Efficacy and safety of liraglutide 3.0 mg in individuals with overweight or obesity and type 2 diabetes treated with basal insulin: the SCALE Insulin trial

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Introduction

- Individuals with type 2 diabetes (T2D) typically find it more difficult to lose weight than matched counterparts without T2D, owing, in part, to the weight-promoting effects of glucose-lowering treatments with sulphonylureas and/or insulin.[1,2]
- Liraglutide 3.0 mg is approved for weight management in individuals with overweight or obesity and has been investigated in individuals with T2D as part of the Satiety and Clinical Adiposity – Liraglutide Evidence (SCALE) phase 3a programme.[3]
- In the SCALE Diabetes trial, liraglutide 1.8 mg and 3.0 mg resulted in clinically significant weight loss (WL) and glycaemic benefits, with an acceptable safety profile.[4] Individuals treated with insulin, however, were excluded from this trial.
- To our knowledge, no pharmacotherapeutic agents approved for weight management have been specifically investigated in individuals with overweight or obesity and insulin-treated T2D.
- The aim of the SCALE Insulin trial was to evaluate the efficacy and safety of liraglutide 3.0 mg for weight management in individuals with overweight or obesity and T2D treated with basal insulin and up to two oral antidiabetic drugs (OADs). This poster reports the measures of body weight and safety data from the trial.

Methods

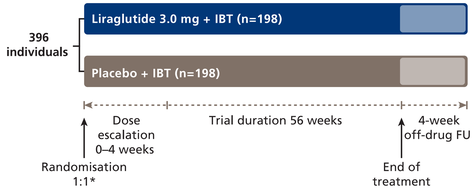
Study design

- SCALE Insulin (NCT02963922) was a 56-week, randomised, double-blind, placebo-controlled, multicentre trial in 396 individuals with T2D (glycated haemoglobin [HbA_{1c}] 6.0–10.0%) and overweight or obesity (body mass index [BMI] ≥27 kg/m^2).
- Individuals were randomised 1:1 to liraglutide 3.0 mg or placebo, both as adjunct to intensive behaviour therapy (IBT) (Figure 1).
- An IBT programme was provided in both arms, which included a hypocaloric diet, increased physical activity goals (increasing up to 250 min/week) and 23 behavioural counselling sessions.
- Primary endpoints were mean change in body weight (%) and proportion with WL ≥5% at week 56; a number of relevant secondary endpoints are reported here.
- All individuals were on stable treatment with basal insulin and up to 2 OADs. It was recommended that doses of sulphonylureas were reduced by 50% at randomisation to avoid the risk of hypoglycaemia.
  - » Individuals on sulphonylureas were stratified between the two treatment arms.
- Similarly, it was recommended that doses of basal insulin be reduced by 15–20% for individuals who had HbA_{1c} ≤8%. The trial was designed to target similar glycaemic control in the two arms by weekly adjustments of insulin dose.
- Weekly dose escalation of the trial drug was implemented during the first 4 weeks following randomisation in accordance with the label.[3]

Statistical analysis

- Outcomes were assessed based on data for all randomised individuals regardless of premature discontinuation of trial product (treatment policy estimand); missing values were handled using a jump-to-reference multiple imputation model.
- Continuous and categorical variables were calculated using analysis of covariance (ANCOVA) and logistic regression, respectively, with treatment arm, gender and BMI as factors and baseline endpoint as a covariate.

Figure 1: Study design



Key inclusion criteria
- T2D on any basal insulin and ≤2 OADs
- BMI ≥27 kg/m^2
- HbA_{1c} 6–10%
- Stable BW

Trial information
- February 2017 – September 2018
- Randomised, placebo-controlled, double-blind trial
- Across 53 sites globally
- Aimed for similar glycaemic target in the two arms

*Insulin dose decreased by 15–20% after randomisation for individuals with HbA_{1c} ≤8% at randomisation; dose adjusted once weekly according to pre-breakfast SMBG target 4.0–5.0 mmol/L (basal insulin dose was not to exceed the entry dose in the first 5 weeks). BMI, body mass index; BW, body weight; FU, follow-up; IBT, intensive behaviour therapy; OAD, oral antidiabetic drug; SMBG, self-measured blood glucose; T2D, type 2 diabetes

