# Effect of liraglutide 3.0 mg on glycaemic parameters in adults with overweight/obesity and T2D treated with basal insulin: SCALE Insulin trial

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## Background

- Liraglutide 3.0 mg is approved for weight management in individuals with overweight or obesity and has been investigated in individuals with type 2 diabetes (T2D) as part of the Satiety and Clinical Adiposity—Liraglutide Evidence (SCALE) phase 3a programme.[1]
- Liraglutide up to 1.8 mg has been used in combination with insulin for treatment of T2D, but combination of a 3.0 mg dose with insulin has not previously been investigated.
- In SCALE Diabetes, a 56-week trial in individuals with overweight or obesity and T2D, liraglutide 1.8 mg and 3.0 mg showed significant weight- and glucose-lowering effects, with an acceptable safety profile.[2] However, individuals treated with insulin were excluded from the trial.
- To our knowledge, no pharmacotherapeutic agents approved for the treatment of obesity have been specifically investigated in individuals with obesity and insulin-treated T2D.
- The aim of the SCALE Insulin phase 3b 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 effect on glycaemic parameters and hypoglycaemic safety data from the trial.

## Methods

### Study design

- SCALE Insulin (NCT02963922) was a 56-week, randomised, double-blind, placebo-controlled, multicentre trial in individuals with obesity.
- A total of 396 adults with T2D (glycated haemoglobin [$HbA_{1c}$] 6.0–10.0%) and overweight or obesity (body mass index [BMI] ≥27 kg/m$^2$) were randomised 1:1 to liraglutide 3.0 mg or placebo, both as adjunct to intensive behaviour therapy (IBT).
- An IBT programme was provided in both arms which included reduced caloric intake, increased physical activity goals (increasing up to 250 min/week) and 23 behavioural counselling sessions.
- The diabetes treatment regimens for all individuals included basal insulin and up to two 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 arms.
- Similarly, doses of basal insulin were recommended to be reduced by 15–20% for individuals who had $HbA_{1c}$ ≤8%. The trial was designed such that glycaemic control was similar between the two arms (e.g. insulin doses adjusted weekly).
- Weekly dose escalation of the trial drug was implemented during the first 4 weeks at randomisation in accordance with the label.[2]

### Statistical analysis

- Outcomes were assessed based on data for all randomised individuals regardless of premature discontinuation of trial product (treatment policy estimand or intention-to-treat [ITT] principle); 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.

## Results

- In total, 396 individuals were randomised (1:1) to liraglutide 3.0 mg or placebo, of which 195 and 197 were exposed, respectively.
- 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 treatment arms (Table 1).
- Estimated mean change in weight at 56 weeks was –5.8% with liraglutide 3.0 mg and –1.5% with placebo (estimated treatment difference [ETD]: –4.3%, 95% CI: –5.5; –3.2, $p$<0.0001). Additional weight loss data available from the trial (see poster 576[3]).
- Mean estimated change in $HbA_{1c}$ at 56 weeks was –1.09% and –0.55% with liraglutide 3.0 mg and placebo, respectively (ETD: –0.53, 95% CI: –0.76; –0.31, $p$<0.0001) (Figure 1).
- Mean estimated change in fasting plasma glucose at 56 weeks was –1.02 and –0.64 mmol/L (ETD: –0.39, 95% CI: –0.91; 0.14, $p$=not significant).
- Change in estimated mean daytime glucose value (based on 7-point self-measured blood glucose profile) at 56 weeks was –2.2 and –1.5 mmol/L for liraglutide 3.0 mg and placebo, respectively (ETD: –0.69, 95% CI: –1.14; –0.23, $p$=0.0032).
- 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 (95% CI: 22; 8, $p$<0.0001).
- At 56 weeks, more liraglutide 3.0 mg- than placebo-treated individuals achieved the composite endpoint of reaching $HbA_{1c}$ target[4] <7.0% + ≥5% weight loss (39.0% vs 13.9%; odds ratio 3.94, $p$<0.0001). Similarly, more liraglutide 3.0 mg- than placebo-treated individuals met the composite endpoint of $HbA_{1c}$ <7.0% + ≥5% weight loss + no documented symptomatic hypoglycaemia[5] (17.8% vs 6.2%; odds ratio 3.28, $p$=0.0006).
- 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%).
- 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 2).
- Documented symptomatic hypoglycaemia (on-drug) occurred at rates of 425 and 299 events per 100 patient-years of exposures, with liraglutide versus placebo respectively, in patients taking sulphonylureas at baseline; and 290 vs 475 events per 100 patient-years of exposure in patients not taking sulphonylureas at baseline with liraglutide versus placebo, respectively.

