Early responders to liraglutide 3.0 mg as adjunct to diet and exercise from the SCALE Maintenance trial

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Introduction

- The SCALE Maintenance trial randomised adults with obesity (body mass index; BMI ≥30 kg/m²) or overweight (BMI ≥27 kg/m²) with comorbidities who lost ≥5% of initial body weight during a 4–12-week low calorie diet (1200–1400 kcal/day) run-in period prior to randomisation to liraglutide 3.0 mg or placebo, as adjunct to diet and exercise (Wadden *et al. Int J Obes (Lond)* 2013;37: 1443–51).
- The European Union summary of product characteristics for liraglutide 3.0 mg states that treatment should be discontinued after 12 weeks on the 3.0 mg/day dose (typically corresponding to 16 weeks) if individuals have not lost ≥5% of their initial body weight (EU SmPC liraglutide 3.0 mg. Available at: <http://www.ema.europa.eu/ema/>. Accessed Oct 2017).
- This *post-hoc* analysis compared outcomes in liraglutide 3.0 mg early responders (ER: ≥5% weight loss at week 16) vs. early non-responders (ENR: <5% weight loss at week 16), after 56 weeks of treatment in the SCALE Maintenance trial.

Methods

- The SCALE Maintenance Trial was a double-blind, randomised Phase 3 trial to assess the efficacy of liraglutide 3.0 mg vs. placebo in maintaining weight loss achieved through low calorie diet (Wadden *et al. Int J Obes (Lond)* 2013;37:1443–51).
- Individuals with overweight or obesity (≥18 years old, BMI ≥30 kg/m² or ≥27 kg/m² with comorbidities) from 36 sites in the USA and Canada were placed on a low calorie diet (1200–1400 kcal per day) for a 12-week run-in period.
 - Key exclusion criteria: diagnosis of diabetes (type 1 or 2); treatment with glucagon-like peptide-1 receptor agonists or medications causing significant weight gain/loss; bariatric surgery; history of idiopathic acute or chronic pancreatitis; history of major depressive disorder or other severe psychiatric disorders; or clinically significant active cardiovascular disease.
- Those who lost ≥5% of their screening body weight during the run-in period were randomised 1:1 to once-daily subcutaneous liraglutide 3.0 mg (n=212) or placebo (n=210) as an adjunct to lifestyle intervention. Diet and exercise counselling were provided throughout the trial.

Statistical analysis

- Efficacy outcomes are observed means or proportions in ER and ENR who completed 56 weeks of treatment following a 12-week run-in period.
- The safety analysis set (all randomised individuals) was used for adverse events (AEs).

Outcome measures

- Efficacy endpoints for liraglutide 3.0 mg ER and ENR:
 - observed weight loss during the trial period;
 - the proportion who maintained their run-in weight loss over 56 weeks of treatment;
 - secondary outcomes: the proportion who regained all their run-in weight by week 56, and observed changes in cardiometabolic risk factors.
- Safety endpoints for liraglutide 3.0 mg ER and ENR:
 - total reported AE;
 - serious AE;
 - severe AE;
 - gastrointestinal AE.
- Serious AE defined as one of the following: death; life-threatening experience; in-patient hospitalisation or prolongation of existing hospitalisation; persistent or significant disability/incapacity; congenital anomaly or birth defect. An important medical event that may not have resulted in death, been life-threatening, or required hospitalisation might be considered a serious AE when, based upon appropriate medical judgement, it jeopardised the subject and required medical or surgical

Figure 1 Mean change in body weight during the run-in period and over 56 weeks of treatment for liraglutide 3.0 mg ER and ENR.

Table 1 Subject characteristics at randomisation.

	Liraglutide 3.0 mg (N=212)	Placebo (N=210)
Age, years ± SD	45.9 ± 11.9	46.5 ± 11.0
Female, n (%)	178 (84)	165 (79)
Weight, kg ± SD	100.4 ± 20.8	98.7 ± 21.2
BMI, kg/m² ± SD	36.0 ± 5.9	35.2 ± 5.9
Race, n (%)		
White	170 (80)	185 (88)
Black or African-American	32 (15)	24 (11)
Asian or other	10 (5)	1 (1)

Full analysis set, observed means and proportions. SD, standard deviation.

