NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
September 2022

Semaglutide for treating obesity-related heart failure

Company/Developer	Novo Nordisk Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 31416	NICE TSID: 11788	UKPS ID: N/A

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Semaglutide is in clinical development for the treatment of obesity-related heart failure with preserved ejection fraction (HFpEF). Obesity is a chronic disease and global public health challenge, and the prevalence of obesity is rising in the UK. Obesity increases the risk of developing a range of health conditions including a predisposition to risk factors associated with HF, such as cardiovascular disease, myocardial infraction and coronary artery disease. Currently, there are very limited effective and durable interventions available to reduce body weight and specifically target the increased cardiovascular risk associated with obesity.

Semaglutide is a medicinal product that acts in the same way as glucagon-like peptide-1 (GLP-1) which is a natural hormone in the body. Semaglutide regulates appetite by increasing a person's feelings of fullness, while reducing their food intake, hunger and cravings. Additionally, GLP-1 has other effects that are potentially promising therapeutic benefits from a cardiovascular risk perspective. If a license extension is approved, semaglutide 2.4mg administered via subcutaneous injection would provide a novel treatment option for adults with obesity-related HFpEF.

Proposed Indication

Adults with obesity-related heart failure with preserved ejection fraction (HFpEF)[1,2]

Technology

Description

Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. GLP-1 is a physiological hormone that has multiple actions in glucose and appetite regulation, and in the cardiovascular system. Semaglutide reduces blood glucose in a glucose dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. Semaglutide reduces body weight and body fat mass by reduction in appetite and lowered energy intake. Semaglutide has direct effects on areas in the brain involved in homeostatic and hedonic regulation of food intake. In addition, semaglutide reduces the preference for high fat foods.[3]

Semaglutide is currently in clinical development for the treatment of adult patients with obesity-related heart failure, which is also known as the obese phenotype of heart failure with preserved ejection fraction (HFpEF).[1,4] In the phase III clinical trials (STEP-HFpEF; NCT04788511 and STEP HFpEF DM; NCT04916470), participants will receive semaglutide subcutaneous injection(s) once-weekly for 52 weeks, with dose escalating from 0.25 mg to the maintenance dose of 2.4mg over a 16 week period.[1,2]

Key Innovation

Obesity is a crucial contributor to cardiovascular disease, but little progress has been made on effective and durable interventions to reduce body weight and specifically target the increased cardiovascular risk associated with obesity.[5] Treatment approaches are changing, with renewed interest in using medications for weight management based on improved understanding of food intake and energy balance regulation. GLP-1 is a gut hormone released in response to food intake that acts as a satiety signal, stimulates insulin release, inhibits glucagon secretion, and regulates gastric emptying. In addition, GLP-1RAs demonstrate a range of effects on the cardiovascular system that are independent of their effects on blood glucose, including reduction in systolic and diastolic blood pressure, lowering plasma cholesterol level and improving endothelial dysfunction, therefore, decreasing atherosclerosis risk and improvements in inflammation.[6]

Semaglutide is a GLP-1 analogue with an extended half-life of approximately 1 week, which permits once-weekly subcutaneous administration.[7] If a license extension is approved, semaglutide 2.4mg would provide a novel treatment option for adults with obesity-related HFpEF.

Regulatory & Development Status

Semaglutide (Wegovy, Ozempic and Rybelsus) has Marketing Authorisation in the EU/UK for the following indications:[3,8,9]

- Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of: ≥30 kg/m2 (obesity), or ≥27 kg/m2 to <30 kg/m2 (overweight) in the presence of at least one weight-related comorbidity.
- Ozempic and Rybelsus are indicated as monotherapy or in combination treatments, for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise.

Semaglutide is currently in phase II and III clinical trials for several indications, some of which include:[10]

- Type 1 and type 2 diabetes mellitus
- Myocardial injury
- Atherosclerosis
- Chronic Kidney Disease
- Non-alcoholic fatty liver disease (NAFLD)
- Atrial fibrillation
- Alzheimer's disease
- Polycystic ovary syndrome (PCOS)

Patient Group

Disease Area and Clinical Need

The term obese describes a person who is very overweight, with abnormal or excessive fat accumulation that presents a risk to health.[11] There are many ways in which a person's health in relation to their weight can be classified, but the most widely used method is body mass index (BMI). Obesity-related factors are estimated to cause 11% of heart failure cases in men and 14% in women.[12] Obesity may result in heart failure by inducing hemodynamic and myocardial changes that lead to cardiac dysfunction, or due to an increased predisposition to other heart failure risk factors such as coronary artery disease (CAD), diabetes mellitus, hypertension, dyslipidaemia, insulin resistance (IR), metabolic syndrome, kidney disease or occur solely as a result of obesity.[12] HFpEF in people with obesity is associated with reduced quality of life, worse heart failure symptoms, greater systemic inflammation and worse exercise capacity compared to HFpEF patients without obesity.[13,14]

