, greater mean reductions in HbA1c and FPG with liraglutide 3.0 mg versus placebo were generally observed across racial subgroups. Whilst the test for interaction was statistically significant for both these glycaemic variables

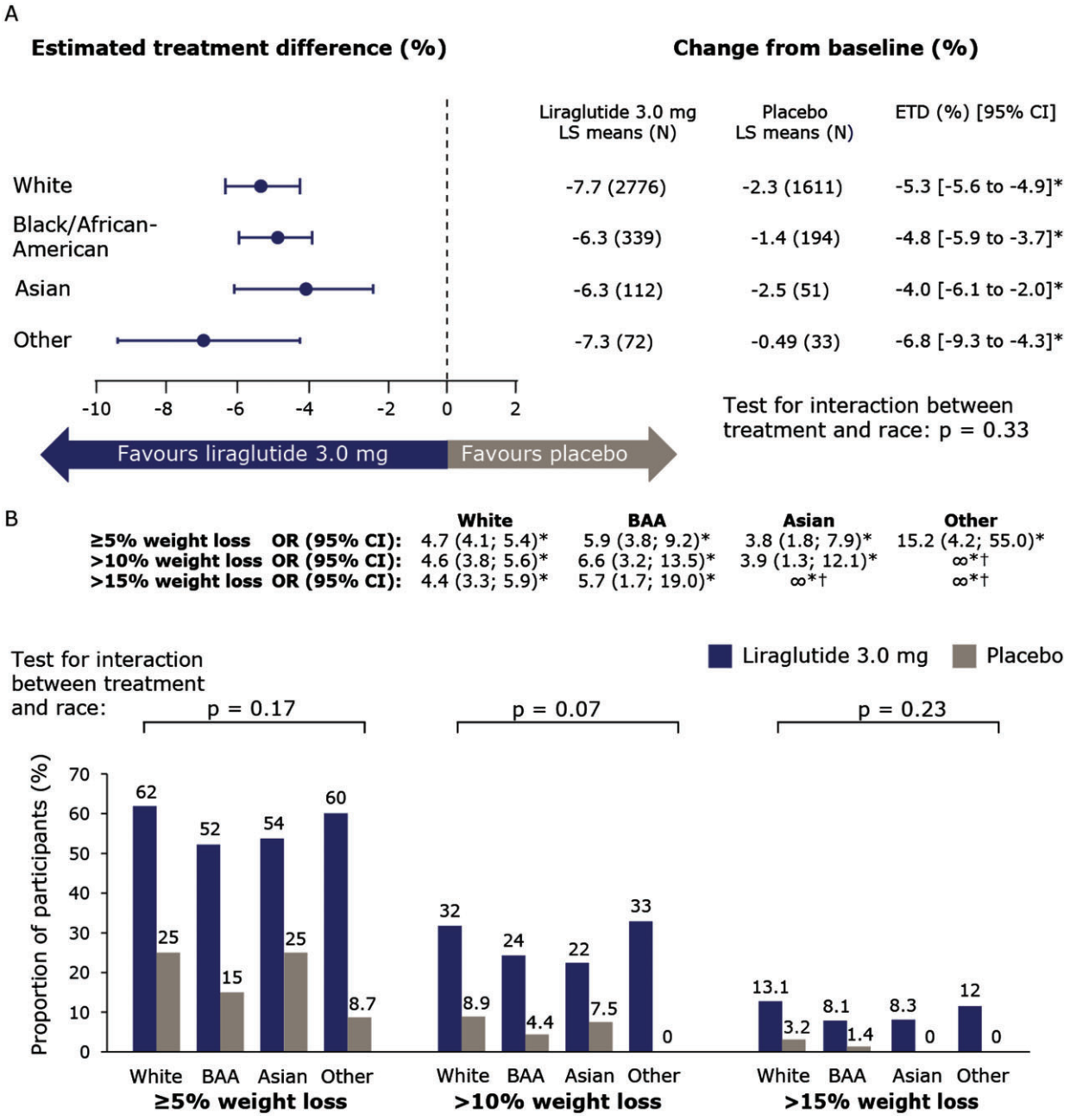

Figure 1. Body weight loss in different racial subgroups treated with liraglutide 3.0 mg or placebo presented as mean relative weight loss from baseline to end of treatment (A) and (B) the proportion of participants achieving ≥5%, >10%, and >15% weight loss. Data are estimated least squares (LS) means from an analysis of covariance (ANCOVA) model (A) and estimated proportions from a logistic regression model (B) for the full analysis set (all exposed individuals with at least one post-baseline efficacy assessment) with last observation carried forward imputation. The 'Other' subgroup includes American Indian or Alaska Native, Native Hawaiian people or other Pacific Islanders, and other. BAA, Black/African-American; CI, confidence interval; ETD, estimated treatment difference; N, number of individuals contributing to the analysis; OR, odds ratio. *Statistically significant treatment difference of $p < 0.02$ versus placebo. †As no participants in the placebo group achieved the weight loss target, the treatment estimate was infinity.

in individuals with prediabetes, the differences between subgroups were minor and are unlikely to be clinically relevant.