Results

- In total, 396 individuals were randomised (1:1) to liraglutide 3.0 mg or placebo, of which 195 and 197 were exposed, respectively. Subject disposition was similar between treatment arms (Table 1).
- To increase retention, the trial allowed individuals to return to study drug after discontinuation. At 56 weeks, 166 (83.8%) and 168 (84.8%) individuals remained on liraglutide 3.0 mg and placebo, respectively.
- Baseline demographics were similar between both treatment groups (Table 1).

Table 1: Subject disposition and baseline characteristics

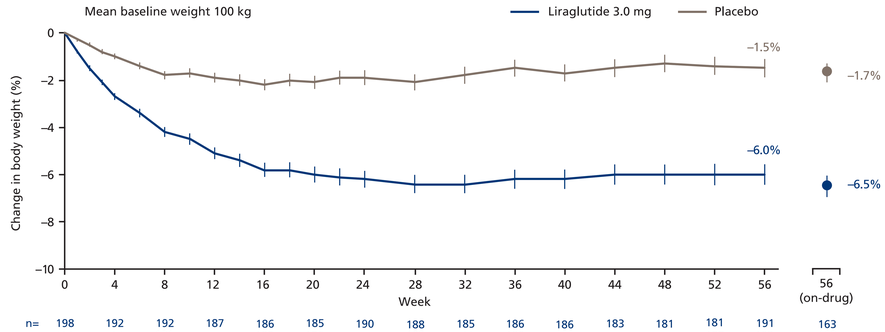
	Liraglutide 3.0 mg (n=198)	Placebo (n=198)
Randomised, n	198	198
Exposed, n	195	197
On drug at week 56 visit, n [%]	166 [83.8]	168 [84.8]
Discontinued trial drug, n [%]	32 [16.2]	30 [15.2]
Withdrawals, n [%]	4 [2.0]	4 [2.0]
With BW measurement at week 56, n [%]	191 [96.5]	193 [97.5]
Sex, male, n [%]	90 [45.5]	99 [50.0]
Mean age, years	55.9 (11.3)	57.6 (10.4)
Race, White, n [%]	174 [87.9]	180 [90.9]
Mean body weight, kg	100.6 (20.8)	98.9 (19.9)
Mean BMI, kg/m^2	35.9 (6.5)	35.3 (5.8)
Mean HbA_{1c}, %	7.9 (1.1)	8.0 (1.0)
Mean diabetes duration, years	11.4 (6.8)	12.8 (6.9)
Mean daily insulin dose, U	38 (27)	38 (29)
Use of sulphonylureas, n [%]	66 [33.3]	70 [35.4]

Discontinued trial drug group includes randomised individuals who were not exposed to trial product. Data are mean (SD) unless otherwise stated. BMI, body mass index; BW, body weight; SD, standard deviation

- Mean estimated change in weight at 56 weeks was –5.8% and –1.5% with liraglutide 3.0 mg and placebo, respectively, corresponding to an estimated treatment difference (ETD) of –4.3% (95% confidence interval [CI]: –5.5; –3.2, p<0.0001) (Figure 2).
- The proportion of individuals achieving WL ≥5% was 51.8% with liraglutide 3.0 mg versus 24.0% with placebo (odds ratio [OR] 3.4, p<0.0001). Values for >10% WL were 22.8% and 6.6% (OR 4.2, p<0.0001), respectively (Table 2).
- Mean estimated change in HbA_{1c} at 56 weeks was –1.1% and –0.6% with liraglutide 3.0 mg and placebo, respectively (ETD: –0.5, 95% CI: –0.8; –0.3, p<0.0001) (Table 2).
- Outcome data for other glycaemic parameters are available from poster 575.[5]
- Treatment with liraglutide 3.0 mg resulted in a smaller increase in mean insulin dose requirement at 56 weeks versus placebo; +2.8U and +17.8U, respectively, from a baseline mean in both groups of 38U. This represented a relative difference of 15U (p<0.0001).
- Total number of hypoglycaemic events (on-drug) occurred at the respective rates of 742 and 938 events per 100 patient-years of exposure with liraglutide and placebo, with three and two severe events, respectively (Table 3).
- Adverse event incidence was similar for liraglutide 3.0 mg and placebo, except for gastrointestinal events (liraglutide 3.0 mg, 62.1%; placebo, 46.7%) (Table 3).