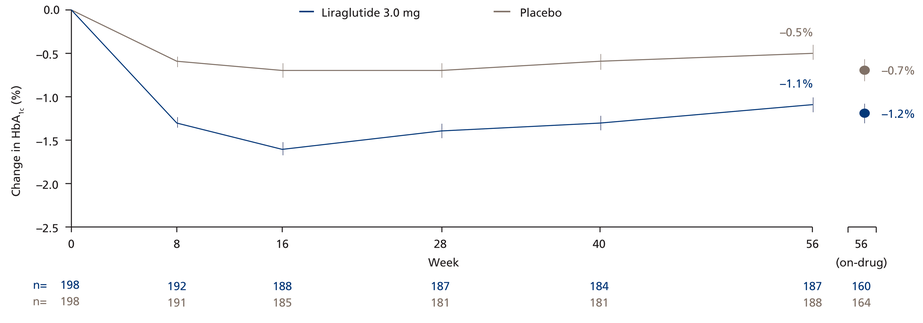
**Table 1**: Baseline demographics and anthropometry

| | Liraglutide 3.0 mg (n=198) | Placebo (n=198) |
|---|---|---|
| Sex, male, n (%) | 90 (45.5) | 99 (50.0) |
| Mean age, years (SD) | 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$^2$ (SD) | 35.9 (6.5) | 35.3 (5.8) |
| Mean $HbA_{1c}$, % (SD) | 7.9 (1.1) | 8.0 (1.0) |
| Mean FPG, mmol/L (SD) | 7.8 (2.2) | 8.1 (2.5) |
| Mean diabetes duration, years | 11.4 (6.8) | 12.8 (6.9) |
| Anti diabetic medications at screening | | |
| SGLT-2is, n (%) | 44 (22.2) | 44 (22.2) |
| Sulphonylureas, n (%) | 68 (34.3) | 71 (35.9) |
| Long-acting basal insulins/analogues, n (%) | 180 (90.9) | 184 (92.9) |
| Intermediate-acting basal insulins/analogues, n (%) | 18 (9.1) | 14 (7.1) |

Values are observed mean (SD) for full analysis set, unless otherwise stated. BMI, body mass index; FPG, fasting plasma glucose; SD, standard deviation; SGLT2-i; sodium-glucose co-transporter-2 inhibitor

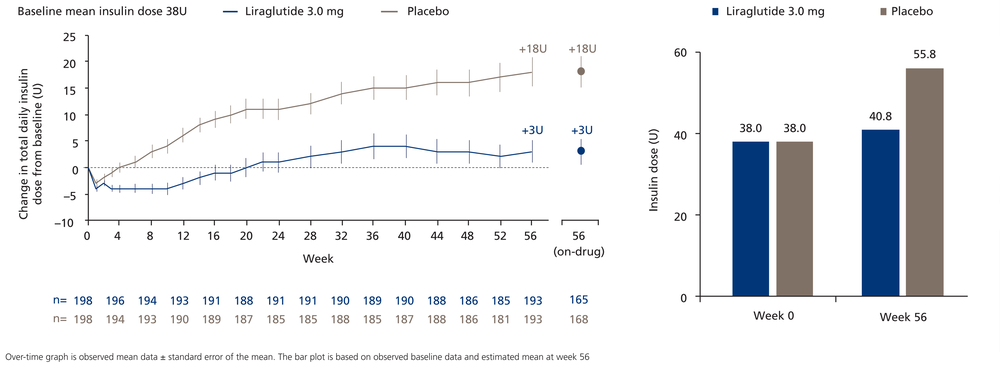
**Figure 1**: Change in $HbA_{1c}$ over time (%)

Key result




Graph is observed mean data ± standard error of the mean

**Figure 2**: Change in total daily insulin dose (U)




Over-time graph is observed mean data ± standard error of the mean. The bar plot is based on observed baseline data and estimated mean at week 56

**Table 2**: Hypoglycaemic episodes* from randomisation to week 56

| | Liraglutide 3.0 mg | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R |
| Number of individuals exposed | 195 | | | | 197 | | | |
| Hypoglycaemic episodes | 140 | (71.8) | 1462 | 742.3 | 140 | (71.1) | 1859 | 937.9 |
| Severe episodes | 3 | (1.5) | 3 | 1.5 | 2 | (1.0) | 2 | 1.0 |
| BG ≤3.9 mmol/L | | | | | | | | |
| Asymptomatic | 116 | (59.5) | 742 | 376.7 | 116 | (58.9) | 988 | 498.4 |
| Documented symptomatic | 92 | (47.2) | 662 | 336.1 | 102 | (51.8) | 816 | 411.7 |

Data are from patients on-drug. Episodes recorded in patient diaries. BG, blood glucose; E, number of events; R, event rate per 100 patient-years of exposure. *Based on American Diabetes Association 2013 criteria[4]

## Conclusions

- In insulin-treated individuals with overweight/obesity and longstanding T2D, treatment with liraglutide 3.0 mg resulted in better glycaemic control versus placebo, in addition to clinically relevant weight loss, with need for less basal insulin.
- Total number of hypoglycaemic episodes was higher in individuals treated with placebo versus liraglutide 3.0 mg.

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September 16–20, 2019, Barcelona, Spain.

**References:** (**1**) Davies *et al. JAMA* 2015;314:687–99; (**2**) Novo Nordisk. Saxenda® EU SmPC. https://www.ema.europa.eu/; (**3**) Migrone *et al.* Poster 576. Presented at EASD 2019; (**4**) American Diabetes Association. *Diabetes Care* 2019;42(Suppl 1):S61–70; (**5**) Seaquist *et al. Diabetes Care* 2013;36:1384–95.