Early weight loss with liraglutide 3.0 mg predicts 1-year weight loss and is associated with improvements in clinical markers

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EARLY RESPONDERS MS: REVIEWER COMMENTS (OBESITY)

Cover note: we thank the reviewers for their positive comments and constructive pointers where the article could be improved or clarified. All of the comments have been discussed, and wherever possible (and just within the word count) the text has been amended.

Comments

Reviewer 1 Comments to the Author

This is a very well written manuscript. Just a few very minor issues to address.

Reviewer 1.1

Keywords: The keywords listed on the cover page (GLP1, quality of life, glycemic control), seem to be different than the keywords listed on page 2 (responders, Health-related QOL, stopping rules, glycemic control). These lists should be reconciled.

Response: The keywords on the cover page of the submission were selected from the submission site's predefined drop-down list; the ones on page 2 are suggestions from the authors. We assume the keywords selected on the submission site (GLP1, quality of life, glycemic control) have internal purposes e.g. selection of appropriate reviewers etc., but it is hoped that in the published manuscript the keywords listed on page 2 will be used.

Reviewer 1.2

Methods: in the description of the individuals in the trial, you reference "3731 overweight or obese individuals." My understanding is that the nomenclature has been shifting to avoid labeling people, and instead referring to them as ""3731 individuals with overweight or obesity." This can be addressed throughout the manuscript.

Response: The language has been changed accordingly.

Reviewer: 2 Comments to the Author

The present report is aimed at identifying an early response criterion for predicting ≥ 5 weight loss with Liraglutide 3 mg at week 56 from data derived from two large clinical trials, whose results have been published elsewhere. As secondary aim a comparison of efficacy outcomes in early responders (ERs) vs early non-responders (ENRs) was performed.

In the field of therapeutic weight loss, prediction still is in its infancy and contributions like this provided by Fujioka and colleagues should be highly acknowledged. Indeed, this kind of analysis supposed to identify tools to predict weight-loss responders, or nonresponders, will clearly provide immediate clinical benefit for physicians and patients, as well. This is the reason why we have highly appreciated the manuscript and the analysis provided in the present publication.

However, we have some still open questions to propose to the Authors and we hope that a pertinent answer to each of these questions are consequently provided. This might help the clinicians to provide a tailored Liraglutide treatment for appropriate overweight and obese patients

Reviewer 2.1

It is well known that a deep knowledge of response-determining markers may contribute to a deeper understanding of underlying biological mechanisms involved in the pathophysiology of overweight and obesity. Thus, taking this into consideration: were the GLP1 circulating levels of ERs at time 0 different to those of ENRs?

Response: We thank the reviewer for their kind comments and thought-provoking questions. We agree with the reviewer's comment that an analysis of the relationship between endogenous GLP-1 levels and subsequent on-treatment weight loss responses would be interesting. However, no measures for circulating GLP-1 values at baseline were [see this article for sampling time points: Overgaard *et al. Clin Pharmacokinet*. 2016; http://link.springer.com/article/10.1007%2Fs40262-016-0410-7]

Reviewer 2.2

The data of the ERs should be provided in Table 2 in different manner. We would like to see the % of ERs and ENRs divided in subcohorts according to patient age (30-40, 40-50. 50-60, 60-70 years), furthermore, we would like to know whether the menopausal status might have any difference in the treatment response.

Response: We would prefer not to include the suggested additional data by age category, as this would suggest age category is a determinant of the likelihood of response, which it is not; age does not influence plasma exposure of liraglutide 3.0 mg (Overgaard *et al. Clin Pharmacokinet*. 2016), nor does it influence the percentage of individuals achieving ≥5% weight loss after 56 weeks (Liraglutide 3.0 mg for weight management, FDA Briefing Information for the September 11, 2014 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee). The only known variables to influence exposure and/or weight loss response to liraglutide 3.0 mg are sex and body weight (Overgaard *et al. Clin Pharmacokinet*. 2016; Wilding *et al. Diabetes Obes Metab*. 2016;18:491-9). Unfortunately, menopausal status was not a part of the information collected at baseline and so an analysis of the effect on response to liraglutide 3.0 mg – if any – could not be made.

R2.3

Similar request for BMI: it would be ideal to have the data about % of ERs and ENRs having the patients divided in overweight and obesity classes. This request hold true having in mind the original publication of Pi-Sunyer X. et al. NEJM 2015 in which a different response was observed among BMI classes.

Response: Similar to our response to R2.2, we would prefer not to include the suggested additional data by overweight/obesity class, as this would suggest overweight/obesity class is a determinant of the likelihood of ≥5% weight loss after 56 weeks, which it is not. Whilst there was a trend towards an interaction between baseline BMI and percentage weight loss in SCALE Obesity and Prediabetes (p=0.054), it was not observed for the proportion of patients who achieved ≥5% weight loss (p=0.19) (Pi-Sunyer *et al. N Engl J Med*. 2015;373:11-22), and there was no interaction between BMI group and ≥5% weight loss in SCALE Diabetes (Aroda et al. ADA. 2015; Late-breaker:307-LB.). Moreover, we know from exposure-response analyses (Wilding *et al. Diabetes Obes Metab*. 2016;18:491-9) that while there was *'…a slight decrease in liraglutide exposure with increasing BMI, … exposure differences across BMI subgroups were not associated with meaningful differences in body weight loss, and exposure–weight loss relationships were virtually identical for the four BMI subgroups*.' Thus, the main determinant of weight loss is liraglutide plasma exposure, and the only identified determinants of exposure are body weight and sex. The addition of more granularity on age or BMI would not be of clinical use for the reader.

Reviewer 2.4

At our opinion, the ethnicity should be categorized in different manner considering Hispanic, non Hispanic white, African/American, American Indians and others.

Response: Ethnicity data (Hispanic/non-Hispanic) has been added to the baseline demographics tables to complement the race data. The categories provided in the original manuscript are consistent with current regulatory requirements and all other liraglutide data/analyses in the public domain; thus, we would prefer to keep as it currently stands.

Reviewer 2.5

By carefully looking the Table S7, nausea is more prominent in ERs than in ENR patients according to the data derived from Scale Diabetes, at least this should be critically discussed.

Response: The greater rates of GI disorders in ERs in the SCALE Diabetes trial is mentioned on pages 14 (Results) and 17 (Discussion). The finding is highlighted but not discussed at length because the finding – whilst a potential mechanism to explain early weight loss responses – was not observed in the much larger SCALE Obesity and Prediabetes (Liraglutide 3.0 mg: N= 423 vs. 2487). Whilst we know from the previously published exposure-response manuscript (Wilding *et al. Diabetes Obes Metab*. 2016;18:491-9) that there is a relationship between higher exposure and occurrence of mild (but not moderate/severe) nausea – it has also been shown that weight loss in patients with and without nausea were comparable (Lean *et al. Int J Obes (Lond).* 2014;38:689-97; Lean *et al. AACE* 2015; Poster 611. Abstract available at: http://am2015.aace.com), so GI adverse events cannot explain all the weight loss seen in subjects on liraglutide – nor could it account for the weight loss difference between ERs and ENRs in SCALE Obesity and Prediabetes.

Reviewer: 3 Comments to the Author

Summary: The authors utilized pooled data from phase III trials of high dose liraglutide to determine an optimal cut-point to identify individuals most likely to achieve clinically-meaningful weight loss at 56 weeks. The best balance of positive and negative predictive value was achieved when ≥4% weight loss was observed at the 16 week time-point. Using this criterion, much greater weight loss was observed in early responders vs. early non-responders. Moreover, early responders experienced greater improvements in many cardiometabolic risk factors and in health-related quality of life. The authors conclude that the use of this criterion might be clinically useful and improve the safety and efficacy of liraglutide as a treatment for obesity.

Comments to the authors: Overall, this is a well-written paper and a practical, clinically-relevant topic of investigation.

Reviewer 3.1

Justification regarding the choice of cutoff is somewhat lacking. Using the positive- and negative predictive values and correctly predicted data presented in Table 1, it seems not much is sacrificed by selecting an earlier time-point. Though the highest numerical correctly-predicted value was 4% weight reduction at 16 weeks, similarly high predictive values were identified at earlier time-points. Therefore, the authors should consider if picking an earlier time-point would save time and money in the clinic and allow those patients least likely to benefit to pursue other treatment options earlier. Alternatively, if the authors wish to stick with their current cut-point, additional justification should be provided with discussion of the pros and cons of choosing this versus other criteria.

Response: We remain firm that 4% weight loss at 16 weeks is the most appropriate cut-off to identify individuals most likely to achieve a ≥5% weight loss after 56 weeks. The FDA reviewed the same data and reached the same conclusion, as also reflected in the US label language. We have explained in some

detail in the manuscript how an 8- or 12-week cut-point would have resulted in significantly more patients being incorrectly discontinued (pages 11-12), and have added new text to the discussion (page 16) to highlight this (short statement, to keep within character limits).

Reviewer 3.2

If weight outcomes are available at the two year time-point (even from one of the trials), it would be interesting to evaluate whether the criterion remains a predictor over a longer period of time.

Response: This manuscript focusses on the 1-year data and uses a large number and broad spectrum of patient profiles to draw its conclusions – and this is reflected in the local label language. Data beyond the 1-year are available from a subset of the original population in SCALE Obesity & Prediabetes (individuals with prediabetes only); therefore the findings – whilst of interest – would be based on smaller target population of mostly 'responders' (the rest would have dropped out) and not be as generally applicable as the larger, broader patient group in the 1 year data set.

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Early weight loss with liraglutide 3.0 mg predicts 1-year weight loss and is associated with improvements in clinical markers

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Suggested running head: Liraglutide 3.0 mg: early response, 1-year outcomes

Keywords: Responders; health-related quality of life; stopping rules; glycemic control

Word Count & figures: ~~3497~~ 3499 words (max 3500); 4 tables and 3 figures (max 8); 30 references (max 40); Supplementary online material

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What is known?

- Early weight loss, whether through lifestyle or pharmacotherapy, is a good predictor of long-term weight loss.
- Consequently, all recently-approved weight loss medication labels include 'stopping rules' for discontinuing medication if a threshold weight loss is not achieved by a specified milestone.
- Few data are available that describe weight loss and other outcomes separately in early weight loss responders and early weight loss non-responders.

What does this study add?

- This study describes how an early response criterion was identified for patients treated with liraglutide 3.0 mg.
- Among early responders to liraglutide 3.0 mg, greater mean weight loss and greater proportions achieving weight-loss thresholds were observed.
- The changes in cardiometabolic risk factors and HRQoL scores observed in early responders to liraglutide 3.0 mg versus early non-responders are compared.

Disclosures:

K. Fujioka has received research grants from Orexigen; has received research grants, has acted as consultant, and has attended speakers' bureaux for Novo Nordisk; has received research grants, and has acted as consultant for Enteromedics; has received research grants, and has attended speakers' bureaux for Shire; has acted as consultant for Zafgen; has attended speakers bureaux for Abbott; has acted as consultant, and has attended speakers' bureaux for Takeda; has received research grants, has acted as consultant, and has attended speakers' bureaux for Eisai; has acted as consultant for Gelesis; and has acted as consultant for Nazura.

P. M. O'Neil has received research grants from Orexigen Therapeutics; has received research grants from, and has attended speakers' bureaux for Weight Watchers International; has received research grants from, and has attended speakers' bureaux for Novo Nordisk; has attended speakers' bureaux for Eisai; has attended advisory panels for Fleishman-Hillard; has attended speakers' bureaux for Vindico CME; has attended speakers' bureaux for Practicing Clinicians Exchange; has attended advisory panels for Medscape CME.

