BMSS6007
April 2025
(7722 words)

THE EFFICACY AND SAFETY OF GLP-1RAS IN PROMOTING LONG-TERM WEIGHT LOSS IN ADULTS WITH OVERWEIGHT OR OBESITY: A NARRATIVE REVIEW

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HEALTH, NUTRITION AND LIFESTYLE

Undergraduate Dissertation Certificate

Name of the Programme of Study: HEALTH, NUTRITION AND LIFESTYLE

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ACKNOWLEDGMENTS

I wish to thank my supervisor, Chris Cashin, and Alison Connaughton and Dave Gardner, lecturers, for their valued support and guidance throughout the development of this project. I also wish to thank Connie Davage, librarian at UWTSD, for advising me in my research, and Afifa Zaman and Jo Kelleher, from UWTSD Study Skills, for providing insightful information for my project.

I also wish to thank the students on my course, my friends, and my family, for their constant encouragement and back-up, and all the lecturers who have taught me in the past 3 years, for giving me the opportunity to further my education and expand my knowledge.

Steph Kiefer

4th April 2025

ABSTRACT

Introduction: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been leading the way in the treatment of type 2 diabetes, and more recently in the treatment of obesity (Javaid *et al.,* 2024). Clinical studies found that patients using GLP-1 RAs not only had improved glycaemic levels, but also manifested reductions in weight (Latif, Lambrinos and Rodriguez, 2021; Watanabe *et al.,* 2024).

Aims: to evaluate the efficacy of GLP-1RAs (specifically liraglutide, semaglutide, and tirzepatide) for weight loss (WL) in adults with obesity or overweight and weight-related complications, without diabetes; to assess their safety profile; and to examine their long-term WL sustainability.

Method: A narrative review was conducted to provide a practical synthesis of the literature, while examining, comparing, and critically appraising the relevant SCALE, STEP and SURMOUNT clinical trials, and reflecting on the limitations and areas for future research in the topic. The following databases were used: PubMed, MedLine, Cochrane Library, Embase, Scopus, Web of Science, Science Direct, UWTSD Library resources and Google Scholar.

Discussion: GLP-1RAs liraglutide, semaglutide and tirzepatide, alongside lifestyle behaviour changes, have shown promising WL results across 14 studies on adult participants with obesity or overweight and associated comorbidities, without diabetes. The SCALE trials demonstrated an average WL efficacy of between 6% and 8.2% with liraglutide 3.0mg. STEP 1, 3,4 and 8 trials show an average WL efficacy of between 14.9 % and 17.4% with semaglutide 2.4mg. SURMOUNT trials resulted in WL of between 18.4% and 25.3% with tirzepatide 10mg or 15 mg. Across all trials, adverse events (AE) were mostly GI related (nausea, constipation, diarrhoea and vomiting), transient, mild to moderate, and during dose escalation. Overall, withdrawal due to AE occurred in around 9% with liraglutide vs 4.9% with placebo, 5% with semaglutide vs 3% with placebo, and 6% of participants with tirzepatide vs 2% with placebo. Participants in all trial groups regained weight following treatment discontinuation.

Conclusion: GLP-1RAs combined with lifestyle behavioural therapy can promote significant WL in adults with overweight or obesity without diabetes, despite common adverse events, but treatment discontinuation leads to weight regain. Future research should explore improvements in average efficacy and tolerability of Anti-Obesity Medication, reduction of AE, and supporting WL maintenance.

Keywords: "GLP-1 receptor agonists", "overweight", "obesity", "weight loss", "efficacy", "safety", “clinical studies”, "long-term outcomes", “maintenance”, "liraglutide", "semaglutide", and “tirzepatide”.

