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Outcomes at week 56 in individuals losing ≥4% weight at week 16 on liraglutide 3.0 mg: SCALE Insulin

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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 behavior 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 United States Food and Drug Administration (FDA) prescribing information for liraglutide 3.0 mg defines a stopping rule for individuals achieving <4% 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 categorized as early responders (ERs) and their outcomes after 56 weeks of treatment.

Methods

- The 56-week SCALE Insulin trial (ClinicalTrials.gov: NCT02963922) randomized individuals with overweight/obesity (BMI ≥27 kg/m²) 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 randomization) and 23 behavioral counseling visits.
- Data are presented for ERs (≥4% weight loss at week 16) and early non-responders (ENRs; <4% 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 randomized 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, 62.1% of randomized individuals had achieved ≥4% weight loss and were classified as ERs (Table 1).
- At week 56, mean estimated weight loss from baseline was 8.8% in the ER subgroup and 1.1% 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, 78.8% and 35.8% of ERs achieved categorical weight loss of ≥5% and >10%, respectively (Figure 1b).
- In general, clinically meaningful improvements in waist circumference and glycemic 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 –5.83U for ERs and +17.66U for ENRs.

Table 1: Baseline demographics and individual disposition

	Liraglutide 3.0 mg (n=198)	
	Early non-responders	Early responders
N randomised to study drug	75	123
N exposed to study drug	72	123
N completing 56 weeks on-drug [% of exposed]	54 [75.0]	112 [91.1]
Sex, male, n [%]	36 [48.0]	54 [43.9]
Age, years	54.5 (11.8)	56.8 (10.9)
Body weight, lbs	218.5 (45.4)	223.8 (46.1)
BMI, kg/m²	35.3 (6.6)	36.3 (6.5)
HbA_{1c}, %	8.1 (1.1)	7.8 (1.0)
SBP, mmHg	131 (14)	129 (15)
DBP, mmHg	79 (10)	78 (9)
Duration of diabetes, years	11.1 (6.8)	11.6 (6.9)
Insulin dose, U	39.0 (27.8)	36.6 (26.1)

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; U, units.

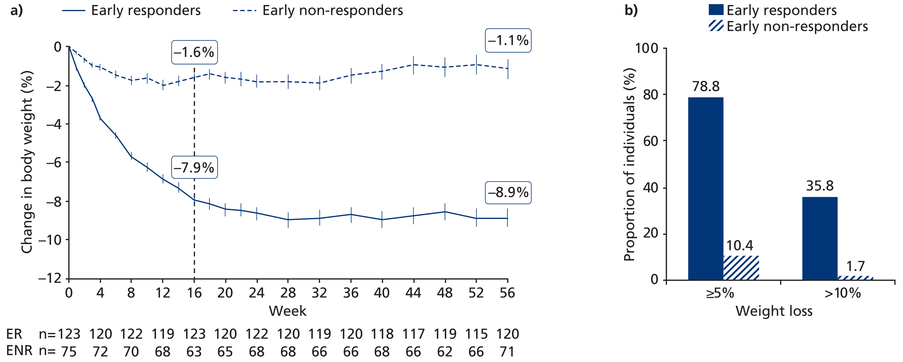
Table 2: Estimated primary and secondary efficacy endpoints

	Liraglutide 3.0 mg (N=198)		
	Early non-responders (n=75)	Early responders (n=123)	Early responders on-drug at week 56
Change in weight (%)	–1.09	–8.75	–8.79
Proportion with ≥5% weight loss (%)	10.37	78.78	78.84
Proportion with >10% weight loss (%)	1.66	35.77	35.52
Change in waist circumference (cm)	–1.40	–7.61	–7.43
Change in HbA_{1c} (% point)	–0.53	–1.40	–1.49
Change in fasting plasma glucose (mg/dL)	2.39	–28.58	–30.77
Change in total daily insulin dose (U)	17.66	–5.83	–6.46
Change in heart rate (beats/min)	2.95	0.71	1.40
Change in systolic blood pressure (mmHg)	–3.09	–6.23	–6.15
Change in diastolic blood pressure (mmHg)	–1.42	–2.97	–2.83
Change in total cholesterol (mg/dL)	–3.11	–5.02	–3.55
Change in LDL cholesterol (mg/dL	–1.85	–3.35	–1.67
Change in HDL cholesterol (mg/dL	–0.18	2.93	2.60
Change in VLDL cholesterol (mg/dL	–0.95	–4.89	–4.66
Change in triglycerides (mg/dL)	–8.39	–26.58	–25.18
Change in free fatty acids (mg/dL)	–3.56	–2.43	–2.31
Change in SF-36 Physical function score	0.81	3.45	3.73
Change in IWQOL-Lite CT Physical function score	2.77	9.69	9.98

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; IWQOL-Lite CT, Impact of Weight on Quality of Life-Lite for Clinical Trials; LDL, low-density lipoprotein; SF-36, short form-36; U, units; VLDL, very-low-density lipoprotein.

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

Key results



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.

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 66.7% of individuals in the ER subset and 54.2% in the ENR subset (Table 3).
- The proportion of individuals experiencing ≥1 hypoglycemic event was 74.8% in the ER subset and 66.7% in the ENR subset (Table 3).

Table 3: Summary of adverse events

	Liraglutide 3.0 mg (n=195)			
	Early non-responders (n=72)		Early responders (n=123)	
	n	(%)	n	(%)
Total adverse events	63	(87.5)	117	(95.1)
Serious adverse events	4	(5.6)	12	(9.8)
Gastrointestinal adverse events	39	(54.2)	82	(66.7)
Hypoglycemic episodes†				
Total	48	(66.7)	92	(74.8)
Severe	1	(1.4)	2	(1.6)
Documented symptomatic	30	(41.7)	62	(50.4)

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

Conclusion

- Over 60% 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 4% at week 16 and were eligible for long-term treatment according to the FDA 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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