M. Davies has attended advisory boards, has acted as consultant, and has attended speakers' bureaux for Sanofi-Aventis, Eli Lilly & Co, Merck Sharp & Dohme, Boerhinger Ingelheim, AstraZeneca, Janssen and Novo Nordisk; and has attended speakers' bureaux for Mitsubishi Tanabe Pharma Corp.

F. Greenway has acted as consultant to AlphaSights; has reviewed a proposal for American Pistachio; has acted as consultant for ClearView Healthcare Partners; has attended medical advisory boards for Curves; has had travel reimbursement for meeting attendance from Diabetes Technology Society has attended editorial board meetings for Diabetic Living; has acted as consultant for Eisai, Inc.; has acted as consultant for Embera; has attended scientific advisory boards for General Nutrition Corporation (GNC); has attended scientif advisory boards, has acted as consultant for, and holds stock options in

MicroBiome Therapeutics; has acted as consultant for, and holds stock options in Neothetics, Inc.; has attended scientific advisory boards for Neurium; holds stock opitions in and patent licences with NeuroQuest, Inc.; has attended advisory boards for Novo Nordisk has attended board meetings for Obesity Medicine Society (OMA); has attended advisory boards, and acted as consultant for Orexigen Therapeutics, Inc., has attended scientific advisory boards for Pamlab, Inc., has acted as medical expert for PlenSat, Inc.; has acted as consultant for Synergy Medical Education; has attended medical scientific boards for Takeda Pharmaceuticals; has attended a GRAS panel for Techenterprises, LLC; has acted as faculty consultant for Vindico Medical Education; has been a witness for Wilson, Sonsini, Goodrich & Rosati Professional Corp; has attended scientific advisory boards for and has acted as consultant for Zafgen, Inc.; is in receipt of research grants from NIH (NIDDK), Novo Nordisk, Hanmi Pharmaceuticals, NIH, Tufts University; has been in receipt of research grants from American Egg Board, Biologene, Pennington Biomedical Research Foundation, MannKind Corporation, Wright Group, NuMe Health, Orexigen Therapeutics, Inc., OmniActive, and Pepsico; and has two patent pending (WO 2016/033063 A1; PCT/US16/15395.

D.C.W. Lau has attended advisory boards and speakers' bureaux for Amgen; has attended advisory boards and speakers' bureaux for Janssen; has attended advisory boards for Roche; has attended advisory boards for Shire; has attended advisory boards and speakers' bureaux for Valeant; has received personal fees from University of Calgary; is President of the Canadian Association of Bariatric Physicians and Surgeons; is President of Obesity Canada; has received research grants from,and has attended advisory boards and speakers' bureaux for AstraZeneca; has received research grants from,and has attended advisory boards and speakers' bureaux for Boehringer-Ingelheim; has received research grants from, and has attended advisory boards and speakers' bureaux for Bristol-Myers Squibb; has received research grants from, and has attended advisory boards and speakers' bureaux for Eli Lilly & Co; has received research grants from, and has attended advisory boards and speakers' bureaux for Merck; has

received research grants from, and has attended advisory boards and speakers' bureaux for Novo Nordisk.

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C. Bjørn Jensen is an employee and shareholder of Novo Nordisk.

J.P.H. Wilding has received research grants from, attended advisory boards and speakers' bureaux for AstraZeneca; has attended advisory panels and speakers' bureau for Boehringer Ingelheim; has received research grants from, attended advisory boards and speakers' bureaux for Bristol-Myers Squibb; has attended advisory panels and speakers' bureaux for Janssen; has attended speakers' bureau for Eli Lilly & Co; has attended advisory panels for Merck Sharpe & Dohme; has received research grants from, and attended advisory boards and speakers' bureaux for Novo Nordisk; has acted as consultant for Pfizer; has attended advisory panels for Sanofi; has attended advisory panels for Orexigen; and has attended advisory panels and speakers' bureaux for Astellas.

Contributions: The decision to examine the outcomes in early responders and early non-responders was a joint one by all the authors, based on trials in which all the academic authors were investigators. The statistical analyses were performed by Novo Nordisk. All authors were involved in discussing the results of the analyses, writing the paper and approving the submitted version.

Abstract

Objective: To identify an early response criterion for predicting ≥5% weight loss with liraglutide 3.0 mg at Week 56, and to compare efficacy outcomes in early responders (ERs) and early non-responders (ENRs).

Methods: Using pooled data from the SCALE Obesity and Prediabetes and SCALE Diabetes trials, weight loss of ≥4% at 16 weeks best predicted ≥5% weight loss after 56 weeks. Weight loss and changes in cardiometabolic risk factors and health-related quality of life (HRQoL) were evaluated in ERs (≥4% weight loss at Week 16) and ENRs (<4% weight loss at Week 16) completing 56 weeks' treatment.

Results: Proportions of ERs/ENRs to liraglutide 3.0 mg were 77.3%/22.7% (individuals without type 2 diabetes [T2D]), and 62.7%/37.3% (those with T2D). Greater mean weight loss was observed in ERs vs. ENRs: 10.8% vs. 3.0% (without T2D), 8.5% vs. 3.1% (T2D). In both trials greater proportions of ERs vs. ENRs achieved ≥5%, >10% and >15% weight loss at Week 56 with liraglutide 3.0 mg. Greater improvements in cardiometabolic risk factors and HRQoL scores were observed in ERs vs. ENRs.

Conclusion: The early response criterion is clinically useful to identify individuals who will achieve clinically-meaningful weight loss at 56 weeks.

Trial registrations: NCT01272219; NCT01272232

Introduction

Managing obesity with pharmacotherapy ~~combined with~~plus lifestyle intervention can help increase the proportion of people reaching ≥5% weight loss ~~of at least 5%~~, the regulatory benchmark for clinically-meaningful weight loss,[1,2] but use of pharmacotherapy must be balanced against potential adverse effects of treatment and costs. One strategy to increase benefit versus risk in obesity pharmacotherapy is through identification of long-term weight-loss predictors. By stopping drug therapy early in patients unlikely to achieve clinical benefit, clinicians can minimize drug exposure, improve the benefit:risk ratio for the patient,[3] and use health resources more effectively. Early weight loss-, whether through lifestyle[4-7] or pharmacotherapy,[8-11] is a good predictor of long-term weight loss. Indeed, all recently-approved weight loss medication labels include 'stopping rules' stating when pharmacotherapy should be discontinued if clinically-relevant weight loss is not, or is unlikely to be, achieved. However, current labels provide ~~no~~ little information on ~~weight loss or other~~ outcomes in those individuals eligible for continued treatment beyond the early milestone; reported results are for all randomized individuals.

Liraglutide is a glucagon-like peptide-1 (GLP-1) analog with 97% homology to human GLP-1, a physiological regulator of appetite.[12,13] Liraglutide at doses up to 1.8 mg once-daily (Victoza®, Novo Nordisk, Bagsvaerd, Denmark) has been licensed for glycemic control in type 2 diabetes (T2D) since 2009. More recently, liraglutide 3.0 mg (Saxenda®; Novo Nordisk), as an adjunct to a reduced-calorie diet and increased physical activity, has been approved for weight management in the USA, EU, and elsewhere.

This paper describes how the early treatment criterion that best predicts ≥5% weight loss with liraglutide 3.0 mg at Week 56 was identified, based on data from the two largest trials in the SCALE

program of phase 3a trials of liraglutide 3.0 mg for weight loss. *Post-hoc* analyses are presented of the efficacy and safety results from these trials by early responder status, using this early response criterion.

Methods

Trial design

The design, methods, patient populations and results of the SCALE Obesity and Prediabetes (NCT01272219) and SCALE Diabetes (NCT01272232) trials were previously published.[14,15] Briefly, in SCALE Obesity and Prediabetes, 3731 ~~overweight or obese~~ individuals with overweight or obesity and without diabetes (BMI ≥30 kg/m^2, or ~~BMI~~ ≥27 kg/m^2 with ≥1 obesity-related comorbidity), were randomized 2:1 to liraglutide 3.0 mg or placebo for 56 weeks.[14] ~~(Individuals with prediabetes remained in the trial for a further 2 years, only the 56-week results are reported here.)~~ In SCALE Diabetes, 846 ~~obese or~~individuals with ~~overweight (~~BMI ≥27 kg/m^2~~)~~ ~~individuals or obesity~~ and ~~with~~ T2D were randomized 2:1:1 to liraglutide 3.0 mg, liraglutide 1.8 mg or placebo for 56 weeks.[15] Both trials were double-blind, placebo-controlled, multicenter trials, and trial drug was given as adjunct to lifestyle intervention (500 kcal/day deficit diet and physical activity ≥~~of at least~~ 150 min/week). ~~In this paper~~Here, only results for liraglutide 3.0 mg and placebo are reported, referred to as 'liraglutide 3.0 mg' or 'placebo' hereafter. Liraglutide was initiated at a dose of 0.6 mg and dose-escalated by 0.6-mg increments weekly to the 3.0-mg treatment dose. This was a forced dose-escalation, with the dose at 3.0 mg for all individuals by Week 4; investigators could delay dose escalation by 7 days in total.

Determination of early response criterion

We used pooled data from SCALE Obesity and Prediabetes and SCALE Diabetes to determine the optimal treatment timepoint and weight-loss threshold for identifying subjects likely to achieve ≥5% loss of initial body weight after 56 weeks' treatment. Given the objective of the analysis (predictive value for 1-

year weight loss), only trials of minimum 1-year duration were eligible. Two of the four phase 3a trials were excluded: SCALE Sleep Apnea because it was a 32-week trial; SCALE Maintenance because it required individuals to lose ≥5% weight through diet and exercise prior to randomization, thus their initial weight loss after randomization would not have represented general practice. The pooled analysis was pre-defined with the FDA before individual trial data became available. For mean weight loss in Table 1, only subjects with body-weight measurements at baseline and the specific timepoint being analyzed (8, 12, 16 weeks) and Week 56 contributed to the analysis. For identifying individuals with ≥5% weight loss at Week 56, missing data were imputed using last observation carried forward (LOCF~~)~~. Reasons for choosing these timepoints are in the Supplementary material.

The ability to predict response status after 56 weeks was evaluated by the positive predictive value (PPV; i.e. proportion of subjects with an early response who had ≥5% weight loss after 56 weeks), and the negative predictive value (NPV; i.e. proportion of subjects with an early non-response who had <5% weight loss after 56 weeks) for ≥3, 4 and 5% weight loss at 8, 12 and 16 weeks. The proportions of 'correctly predicted overall' were calculated from PPV and NPV (Table 1). The sensitivity and specificity of these criteria were also evaluated (Supplementary material).

The pooled analysis was repeated for male and female subjects, and the results were also analyzed separately by trial, to ensure that the identified cut-point for defining early response would be valid for both sexes and for subjects with or without T2D. A sensitivity analysis was also performed in which missing Week 56 responses were imputed as non-response, rather than using LOCF.

Post-hoc analysis of endpoints by early response status

Once the optimal early response criterion was identified, subjects were classified as early responders (ERs) or early non-responders (ENRs). We then assessed efficacy outcomes at Week 56 for ERs and ENRs, based on individuals who completed 56 weeks' treatment. Weight endpoints were mean change in body weight from baseline and the proportion of patients with a weight loss of ≥5%, >10% and >15% at Week 56. Secondary efficacy outcomes were the changes from baseline to Week 56 in HbA_{1c}, fasting plasma glucose (FPG), systolic (SBP) and diastolic blood pressure (DBP), BMI, waist circumference, heart rate, fasting lipid profile, and various additional cardiometabolic biomarkers. Changes in the following health-related quality of life (HRQoL) scores were also evaluated: Impact of Weight on Quality of Life-Lite (IWQOL-Lite) total score and physical function score[16] (both trials); and Short Form-36 (SF-36) physical component summary score[17] (SCALE Obesity and Prediabetes only).

