Once-Weekly Semaglutide 2.4 mg Improved Glucose Metabolism and Prediabetes in Adults with Overweight/Obesity in the STEP 1 Trial

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Aim

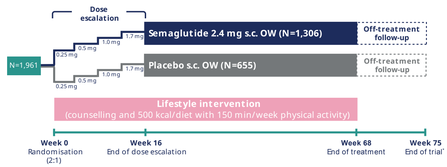
- To evaluate the effects of subcutaneous (s.c.) semaglutide 2.4 mg on prediabetes and glucose metabolism in participants with overweight/obesity in the Semaglutide Treatment Effect in People (STEP) 1 trial.

Introduction

- Obesity is a well-established risk factor for prediabetes, and people with prediabetes are at increased risk of developing type 2 diabetes (T2D) and cardiovascular disease (CVD).[1–3]
- In individuals with prediabetes, weight loss and prevention of diabetes are often accompanied by improvements in cardiometabolic risk factors.[4]
- In the STEP 1 trial, s.c. semaglutide 2.4 mg plus lifestyle intervention in participants with overweight/obesity was associated with:
  - Sustained clinically meaningful reductions in body weight.[5]
  - Benefits beyond weight loss on cardiometabolic parameters and patient-reported outcomes.[5]

Methods

Figure 1: STEP 1 trial design: a randomised, double-blind, multicentre, placebo-controlled trial



*End of trial for the main phase. OW, once weekly; s.c., subcutaneous.

- STEP 1 trial participants (N=1,961) (Figure 1):
  - Were male or female and ≥18 years old.
  - Had made ≥1 unsuccessful dietary effort to lose weight.
  - Had a body mass index (BMI) ≥30 kg/m^2, or ≥27 kg/m^2 with ≥1 weight-related comorbidity (i.e., hypertension, dyslipidaemia, obstructive sleep apnoea, or CVD), without diabetes.
- Supportive secondary efficacy endpoints and prespecified exploratory endpoints of the STEP 1 trial included change from baseline to week 68 in HbA_{1c}, fasting plasma glucose (FPG), and glycaemic status.
  - Glycaemic status (normoglycaemia, prediabetes or T2D) was assessed by investigators at baseline and at week 68, according to American Diabetes Association definitions and based on all available relevant information.
- *Post hoc* analyses assessed change from baseline to week 68 in the following according to glycaemic status at week 0:
  - HbA_{1c}, FPG, glycaemic status, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and Homeostatic Model Assessment of β-cell function (HOMA-B).
  - Percentage body weight.
- Statistical analyses were not adjusted for multiplicity.

Results

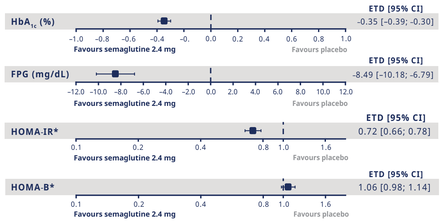
Table 1: Demographics and baseline characteristics of participants with prediabetes at baseline*

	Semaglutide 2.4 mg (n=593)	Placebo (n=263)
Sex, female, %	68.6	74.5
Age, mean, years	48	49
Race, %		
White	70.3	69.6
Black or African American	7.1	8.4
Asian	16.9	15.6
Other†	5.7	6.5
Hispanic or Latino ethnicity, %	12.6	15.6
Body weight, mean, kg (lbs)	106.9 (235.7)	106.9 (235.7)
BMI, mean, kg/m^2	38.4	38.9
HbA_{1c}, mean, % (mmol/mol)	5.9 (41.2)	5.9 (41.4)
FPG, mean, mg/dL	98.7	97.6

*Glycaemic status was determined by investigators based on available information (e.g. medical records, concomitant medication, and blood glucose parameters) and in accordance with the American Diabetes Association criteria.
†Including Native American or other Pacific Islander, other, and not applicable, the last of which is how race was recorded in France.
BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin.

- At baseline, 856 (43.7%) participants in the STEP 1 trial had prediabetes.
- Baseline characteristics among participants with prediabetes are reported in Table 1.
- In the overall STEP 1 trial population, mean change from baseline to week 68 in body weight was –14.9% with semaglutide 2.4 mg vs –2.4% with placebo (estimated treatment difference [ETD]: –12.4 %-points [95% confidence interval (CI): –13.4; –11.5]; p<0.0001).
- Among participants with prediabetes at baseline, mean change from baseline to week 68 in body weight was –13.7% with semaglutide 2.4 mg vs –2.4% with placebo (ETD: –11.3 %-points [95% CI: –12.7; –10.0]; p<0.0001).

