T4P118

High number of responders with pharmacotherapy-induced weight loss of at least 15% in a placebo-controlled, dose-ranging study of semaglutide in people with obesity

John Wilding[1], Andreas L. Birkenfeld[2], Barbara McGowan[3], Ofri Mosenzon[4], Sue D. Pedersen[5], Sean Wharton[6], Lars Endahl[7], Cecilie H. Jepsen[7], Patrick M. O'Neil[8]

[1]University of Liverpool, Liverpool, UK;
[2]University Clinic Dresden, TU Dresden, Dresden, Germany;
[3]Guy's and St Thomas' NHS Foundation Trust, London, UK;
[4]Hadassah Hebrew University Hospital, Jerusalem, Israel;
[5]C-ENDO Diabetes & Endocrinology Clinic, Calgary, AB, Canada;
[6]York University & Wharton Weight Management Clinic, Toronto, ON, Canada;
[7]Novo Nordisk A/S, Søborg, Denmark;
[8]Medical University of South Carolina, Charleston, SC, USA.

Background

- New therapeutic agents are needed to treat obesity[1]
- Glucagon-like peptide 1 (GLP-1), and pharmacological activation of the GLP-1 receptor, modulate satiety and appetite, as well as glucose-dependent insulin secretion, through receptors in the brain, gut, pancreas and elsewhere
- Semaglutide is a GLP-1 receptor agonist recently approved in the US, EU, Canada and Japan in weekly doses of 0.5 and 1.0 mg to treat type 2 diabetes, and it is currently under investigation at higher doses for weight management
- A recent phase 2 trial (NCT02453711) showed dose-dependent, mean weight losses of -6.0% to -13.8% of baseline body weight among people with obesity, without diabetes, who received once-daily subcutaneous semaglutide as an adjunct to lifestyle intervention for 52 weeks, at final doses between 0.05 mg and 0.4 mg/day (following sequential escalation every 4 weeks), compared with -2.3% on placebo and -7.8% on liraglutide 3.0 mg[2]
  - The primary analysis (ANCOVA model) used all available in-trial data at week 52, with missing data imputed from the placebo pool by a multiple imputation jump-to-reference approach
  - In that analysis, at the highest dose of semaglutide (0.4 mg), 83% of participants were estimated to have achieved a weight loss ≥5% of baseline, and 65% a loss ≥10% by logistic regression in prespecified analyses, compared with 23% and 10%, respectively, with placebo

Aims

- To undertake *post-hoc* analyses to evaluate categorical weight loss at the higher thresholds of ≥15% and ≥20%, and combine with data from the prespecified categorical weight losses of ≥5% and ≥10% (without imputation), to produce data for the categorical weight losses of ≥5% to ≥20% among participants on- and off-treatment at week 52 in this phase 2 trial

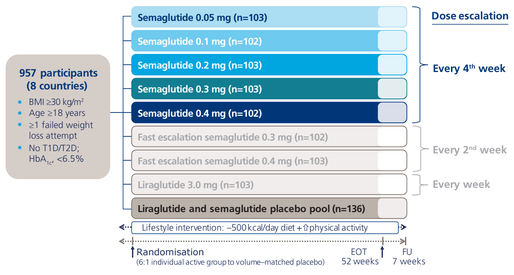
Glossary. Definitions used for data outputs in this analysis.

In trial/ observed	All participants who received at least one dose of study treatment and then returned for body weight assessment at the end of treatment (week 52). This includes those who discontinued treatment for any reason before week 52
On treatment	Participants who continued treatment for 52 weeks according to the trial protocol
Off treatment	Participants who discontinued their assigned treatment for any reason but returned for assessment at week 52

Methods

- The study design is shown in Fig 1

Figure 1. Study design.



BMI, body mass index; EOT, end of treatment; FU, follow-up; T1D/T2D, type 1/type 2 diabetes.

- Data are presented for the five semaglutide dosing arms (0.05, 0.1, 0.2, 0.3, 0.4 mg/day), with dose escalation every 4 weeks, and for the pooled placebo arm
  - Data are not shown for the 0.3 and 0.4 mg/day semaglutide arms escalated every 2 weeks, or for the liraglutide 3.0 mg comparator
- The proportion of participants in trial at week 52 who achieved a weight loss of ≥5% or ≥10% of baseline (prespecified analyses), or ≥15% or ≥20% of baseline (*post-hoc* analyses), were evaluated overall and for those on-treatment or off-treatment at week 52

Results

Participant characteristics and disposition

- In the 6 presented arms, 649 people with obesity (35% male) were enrolled on the above schedule, including those who did not return for assessment at Week 52
- The mean age was 44–48 years across all dosing groups (overall range: 18–77); mean weight was 111–114 kg (range: 73–244) and mean BMI was 39–40 kg/m² (range: 30–80)
- Week 52 data were available for 600 participants (92%), including 525 on-treatment and 75 off-treatment; 49 patients did not return for a final assessment
  - Reasons for discontinuation are given in Table 1

Table 1. Discontinuations by treatment group.