Efficacy outcomes are reported for ERs and ENRs who completed 56 weeks' treatment. Safety is reported based on the safety analysis set for ERs and ENRs (i.e. all subjects with data at Week 16, regardless of whether they completed 56 weeks' treatment) (Figure 1). The results are reported by trial for ERs and ENRs to liraglutide 3.0 mg or placebo so that any potential differences in clinical outcomes in patients with T2D would not be masked due to the relatively small size of this study population.

Statistical analysis

For the pooled analysis to assess the optimal response criterion, no covariate adjustments were made. Missing response status after 56 weeks was imputed using LOCF. The observed mean weight loss was plotted during the course of the trial (Figure 2).

Analyses of outcomes at Week 56 were performed in trial completers split by ER and ENR status. The analyses of outcomes used the same model as in the individual trials.[14,15] The model included treatment,

country, sex, and interaction between BMI strata and prediabetes status as fixed effects, with baseline body weight as covariate. In SCALE Diabetes, an interaction between HbA_{1c} stratification and background medication was also included. Continuous variables were estimated using ANCOVA, as described above; categorical variables were estimated using a logistic regression model with the same fixed effects and covariates as the relevant ANCOVA. Efficacy data are estimated means or estimated proportions; safety data are observed proportions or observed means.

Statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc, Cary, NC, USA). As ERs and ENRs are not randomized populations, differences between them were not quantified or analyzed statistically.

Results

Subject disposition by trial for the individuals covered in these analyses (i.e. those with body-weight measurement at baseline and Weeks 16 and 56) is shown in Figure 1.

Optimal early response criterion for ≥5% weight loss after 56 weeks

The proportion of subjects treated with liraglutide 3.0 mg who lost ≥3%, ≥4% or ≥5% weight at 8, 12 and 16 weeks in the pooled analysis of SCALE ~~Prediabetes and~~ Obesity and Prediabetes and SCALE Diabetes and associated PPVs and NPVs are shown in Table 1. The sensitivity and specificity of each criterion were also calculated (Table S1).

The analyses showed that 4% weight loss at 16 weeks yielded the highest correctly predicted value (80.1%), consistent with high values for both PPV (81.4%) and NPV (76.0%) (Table 1). The criteria based on the 8-week timepoint were associated with lower overall correctly predicted values and, in

particular, low NPVs, meaning that treatment would have been incorrectly discontinued in a notable number of individuals who would have gone on to achieve ≥5% weight loss after 56 weeks. For example, using NPV for 4% weight loss at 8 weeks, 34.7% (350 of 1009 subjects identified as ENRs) would have been incorrectly discontinued, versus 24% (150 of 626 subjects) using the 16-week value (Table 1). The 12-week timepoint criteria had PPVs similar to those at the 16-week timepoint but comparatively lower NPVs (Table 1). Thus, using NPV for 4% weight loss at 12 weeks, 29.2% (221 of 757 subjects identified as ENRs) would have been incorrectly discontinued, versus 24% (150 of 626 subjects) using the 16-week value (Table 1). Furthermore, the choice of Week 16 meant that individuals would have received treatment-dose liraglutide 3.0 mg for 12 weeks, consistent with the exposure period generally recommended for other anti-obesity medications.

Consistent results and conclusions were reached when the pooled analysis was conducted separately for males and females, or for each trial, and from a sensitivity analysis with missing Week 56 responses imputed as non-response (Tables S2-S4).

A separate analysis showed that ≥4% weight loss at 16 weeks was also a good criterion for predicting weight loss with placebo, yielding a high overall correctly predicted value (80.0%), consistent with a reasonably high PPV (66.1%) and NPV (85.8%) (Table S5).

Early responder populations

Among individuals on liraglutide 3.0 mg with a Week 16 measurement, 77.3% without T2D and 62.7% with T2D were ERs, and 22.7% and 37.3% were ENRs. The proportions of individuals who were ERs to placebo were much lower than with liraglutide 3.0 mg: 30.5% of individuals without T2D and 20.5% with T2D.

Demographic and other baseline characteristics of all randomized subjects, as well as ERs and ENRs in each trial, are shown in Table 2. The 'all-randomized' group ~~includes~~ included individuals who discontinued the trial prior to Week 16, while the ER/ENR groups ~~do~~ did not (by definition they could not be classified as ER or ENR).

In general, baseline characteristics in the ER and ENR groups appeared similar across treatment groups within each trial. In both liraglutide 3.0 mg and placebo groups, individuals of White origin appeared more prevalent in the ER vs ENR groups, and female sex appeared consistently associated with early response to liraglutide 3.0 mg (see percentages, Table S3) but not to placebo in individuals with and without T2D.

Weight loss at Week 56 in ERs and ENRs

In SCALE Obesity and Prediabetes, weight loss in ERs to liraglutide 3.0 mg was 10.8% (11.2 kg) vs. 3.0% (3.2 kg) for ENRs (Figure 2a). Similarly, in SCALE Diabetes, ERs had a greater mean weight loss than ENRs (8.5% [9.0 kg] vs. 3.1% [3.2 kg]) at 56 weeks (Figure 2b). ERs to placebo also achieved greater weight loss than ENRs to placebo (Figure 2).

The proportions of ERs and ENRs achieving ≥5%, >10% and >15% weight loss at Week 56 in both trials were always greater for ERs vs ENRs to liraglutide 3.0 mg (Figure 3). The same pattern was observed for placebo, although proportions achieving each category were smaller than for liraglutide 3.0 mg.

Secondary endpoints at Week 56 in ERs and ENRs

In SCALE Obesity and Prediabetes, changes in all cardiometabolic biomarkers examined, except heart rate, appeared to be more favorable in ERs than ENRs to liraglutide 3.0 mg, consistent with greater weight loss (Table 3a, Table S6a). In particular, greater improvements were observed in ERs vs. ENRs to liraglutide 3.0 mg for SBP, HDL-cholesterol, LDL-cholesterol, total cholesterol, and triglycerides. Most changes were also more favorable in ERs vs. ENRs to placebo. With liraglutide 3.0 mg, pulse rate increased by 2.7 beats per minute (bpm) in ERs and 2.6 bpm in ENRs. With placebo, pulse rate changes were -1.2 and +0.2 bpm, respectively. Improvements in the IWQoL-Lite total score and physical function score and the SF-36 physical component summary score were reported by all groups, but appeared greater ~~with~~ in ERs vs. ENRs to both liraglutide 3.0 mg and placebo (Tables 3a, S6a).

Similarly in SCALE Diabetes, changes in most cardiometabolic biomarkers and HRQoL scores appeared more favorable in ERs than ENRs (Tables 3b, S6b). Notably, improvements in glycemic markers were observed in both ERs and ENRs to liraglutide 3.0 mg.

Safety

Safety results for the randomized populations in both trials were reported previously.[14,15] The most common adverse events (AEs), occurring more frequently with liraglutide 3.0 mg vs. placebo, were gastrointestinal.

An overview of safety results by early responder status is shown in Table 4. AEs occurring in ≥5% of individuals treated with liraglutide 3.0 mg and more frequently with liraglutide 3.0 mg than placebo are listed by preferred term in Table S7. AE rates were generally comparable between ERs and ENRs to liraglutide 3.0 mg, and comparable to the overall trial population, except that in SCALE Diabetes, rates of gastrointestinal- or appetite-related AEs were higher in ERs vs. ENRs.

In SCALE Obesity and Prediabetes, pancreatitis was uncommon in ERs (<0.1/100-patient-years' exposure [PYE]) and ENRs (0.2/100-PYE) to liraglutide 3.0 mg. Gallbladder disorders were more frequent in ERs (2.8% of individuals; 2.9/100-PYE) vs. ENRs to liraglutide 3.0 mg (1.4%; 1.9/100 PYE). Psychiatric AEs appeared similar in ER and ENRs.

In SCALE Diabetes, no events of pancreatitis were reported, and there were too few gallbladder-related and psychiatric AEs to allow any conclusions to be drawn. Documented symptomatic hypoglycemia, defined according to ADA criteria,[18] was similar in ERs vs. ENRs to liraglutide 3.0 mg (event rates of 79.5/100-PYE and 93.3/100-PYE), respectively.

For ERs and ENRs to placebo, results were as follows: in SCALE Obesity and Prediabetes, no pancreatitis was reported in either ERs or ENRs; gallbladder disorders occurred in 1.6% of ERs (2.2/100-PYE) and 0.5% of ENRs (0.6/100-PYE); and psychiatric AEs appeared similar in ER and ENRs. In SCALE Diabetes, documented hypoglycemia occurred at event rates of 20.5/100-PYE (ERs to placebo) and 31.1/100-PYE (ENRs to placebo).

Discussion

It is well documented that early response to a weight-loss intervention can predict long-term weight loss;[8-11] this is the basis for the stopping rules for all recently approved weight-loss medications.[19-21] Weight-loss response after 1-4 months has been used to predict weight loss at 1 year. Interestingly, in the Look AHEAD study, 1- and 2-month weight loss was associated with weight loss through Year 8 among individuals with T2D who received an intensive lifestyle intervention.[7]

In order to identify an optimal early response criterion for liraglutide 3.0 mg, we examined weight loss of ≥3%, 4% or 5% at 8, 12 or 16 weeks in a pooled analysis pre-defined with the US FDA before trial data became available. Weight loss of ≥4% at Week 16 was shown to be the best predictor of ≥5% weight loss at 56 weeks and to be appropriate for individuals with and without T2D and for both genders (Table 1, Table S1). Earlier timepoints would result in discontinuation of treatment in a significant number of individuals who would indeed achieve ≥5% weight loss after 56 weeks, whilst later timepoints ~~Earlier timepoints would result in more patients who could potentially acheive 5% weight loss at 56 weeks after failing to achieve the 16 -weekearly weight loss target. Whilst L~~later timepoints would likely have achieved even greater predictive accuracy, but were not considered as they would have entailed additional unnecessary exposure in non-responders. Accordingly, the 'stopping rule' in the USA specifies a weight loss of ≥4% at 16 weeks.[22] While health authorities across the world focus on limiting treatment to those who will benefit, their approaches differ slightly. The European Medicines Agency required an early response criterion optimized to exclude individuals who were unlikely to achieve ≥10% weight loss at 56 weeks; this was best fulfilled by weight loss of ≥5% after 16 weeks (data not shown). Accordingly, the European label requires ≥5% weight loss after 12 weeks on the full 3.0-mg dose to qualify for continued treatment.[23]

In both trials, higher proportions of subjects were early responders to liraglutide 3.0 mg than to placebo. Early responders to liraglutide achieved greater mean weight loss than early non-responders, and were more likely to achieve ≥5%, >10% and >15% weight loss at 56 weeks. Greater responses were also seen among early responders vs. early non-responders to placebo; but fewer subjects were early responders to placebo compared with liraglutide 3.0 mg.