INTRODUCTION

The following review aims to investigate the efficacy and safety of glucagon-like peptide -1 receptor agonists (GLP-1 RAs) for long-term weight-loss in adults with obesity or overweight and associated comorbidities, without diabetes. Specifically, the roles of the GLP-1 RAs liraglutide, semaglutide, and tirzepatide in the therapeutic treatment option for the management of obesity will be appraised in the context of the current obesity pandemic, and evidence on their efficacy and safety will be synthesised through an analysis of the relevant studies. Furthermore, this review will examine the long-term sustainability of weight loss and explore the broader health benefits of GLP-1 RAs while considering practical implications, and reflecting on limitations and areas for future research.

Obesity has become a global epidemic, with rates almost tripling in the past forty years (Haththotuwa *et al.*, 2020). In 2022, 43% of adults were overweight, with 17.9% females and 13.6% males living with obesity worldwide (WHO, 2024). Overweight and obesity rates are impacting global economy and affecting not only high-income countries but also lower income countries, prompting an urgent call for action from the World Obesity Federation (World Obesity, 2023).

Obesity is a multi-etiological chronic disease defined by an excess accumulation or distribution of adiposity, resulting from complex interactions between genetic, metabolic, neuroendocrine, behavioural, and environmental factors (Heymsfield and Wadden, 2017). Epigenetics and the gut microbiome may also have a role in the incidence of obesity (Mechanick *et al.*, 2017; Theilade *et al.,* 2021). Obesity affects every organ system and is associated with over 200 major chronic diseases, as well as premature mortality (Jastreboff *et al.,* 2019; Rubino *et al.*, 2025; The Obesity Society, 2022).

Body Mass Index (BMI) is used to classify the degree of overweight or obesity: a BMI between 25 kg/m^2 and 29.9 kg/m^2 is categorised as overweight, between 30 kg/m^2 and 34.9 kg/m^2 is categorised as obesity class 1, 35 kg/m^2 to 39.9 kg/m^2 is obesity class 2 and ≥40 kg/m^2 is class 3 (NICE, 2025). Age, ethnicity and health status are essential to define an individual's optimal BMI (Müller *et al.,* 2016). High body mass index (BMI) has been associated with increased risks of sleep apnoea, type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and conditions (hypertension, dyslipidaemia, coronary heart disease, stroke, myocardial infarction), gallbladder disease, and osteoarthritis (Haase *et al.,* 2021; Khan *et al.,* 2018). However, BMI alone cannot determine whether an individual is at increased risk of comorbidities (Müller *et al.,* 2016; Sarma *et al.*, 2021). Other methods such as imaging techniques and bioelectrical impedance analysis are more accurate and precise for measuring body composition, but are costly and require technical skills (Kuriyan, 2018; Heymsfield, 2024).

Weight loss (WL) can improve obesity-related diseases and quality of life (Kaplan *et al.,* 2024). Studies have shown that for individuals with overweight or obesity, 10% WL can reduce the risk of future T2DM by ~80%; 7 to 11% or more can improve obstructive sleep

apnoea (OSA), 5 to 15% can reduce hypertension, and 10% or more can be effective in treating osteoarthritis (Garvey *et al.,* 2016). However, WL also results in a decrease in both fat mass (FM) and fat-free mass (FFM) in varying ratios, and can affect muscle mass, health and function, particularly in vulnerable patients; therefore, support to adhere to an adequate nutrition and exercise regime during a period of weight-loss are advised (Mechanick *et al.*, 2025; Neagu and Neagu, 2025). Furthermore, WL also leads to a reduction in energy expenditure due to the homeostatic control of body weight, which can result in weight regain (Neeland *et al.*, 2024).

Lifestyle interventions alone, involving a reduced-calorie diet and optimal physical activity, have shown limited efficacy for long-term WL (Blüher, 2019; Yang *et al.*, 2022). Bariatric surgery is effective for WL in patients with class 3 or 4 obesity but is an invasive procedure with associated risks and complications and often results in weight regain post-surgery (Maciejewski *et al.,* 2016; Tolvanen *et al.,* 2022). Pharmacotherapy is recommended alongside lifestyle modifications and behavioural therapy as a treatment for class 3 obesity, and class 2 with at least one excess weight associated comorbidity, for patients who had unsuccessful WL following lifestyle interventions alone (Apovian *et al.,* 2015; Chakhtoura *et al.,* 2023). However, anti-obesity medications (AOM) came under scrutiny following reports of serious adverse events, which begot the revision of the Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulatory approval criteria of AOM (Chakhtoura *et al.,* 2023; FDA, 2022).

