Outcomes in early responders achieving ≥5% weight loss at 16 weeks with treatment with liraglutide 3.0 mg in people with overweight or obesity and basal insulin-treated type 2 diabetes (T2D) in the SCALE Insulin trial

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Background

- The SCALE Insulin study demonstrated the superiority of liraglutide 3.0 mg for weight reduction versus placebo in individuals with basal insulin-treated type 2 diabetes (T2D) as an adjunct to intensive behaviour therapy (IBT) after 56 weeks of treatment (–5.9% vs. –1.5%; estimated treatment difference –4.3% [95% CI: –5.5; –3.2], $p<0.0001$).[1]
- The European Medicines Agency (EMA) prescribing information for liraglutide 3.0 mg defines a stopping rule for individuals achieving <5% body weight reduction after 16 weeks' treatment (including 4 weeks of dose escalation).[2]
- This *post hoc* analysis explored the effect of intervention in the subgroup of liraglutide-treated individuals categorised as early responders (ERs) and their outcomes after 56 weeks of treatment.

Methods

- The 56-week SCALE Insulin trial (ClinicalTrials.gov: NCT02963922) randomised individuals with overweight/obesity (BMI ≥27 kg/m^2) and T2D (HbA_{1c} 6.0–10.0%) treated with basal insulin and ≤2 oral antidiabetic drugs to liraglutide 3.0 mg or placebo, both as an adjunct to IBT.
- IBT consisted of physical activity (escalating up to 250 min/week), reduced caloric intake (1200–1800 kcal/day, based on body weight at randomisation) and 23 behavioural counselling visits.
- Data are presented for ERs (≥5% weight loss at week 16) and early non-responders (ENRs; <5% weight loss at week 16) after 56 weeks of treatment with liraglutide 3.0 mg.
  - » Individuals who withdrew from the trial before 16 weeks, or had a missing weight measurement at week 16, were classified as non-responders.
- Efficacy outcomes are estimated means or proportions from all randomised individuals based on the intention-to-treat principle. Safety outcomes are based on observed data from individuals exposed to the study drug.
- Data presented for the two subsets are for descriptive purposes only. As data are not placebo-adjusted, any differences in outcomes between ERs and ENRs should be interpreted with caution.

Results

Efficacy

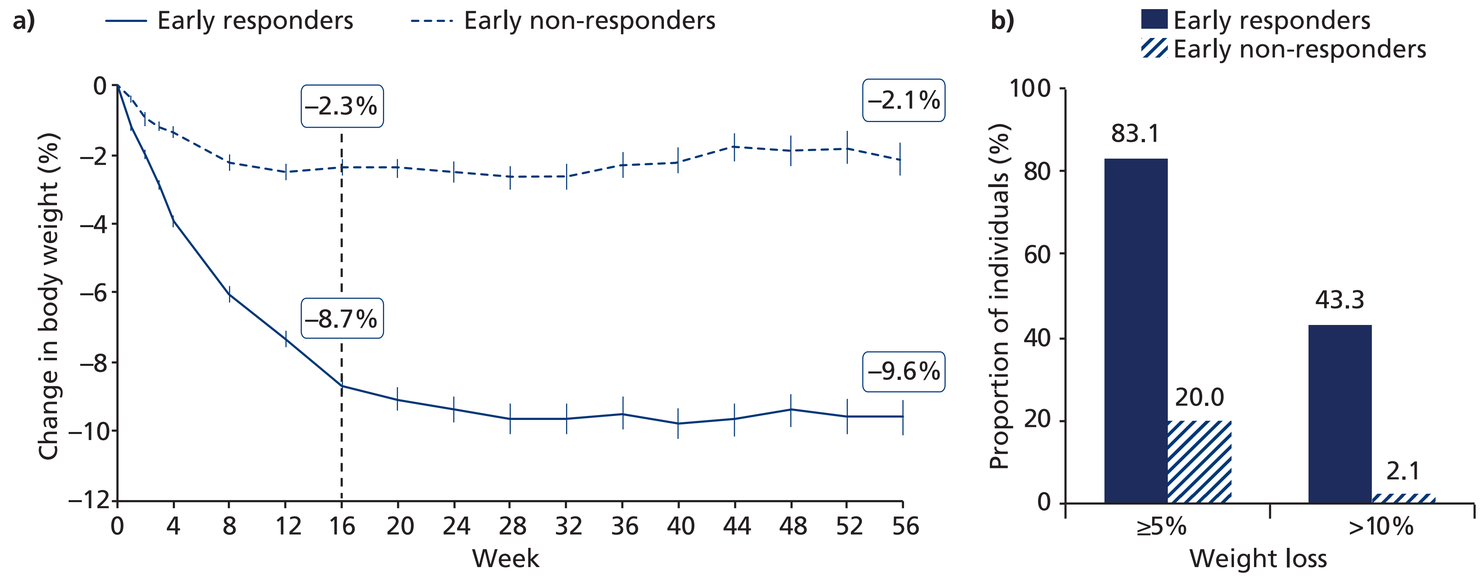
- The baseline characteristics of ERs and ENRs for liraglutide 3.0 mg-treated individuals, as well as the subset of individuals who were on-drug at week 56, are presented in Table 1.
- At week 16, 51.5% of randomised (52.3% of exposed) individuals had achieved ≥5% weight loss and were classified as ERs (Table 1).
- At week 56, mean estimated weight loss from baseline was 9.6% in the ER subgroup and 1.9% in the ENR group (Table 1). Mean observed weight loss over time for ER and ENRs can be seen in Figure 1a.
- At week 56, 83.1% and 43.3% of ERs achieved categorical weight loss of ≥5% and >10%, respectively (Figure 1b).