The greater weight loss in early responders was accompanied by a trend toward greater improvements in cardiometabolic biomarkers. Decreases in mean SBP and DBP and favorable changes in lipid profile, in particular, are expected effects of weight loss, contributing to a decreased risk of developing cardiovascular disease.[24] In SCALE Diabetes, clinically-meaningful reductions in HbA_{1c} and FPG were seen in both early responders and early non-responders to liraglutide, due to its direct glucose-lowering effect;[25] in early responders, this effect appeared further enhanced by the greater weight loss versus early non-responders. The combination of direct effects of liraglutide on glycemia, as well as further improvement likely mediated by enhanced weight loss in early responders, may be particularly beneficial for slowing progression to T2D, and increasing regression to normoglycemia in individuals with prediabetes, which further reduces the risk of conversion to T2D.[26]

It has been suggested that, in trials of anti-obesity drugs, improvements in feeling and functioning should be measured when validated measures exist.[27] Improvements in HRQoL were recorded as assessed by IWQOL-Lite, a questionnaire developed specifically to evaluate the impact of weight on quality of life (both trials), and SF-36, a more general HRQoL questionnaire (SCALE Obesity and Prediabetes only). For both liraglutide 3.0 mg and placebo, improvements were greater in early responders than early non-responders. The changes recorded for early responders (to either intervention) were clinically relevant. (Clinically relevant improvements for an individual are increases of 7.7-12 points for IWQOL-Lite total score, depending on baseline score,[28] and ≥2 points for SF-36 physical component summary score.[17])

The greater improvements observed in early responders, compared with early non-responders, were generally not accompanied by an increase in AEs: the safety profiles of early responders and early non-responders were similar within each trial, except that early responders reported higher rates of

gastrointestinal disorders in SCALE Diabetes, and higher rates of gallbladder disorders in SCALE Obesity and Prediabetes. No new safety signals arose among early responders or early non-responders.

In pooled analyses of the SCALE trials, women had slightly greater weight loss than men with liraglutide 3.0 mg;[29] however, both men and women experienced a clinically-meaningful weight loss. Consistent with this, there appeared to be more women than men among early responders to liraglutide 3.0 mg in both trials. Greater weight loss in women may in part be explained by higher plasma liraglutide exposure in women vs. men.[30]

The comparisons between early responders and early non-responders must be interpreted with caution as they are not comparisons between randomized groups and were therefore not subjected to significance testing. In the case of the diabetes trial, conclusions are further limited by the low number of individuals in the liraglutide early non-responder and placebo early responder groups. An additional limitation is the use of a forced dose escalation of liraglutide from 0.6 mg daily to 3.0 mg daily in 0.6-mg increments over 4 weeks (with 1 additional week at investigator's discretion) in the original trials. Also, early non-responders in these trials were continued on treatment for 56 weeks; in clinical practice their treatment would be discontinued after 16 weeks, and improvements in endpoints might therefore be smaller than those reported here.

From a clinical perspective, use of the stopping rules should help optimize the use of liraglutide 3.0 mg for weight management. Patients can be informed that, if they respond well during the first 16 weeks, it is likely they will continue to do so. It is reassuring that most adverse events were no more frequent in early responders compared with early non-responders, even with greater weight loss, with the

exception of gallbladder disorders, perhaps reinforcing the suggestion that at least part of the increased risk of gallbladder disorders seen in SCALE Obesity and Prediabetes was related to weight loss.[14]

Conclusions

Weight loss of ≥4% after 16 weeks of treatment is a strong predictor of a clinically-meaningful weight loss at 56 weeks. More individuals without or with T2D were early responders to liraglutide 3.0 mg in combination with lifestyle intervention compared with lifestyle intervention alone.

Among early responders to liraglutide 3.0 mg, greater mean weight loss, greater proportions achieving weight-loss thresholds, and generally greater improvements in cardiometabolic risk factors and HRQoL scores were observed compared with early non-responders.

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Table 1. Positive and negative predictive values for achieving ≥5% weight loss with liraglutide 3.0 mg at 56 weeks using different early response criteria: pooled analysis of the SCALE Obesity and Prediabetes and SCALE Diabetes trials.

Week	Early response criterion	N	Early response n (%)	Mean week 56 weight change (%) in early responders	Positive predictive value (a) n (%)	Early non-response n (%)	Mean week 56 weight change (%) in early non-responders	Negative predictive value (b) n (%)	Correctly predicted (c) n (%)
8	3%	2653	2035 (76.7%)	-10.09	1544 (75.9%)	618 (23.3%)	-3.69	439 (71.0%)	1983 (74.7%)
	4%		1644 (62.0%)	-11.00	1373 (83.5%)	1009 (38.0%)	-4.53	659 (65.3%)	2032 (76.6%)
	5%		1245 (46.9%)	-12.10	1096 (88.0%)	1408 (53.1%)	-5.46	781 (55.5%)	1877 (70.8%)
12	3%	2578	2084 (80.8%)	-9.98	1601 (76.8%)	494 (19.2%)	-2.79	389 (78.7%)	1990 (77.2%)
	4%		1821 (70.6%)	-10.68	1485 (81.5%)	757 (29.4%)	-3.56	536 (70.8%)	2021 (78.4%)
	5%		1515 (58.8%)	-11.55	1312 (86.6%)	1063 (41.2%)	-4.37	669 (62.9%)	1981 (76.8%)
16	3%	2519	2099 (83.3%)	-9.95	1609 (76.7%)	420 (16.7%)	-2.29	338 (80.5%)	1947 (77.3%)
	4%		1893 (75.1%)	-10.46	1541 (81.4%)	626 (24.9%)	-3.02	476 (76.0%)	2017 (80.1%)
	5%		1637 (65.0%)	-11.21	1411 (86.2%)	882 (35.0%)	-3.78	602 (68.3%)	2013 (79.9%)

Week 56 response is defined as at least a 5% reduction in body weight. If data were missing for Week 56, the last available body weight measurement was used (i.e. missing data were imputed using last observation carried forward). Mean weight loss is based on observed data only.

[a] Positive predictive value is defined as the percentage of early responders who were Week 56 responders.

[b] Negative predictive value is defined as the percentage of early non-responders who were Week 56 non-responders.

[c] Correctly predicted proportion = (number of correctly predicted week 56 responders + number of correctly predicted week 56 non-responders)/(total number of subjects)

Table 2. Demographics and baseline characteristics of patients by early responder status.

a. SCALE Obesity and Prediabetes.

	Liraglutide 3.0 mg			Placebo		
	All randomized (N=2487)	**Early responders (N=1433)**	**Early non-responders (N=355)**	**All randomized (N=1244)**	**Early responders (N=265)**	**Early non-responders (N=535)**
Female sex, n (%)	1957 (78.7)	1151 (80.3)	251 (70.7)	971 (78.1)	205 (77.4)	415 (77.6)
Mean age, years [SD]	45.2 [12.1]	46.4 [11.6]	45.4 [11.8]	45.0 [12.0]	47.0 [11.7]	45.6 [12.1]
Race, n (%)						
White	2107 (84.7)	1238 (86.4)	289 (81.4)	1061 (85.3)	240 (90.6)	455 (85.0)
Black/African American	242 (9.7)	126 (8.8)	41 (11.5)	114 (9.2)	15 (5.7)	51 (9.5)
Other	138 (5.5)	69 (4.8)	25 (7.0)	69 (5.5)	10 (3.8)	29 (5.4)
Ethnicity, n (%)						
Hispanic/Latino	259 [10.4]	126 [8.8]	31 [8.7]	134 [10.8]	31 [11.7]	46 [8.6]
Non-Hispanic/Latino	2228 [89.6]	1307 [91.2]	324 [91.3]	1110 [89.2]	234 [88.3]	489 [91.4]
Mean weight, kg [SD]	106.2 [21.2]	105.3 [20.4]	109.8 [23.7]	106.2 [21.7]	107.4 [23.6]	106.7 [22.3]
Mean BMI, kg/m^2 [SD]	38.3 [6.4]	38.1 [6.3]	38.9 [6.8]	38.3 [6.3]	38.7 [7.1]	38.3 [6.4]
Glycemic status, n (%)						
Normoglycemic	959 (38.6)	528 (36.8)	151 (42.5)	487 (39.1)	100 (37.7)	196 (36.6)
With prediabetes	1528 (61.4)	905 (63.2)	204 (57.5)	757 (60.9)	165 (62.3)	339 (63.4)
Mean HbA_{1c}, %-points [SD]	5.6 [0.4]	5.6 [0.4]	5.6 [0.4]	5.6 [0.4]	5.6 [0.4]	5.6 [0.4]
Mean FPG, mg/dl [SD]	95.9 [10.6]	96.1 [10.4]	97.2 [11.3]	95.5 [9.8]	95.7 [9.2]	95.9 [9.9]

b. SCALE Diabetes.

	Liraglutide 3.0 mg			Placebo		
	All randomized (N=423)	**Early responders (N=214)**	**Early non-responders (N=110)**	**All randomized (N=212)**	**Early responders (N=31)**	**Early non-responders (N=101)**
Female sex, n (%)	203 (48.0)	112 (52.3)	43 (39.1)	115 (54.2)	15 (48.4)	61 (60.4)
Mean age, years [SD]	55.0 [10.8]	55.5 [10.1]	54.1 [9.8]	54.7 [9.8]	57.9 [9.4]	55.7 [8.8]
Race, n (%)						
White	353 (83.5)	184 (86.0)	86 (78.2)	175 (82.5)	27 (87.1)	83 (82.2)
Black/African American	44 (10.4)	16 (7.5)	14 (12.7)	27 (12.7)	3 (9.7)	13 (12.9)
Other	26 (6.1)	14 (6.5)	10 (9.1)	10 (4.7)	1 (3.2)	5 (5.0)
Ethnicity, n (%)						
Hispanic/Latino	46 [10.9]	19 [8.9]	15 [13.6]	24 [11.3]	3 [9.7]~~6 [8.3]~~	9 [8.9]~~3 [9.7]~~
Non-Hispanic/Latino	375 [88.7]	193 [90.2]	95 [86.4]	187 [88.2]	28 [90.3]~~66 [91.7]~~	92 [91.1]~~28 [90.3]~~
Mean weight, kg [SD]	105.7 [21.9]	106.8 [21.3]	102.8 [19.5]	106.5 [21.3]	109.3 [18.6]	104.7 [22.1]
Mean BMI, kg/m^2 [SD]	37.1 [6.5]	37.7 [6.5]	36.1 [6.3]	37.4 [7.1]	37.7 [5.7]	37.4 [7.6]
Mean HbA_{1c}, %-points [SD]	7.9 [0.8]	7.9 [0.8]	8.0 [0.8]	7.9 [0.8]	7.6 [0.5]	7.8 [0.7]
Mean FPG, mg/dl [SD] [a]	158.4 [32.8]	158.5 [34.8]	157.7 [27.9]	155.5 [33.0]	151.4 [33.0]	149.6 [30.0]

[a] Overall values are based on the full analysis set (N=407 and 211, respectively).

Early responders, individuals who achieved ≥4% weight loss from baseline at 16 weeks; early non-responders, individuals who achieved <4% weight loss from baseline at 16 weeks. Based on individuals with a fasting body weight measurement at baseline and week 16 and who completed 56 weeks of treatment. 'All randomized' refers to all randomized patients in the overall trial.

BMI, body-mass index; FPG, fasting plasma glucose; SD, standard deviation.