Obesity is a common problem in the UK that is estimated to affect around one in every four adults.[15] In England, in 2018-2019, 26% of men and 29% of women were obese.[16] In England (2020-21), there were 5,289 finished consultant episodes (FCEs) and 4,487 admissions for obesity (ICD-10 code E66) which resulted in 10,282 FCE bed days and 1,371 day cases.[16] Furthermore, there were 26,674 FCEs and 14,821 admissions for heart disease (ICD-110 code I50.9) which resulted in 75,859 FCE bed days and 2,559 day cases.[17] There are approximately 60,000 new cases of HF per year in the UK, with 40-50% of HF cases have preserved ejection fraction.[18,19] With 11% of heart failures in men and 14% of heart failures in women being obesity-related, obesity-related HFpEF incidence in UK estimated at 2,640-3,300 per year in men, 3,360-4,200 in women.[12]

Recommended Treatment Options

NICE recommends prevention and lifestyle weight management services for adults who are becoming overweight or obese.[20] Drug treatment should only be considered once dietary and physical activity interventions have been started and evaluated, or as part of an integrated approach to weight management.[21]

NICE recommends the following treatment options for managing a person who is overweight or obese:[22,23]

- Orlistat in conjunction with a mildly hypocaloric diet
- Liraglutide 3mg as an adjunct to a reduced-calorie diet and increased physical activity
- Bariatric surgery
- Semaglutide 2.4mg once-weekly subcutaneous injection as an adjunct to a reduced-calorie diet and increased physical activity

Clinical Trial Information

Trial	**STEP-HFpEF,** NCT04788511, EudraCT2019-004452-11; Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects With Obesity-related Heart Failure With Preserved Ejection Fraction **Phase III:** Active, not recruiting **Location(s):** 7 EU countries, UK, USA, Canada and other countries **Primary completion date:** April 2023
Trial Design	Randomised, parallel assignment, double masking
Population	N = 516 (estimated); adults aged 18 years and older; body mass index (BMI) ≥ 30.0 kg/m^2; left ventricular ejection fraction (LVEF) ≥45% at screening; New York Heart Association (NYHA) Class II-IV
Intervention(s)	Semaglutide 2.4 mg (injected into a skin fold, in the stomach, thigh or upper arm) once weekly as add-on to standard of care. Treatment duration of 52 weeks (with a 5 week follow up) including a 16 week dose escalation phase with semaglutide, starting at 0.25mg once weekly to the maintenance dose of 2.4mg once weekly.
Comparator(s)	Matched placebo once weekly via SC injection
Outcome(s)	**Primary outcome(s):** • Change in KCCQ (Kansas City Cardiomyopathy Questionnaire) clinical summary score [Time frame: from baseline (week 0) to end of treatment (week 52)] • Change in body weight [Time frame: from baseline (week 0) to end of treatment (week 52)] See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-
Clinical Trial Information	
Trial	**STEP HFpEF DM;** NCT04916470, EudraCT2020-004170-22; Effect of Semaglutide 2.4 mg Once-weekly on Function and Symptoms in Subjects With Obesity-related Heart Failure With Preserved Ejection Fraction, and Type 2 Diabetes **Phase III:** Recruiting **Location(s):** 7 EU countries, UK, USA, Canada and other countries **Primary completion date:** June 2023
Trial Design	Randomised, parallel assignment, quadruple masking
Population	N = 610 (estimated); adults aged 18 years and older; BMI ≥ 30.0 kg/m^2; NYHA Class II-IV; LVEF ≥ 45% at screening; diagnosed with T2D; hbA1c of below or equal to 10.0%
Intervention(s)	Participants will receive semaglutide SC injection(s) once-weekly for 52 weeks. Dose will be gradually increased to 2.4 mg: 0.25 mg from week 1 to 4, 0.5 mg