Table 1: Baseline demographics and individual disposition

	Liraglutide 3.0 mg (n=198)	
	Early non-responders	Early responders
N randomised to study drug	96	102
N exposed to study drug	93	102
N completing 56 weeks on-drug [% of exposed]	73 [78.5]	93 [91.2]
Sex, male, n [%]	43 [44.8]	47 [46.1]
Age, years	54.9 (11.9)	56.9 (10.6)
Body weight, kg	98.4 (20.3)	102.6 (21.1)
BMI, kg/m^2	35.3 (6.8)	36.6 (6.3)
HbA_{1c}, %	8.1 (1.0)	7.8 (1.1)
SBP, mmHg	130 (13)	129 (15)
DBP, mmHg	78 (10)	78 (9)
Duration of diabetes, years	11.0 (6.8)	11.7 (6.9)
Insulin dose	36.3 (26.1)	38.7 (27.4)

Data are mean (±SD) unless otherwise stated. BMI, body mass index; DBP, diastolic blood pressure; N, number of individuals; SBP, systolic blood pressure; SD, standard deviation.

Figure 1: a) Change in body weight from baseline to week 56; b) Categorical weight loss



Data are observed means ± SEM. ER, early responders; ENR, early non-responders.

Data are estimated proportions; missing values were handled using a jump-to-reference multiple imputation model.

Key results

- In general, clinically meaningful improvements in waist circumference and glycaemic parameters were observed in ERs, as was a clinically meaningful reduction in total daily insulin dose (Table 2).
  - » Change in total daily insulin dose was –9.45U for ERs and 16.37U for ENRs.

Safety

- The proportion of ERs and ENRs reporting adverse events and serious adverse events was similar to that reported in the overall trial population.
- The most frequent adverse events were gastrointestinal events, reported for 67.6% of individuals in the ER subset and 55.9% in the ENR subset (Table 3).
- The proportion of individuals experiencing ≥1 hypoglycaemic event was 74.5% in the ER subset and 68.8% in the ENR subset (Table 3).

Table 3: Summary of adverse events

	Liraglutide 3.0 mg (n=195)			
	Early non-responders (n=93)		Early responders (n=102)	
	n	(%)	n	(%)
Total adverse events	81	(87.1)	99	(97.1)
Serious adverse events	6	(6.5)	10	(9.8)
Gastrointestinal adverse events	52	(55.9)	69	(67.6)
Hypoglycaemic episodes[†]				
Total	64	(68.8)	76	(74.5)
Severe	2	(2.2)	1	(1.0)
Documented symptomatic	40	(43.0)	52	(51.0)

On-drug AEs: adverse events with onset date no more than 14 days after any trial product administration. [†]Hypoglycaemic episodes are based on American Diabetes Association criteria.[3]

Table 2: Estimated primary and secondary efficacy endpoints

	All randomised individuals		Early responders on-drug at week 56
	Early non-responders (n=96)	Early responders (n=102)	
Change in weight (%)	–1.89	–9.57	–9.63
Proportion with ≥5% weight loss (%)	20.04	83.05	82.68
Proportion with >10% weight loss (%)	2.08	43.32	42.84
Change in waist circumference (cm)	–2.13	–8.21	–8.01
Change in HbA_{1c} (% point)	–0.74	–1.38	–1.46
Change in fasting plasma glucose (mmol/L)	-0.21	–1.62	–1.72
Change in total daily insulin dose (U)	16.37	–9.45	–9.58
Change in heart rate (beats/min)	2.85	0.35	1.10
Change in systolic blood pressure (mmHg)	–3.81	–6.19	–6.12
Change in diastolic blood pressure (mmHg)	–1.37	–3.33	–3.21
Change in total cholesterol (mmol/L)	–0.06	–0.15	–0.11
Change in LDL cholesterol (mmol/L)	–0.05	–0.10	–0.05
Change in HDL cholesterol (mmol/L)	0.00	0.09	0.08
Change in VLDL cholesterol (mmol/L)	–0.01	–0.16	–0.15
Change in triglycerides (mmol/L)	–0.06	–0.38	–0.36
Change in free fatty acids (mmol/L)	–0.10	–0.10	–0.09
Change in SF-36 Physical function score	1.07	3.75	4.14
Change in IWQoL-Lite CT Physical function score	4.05	9.90	10.28

Data are estimated means. Analysis of in-trial data with missing observations imputed from the placebo arm based on a jump-to-reference multiple (x100) imputation approach. HDL, high-density lipoprotein cholesterol; IWQoL-Lite CT, Impact of Weight on Quality of Life-lite for clinical trials; LDL, low-density lipoprotein cholesterol; SF-36, short form-36; VLDL, very low-density lipoprotein cholesterol.

Conclusion

- More than half of individuals with overweight/obesity and basal insulin-treated T2D receiving liraglutide 3.0 mg as an adjunct to IBT achieved clinically meaningful weight loss of at least 5% at week 16 and were eligible for long-term treatment according to the EMA prescribing information.
- Of these, the majority continued on therapy to 56 weeks, achieving clinically relevant reductions in body weight and other endpoints.

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