Table 3. Changes from baseline in selected secondary endpoints.

a) SCALE Obesity and Prediabetes

	Liraglutide 3.0 mg				Placebo			
	Early responders (N=1433)		Early non-responders (N=355)		Early responders (N=265)		Early non-responders (N=535)	
	Baseline	Change at 56 weeks [SE]	Baseline	Change at 56 weeks [SE]	Baseline	Change at 56 weeks [SE]	Baseline	Change at 56 weeks [SE]
HbA_{1c} (% points)	5.6	-0.36 [0.01]	5.6	-0.23 [0.01]	5.6	-0.17 [0.02]	5.6	-0.06 [0.01]
FPG (mg/dL)	96.1	-8.2 [0.2]	97.2	-6.3 [0.5]	95.7	-2.3 [0.5]	95.9	0.9 [0.4]
SBP (mmHg)	123.4	-5.1 [0.3]	123.8	-2.0 [0.6]	123.0	-2.3 [0.7]	124.0	-1.8 [0.5]
DBP (mmHg)	78.9	-3.3 [0.2]	78.6	-1.4 [0.4]	78.3	-3.0 [0.5]	79.4	-2.1 [0.3]
Pulse, bpm	71.2	+2.7 [0.2]	70.8	+2.6	71.0	-1.2	71.0	+0.2
HDL-cholesterol, mg/dL (%)[a]	51.8	+3.9 [0.4]	52.0	+0.0 [0.8]	51.9	4.8 [0.9]	50.9	–1.0 [0.6]
LDL-cholesterol,	111.4	-3.6 [0.5]	113.2	-0.9 [1.1]	115.6	-2.0 [1.3]	111.7	-1.0 [0.9]

mg/dL (%)[a]								
Total cholesterol, mg/dL (%)[a]	193.0	-3.2 [0.3]	196.7	-1.7 [0.7]	198.6	-1.7 [0.8]	193.9	-0.9 [0.6]
Triglycerides, mg/dL (%)[a]	125.2	-15.3 [0.7]	129.4	-7.1 [1.6]	128.3	-12.8 [1.8]	130.3	-2.5 [1.4]
IWQOL-Lite total score	73.0	+12.7	70.7	+8.2	72.7	+13.0	73.9	+6.3

b) SCALE Diabetes.

	Liraglutide 3.0 mg				Placebo			
	Early responders (N=214)		Early non-responders (N=110)		Early responders (N=31)		Early non-responders (N=101)	
	Baseline	Change at 56 weeks [SE]	Baseline	Change at 56 weeks [SE]	Baseline	Change at 56 weeks [SE]	Baseline	Change at 56 weeks [SE]
HbA1c (% points)	7.9	-1.60 [0.05]	8.0	-1.11 [0.08]	7.6	-1.17 [0.14]	7.7	-0.30 [0.09]
FPG (mg/dL)	158.5	-44.2 [2.4]	157.7	-30.1 [30.3]	151.4	-30.4 [6.2]	151.4	-1.9 [3.7]
SBP (mmHg)	128.4	-3.3 [0.8]	129.1	-1.3 [1.1]	128.7	-3.2 [2.1]	129.8	+0.7 [1.2]
DBP (mmHg)	78.5	-0.6 [0.5]	79.9	-1.8 [0.8]	78.5	-2.1 [0.4]	79.3	-1.0 [0.8]
Pulse, bpm	74.0	+1.7 [0.6]	72.1	+3.1 [0.8]	74.3	-3.8 [1.5]	73.4	-1.4 [0.8]
HDL-cholesterol, mg/dL (%)[a]	45.3	+7.2 [1.0]	46.2	+0.7 [1.3]	43.7	+7.7 [2.6]	45.6	+0.6 [1.3]
LDL-cholesterol, mg/dL (%)[a]	85.1	+1.6 [1.9]	91.7	-0.3 [2.5]	76.7	+2.5 [4.9]	79.8	+4.1 [2.7]

Total cholesterol, mg/dL(%)[a]	169.1	-1.5 [1.0]	175.6	-1.1 [1.5]	159.3	+0.3 [2.8]	164.2	+3.9 [1.6]
Triglycerides, mg/dL (%)[a]	162.0	-19.2 [2.1]	155.8	-6.9 [3.3]	163.6	-12.7[5.9]	157.2	+3.2 [3.8]
IWQOL-Lite total score	69.7	+13.2 [0.8]	79.5	+7.9 [1.1]	73.8	+10.8 [2.1]	75.9	+7.2 [1.2]

[a] Baseline value is in mg/dL and change is presented as relative change.

Early responders, individuals who achieved ≥4% weight loss from baseline at 16 weeks; early non-responders, individuals who achieved <4% weight loss from baseline at 16 weeks. Based on individuals with a fasting body weight measurement at baseline and week 16 and who completed 56 weeks of treatment. Changes are estimated mean changes from baseline to week 56 from an ANCOVA. Missing values post-baseline were imputed using last observation carried forward. Additional endpoints are reported in Tables S6a, b.

DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IWQOL-Lite, Impact of Weight on Quality of Life-Lite; SBP, systolic blood pressure.

Table 4. Overview of AEs in the overall trial and in early responders and early non-responders. The 'All-randomized' column covers all randomized patients in the overall trial.

a) SCALE Obesity and Prediabetes

	Liraglutide 3.0 mg			Placebo		
AE, n (% of patients)	**All randomized N=2481**	**ERs N=1668**	**ENRs N=491**	**All randomized N=1242**	**ERs N=322**	**ENRs N=735**
Adverse events	2285 (92.1)	1559 (93.5)	453 (92.3)	1043 (84.0)	285 (88.5)	651 (88.6)
Serious adverse events	154 (6.2)	106 (6.4)	24 (4.9)	62 (5.0)	21 (6.5)	33 (4.5)
Severe adverse events	304 (12.3)	190 (11.4)	51 (10.4)	113 (9.1)	36 (11.2)	66 (9.0)
Fatal	1 (0.0)	0 (0.0)	1 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)
Leading to withdrawal[a]	244 (9.8)	54 (3.2)	20 (4.1)	47 (3.8)	4 (1.2)	17 (2.3)

b) SCALE Diabetes.

	Liraglutide 3.0 mg			Placebo		
AE, n (% of patients)	**All randomized N=422[b]**	**ERs N=229**	**ENRs N=136**	**All randomized N=212**	**ERs N=34**	**ENRs N=132**
Adverse events	392 (92.9)	222 (96.9)	124 (91.2)	182 (85.8)	32 (94.1)	120 (90.9)
Serious adverse events	37 (8.8)	17 (7.4)	15 (11.0)	13 (6.1)	1 (2.9)	10 (7.6)
Severe adverse events	52 (12.3)	30 (13.1)	14 (10.3)	21 (9.9)	1 (2.9)	17 (12.9)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to withdrawal[a]	39 (9.2)	7 (3.1)	6 (4.4)	7 (3.3)	0 (0.0)	3 (2.3)

[a] Withdrawal rates cover the entire trial period for 'All randomized' and Week 16 onwards for ERs and ENRs.

[b] One subject did not receive treatment and was excluded from the safety analysis set for SCALE Diabetes.

Safety analysis set (for ERs and ENRs, all subjects with data at week 16).

ERs, early responders (individuals who achieved ≥4% weight loss from baseline at 16 weeks); ENRs, early non-responders (individuals who achieved <4% weight loss from baseline at 16 weeks).

Figure 1. Subject disposition for results of post-hoc analyses.

Early responders (ERs), individuals who achieved ≥4% weight loss from baseline at 16 weeks; early non-responders (ENRs), individuals who achieved <4% weight loss from baseline at 16 weeks.

- Full analysis set (FAS): in order to be defined as ER/ENR at Week 16, individuals had to have a fasting body weight measurement at baseline and the Week 16 visit.
- Completers at Week 56 were individuals with a body weight measurement at Week 56.

Only individuals satisfying the respective criteria are shown.

Figure 2. Fasting body weight loss by early responder status.

Line graphs are observed means (±SE) for ERs/ENRs who completed 56 weeks. Fasting visit data only. ERs, early responders (individuals who achieved ≥4% weight loss from baseline at 16 weeks); ENRs, early non-responders (individuals who achieved <4% weight loss from baseline at 16 weeks); SE, standard error. Note that ENRs continued on treatment till week 56; in clinical practice, treatment would cease for ENRs in line with the stopping rule.

Figure 3. Categorical weight loss at Week 56.

Proportions of subjects are estimated proportions from a logistic regression model for ERs/ENRs who completed 56 weeks of treatment. ERs, early responders (individuals who achieved ≥4% weight loss from baseline at 16 weeks); ENR, early non-responders (individuals who achieved <4% weight loss from baseline at 16 weeks).

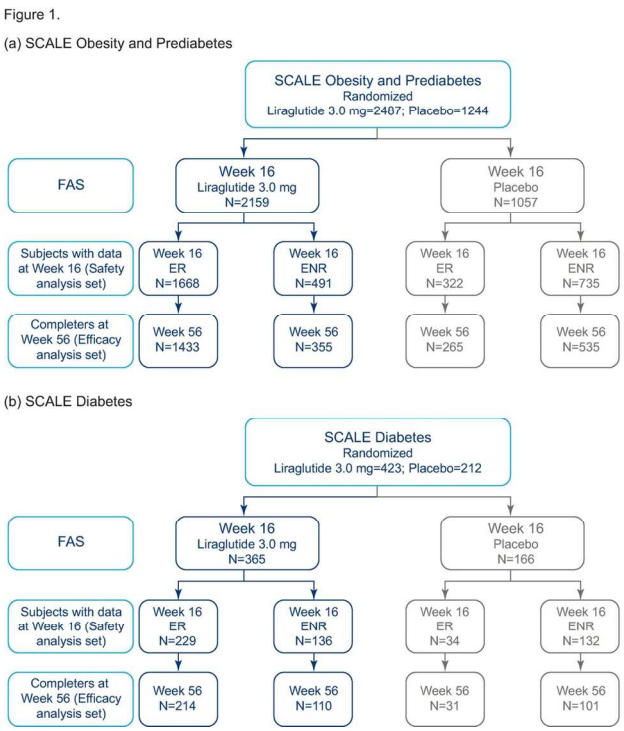

Figure 1. Subject disposition for results of post-hoc analyses.
Early responders (ERs), individuals who achieved ≥4% weight loss from baseline at 16 weeks; early non-responders (ENRs), individuals who achieved <4% weight loss from baseline at 16 weeks.
• Full analysis set (FAS): in order to be defined as ER/ENR at Week 16, individuals had to have a fasting body weight measurement at baseline and the Week 16 visit.
• Completers at Week 56 were individuals with a body weight measurement at Week 56.
Only individuals satisfying the respective criteria are shown.
Figure 1
142x102mm (300 x 300 DPI)