Few data are available comparing the safety profiles of GLP-1 receptor agonists in different racial subgroups; however, racial differences did not influence the safety or efficacy of liraglutide or exenatide in two previous studies [12,13].

Limitations of this *post hoc*, exploratory analysis include the fact that the trials were neither designed nor powered for comparisons across racial subgroups, and there were disproportionately more white individuals than those of other races. Strengths include the use of individual participant data from each of the trials, in contrast to typical meta-analyses that use summary statistics.

Table 1. Changes in body weight and cardiovascular risk markers between baseline and end of treatment.

	Racial group				
Pooled trials*	White Liraglutide 3.0 mg/placebo	Black/African-American Liraglutide 3.0 mg/placebo	Asian Liraglutide 3.0 mg/placebo	Other† Liraglutide 3.0 mg/placebo	Test for interaction p value
Weight, kg	n = 2776/1611	n = 339/94	n = 112/51	n = 72/33	0.19
Estimated mean	−8.1/−2.5	−6.6/−1.6	−6.1/−2.5	−7.7/−0.49	
ETD (95% CI)	−5.4 (−5.9 to −5.0)‡	−5.0 (−6.1 to −3.8)‡	−3.6 (−5.8 to −1.4)‡	−7.2 (−10.0 to −4.5)‡	
BMI, kg/m^2	n = 2796/1635	n = 342/198	n = 112/51	n = 73/33	0.26
Estimated mean	−2.9/−0.88	−2.4/−0.56	−2.3/−0.91	−2.8/−0.21	
ETD (95% CI)	−2.0 (−2.1; −1.8)‡	−1.8 (−2.2; −1.4)‡	−1.4 (−2.2; −0.63)‡	−2.6 (−3.6; −1.6)‡	
Waist circumference, cm	n = 2793/1632	n = 342/198	n = 112/51	n = 72/33	0.36
Estimated mean	−7.8/−3.6	−6.8/−2.2	−6.8/−4.4	−6.9/−1.4	
ETD (95% CI)	−4.0 (−4.4; −3.5)‡	−4.5 (−5.7; −3.3)‡	−2.5 (−4.8; −0.3)‡	−5.4 (−8.2; −2.6)‡	
SBP, mmHg	n = 2785/1630	n = 341/198	n = 112/51	n = 73/33	0.59
Estimated mean	−4.0/−0.9	−2.2/0.5	−3.1/−2.4	−2.9/−0.1	
ETD (95% CI)	−2.9 (−3.6; −2.3)‡	−3.6 (−5.5; −1.7)‡	−0.7 (−4.3; 2.8)	−3.1 (−7.5; 1.3)	
DBP, mmHg	n = 2785/1630	n = 341/198	n = 112/51	n = 73/33	0.62
Estimated mean	−2.1/−1.2	−1.0/0.4	−2.9/−2.4	−2.1/−3.6	
ETD (95% CI)	−0.9 (−1.3; −0.4)‡	−1.3 (−2.6; 0.0)	−0.2 (−2.7; 2.3)	0.7 (−2.3 3.8)	
Pulse, beats/min	n = 2821/1639	n = 343/198	n = 113/51	n = 73/34	0.26
Estimated mean	2.7/0.24	1.6/−0.08	−0.28/−0.96	3.9/1.2	
ETD (95% CI)	2.7 (2.1 ; 3.2)‡	1.5 (0.04; 3.0)‡	0.64 (−2.1; 3.4)	3.2 (−0.17; 6.6)	
Total cholesterol,%	n = 2432/1385	n = 293/161	n = 94/43	n = 60/23	0.58
Relative changes	−2.5/0.3	−1.8/1.1	−2.4/−0.5	1.1/−2.7	