	from week 5 to 8, 1.0 mg from week 9 to 12, 1.7 mg from week 13 to 16 and 2.4 mg from week 17 to week 52
Comparator(s)	Matching placebo SC injection(s) once-weekly for 52 weeks
Outcome(s)	**Primary outcome(s):** • Change in KCCQ clinical summary score [Time frame: from baseline (week 0) to end of treatment (week 52)] • Change in body weight [Time frame: from baseline (week 0) to end of treatment (week 52)] See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	NCT05371496; Evaluation of the Cardiac and Metabolic Effects of Semaglutide in Heart Failure With Preserved Ejection Fraction (CAMEO-SEMA) A Phase II, Prospective, Double-Blind Randomized Trial **Phase II:** Recruiting **Location(s):** US **Primary completion date:** August 2026
Trial Design	Randomised, parallel assignment, double masking
Population	N=81; adults ages 18 years and over; BMI ≥ 30.0 kg/m^2; NYHA Class II-IV; LVEF ≥ 50 % within the preceding year; no hospitalisations due to heart failure in the preceding 30 days
Intervention(s)	Subjects will receive Semaglutide once weekly in addition to counselling on healthy lifestyle intervention. 3.0 mg/ml (titrated to 2.4 mg) SC once weekly for 12 months
Comparator(s)	Subjects will receive matching placebo once weekly in addition to counselling on healthy lifestyle intervention
Outcome(s)	Primary outcome(s): • Pulmonary Capillary Wedge Pressure (PCWP) [time frame: baseline, 12 months]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Semaglutide is already marketed in the UK for the treatment of type 2 diabetes mellitus; the 0.25mg/0.19ml, 0.5mg/0.37ml, and 1mg/0.74ml solution for injection (Ozempic) costs £73.25.[24]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction (ID3945). Expected date of issue to be confirmed.
- NICE technology guidance in development. Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction (ID1648). Expected date of issue to be confirmed.
- NICE technology appraisal. Semaglutide for managing overweight and obesity (ID3850). Expected date of issue to be confirmed.
- NICE technology appraisal. Liraglutide for managing overweight and obesity (TA664). December 2020.
- NICE technology appraisal. Naltrexone–bupropion for managing overweight and obesity (TA494). December 2017.
- NICE guideline. Chronic heart failure in adults: diagnosis and management (NG106). September 2018.
- NICE clinical guideline. Obesity prevention (CG43). March 2015.
- NICE clinical guideline. Obesity: identification, assessment and management (CG189). November 2014.
- NICE quality standard. Chronic heart failure in adults (QS9). September 2018.
- NICE quality standard. Obesity: clinical assessment and management (QS127). August 2016.
- NICE quality standard. Obesity in adults: prevention and lifestyle weight management programmes (QS111). January 2016.
- NICE public health guidance. Weight management: lifestyle services for overweight or obese adults (PH53). May 2014.

NHS England (Policy/Commissioning) Guidance

- NHS England. NHS Standard Contract for Severe and Complex Obesity – All Ages (A05/S/a). October 2013.
- NHS England. Clinical Commissioning Policy: Complex and Specialised Obesity Surgery. NHSCB/A05/P/a. April 2013.

Other Guidance

- European Society of Cardiology (ESC). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. 2021.[25]
- Yumuk V et al. European Guidelines for Obesity Management in Adults. December 2015.[26]
- Scottish Intercollegiate Guidelines Network. Management of Obesity – A national clinical guideline. 2010.[27]

Additional Information

Novo Nordisk Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 Clinicaltrails.gov. *Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects With Obesity-related Heart Failure With Preserved Ejection Fraction*. *Trial ID: NCT04788511*. 2021. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04788511 [Accessed 19th August 2022]

2 Clinicaltrails.gov. *Effect of Semaglutide 2.4 mg Once-weekly on Function and Symptoms in Subjects With Obesity-related Heart Failure With Preserved Ejection Fraction, and Type 2 Diabetes*. *Trial ID: NCT04916470*. 2021. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04916470 [Accessed 19th August 2022]

3 Electronic Medicines Compendium (EMC). *Ozempic 0.25 mg solution for injection in pre-filled pen*. 2021. Available from: https://www.medicines.org.uk/emc/product/9748/smpc#PHARMACOLOGICAL_PROPS [Accessed 19th August 2022].

4 Sabbah MS, Fayyaz AU, Denus Sd, Felker GM, Borlaug BA, Dasari S, et al. Obese-Inflammatory Phenotypes in Heart Failure With Preserved Ejection Fraction. *Circulation: Heart Failure*. 2020;13(8):e006414. Available from: https://doi.org/10.1161/CIRCHEARTFAILURE.119.006414.

5 Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med*. 2017;377(1):13-27. Available from: https://doi.org/10.1056/NEJMoa1614362.