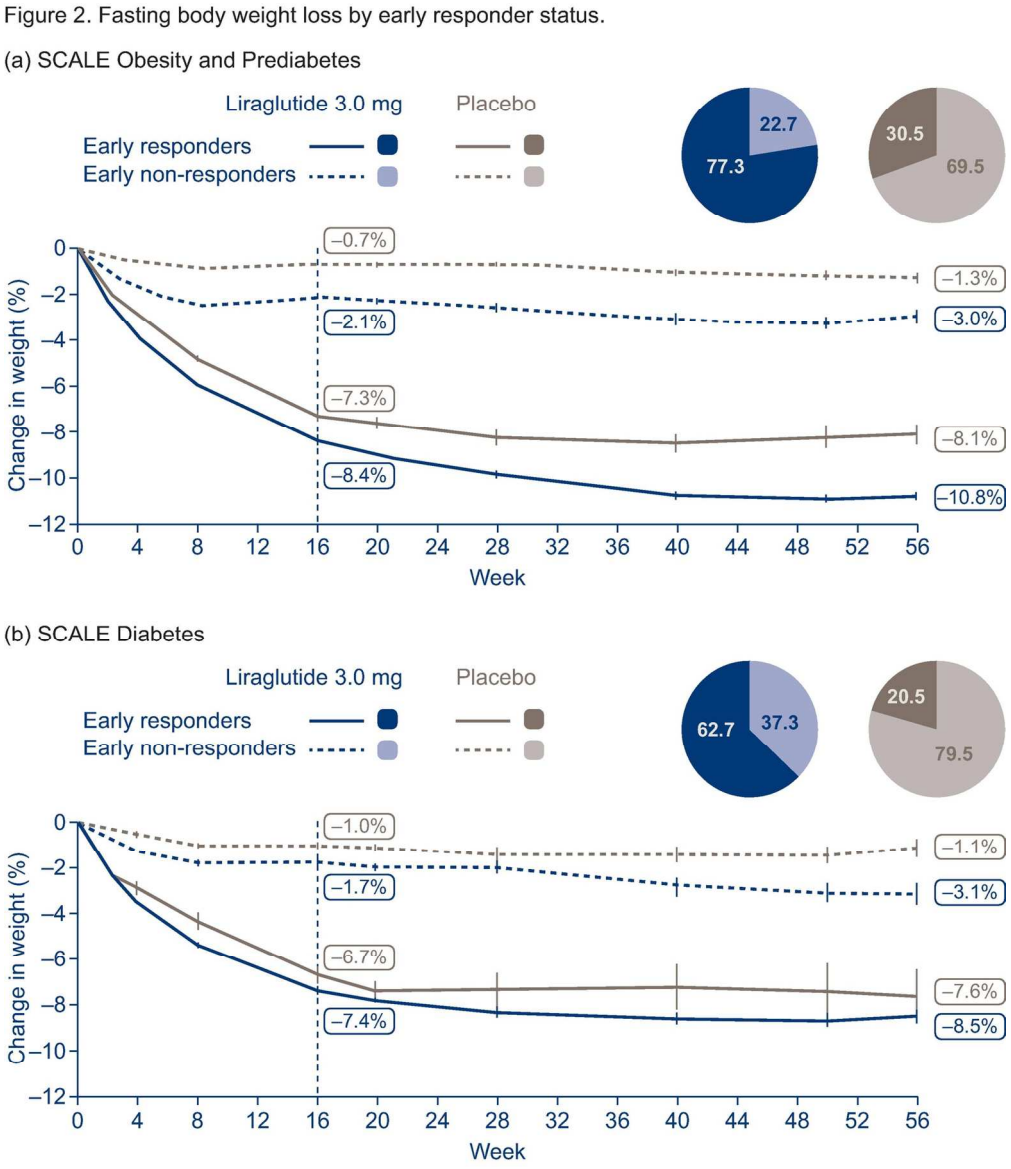

Figure 2. Fasting body weight loss by early responder status.
Line graphs are observed means (±SE) for ERs/ENRs who completed 56 weeks. Fasting visit data only. ERs, early responders (individuals who achieved ≥4% weight loss from baseline at 16 weeks); ENRs, early non-responders (individuals who achieved <4% weight loss from baseline at 16 weeks); SE, standard error. Note that ENRs continued on treatment till week 56; in clinical practice, treatment would cease for ENRs in line with the stopping rule.
Figure 2
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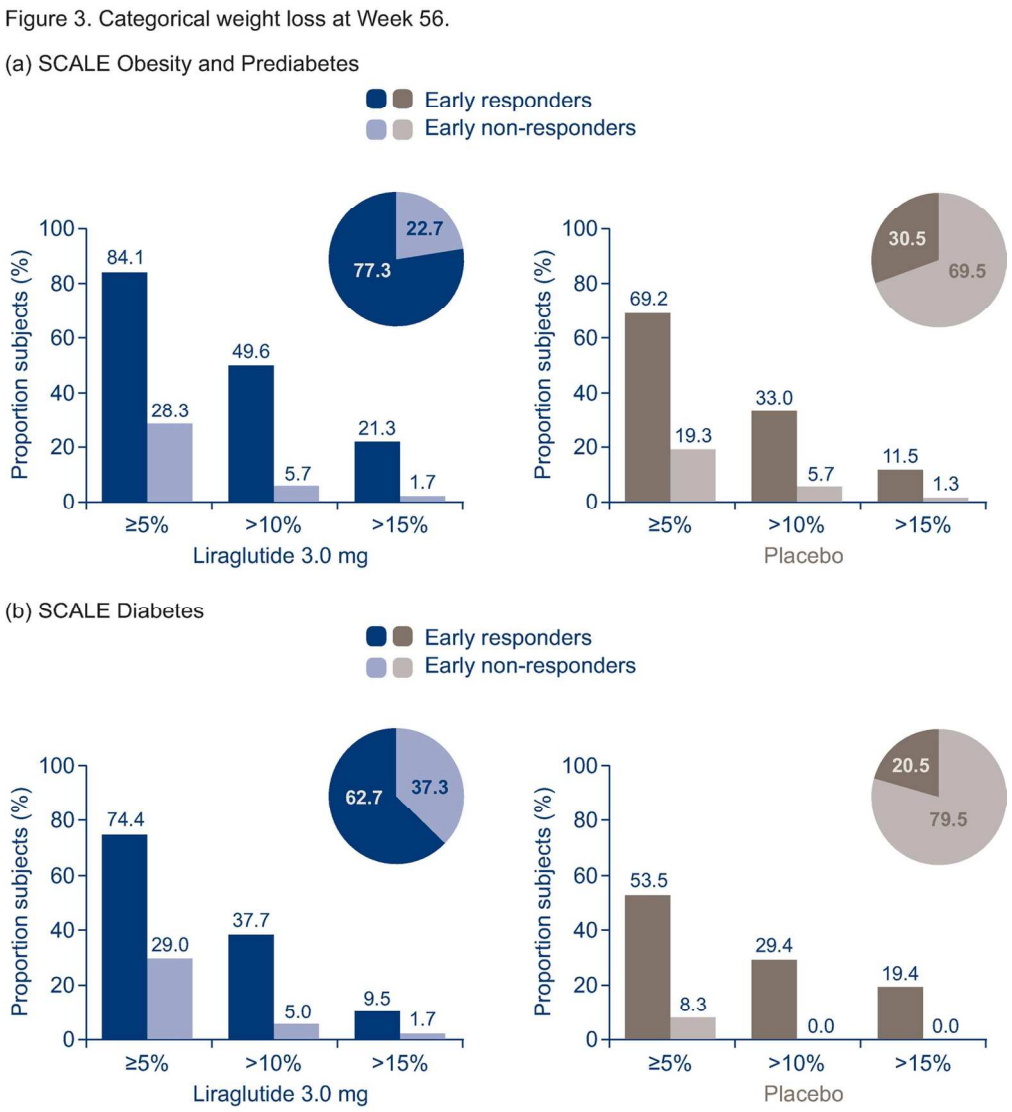


Figure 3. Categorical weight loss at Week 56.
Proportions of subjects are estimated proportions from a logistic regression model for ERs/ENRs who completed 56 weeks of treatment. ERs, early responders (individuals who achieved ≥4% weight loss from baseline at 16 weeks); ENR, early non-responders (individuals who achieved <4% weight loss from baseline at 16 weeks).
Figure 3
140x154mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL

METHODS

Reasons for choosing 8, 12 and 16 weeks as the timepoints for evaluating early response

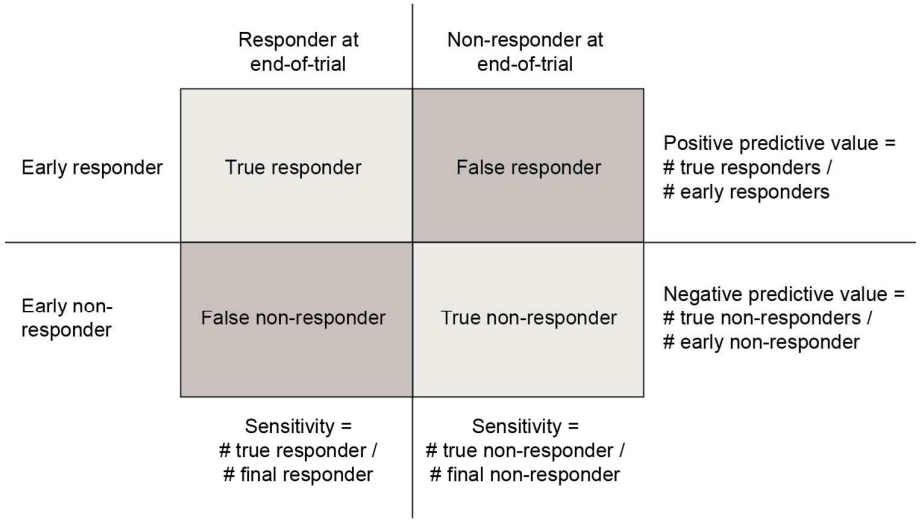
Any timepoint earlier than 8 weeks would have represented 4 weeks or less of full-dose treatment, as a minimum of 4 weeks are needed to reach the full 3.0 mg dose of liraglutide. 16 weeks corresponds to the recommended dose escalation phase of 4 weeks plus 12 weeks on full therapy, and was also the latest timepoint examined. For any weight loss criterion, the later the timepoint, the better the predictive value; periods longer than 16 weeks would therefore be expected to increase the predictive accuracy, but would entail unnecessary drug exposure in patients unlikely to respond successfully.

Identification of individuals likely to achieve and sustain a clinically meaningful weight loss

The sensitivity and specificity of various early response criteria (≥3, 4 and 5% weight loss at 8, 12 and 16 weeks) were evaluated. Figure S1 illustrates how the positive predictive value, negative predictive value, sensitivity and specificity are related.

In evaluating correctly predicted values, equal weight was put on positive and negative predictive values. With a low positive predictive value, a large number of subjects would be continued who would not in the end achieve a response, while with a low negative predictive value, a large number of subjects would be stopped who would eventually have achieved response. Both are undesirable.

Figure S1. Calculation of positive predictive value, negative predictive value, sensitivity and specificity.



A 'true positive' occurred when the test made a positive prediction and the subject had a positive result (having >5% body weight loss at Week 56).
The positive predictive value was defined as:

$$\frac{\text{number of true positives}}{\text{number of true positive + number of false positives}} = \frac{\text{number of true positives}}{\text{number of positive calls}}$$

where a 'true positive' was the event that the test made a positive prediction (of meeting the early response criteria), and the subject had a positive result under the gold standard (having >5% body weight loss at Week 56), and a 'false positive' was the event that the test made a positive prediction (of not meeting the early response criteria), and the subject had a negative result under the gold standard (not having ≥5% body weight loss at Week 56).
A 'correct prediction' occurred when the test made a correct positive prediction or a correct negative prediction. The percentage of correct predictions is also referred to as the accuracy.

Table S1. Prediction of ≥5% weight loss at 56 weeks based on early response to liraglutide 3.0 mg: SCALE Obesity and Prediabetes and Scale Diabetes: sensitivity and specificity of the different criteria.

Week	Early response criterion	N	Early response n (%)	Early non-response n (%)	Sensitivity n (%)	Specificity n (%)
8	3%	2653	2035 (76.7%)	618 (23.3%)	1544 (89.6%)	439 (47.2%)
	4%		1644 (62.0%)	1009 (38.0%)	1373 (79.7%)	659 (70.9%)
	5%		1245 (46.9%)	1408 (53.1%)	1096 (63.6%)	781 (84.0%)
12	3%	2578	2084 (80.8%)	494 (19.2%)	1601 (93.8%)	389 (44.6%)
	4%		1821 (70.6%)	757 (29.4%)	1485 (87.0%)	536 (61.5%)
	5%		1515 (58.8%)	1063 (41.2%)	1312 (76.9%)	669 (76.7%)
16	3%	2519	2099 (83.3%)	420 (16.7%)	1609 (95.2%)	338 (40.8%)
	4%		1893 (75.1%)	626 (24.9%)	1541 (91.1%)	476 (57.5%)
	5%		1637 (65.0%)	882 (35.0%)	1411 (83.4%)	602 (72.7)

Missing Week 56 responses are imputed using last observation carried forward.
Sensitivity of prediction is defined as the percentage of true positives out of the total number of positives. Specificity of prediction is defined as the percentage of true negatives out of the total number of negatives.