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been leading the way in the treatment of T2DM, and more recently in the treatment of obesity (Javaid *et al.,* 2024). Clinical studies found that patients using GLP-1 RAs not only had improved glycaemic levels, but also manifested weight reduction of 10% of body weight or more, showed improvement in cardiovascular and kidney health, and a reduction in the risk of cardiovascular mortality, along with relative tolerability and safety for adults with overweight and associated comorbidity, or with obesity (Garvey *et al.,* 2022; Grunvald *et al.,* 2022; Holst, 2019; Host, 2024; Latif *et al*, 2021; Müller *et al.,* 2022; Müller *et al.,* 2017; 2021; O'Neil *et al.,* 2018; Rubino *et al.,* 2021; Rubino *et al.,* 2022; Ussher and Drucker, 2023; Wadden *et al.,* 2021; Watanabe *et al.,* 2024; Wilding *et al.,* 2021; Zushin and Wu, 2024).

Glucagon-Like Peptide-1 (GLP-1) is a hormone released from gut cells which stimulates insulin secretion, inhibits glucagon secretion, restrains appetite and food intake, and slows gastric emptying (Drucker, 2018). GLP-1 receptors are also found in areas of the brain linked to appetite regulation (Cerillo and Parmar, 2024). Due to the short half-life of GLP-1 in humans, long-term injectable GLP-1analogues, or GLP-1 receptor agonists (RAs), were synthesised (Holst, 2019). The FDA approved the use of the GLP-1 RAs liraglutide and semaglutide, and the dual receptor agonist tirzepatide (glucose-dependent insulinotropic polypeptide (GIP) and GLP-1) for weight loss in the treatment of obesity in 2014, 2021 and 2023 respectively (FDA, 2023; Moore *et al.,* 2023; Tchang *et al.,* 2024).

Different GLP1-RAs vary in molecular size, structure and duration of action (short or long acting), which affect glycaemic control, weight loss capacities, tolerability and cardiovascular effects in obesity and diabetes (Cornell, 2020). Liraglutide 3.0mg dose-escalated daily injections, semaglutide 2.4mg dose-escalated weekly injections and tirzepatide 5mg, 10mg or 15mg weekly injections, have shown promising results for WL (Cercato and Fonseca, 2019; Friedrichsen *et al.,* 2021). Evidence from studies examining the mechanisms of GLP-1RAs in reducing body weight shows improvements in eating control, a decrease in cravings, a change in food reward pathways, a decrease in appetite and hunger, and a decreased preference for foods high in energy (Ard *et al.,* 2021; Burcelin and Gourdy, 2017). Furthermore, with tirzepatide, the GIP part of the dual receptor activation may help improve WL caused by GLP-1; GIP is thought to target white fat tissue to better manage dietary fats and prevent excess fat from entering the bloodstream (Jastreboff *et al.,* 2022; le Roux *et al.,* 2023; Samms *et al.,* 2020). However, the prevalence of adverse events such as nausea, hypoglycaemia, diarrhoea, constipation, vomiting, pancreatitis, and headaches, have resulted in discontinuation of treatment in some cases (Bettge *et al.,* 2017; Dodangeh and Hasani-Ranjbar, 2024; Smits and Van Raalte, 2021). Additionally, weight loss maintenance is an issue: weight regain following cessation of AOM is common due to physiological and psychological changes, which raises the issue of sustainability of GLP-1 RAs (Ard *et al.,* 2021; MacLean *et al.,* 2015; Montesi *et al.,* 2016).