6 Ryan DH, Lingvay I, Colhoun HM, Deanfield J, Emerson SS, Kahn SE, et al. Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) rationale and design. *American Heart Journal*. 2020;229:61-9. Available from: https://doi.org/https://doi.org/10.1016/j.ahj.2020.07.008.

7 Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine*. 2016;375(19):1834-44. Available from: https://doi.org/10.1056/NEJMoa1607141.

8 European Medicines Agency (EMA). *Wegovy*. 2022. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/wegovy [Accessed 19th August 2022].

9 Electronic Medicines Compendium (EMC). *Rybelsus*. 2020. Available from: https://www.medicines.org.uk/emc/product/11507/smpc#INDICATIONS [Accessed 19th August 2022].

10 Clinicaltrails.gov. *Search: semaglutide | Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies | Phase 2, 3*. 2022. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=semaglutide&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort [Accessed 19th August 2022].

11 World Health Organization (WHO). *Obesity*. Available from: https://www.who.int/health-topics/obesity#tab=tab_1. [Accessed 19th August 2022].

12 Ebong IA, Goff DC, Jr., Rodriguez CJ, Chen H, Bertoni AG. Mechanisms of heart failure in obesity. *Obes Res Clin Pract*. 2014;8(6):e540-8. Available from: https://doi.org/10.1016/j.orcp.2013.12.005.

13 Pandey A, Patel KV, Vaduganathan M, Sarma S, Haykowsky MJ, Berry JD, et al. Physical Activity, Fitness, and Obesity in Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail*. 2018;6(12):975-82. Available from: https://doi.org/10.1016/j.jchf.2018.09.006.

14 Tanase DM, Radu S, Al Shurbaji S, Baroi GL, Florida Costea C, Turliuc MD, et al. Natriuretic Peptides in Heart Failure with Preserved Left Ventricular Ejection Fraction: From Molecular Evidences to Clinical Implications. *Int J Mol Sci*. 2019;20(11). Available from: https://doi.org/10.3390/ijms20112629.

15 NHS Inform. *Obesity*. 2021. Available from: https://www.nhsinform.scot/illnesses-and-conditions/nutritional/obesity [Accessed August 5th 2022].

16 NHS Digital. *Statistics on Obesity, Physical Activity and Diet, England, 2020*. 2020. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-obesity-physical-activity-and-diet/england-2020.

17 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21*. 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 19th August 2022].

18 NHS Improving Quality. *End of life care in heart failure - A framework for implementation*. Available from: https://www.england.nhs.uk/improvement-hub/wp-content/uploads/sites/44/2017/11/heart-failure.pdf [Accessed 23rd August 2022].

19 British Cardiovascular Society. *Heart failure with preserved ejection fraction*. Available from: https://www.britishcardiovascularsociety.org/resources/editorials/articles/heart-failure-preserved-ejection-fraction [Accessed 23rd August 2022].

20 National Institute for Health and Care Excellence (NICE). *Obesity in adults: prevention and lifestyle weight management programmes*. 2016. Available from: https://www.nice.org.uk/guidance/qs111 [Accessed 19th August 2022].

21 National Institute for Health and Care Excellence (NICE). *Obesity: Scenario: Management*. 2022. Available from: https://cks.nice.org.uk/topics/obesity/management/management/#drug-treatment [Accessed 19th August 2022].

22 National Institute for Health and Care Excellence (NICE). *Liraglutide for managing overweight and obesity*. 2020. Available from: https://www.nice.org.uk/guidance/ta664 [Accessed 23rd August 2022].

23 National Institute for Health and Care Excellence (NICE). *Semaglutide for managing overweight and obesity*. 2022. Available from: https://www.nice.org.uk/guidance/gid-ta10765/documents/final-appraisal-determination-document.

24 National Institute for Health and Care Excellence (NICE). *Semaglutide - Medicinal forms*. Available from: https://bnf.nice.org.uk/drugs/semaglutide/medicinal-forms/ [Accessed 19th August 2022].

25 McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-726. Available from: https://doi.org/10.1093/eurheartj/ehab368.

26 Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, et al. European Guidelines for Obesity Management in Adults. *Obes Facts*. 2015;8(6):402-24. Available from: https://doi.org/10.1159/000442721.

27 Scottish Intercollegiate Guidelines Network (SIGN). *Management of Obesity - A national clinical guideline*. 2010. Available from: https://www.sign.ac.uk/assets/sign115.pdf.

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