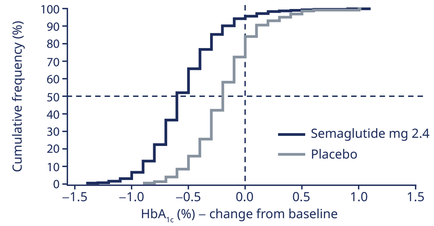
Figure 2: Effects on glucose metabolism in participants with prediabetes at baseline



*Log-transformed baseline values used as covariate.
CI, confidence interval; ETD, estimated treatment difference; ETR, estimated treatment ratio; HbA_{1c}, glycated haemoglobin; FPG, fasting plasma glucose; HOMA-B: Homeostatic Model Assessment of β-cell function; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance.

- Among participants with prediabetes at baseline:
  - Treatment with semaglutide 2.4 mg improved HbA_{1c}, FPG, and HOMA-IR compared with placebo (Figure 2). There was no difference between treatment groups for HOMA-B.
  - Most patients experienced reductions in HbA_{1c} from baseline to week 68, with greater reductions with semaglutide vs placebo (Figure 3).

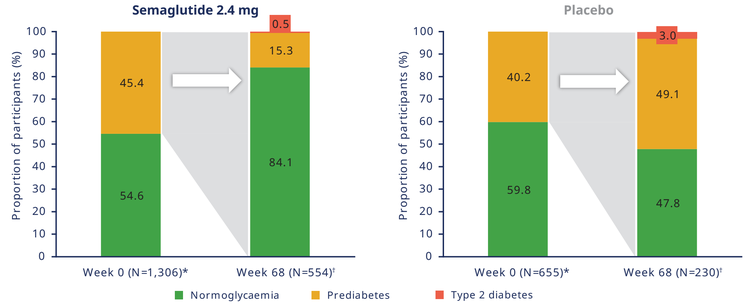
Figure 3: Cumulative distribution of observed change from baseline to week 68 in HbA_{1c} in participants with prediabetes at baseline



Vertical dotted line at 0% indicates zero change from baseline. Horizontal dotted line indicates 50% cumulative frequency.
HbA_{1c}, glycated haemoglobin.

Figure 4: Shift in glycaemic status from baseline to week 68 in participants with prediabetes at baseline

Key result



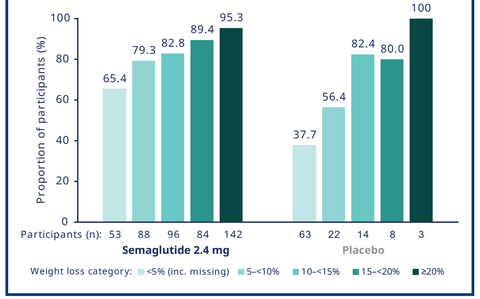
Data are observed during the in-trial period (regardless of treatment discontinuation or rescue intervention). Glycaemic category was evaluated by the investigator based on all available relevant information (e.g. concomitant medication, medical records, and blood glucose parameters) in accordance with American Diabetes Association definitions.

*Number of participants in the overall population.

†Number of participants with prediabetes at baseline and evaluable data at week 68.

- By week 68, 84.1% of participants with prediabetes at baseline were normoglycaemic with semaglutide 2.4 mg vs 47.8% with placebo (Figure 4).
- The proportion of participants with prediabetes at baseline who reverted to normoglycaemia by week 68 with semaglutide 2.4 mg increased in subgroups with larger losses of baseline body weight (Figure 5).

Figure 5: Shift from prediabetes to normoglycaemia from baseline to week 68 by weight loss category



- Among participants with normoglycaemia at baseline:
  - By week 68, 97.1% remained normoglycaemic with semaglutide 2.4 mg vs 89.1% with placebo.
  - By week 68, 2.9% had progressed to prediabetes with semaglutide 2.4 mg vs 10.9% with placebo.

Conclusion

- Once-weekly semaglutide 2.4 mg allowed most participants with overweight/obesity and prediabetes to revert to normoglycaemia at week 68.
  - In addition, semaglutide 2.4 mg prevented more participants with normoglycaemia from progressing to prediabetes vs placebo.
- The proportion of patients who reverted from prediabetes to normoglycaemia with semaglutide 2.4 mg increased with larger losses of baseline body weight.
- Treatment with semaglutide 2.4 mg improved glucose metabolism vs placebo, assessed by HbA_{1c}, FPG and HOMA-IR.
- These results indicate that semaglutide 2.4 mg can reverse or prevent the progression to prediabetes.
- Semaglutide-induced weight loss was also associated with improvement in insulin sensitivity.

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References:

(**1**) Miao Z, et al. PLoS Genet. 2020;16:e1009018; (**2**) Braga T, et al. Minerva Med. 2019;110:52–61; (**3**) Huang Y, et al. BMJ. 2016;355:i5953; (**4**) Garvey WT, et al. Diabetes Care. 2014;37:912–21; (**5**) Wilding JPH, et al. N Engl J Med. 2021;384:989.