Beyond glycaemic control: Weight loss Benefits

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Radcliffe Medical Education

In addition to their anti-hyperglycaemic properties, GLP-1 RAs have established weight loss benefits

Mechanisms through which GLP-1 RAs exert their weight loss effects include

- Reducing the energy intake through increasing satiety and reducing hunger
- Enhancing glycaemic control[1]

GLP-1 RAs have shown their weight loss benefits during several CVOTs[2]

- A phase 2 trial with semaglutide 0.4 mg daily resulted in greater weight loss at wk 52 compared to placebo (−13.8% vs −2.3%)
- While the mean weight loss with liraglutide 3.0 mg was −7.8% [3]

Major guidelines have recommended GLP-1 RAs for obesity management

- ADA and EASD recommended GLP-1 RAs[4]
- FDA and EMA approved liraglutide 3.0 mg once daily[1,5]
- FDA also approved semaglutide 2.4 mg once weekly SQ[6]

The STEP trials

The **STEP programme** was designed to assess the use of **injectable semaglutide** for **treatment of obesity**[7-12]

5000
enrolled patients

Primary endpoints for STEP 1 – STEP 5 were **weight loss**

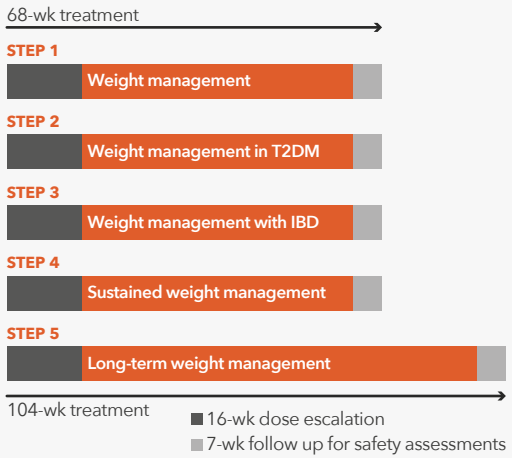
STEP 1, 2, 4, & 5 trials included **lifestyle interventions**

- Physical activity 150 min/wk
- Diet ~500 kcal/day

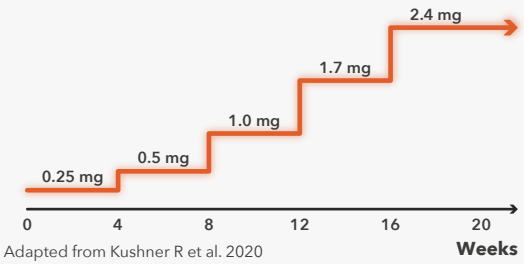
STEP 3 trial had **intensive behavior therapy**

- Dietitian counselling
- Increased physical activity
- Initial 8-wk low-calorie diet 60-wk hypocaloric diet

Trial designs



Dose escalation plan for STEP program



Adapted from Kushner R et al. 2020

Eligibility criteria included

- unsuccessful diet history
- age ≥18 years
- no >5 kg weight change <90 days before screening
- BMI ≥30 kg/m² or ≥27 kg/m² + weight-related complications

Baseline characteristics included

- adults
- high BMI (36 – 38)
- aged 40 – 50 yrs
- no history of DM[12]
  - Only STEP 2 included pts with DM (≥27 kg/m²+T2DM)

Key findings

Injectable semaglutide at dose of 2.4 mg once-weekly produce clinically meaningful and statistically significant reduction in body weight

- -12.4% in STEP 1[7]
- -6.2% in STEP 2[8]
- -10.3% in STEP 3[9]
- -14.8% in STEP 4[10]
- STEP 5 results are awaited[11]

Ongoing STEP trials

- **STEP 6** (NCT03811574), **STEP TEENS** (NCT04102189), **STEP 7** (NCT04251156) trials are enrolling pts with **different demographic** populations
- **STEP 8** (NCT04074161) will assess the efficacy and safety of **semaglutide** 2.4 mg once-weekly compared with **liraglutide** 3.0 mg once daily in **obese** pts[4]
- **SELECT trial** (NCT03574597) will assess **CV benefits** in pts at with **obesity and established CVD without DM**

Data from these trials may change the treatment paradigm of obesity management to concentrate on not only the weight loss, but also key complications of obesity, including CVD

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DM, diabetes; EASD, European Association for the Study of Diabetes; EMA, European Medicines Agency; FDA, Food Drug Administration; GLP-1RA, glucagon-like peptide 1 receptor agonist; IBD, inflammatory bowel disease; NCT, national clinical trial; pts, patients; SQ, subcutaneous; T2DM, type 2 diabetes mellitus; wk, week.

References: **1.** Davies MJ et al *JAMA* 2015, 314(7):687. **2.** Foley JE et al. *Vasc Health Risk Manag* 2010, 6:541. **3.** O'Neil PM et al. *Lancet* 2018, 392:637. **4.** Davies MJ et al. *Diabetes Care* 2018, 41(12):2669. **5.** Iepsen EW et al. *Expert Rev Cardiovasc Ther* 2015, 13(7):753. **6.** U.S. Food and Drug Administration Web site. www.fda.gov. Accessed October 6, 2021. **7.** Wilding JPH et al. *N Engl J Med* 2021, 384(11):989 (STEP 1). **8.** Davies M et al. *Lancet* 2021, 397(10278):971(STEP 2). **9.** Wadden TA et al. *JAMA* 2021, 325(14):1403 (STEP 3). **10.** Rubino D et al. *JAMA* 2021, 325(14):1414 (STEP 4). **11.** NCT03693430 (STEP 5). **12.** Kushner R et al. *Obesity (Silver Spring)* 2020, 28(6):1050.