There appears to be limited reviews in the literature comparing different types of GLP1-RAs for both efficacy and safety, specifically in non-diabetic overweight or obese adult populations. Consequently, the objective of this narrative review is to provide an in-depth interpretation, contextual analysis and synthesis of evolving evidence on the efficacy, safety and sustainability of GLP-1 RAs for weight loss, from clinical trials such as the SCALE (Safety and Clinical Adiposity-Liraglutide Evidence), STEP (Semaglutide Treatment Effect in People with obesity) and SURMOUNT studies (series of clinical trials conducted to evaluate the efficacy and safety of tirzepatide for the treatment of obesity), while presenting previous and current data on the topic, identifying gaps in knowledge, to ultimately inform the review's conclusion (Blackman *et al.,* 2016; Davies *et al.,* 2015; Garvey *et al.,* 2022; Grunvald *et al.,* 2022; Holst, 2019; Holst, 2024; Pratley *et al.,* 2019; Rubino *et al.,* 2021; Rubino *et al.,* 2022; Sukhera, 2022a; Sukhera, 2022b; Wadden *et al.,* 2021; Wadden *et al.,* 2013; Wadden *et al.,* 2020; Wilding *et al.,* 2021). The narrative review format of this paper will enable an extensive description of the topic by incorporating a comparison of multiple studies and facilitate a broad scope of research owing to the flexibility of its methodology, which is described in the following chapter (Greenhalgh *et al.*, 2018).

METHODOLOGY

A narrative review was conducted to provide a practical synthesis of the literature concerning the use of GLP-1RAs for weight loss in overweight and obesity, while examining, comparing, and critically appraising clinical studies, and reflecting on the limitations and areas for future research in the topic. The focus of this review was on the efficacy, safety and sustainability of liraglutide, semaglutide and tirzepatide for weight loss, concentrating on adults with obesity or overweight and a weight related condition, but without diabetes.

Research strategy and data collection

The literature was searched using the following databases:

PubMed, MedLine, Cochrane Library, Embase, Scopus, Web of Science, Science Direct, UWTSD Library resources and Google Scholar.

Key words:

The key words for the search included: *"GLP-1 receptor agonists"*, *"overweight"*, *"obesity"*, *"weight loss"*, *"efficacy"*, *"safety"*, *"clinical studies", "long-term outcomes"*, *"maintenance", "liraglutide"*, *"semaglutide", and "tirzepatide"*.

Key words and MeSH terms were combined with Boolean operators "AND", "OR", and "NOT", to filter relevant studies for this topic (Aliyu, 2017).

Inclusion and exclusion criteria:

The inclusion criteria focused on adult population with obesity or overweight and 1 or more comorbidities, but without diabetes; GLP-1 receptor agonists liraglutide, semaglutide and tirzepatide intervention; and the outcomes included efficacy, safety, and sustainability of weight loss.

Studies including children and young people under 18 years old, adults without overweight or obesity, populations with overweight or obesity and diabetes, studies prior to 2010, and animal studies, were excluded from the research.

The research used in this review ranged from clinical trials, randomised control trials (RCTs), systematic reviews and meta-analysis, to peer-reviewed articles, observational studies, and real-world evidence relating to GLP-1 RAs and overweight and obesity in adults, dating back to 2010 and up to 2025 to ensure up-to-date relevance. The variety of the research performed ensured diversity, depth, and nuances of the issue being investigated (Green *et al.*, 2006).

Studies were researched following a screening of titles and abstracts in the current literature, and selected based on the previously stated inclusion and exclusion criteria. Ultimately, fourteen studies were included in this review: 5 on liraglutide (SCALE studies), 6 on

semaglutide (STEP 1, 3, 4, 5 and 8 studies), and 3 on tirzepatide (SURMOUNT 1, 3 and 4 studies).