Table S2. Prediction of Week 56 response based on early response - by trial (liraglutide 3.0 mg only).

Week	Early response criterion	N	Early response n (%)	Mean Week 56 weight change (%) in early responders	Positive predictive value (a) n (%)	Early non-response n (%)	Mean Week 56 weight change (%) in early non-responders	Negative predictive value (b) n (%)	Correctly predicted n (%)
SCALE Obesity and Prediabetes									
8	3%	2268	1787 (78.8%)	-10.34	1374 (76.9%)	481 (21.2%)	-3.86	335 (69.6%)	1709 (75.4%)
	4%		1457 (64.2%)	-11.23	1228 (84.3%)	811 (35.8%)	-4.74	519 (64.0%)	1747 (77.0%)
	5%		1112 (49.0%)	-12.34	987 (88.8%)	1156 (51.0%)	-5.65	623 (53.9%)	1610 (71.0%)
12	3%	2203	1824 (82.8%)	-10.24	1420 (77.9%)	379 (17.2%)	-2.99	293 (77.3%)	1713 (77.8%)
	4%		1608 (73.0%)	-10.93	1325 (82.4%)	595 (27.0%)	-3.68	414 (69.6%)	1739 (78.9%)
	5%		1346 (61.1%)	-11.79	1175 (87.3%)	857(38.9%)	-4.54	526 (61.4%)	1701 (77.2)
16	3%	2154	1842 (85.5%)	-10.22	1433 (77.8%)	312 (14.5%)	-2.19	252 (80.8%)	1685 (78.2%)
	4%		1664 (77.3%)	-10.75	1378 (82.8%)	490 (22.7%)	-2.99	375 (76.5%)	1753 (81.4%)
	5%		1453 (67.5%)	-11.48	1265 (87.1%)	701 (32.5%)	-3.83	473 (67.5%)	1738 (80.7%)
SCALE Diabetes									
8	3%	385	248 (64.4%)	-8.36	170 (68.5%)	137 (35.6%)	-3.17	104 (75.9%)	274 (71.2%)
	4%		187 (48.6%)	-9.30	145 (77.5%)	198 (51.4%)	-3.74	140 (70.7%)	285 (74.0%)
	5%		133 (34.5%)	-10.18	109 (82.0%)	252 (65.5%)	-4.64	158 (62.7%)	267 (69.4%)
12	3%	375	260 (69.3%)	-8.25	181 (69.6%)	115 (30.7%)	-2.16	96 (83.5%)	277 (73.9%)
	4%		213 (56.8%)	-8.95	160 (75.1%)	162 (43.2%)	-3.13	122 (75.3%)	282 (75.2%)
	5%		169 (45.1%)	-9.72	137 (81.1%)	206 (54.9%)	-3.67	143 (69.4%)	280 (74.7%)
16	3%	365	257 (70.4%)	-8.15	176 (68.5%)	108 (29.6%)	-2.56	86 (79.6%)	262 (71.8%)
	4%		229 (62.7%)	-8.49	163 (71.2%)	136 (37.3%)	-3.10	101 (74.3%)	264 (72.3%)
	5%		184 (50.4%)	-9.25	146 (79.3%)	181 (49.6%)	-3.57	129 (71.3%)	275 (75.3%)

Week 56 response is defined as at least a 5% reduction in body weight. If data were missing for Week 56, the last available body weight measurement was used (i.e. missing data were imputed using last observation carried forward). Mean weight loss is based on observed data only.

[a] Positive predictive value is defined as the percentage of early responders who were Week 56 responders.

[b] Negative predictive value is defined as the percentage of early non-responders who were Week 56 non-responders.

The number of subjects for liraglutide 3.0 mg with 4% weight loss at Week 16 in SCALE Obesity and Prediabetes does not exactly match the number of subjects shown in Figure 1. The values used here for prediction are based on subjects who have a body weight (BW) measurement at the relevant week (8, 12 or 16) as well as a fasting BW at baseline and Week 56 (or at least one post-baseline fasting BW that could be carried forward), while all subjects who had lost ≥4% of their baseline body weight after 16 weeks were included in Figure 1. The small differences are subjects that have a non-fasting BW at Week 0.

Table S3. Prediction of Week 56 response based on early response - by sex (liraglutide 3.0 mg only).

Week	Early response criterion	N	Early response n (%)	Mean Week 56 weight change (%) in early responders	Positive predictive value (a) n (%)	Early non-response n (%)	Mean Week 56 weight change (%) in early non-responders	Negative predictive value (b) n (%)	Correctly predicted n (%)
Female									
8	3%	1961	1555 (79.3%)	-10.62	1214 (78.1%)	406 (20.7%)	-4.27	277 (68.2%)	1491 (76.0%)
	4%		1265 (64.5%)	-11.52	1084 (85.7%)	696 (35.5%)	-5.02	437 (62.8%)	1521 (77.6%)
	5%		954 (48.6%)	-12.66	857 (89.8%)	1007 (51.4%)	-6.03	521 (51.7%)	1378 (70.3%)
12	3%	1904	1588 (83.4%)	-10.49	1259 (79.3%)	316 (16.6%)	-3.36	245 (77.5%)	1504 (79.0%)
	4%		1410 (74.1%)	-11.12	1176 (83.4%)	494 (25.9%)	-3.98	340 (68.8%)	1516 (79.6%)
	5%		1180 (62.0%)	-11.96	1040 (88.1%)	724 (38.0%)	-4.84	434 (59.9%)	1474 (77.4%)
16	3%	1859	1609 (86.6%)	-10.42	1264 (78.6%)	250 (13.4%)	-2.70	195 (78.0%)	1459 (78.5%)
	4%		1454 (78.2%)	-10.95	1215 (83.6%)	405 (21.8%)	-3.42	301 (74.3%)	1516 (81.5%)
	5%		1274 (68.5%)	-11.64	1118 (87.8%)	585 (31.5%)	-4.21	384 (65.6%)	1502 (80.8%)
Male									
8	3%	692	480 (69.4%)	-8.42	330 (68.8%)	212 (30.6%)	-2.65	162 (76.4%)	492 (71.1%)
	4%		379 (54.8%)	-9.26	289 (76.3%)	313 (45.2%)	-3.52	222 (70.9%)	511 (73.8%)
	5%		291 (42.1%)	-10.26	239 (82.1%)	401 (57.9%)	-4.07	260 (64.8%)	499 (72.1%)
12	3%	674	496 (73.6%)	-8.36	342 (69.0%)	178 (26.4%)	-1.86	144 (80.9%)	486 (72.1%)
	4%		411 (61.0%)	-9.17	309 (75.2%)	263 (39.0%)	-2.83	196 (74.5%)	505 (74.9%)
	5%		335 (49.7%)	-10.06	272 (81.2%)	339 (50.3%)	-3.43	235 (69.3%)	507 (75.2%)
16	3%	660	490 (74.2%)	-8.42	345 (70.4%)	170 (25.8%)	-1.71	143 (84.1%)	488 (73.9%)
	4%		439 (66.5%)	-8.85	326 (74.3%)	221 (33.5%)	-2.31	175 (79.2%)	501 (75.9%)
	5%		363 (55.0%)	-9.71	293 (80.7%)	297 (45.0%)	-2.95	218 (73.4%)	511 (77.4%)

Week 56 response is defined as at least a 5% reduction in body weight. If data were missing for Week 56, the last available body weight measurement was used (i.e. missing data were imputed using last observation carried forward). Mean weight loss is based on observed data only.

[a] Positive predictive value is defined as the percentage of early responders who were Week 56 responders.

[b] Negative predictive value is defined as the percentage of early non-responders who were Week 56 non-responders.

Table S4. Prediction of ≥5% weight loss at 56 weeks based on early response to liraglutide 3.0 mg: Sensitivity analysis with missing values imputed as non-response.

Week	Early response criterion	N	Early response n (%)	Mean week 56 weight change (%) in early responders	Positive predictive value (a) n (%)	Early non-response n (%)	Mean week 56 weight change (%) in early non-responders	Negative predictive value (b) n (%)	Correctly predicted n (%)
8	3%	2653	2035 (76.7%)	-10.09	1346 (66.1%)	618 (23.3%)	-3.69	463 (74.9%)	1809 (68.2%)
	4%		1644 (62.0%)	-11.00	1198 (72.9%)	1009 (38.0%)	-4.53	706 (70.0%)	1904 (71.8%)
	5%		1245 (46.9%)	-12.10	951 (76.4%)	1408 (53.1%)	-5.46	858 (60.9%)	1809 (68.2%)
12	3%	2578	2084 (80.8%)	-9.98	1406 (67.5%)	494 (19.2%)	-2.79	397 (80.4%)	1803 (69.9%)
	4%		1821 (70.6%)	-10.68	1308 (71.8%)	757 (29.4%)	-3.56	562 (74.2%)	1870 (72.5%)
	5%		1515 (58.8%)	-11.55	1160 (76.6%)	1063 (41.2%)	-4.37	720 (67.7%)	1880 (72.9%)
16	3%	2519	2099 (83.3%)	-9.95	1425 (67.9%)	420 (16.7%)	-2.29	343 (81.7%)	1768 (70.2%)
	4%		1893 (75.1%)	-10.46	1368 (72.3%)	626 (24.9%)	-3.02	492 (78.6%)	1860 (73.8%)
	5%		1637 (65.0%)	-11.21	1254 (76.6%)	882 (35.0%)	-3.78	634 (71.9%)	1888 (75.0%)

Week 56 response is defined as at least a 5% reduction in body weight. If data were missing for Week 56, the last available body weight measurement was used (i.e. missing data were imputed using last observation carried forward). Mean weight loss is based on observed data only.

[a] Positive predictive value is defined as the percentage of early responders who were Week 56 responders.

[b] Negative predictive value is defined as the percentage of early non-responders who were Week 56 non-responders.

Table S5.Prediction of ≥5% weight loss at 56 weeks based on early response - placebo group: pooled analysis of SCALE Obesity and Prediabetes and SCALE Diabetes.

Week	Early response criteria	N	Early response n (%)	Mean week 56 weight change (%) in early responders	Positive predictive value n (%)	Early non-response n (%)	Mean week 56 weight change (%) in early non-responders	Negative predictive value n (%)	Correctly predicted n (%)
8	3%	1338	377 (28.2%)	-7.23	213 (56.5%)	961 (71.8%)	-1.57	816 (84.9%)	1029 (76.9%)
	4%		245 (18.3%)	-8.56	169 (69.0%)	1093 (81.7%)	-1.95	904 (82.7%)	1073 (80.2%)
	5%		161 (12.0%)	-10.09	128 (79.5%)	1177 (88.0%)	-2.30	947 (80.5%)	1075 (80.3%)
12	3%	1285	424 (33.0%)	-7.30	236 (55.7%)	861 (67.0%)	-1.17	742 (86.2%)	978 (76.1%)
	4%		311 (24.2%)	-8.44	205 (65.9%)	974 (75.8%)	-1.50	824 (84.6%)	1029 (80.1%)
	5%		221 (17.2%)	-9.36	160 (72.4%)	1064 (82.8%)	-1.87	869 (81.7%)	1029 (80.1%)
16	3%	1218	460 (37.8%)	-7.03	261 (56.7%)	758 (62.2%)	-0.91	662 (87.3%)	923 (75.8%)
	4%		354 (29.1%)	-8.10	234 (66.1%)	864 (70.9%)	-1.25	741 (85.8%)	975 (80.0%)
	5%		257 (21.1%)	-9.41	195 (75.9%)	961 (78.9%)	-1.54	799 (83.1%)	994 (81.6%)

Week 56 response is defined as at least a 5% reduction in body weight. If data were missing for Week 56, the last available body weight measurement was used (i.e. missing data were imputed using last observation carried forward). Mean weight loss is based on observed data only.