RTD (95% CI)	−2.6 (−3.5; −1.7)‡	−2.3 (−4.8; 0.4)	−2.4 (−7.1; 2.6)	2.1 (−4.4; 9.1)	
LDL cholesterol,%	n = 2430/1384	n = 293/161	n = 94/43	n = 60/23	0.23
Relative changes	−2.6/0.4	−1.7/1.5	−0.9/−6.1	4.6/1.0	
RTD (95% CI)	−3.1 (−4.5; −1.7)‡	−2.3 (−6.3; 1.8)	4.8 (−3.1; 13.3)	1.0 (−9.0; 12.1)	
HDL cholesterol,%	n = 2432/1385	n = 293/161	n = 94/43	n = 60/23	0.75
Relative changes	3.3/2.2	3.4/3.3	2.0/1.8	5.4/0.6	
RTD (95% CI)	1.7 (0.8; 2.7)‡	1.0 (−1.8; 3.9)	−0.1 (−5.2; 5.3)	4.5 (−2.6; 12.1)	
VLDL cholesterol,%	n = 2426/1384	n = 293/161	n = 94/43	n = 60/23	0.44
Relative changes	−10.3/−0.7	−12.5/−3.0	−12.7/−3.8	−13.8/−19.4	
RTD (95% CI)	−8.7 (−11.0; −6.4)‡	−10.0 (−16.3; −3.1)‡	−9.1 (−20.7; 4.3)	6.0 (−11.7; 27.3)	
Triglycerides,%	n = 2432/1385	n = 293/161	n = 94/43	n = 60/23	0.39
Relative changes	−12.7/−3.8	−11.3/0.1	−12.7/−3.5	−11.8/−16.8	
RTD (95% CI)	−9.5 (−11.6; −7.5)‡	−11.1 (−16.7; −5.1)‡	−9.3 (−19.7; 2.5)	3.7 (−11.9; 22.1)	
FFA,%	n = 2304/1258	n = 260/125	n = 82/39	n = 57/19	0.60
Relative changes	−3.6/−3.3	−4.0/−1.6	0.37/−7.5	8.6/0.97	
RTD (95% CI)	−4.1 (−7.0; −1.1)‡	−5.9 (−14.4; 3.5)	3.3 (−12.8; 22.4)	8.1 (−14.2; 36.2)	
hsCRP (%)	n = 2384/1335	n = 287/158	n = 92/42	n = 61/22	0.86
Relative changes	−36.6/−10.3	−34.3/−4.3	−34.7/−12.5	−26.6/0.9	
RTD (95% CI)	−28.2 (−31.7; −24.5)‡	−31.9 (−41.0; −21.5)‡	−24.7 (−42.3; −1.6)‡	−23.8 (−46.7; 8.9)	
Glycaemic variables					
Individuals with normoglycaemia					
HbA1c (%)	n = 937/561	n = 103/54	n = 15/8	n = 27/12	0.23
Estimated mean	−0.22/−0.02	−0.20/0.00	−0.14/−0.24	−0.20/−0.06	
ETD (95% CI)	−0.19 (−0.21; −0.16)‡	−0.18 (−0.26; −0.10)‡	0.03 (−0.18; 0.24)	−0.17 (−0.33; −0.01)‡	
FPG, mmol/l	n = 953/576	n = 103/57	n = 17/8	n = 27/12	0.63
Estimated mean	−0.27/0.02	−0.24/−0.03	−0.03/0.10	−0.28/0.00	
ETD (95% CI)	−0.27 (−0.31; −0.22)‡	−0.21 (−0.35; −0.08)‡	−0.11 (−0.47; 0.24)	−0.36 (−0.65; −0.08)‡	
Individuals with prediabetes					
HbA1c, %	n = 1453/845	n = 192/109	n = 80/38	n = 31/15	0.01
Estimated mean	−0.33/−0.06	−0.30/−0.12	−0.41/−0.02	−0.28/−0.05	
ETD (95% CI)	−0.26 (−0.29; −0.24)‡	−0.19 (−0.26; −0.13)‡	−0.40 (−0.51; −0.29)‡	−0.20 (−0.38; −0.02)‡	
FPG, mmol/l	n = 1480/861	n = 194/110	n = 84/39	n = 32/16	0.007
Estimated mean	−0.48/0.00	−0.40/−0.12	−0.43/0.09	−0.27/−0.01	
ETD (95% CI)	−0.48 (−0.53; −0.44)‡	−0.27 (−0.40; −0.14)‡	−0.50 (−0.71; −0.29)‡	−0.16 (−0.50; 0.17)	

Table 1. Continued.