Figure 2: Change in body weight, over time (%)

Key result



Full analysis set. Over time graph is observed mean data ± SEM. SEM, standard error of the mean

Table 2: Endpoints at 56 weeks

	Liraglutide 3.0 mg (n=198)	Placebo (n=198)	ETD/OR* [95% CI]	p-value
Change in body weight from baseline (%)	–5.8	–1.5	–4.3 [–5.5; –3.2]	<0.0001
Percentage of ≥5% responders* (%)	51.8	24.0	3.4 [2.2; 5.3]	<0.0001
Percentage of >10% responders* (%)	22.8	6.6	4.2 [2.2; 8.2]	<0.0001
Change in waist circumference from baseline (cm)	–5.3	–2.6	–2.7 [–3.9; –1.5]	<0.0001
Change in HbA_{1c} from baseline (%)	–1.1	–0.6	–0.5 [–0.8; –0.3]	<0.0001
Change in heart rate (beats/min)	1.4	–0.2	1.5 [–0.2; 3.2]	NS
Change in systolic blood pressure (mmHg)	–5.6	–1.6	–4.0 [–6.4; –1.5]	0.0014
Change in diastolic blood pressure (mmHg)	–2.3	–0.9	–1.4 [–3.0; 0.2]	NS
Change in SF-36 Physical Functioning score from baseline	2.7	2.3	0.4 [–1.0; 1.8]	NS
Change in IWQOL-Lite-CT Physical Function domain score from baseline	8.2	5.7	2.5 [–1.5; 6.4]	NS

*The endpoint is analysed in a logistic regression model. CI, confidence interval; ETD, estimated treatment difference; IWQOL-Lite-CT, impact of weight on quality of life-lite clinical trial version; NS, non-significant; OR, odds ratio; SF-36, short-form 36

Table 3: Safety outcomes

	Liraglutide 3.0 mg			Placebo		
	N	(%)	E/100 yr	N	(%)	E/100 yr
Exposed to trial product, n	195	-	-	197	-	-
Adverse events	180	(92.3)	578.3	175	(88.8)	531.2
Serious	16	(8.2)	11.7	19	(9.6)	12.6
Fatal	0	(0.0)	-	0	(0.0)	-
Leading to discontinuation	15	(7.7)	8.6	6	(3.0)	3.0
Gastrointestinal disorders	121	(62.1)	207.1	92	(46.7)	101.9
Hypoglycaemic episodes*	140	(71.8)	742.3	140	(71.1)	937.9
Severe episodes	3	(1.5)	1.5	2	(1.0)	1.0
Documented symptomatic	92	(47.2)	336.1	102	(51.8)	411.7

Data are from individuals on-drug. *Hypoglycaemic episodes recorded in patient diaries and are based on the American Diabetes Association classification.[6] Documented symptomatic hypoglycaemia: measured plasma glucose concentration ≤3.9 mmol/L with typical symptoms of hypoglycaemia apparent. E/100 yr, event rate per 100 patient-years of exposure

Conclusions

- In individuals with overweight/obesity and insulin-treated T2D, liraglutide 3.0 mg was superior to placebo with respect to mean WL and the proportion of individuals achieving ≥5% and >10% WL at week 56.
- Additionally, liraglutide 3.0 mg was associated with significant improvements in glycaemic control, such as reduction in HbA_{1c} and a reduced need for basal insulin.
- More hypoglycaemic episodes were reported in individuals in the placebo versus liraglutide 3.0 mg group, and no new safety or tolerability issues were observed.
- Liraglutide 3.0 mg is effective for weight management, with an acceptable safety profile, in individuals with overweight/obesity and insulin-treated T2D.

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