[a] Positive predictive value is defined as the percentage of early responders who were Week 56 responders.

[b] Negative predictive value is defined as the percentage of early non-responders who were Week 56 non-responders.

Table S6. Changes from baseline in secondary endpoints: additional endpoints not shown in main article.
a) SCALE Obesity and Prediabetes

	Liraglutide 3.0 mg				Placebo			
	Early responders (N=1433)		Early non-responders (N=355)		Early responders (N=265)		Early non-responders (N=535)	
	Baseline	Change at 56 weeks [SE]	Baseline	Change at 56 weeks [SE]	Baseline	Change at 56 weeks [SE]	Baseline	Change at 56 weeks [SE]
BMI (kg/m^2)	38.1	-4.1 [0.1]	38.9	-1.2 [0.1]	38.7	-3.2 [0.1]	38.3	-0.5 [0.1]
Waist circumference (cm)	114.3	-10.5 [0.2]	116.8	-4.8 [0.4]	115.0	-8.6 [0.4]	114.5	-3.0 [0.3]
FPG (mmol/L)	5.3	-0.45 [0.01]	5.4	-0.35 [0.03]	5.3	-0.13 [0.03]	5.3	0.05 [0.02]
Free fatty acids, mg/dL (%)[a]	12.7	+1.2 [1.2]	12.3	+6.7 [2.5]	13.8	-3.1 [2.6]	12.9	8.3 [2.1]
VLDL-cholesterol, mg/dL (%)[a]	24.9	-15.2 [0.7]	25.8	-7.0 [1.6]	25.6	-12.7 [1.8]	26.0	-2.[1.4]
hsCRP, mg/L (%)[a]	3.9	-43.9 [1.1]	3.8	-20.4 [3.2]	3.5	-23.0 [3.5]	3.9	-5.9 [3.1]
Adiponectin, ug/mL (%)[a]	7.6	+14.4 [1.2]	7.9	+1.5 [2.1]	7.1	10.6 [2.6]	7.3	-1.7 [1.6]
Fibrinogen, g/L (%)[a]	4.3	+0.5 [0.6]	4.4	+2.0[1.2]	4.4	-0.9 [1.3]	4.3	+0.8 [1.0]
IWQOL-Lite physical function score	68.5	+16.1 [0.4]	70.7	+9.6 [0.8]	66.1	+15.6 [0.9]	70.7	+6.4 [0.6]
SF-36 overall physical health score	47.9	+4.1 [0.2]	49.1	+2.4 [0.4]	46.4	+3.9 [0.4]	48.2	+1.4 [0.3]

b) SCALE Diabetes

	Liraglutide 3.0 mg				Placebo			
	Early responders (N=214)		Early non-responders (N=110)		Early responders (N=31)		Early non-responders (N=101)	
	Baseline	Change at 56 weeks [SE]	Baseline	Change at 56 weeks [SE]	Baseline	Change at 56 weeks [SE]	Baseline	Change at 56 weeks [SE]
BMI (kg/m^2)	37.7	-3.2 [0.1]	36.1	-1.1 [0.2]	37.7	-2.8 [0.3]	37.4	-0.5 [0.2]
Waist circumference (cm)	118.9	-8.6 [0.4]	116.9	-3.3 [0.6]	119.0	-6.9 [1.0]	117.3	-2.3 [0.6]
FPG (mmol/L)	8.8	-2.45 [0.13]	8.8	-1.67 [0.18]	8.4	-1.69 [0.34]	8.3	-0.11 [0.20]
Free fatty acids, mg/dL (%)[a]	15.8	-15.1 [2.2]	15.4	-12.0 [3.2]	16.6	-21.3 [5.3]	15.7	-5.2 [3.5]
VLDL-cholesterol, mg/dL (%)[a]	32.0	-18.7 [2.0]	30.9	-6.8 [3.2]	31.9	-10.4 [5.7]	30.9	+2.8 [3.6]
hsCRP, mg/L (%)[a]	3.6	-45.1 [2.7]	3.0	-13.1 [6.1]	3.2	-33.1 [8.7]	3.9	-7.0 [6.6]
Adiponectin, ug/mL (%)[a]	5.8	6.4 [3.5]	5.7	+8.5 [5.0]	5.7	+6.6 [9.1]	5.6	-4.2 [4.6]
Fibrinogen, g/L (%)[a]	4.2	+2.6 [1.6]	3.9	+4.2 [2.2]	4.3	+3.1 [4.2]	4.4	-4.9 [2.1]
UACR, mg/mmol (%)[a]	0.9	-23.8 [4.9]	1.1	-8.4 [8.2]	1.0	-28.7 [12.1]	1.2	-0.5 [9.2]
IWQOL-Lite physical function score	60.7	+17.6 [1.0]	71.4	+11.4 [1.4]	65.3	+14.5 [2.7]	68.1	+7.8 [1.5]

[a] Baseline value is in unit shown and change is presented as relative change.

Changes are estimated mean changes from baseline to week 56 using ANCOVA. Missing values post-baseline were imputed using last observation carried forward.

BMI, body-mass index; FPG, fasting plasma glucose; hsCRP, high sensitivity C-reactive protein; IWQOL-Lite, Impact of Weight on Quality of Life-Lite; SF-36, Short Form-36; UACR, urinary albumin-creatinine ratio; VLDL, very low-density lipoprotein.

Table S7. Adverse events occurring in the main treatment period (0 to 56 weeks) of the overall trial in ≥5% of individuals treated with liraglutide 3.0 mg, and more common than in individuals treated with placebo; listed by preferred term.

a) SCALE Obesity and Prediabetes

	Liraglutide 3.0 mg			Placebo		
AE, n (% of patients)	**All subjects N=2481**	**ERs N=1668**	**ENRs N=491**	**All subjects N=1242**	**ERs N=322**	**ENRs N=735**
Gastrointestinal disorders						
Nausea	997 (40.2)	660 (39.6)	186 (37.9)	183 (14.7)	49 (15.2)	109 (14.8)
Vomiting	404 (16.3)	259 (15.5)	79 (16.1)	51 (4.1)	19 (5.9)	27 (3.7)
Dyspepsia	236 (9.5)	161 (9.7)	45 (9.2)	39 (3.1)	8 (2.5)	29 (3.9)
Abdominal pain upper	141 (5.7)	103 (6.2)	24 (4.9)	43 (3.5)	13 (4.0)	24 (3.3)
Abdominal pain	130 (5.2)	85 (5.1)	25 (5.1)	43 (3.5)	10 (3.1)	31 (4.2)
Diarrhoea	518 (20.9)	352 (21.1)	100 (20.4)	115 (9.3)	33 (10.2)	75 (10.2)
Constipation	495 (20.0)	363 (21.8)	81 (16.5)	108 (8.7)	44 (13.7)	61 (8.3)
Infections and infestations						
Influenza	144 (5.8)	103 (6.2)	35 (7.1)	66 (5.3)	17 (5.3)	43 (5.9)
Metabolism and nutrition disorders						
Decreased appetite	267 (10.8)	207 (12.4)	38 (7.7)	38 (3.1)	14 (4.3)	23 (3.1)
Nervous system disorders						
Headache	327 (13.2)	241 (14.4)	47 (9.6)	154 (12.4)	48 (14.9)	91 (12.4)
Dizziness	167 (6.7)	114 (6.8)	29 (5.9)	60 (4.8)	19 (5.9)	37 (5.0)
General disorders and administration site conditions						
Fatigue	185 (7.5)	134 (8.0)	29 (5.9)	65 (5.2)	16 (5.0)	44 (6.0)

b) SCALE Diabetes

	Liraglutide 3.0 mg			Placebo		
AE, n (% of patients)	**All subjects N=422**	**ERs N=229**	**ENRs N=136**	**All subjects N=212**	**ERs N=34**	**ENRs N=132**
Gastrointestinal disorders						
Nausea	138 (32.7)	84 (36.7)	36 (26.5)	29 (13.7)	2 (5.9)	19 (14.4)
Vomiting	66 (15.6)	36 (15.7)	22 (16.2)	12 (5.7)	3 (8.8)	6 (4.5)
Dyspepsia	47 (11.1)	32 (14.0)	12 (8.8)	5 (2.4)	1 (2.9)	4 (3.0)
Abdominal distension	26 (6.2)	16 (7.0)	6 (4.4)	3 (1.4)	0 (0.0)	2 (1.5)
Abdominal pain	26 (6.2)	13 (5.7)	6 (4.4)	9 (4.2)	1 (2.9)	8 (6.1)
Flatulence	22 (5.2)	11 (4.8)	9 (6.6)	4 (1.9)	0 (0.0)	3 (2.3)
Diarrhea	108 (25.6)	62 (27.1)	33 (24.3)	27 (12.7)	6 (17.6)	16 (12.1)
Constipation	68 (16.1)	48 (21.0)	15 (11.0)	13 (6.1)	2 (5.9)	8 (6.1)
Infections and infestations						
Nasopharyngitis	88 (20.9)	54 (23.6)	32 (23.5)	41 (19.3)	6 (17.6)	30 (22.7)
Upper resp tract infection	40 (9.5)	24 (10.5)	15 (11.0)	18 (8.5)	3 (8.8)	11 (8.3)
Metabolism and nutrition disorders						
Decreased appetite	40 (9.5)	22 (9.6)	11 (8.1)	4 (1.9)	1 (2.9)	3 (2.3)
Musculoskeletal and connective tissue disorders						
Back pain	42 (10.0)	27 (11.8)	11 (8.1)	20 (9.4)	3 (8.8)	15 (11.4)
Musculoskeletal pain	22 (5.2)	14 (6.1)	8 (5.9)	6 (2.8)	2 (5.9)	4 (3.0)
Arthralgia	30 (7.1)	22 (9.6)	7 (5.1)	12 (5.7)	1 (2.9)	11 (8.3)
Nervous system disorders						
Headache	66 (15.6)	44 (19.2)	17 (12.5)	29 (13.7)	4 (11.8)	19 (14.4)
Dizziness	30 (7.1)	20 (8.7)	7 (5.1)	6 (2.8)	0 (0.0)	5 (3.8)
General disorders and administration site conditions						
Fatigue	35 (8.3)	19 (8.3)	14 (10.3)	7 (3.3)	1 (2.9)	5 (3.8)
Investigations						
Lipase increased	50 (11.8)	30 (13.1)	16 (11.8)	14 (6.6)	3 (8.8)	11 (8.3)

Safety analysis set. For all subjects, this corresponded to all randomized subjects who had been exposed to at least one dose of trial product. For ERs and ENRs, this corresponded to all subjects with data at Week 16.

NR, not reported. For the purposes of this analysis, only AEs occurring from 0 to 56 weeks in the overall trial in ≥5% of individuals treated with liraglutide 3.0 mg, and more common than in individuals treated with placebo, are listed.