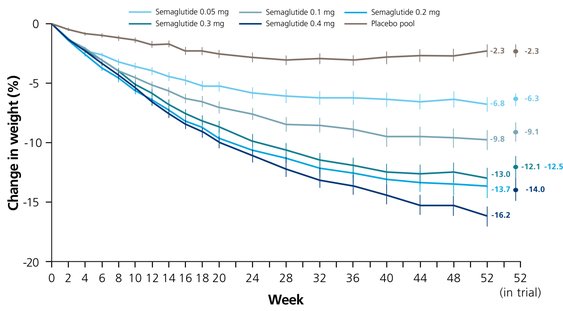
	Placebo (N=136)	0.05 mg (N=103)	0.1 mg (N=102)	0.2 mg (N=103)	0.3 mg (N=103)	0.4 mg (N=102)
Discontinued, n (%)	33 (24.3)	26 (25.2)	14 (13.7)	16 (15.5)	15 (14.6)	20 (19.6)
Adverse event	4 (2.9)	7 (6.8)	8 (7.8)	5 (4.9)	4 (3.9)	15 (14.7)
Protocol violation	4 (2.9)	6 (5.8)	1 (1.0)	2 (1.9)	3 (2.9)	1 (1.0)
Pregnancy	0	0	0	1 (1.0)	0	0
Other	25 (18.4)	13 (12.6)	5 (4.9)	8 (7.8)	8 (7.8)	4 (3.9)
Discontinued with Week 52 data, yes/n (%)	20/33 (60.6)	15/26 (57.7)	7/14 (50.0)	7/16 (43.8)	8/15 (53.3)	18/20 (90.0)

- Discontinuations categorised as "Other" included patient requests to halt treatment
- Reasons for patient requests to discontinue were not systematically captured; however, of 29 "Other" discontinuations with data at week 52, 9 were documented as patient requests for lack of efficacy or dissatisfaction with weight loss
  - All were in the placebo (n=7) or semaglutide 0.05 mg (n=2) groups
  - One patient in the semaglutide 0.4 mg group opted to discontinue study treatment due to excessive weight loss

Response over time

- Mean weight loss continued through week 52 for semaglutide-treated groups; this effect was more pronounced in the higher-dose groups (Fig 2)
- At the final visit at week 52, the mean weight loss was numerically higher among participants in the on-treatment group than for those in the in-trial group, in each semaglutide dose group

Figure 2. Mean (±SEM) changes from baseline in percentage body weight by visit and treatment group (observed data).



The line graph up to Week 52 represents the on-treatment cohort (n=525). The data point on the right-hand side of the graph represent the in-trial group (n=600). SEM, standard error of the mean.

- The on-treatment weight loss on semaglutide at week 52 ranged from -6.8% to -16.2%, vs -2.3% in participants who received placebo; the overall in-trial weight loss ranged from -6.3% to -14.0% on semaglutide vs -2.3% on placebo (Fig 2)

Proportion of participants achieving categorical weight loss

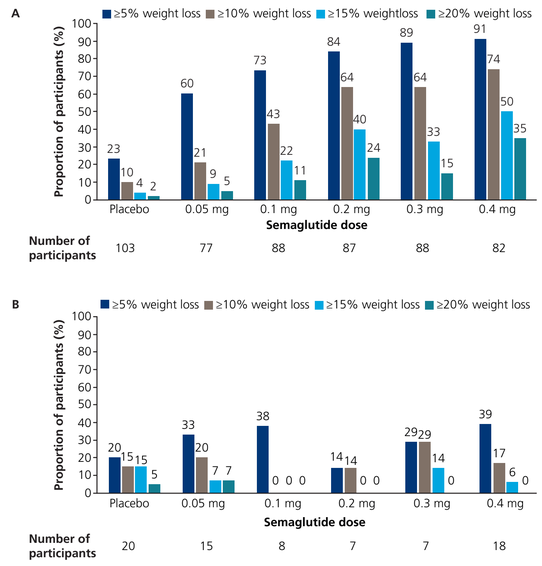
- In the prespecified analyses, 55–84% of participants in-trial lost ≥5% of baseline weight on semaglutide, and 21–64% lost ≥10%, vs 23% and 11% on placebo, respectively (Table 2)
- In the *post-hoc* analyses, 9–42% of participants in-trial lost ≥15% of baseline weight and 5–29% lost ≥20%, vs 6% and 2%, respectively, on placebo.
- The majority of participants who lost at least 15% of baseline weight were still on treatment at week 52, especially those who received higher doses of semaglutide

Table 2. Overall response by semaglutide dose and the proportion of those responding who were still on treatment at the end of treatment.