Pooled trials*	Racial group: White Liraglutide 3.0 mg/placebo	Black/African-American Liraglutide 3.0 mg/placebo	Asian Liraglutide 3.0 mg/placebo	Other† Liraglutide 3.0 mg/placebo	Test for interaction p value
Individuals with T2DM (SCALE diabetes)					
HbA1c, %	n = 335/169	n = 41/27	n = 11/4	n = 13/5	0.34
Estimated mean	−1.4/−0.3	−1.3/−0.5	−0.9/−0.6	−1.1/−0.5	
ETD (95% CI)	−1.0 (−1.2; −0.8)‡	−0.8 (−1.2; −0.3)‡	−0.4 (−1.3; 0.6)	−0.5 (−1.4; 0.4)	
FPG, mmol/l	n = 339/172	n = 42/27	n = 11/4	n = 12/5	0.08
Estimated mean	−1.99/0.08	−1.54/−0.44	−0.70/−1.85	−1.56/0.56	
ETD (95% CI)	−1.95 (−2.30; −1.60)‡	−0.94 (−1.86; −0.02)‡	0.05 (−2.14; 2.23)	−1.54 (−3.53; 0.45)	

Data are estimated means and treatment differences (95% CI) from an analysis of covariance using the full analysis set (all exposed individuals with at least one post-baseline efficacy assessment) with last observation carried forward imputation. Lipids and hsCRP are log-transformed for analysis and presented as relative changes and relative treatment differences (95% CI). p values are from a test for interaction between race and treatment. FFA were reported in all trials, except trial 3970 in individuals with obstructive sleep apnoea (n = 355).

BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; ETD, estimated treatment difference; FFA, free fatty acids; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; hsCRP, high-sensitivity C-reactive protein n, number of individuals included in the analysis; RTD, relative treatment difference; SBP, systolic blood pressure; SCALE, Satiety and Clinical Adiposity–Liraglutide Evidence; T2DM, type 2 diabetes mellitus; VLDL, very low-density lipoprotein.

*Including data from the phase II trial at 52 weeks [5] and the four phase IIIa SCALE trials (SCALE Obesity and Prediabetes [6], SCALE Diabetes [7] and SCALE Maintenance [8] 56-week trials; SCALE Sleep Apnoea 32-week trial [9]).

†Includes American-Indian or Alaska Native, Native Hawaiian people or other Pacific Islanders, and other (including unknown or not applicable, such as individuals from France who did not report race information).

‡Statistically significant treatment difference of $p < 0.05$ versus placebo.

In summary, the efficacy and safety of liraglutide 3.0 mg for weight management were generally similar across races in this *post hoc* pooled analysis, with overall consistent positive effects on body weight, cardiometabolic risk factors and health-related quality of life. With liraglutide 3.0 mg, more than half the individuals across the racial subgroups achieved a clinically meaningful weight loss of at least 5%, which is associated with a variety of health benefits and improvements in obesity-related comorbidities such as diabetes and hypertension [4], as well as in quality of life and physical mobility [14,15]. In each racial subgroup, and consistent with previous findings [5–9], gastrointestinal disorders were more commonly reported with liraglutide 3.0 mg than with placebo.

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Conflict of Interest

J. A. has received consultant honoraria from Novo Nordisk. A. C. has nothing to disclose. C. E. L. has received research funding support from the US National Institutes of Health and Novo Nordisk. H. L. has received consultant honoraria and holds stock in Novo Nordisk, and has received speaker honoraria from Vivus. X. P. has received consultant honoraria and research funding support from Novo Nordisk and honoraria from Johnson and Johnson, Lilly and Zafgen. T. V. S. and B. S. are employed by and hold stock in Novo Nordisk.

Novo Nordisk provided overall management of the trials, performed the statistical analyses and verified the accuracy of the data presented. Novo Nordisk was also responsible for the overall trial designs, and provided a formal review of the manuscript, but the authors had final authority, including choice of journal. Under the direction of the authors and according to an agreed outline, the medical writer Angela Stocks drafted the initial version of the manuscript. T. V. S. and X. P. participated in the concept and design of the studies. X. P. was signatory investigator on one of the trials and C. E. L. was also an investigator on one of the trials; both were involved in data acquisition. All authors were involved in the analysis or interpretation of the data, and all critically reviewed the manuscript and approved the final version for submission. All authors also agreed to be accountable for all aspects of the work.

Supporting Information

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

File S1. Supplementary methods, results and references.

Figure S1. Adverse event profile in different racial subgroups treated with liraglutide 3.0 mg or placebo presented as (A) the proportion of participants with overall adverse events and (B) the most frequent adverse events with an incidence of at least 5% in any group, by preferred terms.

Table S1. Characteristics of randomized, placebo-controlled trials included in the pooled analysis.

Table S2. Demographics and baseline characteristics.

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