- intervention to prevent one of the outcomes listed in this definition.
- Severe AE defined as an AE that results in considerable interference with the subject's daily activities (i.e. to an unacceptable degree).

Results

- After 12 weeks of low-calorie diet run-in period, mean weight loss in the total population who achieved the ≥5% weight loss target was 6.0% of screening body-weight (Wadden *et al. Int J Obes (Lond)* 2013;37: 1443–51). Individuals were then randomised 1:1 either to liraglutide 3.0 mg or to placebo, with baseline characteristics shown in Table 1.
- Of all randomised individuals treated with liraglutide 3.0 mg completing 16 weeks of treatment (n=190), 123 (65%) were ER and 67 (35%) were ENR (safety analysis set).
- Of those who further completed 56 weeks of treatment (n=159), 108 (68%) were ER and 51 (32%) ENR.
- For the 56 weeks of treatment, greater mean weight loss was observed in ER to liraglutide 3.0 mg vs. ENR (Figure 1). Greater categorical weight loss was also observed for ER vs. ENR at week 56 (Table 2).
- Of the ER, 91.7% maintained their run-in weight loss over 56 weeks. For ENR, 47.1% maintained their run-in weight loss over 56 weeks.
- At week 56, a smaller proportion of ER had regained all their run-in weight loss (Table 2) compared with ENR. Similar improvements in cardiometabolic risk factors were observed in ERs vs. ENRs from the post-run-in randomization period to week 56 (Table 2).
- AEs for ER and ENR to liraglutide 3.0 mg are shown in Table 3.

Table 2 Change from randomisation to week 56 in categorical weight loss and cardiometabolic risk factors for liraglutide 3.0 mg ER and ENR completers.

	Liraglutide 3.0 mg ER (N=108)	Liraglutide 3.0 mg ENR (N=51)
Change in body weight (%)	-9.9	0.0
Change in body weight (kg)	-9.6	0.1
Proportion regaining run-in weight loss (%)	0.0	3.9
≥5% weight loss at Week 56 (%)	73.1	11.8
>10% weight loss at Week 56 (%)	47.2	0.0
>15% weight loss at Week 56 (%)	20.4	0.0
Change in mean waist circumference (cm)	-7.9	0.0
Change in FPG (mmol/L)	-0.6	-0.5
Change in HbA _{1c} (%)	-0.2	-0.1
Change in SBP (mmHg)	-0.1	-0.5
Change in DBP (mmHg)	+2.0	+1.3

Completer analysis set, observed proportions and means. Randomisation occurred after initial LCD weight loss of ≥5%. DBP, diastolic blood pressure; ER, early responders; ENR, early non-responders; FPG, fasting plasma glucose; SBP, systolic blood pressure.

Table 3 Adverse events for ER and ENR to liraglutide 3.0 mg.

	Liraglutide 3.0 mg ER (N=123)			Liraglutide 3.0 mg ENR (N=67)		
	%	E	R	%	E	R
Adverse events	92.7	884	694.7	91.0	402	624.4
Serious adverse events	4.9	6	4.7	0.0	0	0.0
Severe adverse events	18.7	35	27.5	14.9	11	17.1
Gastrointestinal adverse events	78.9	328	257.7	62.7	117	181.7

Safety analysis set. %, percent of subjects based on total N; E, number of events; R, event rate per 100 years of exposure.

Conclusions

- Following ≥5% weight loss pre-randomisation, liraglutide 3.0 mg ER achieved greater additional mean and categorical weight loss than liraglutide 3.0 mg ENR, among those who completed 56 weeks of treatment.
- Reported total AEs were similar between ER and ENR, however there was a higher rate of serious, severe, and gastrointestinal AEs between ER vs. ENR.

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