Observed data	Placebo (N=123)	0.05 mg (N=92)	0.1 mg (N=96)	0.2 mg (N=94)	0.3 mg (N=95)	0.4 mg (N=100)
In-trial responders at week 52, n (%)						
≥5% response	28 (23)	51 (55)	67 (70)	74 (79)	80 (84)	82 (82)
≥10% response	13 (11)	19 (21)	38 (40)	57 (61)	58 (61)	64 (64)
≥15% response	7 (6)	8 (9)	19 (20)	35 (37)	30 (32)	42 (42)
≥20% response	3 (2)	5 (5)	10 (10)	21 (22)	13 (14)	29 (29)
Proportion of responders still on treatment at week 52, yes/n (%)						
≥5% response	24/28 (86)	46/51 (90)	64/67 (96)	73/74 (99)	78/80 (98)	75/82 (91)
≥10% response	10/13 (77)	16/19 (84)	38/38 (100)	56/57 (98)	56/58 (97)	61/64 (95)
≥15% response	4/7 (57)	7/8 (88)	19/19 (100)	35/35 (100)	29/30 (97)	41/42 (98)
≥20% response	2/3 (67)	4/5 (80)	10/10 (100)	21/21 (100)	13/13 (100)	29/29 (100)

- Weight loss was dose-related and the proportion of responders in the higher weight-loss categories was higher at doses of 0.2–0.4 mg/day (Fig 3)
- Very few participants who discontinued semaglutide before week 52 achieved a ≥15% or ≥20% weight loss
- Among participants who completed the full 52-week treatment period, 33–50% who received 0.2–0.4 mg/day semaglutide achieved ≥15% weight loss, and 15–35% achieved ≥20% weight loss

Figure 3. Proportion of trial participants with ≥5% and ≥10% (prespecified) and ≥15% and ≥20% (*post-hoc*) weight loss at week 52 in a) participants treated for 52 weeks and b) participants who discontinued treatment before week 52.



Conclusions

- Observed weight loss among participants who remained on treatment was dose-related and appeared to continue through the entire 52-week treatment period
  - Longer studies may be needed to determine the full semaglutide treatment effect
- A high proportion of patients achieved ≥15% weight loss on higher doses of semaglutide (≥0.2 mg)
  - While some participants achieved ≥5% or ≥10% weight loss on placebo, higher levels of ≥15% or above were achieved almost exclusively by participants who received semaglutide
- At week 52, the proportion of responders in each of the four weight loss categories was also dose-related and high among in-trial participants, particularly those who received semaglutide doses of 0.2 mg or higher
- Almost all responders, particularly in higher weight loss categories of ≥15 or ≥20%, remained on treatment at week 52
- At the highest evaluated dose of semaglutide (0.4 mg/day), 50% of those still on treatment at week 52 achieved ≥15% weight loss, and 35% achieved ≥20% weight loss
- The data indicate that weight loss ≥15% of baseline is achievable by a high proportion of people with obesity after 1 year on daily semaglutide treatment for obesity, provided treatment is maintained for the full duration

References

1. World Obesity Federation. World Obesity Day 2017: Global Data on Costs of Consequences. Available at: http://www.obesityday.worldobesity.org/ourdata2017 (accessed Apr 25, 2018).
2. Wilding J, *et al*. *ECO* 2018; Vienna, Austria; Abstract O8.1.

Contact information
Prof. John Wilding
Obesity and Endocrinology Research, Institute of Ageing and Chronic Disease, University of Liverpool, Clinical Sciences Centre, University Hospital Aintree, Longmoor Lane, Liverpool L9 7AL, United Kingdom
e-mail: J.P.H.Wilding@liverpool.ac.uk

qrs.ly/pq6vlu3

Acknowledgements and Disclosures

- Clinical trial NCT02453711 (Study NN9536-4153) was conducted by Novo Nordisk A/S, Denmark
- The authors thank the trial investigators, site staff and trial participants for their contributions to the data, and Dr Charlotte Giwercman Carson of Novo Nordisk A/S (Denmark) for her review and input
- Editorial assistance with this poster was provided by John Munro, BSc (Hons), of ArticulateScience Ltd, London, UK
- John Wilding has received honoraria as an advisory board member/consultant for Astellas, AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Napp, Novo Nordisk, Orexigen and Sanofi; as a speaker for AstraZeneca, Biologix, Boehringer Ingelheim, Janssen, Lilly, Napp, Novo Nordisk, Orexigen, Sanofi and Takeda; and has received grants from AstraZeneca, Novo Nordisk and Takeda