Ethical considerations

Ethical considerations and approval were not required for this narrative review due to involving the analysis of previously published and publicly available data. Nonetheless, any unethical literature was not considered during the research process. In addition, due to the potential of bias attached to narrative reviews, it is important to note that not all literature specific to the subject was included in this review. The researcher carefully selected the studies which were relevant to the specific topic of this paper with thoughtful considerations and the intent to bring objectivity and impartiality to the research.

Results

There will be no formal results section in this paper due to the narrative format. However, the following data was extracted from each study and organised in tables for analysis and critical appraisal: study design, intervention (type of GLP1-RA, dosage and timescale), outcome (mean weight loss, participants who achieved baseline weight loss of ≥5%, ≥10%, ≥15%, ≥20% and ≥25% where applicable), and adverse events. Additionally, evidence of the sustainability of weight loss was investigated, but data were limited due to the recentness of the studies.

The next chapter will aim to assess the efficacy and safety of liraglutide, semaglutide and tirzepatide for weight loss, by reviewing and comparing the relevant studies. The first section will focus on liraglutide, with a review of the SCALE studies; the second section will focus on semaglutide and the relevant STEP studies, and the third section will focus on tirzepatide and the relevant SURMOUNT studies. The fourth section will address the issue of weight loss sustainability, followed by an overall critical appraisal of the studies included in this review, and will conclude with practical implications and areas for future research.

DISCUSSION

Combined lifestyle intervention and pharmacotherapy have shown favourable outcomes for weight management in the treatment of obesity (Mechanick *et al.,* 2025; Singh and Singh, 2020; Zheng *et al.,* 2024). In randomised controlled trials, Magkos *et al.* (2016) found that 5% weight loss resulted in considerable health benefits such as improves insulin sensitivity and b cell function, and additional weight loss of 11%-16% could produce further health benefits (Magkos *et al.,* 2016). Similarly, Ryan and Yockey (2017) found that greater weight loss resulted in greater overall health improvements (Ryan and Yockey, 2017). The following chapters will investigate the weight loss efficacy of liraglutide, semaglutide and tirzepatide alongside lifestyle behaviours, and their safety profiles, followed by an assessment of the sustainability of weight loss.

SCALE STUDIES

The Satiety and Clinical Adiposity- Liraglutide Evidence in non-diabetic and diabetic individuals with overweight or obesity (SCALE) studies have demonstrated the benefits of the GLP-1RA liraglutide for the treatment of diabetes and obesity. Specifically, Wadden *et al.* (2013) (study 1), Pi-Sunyer *et al.* (2015) (study 2), le roux *et al.* (2017) (study 3), Wadden *et al.* (2019) (study 4) and Wadden *et al.* (2020) (study 5), have focused on liraglutide for weight management in adults over 18 with a BMI of 30 or a BMI 27 with comorbidities, without diabetes, or with prediabetes (Table 1). Study 1 aimed to assess the efficacy of liraglutide vs placebo in maintaining weight loss (WL) achieved with a low-calorie diet (LCD); study 2 focused on the efficacy and safety of liraglutide vs placebo as an adjunct to a reduced-calorie diet and increased physical activity (PA); study 3 aimed to evaluate the proportion of individuals with pre-diabetes (from study 2) who were diagnosed with T2D following treatment with liraglutide vs placebo, and the WL efficacy of liraglutide compared to placebo; in addition, participants were followed for 12-weeks off-treatment. Study 4 had an open-label design, was delivered in a specialist setting, and aimed to compare the efficacy of liraglutide alongside intensive behavioural therapy (IBT), IBT alone, and IBT-liraglutide combined with a low-calorie meal replacement diet (multicomponent), for WL in adults with obesity; and study 5 aimed to evaluate the efficacy of IBT and placebo versus IBT and liraglutide, for WL in adults with obesity in a primary care setting.

Liraglutide is a synthetic analogue of human glucagon-like peptide-1 (GLP-1) hormone which binds to the GLP-1 receptors in the cells of the pancreas, promoting euglycemia and leading to appetite reduction and decreased calorie intake (Cerillo and Parmar, 2024). Liraglutide is administered subcutaneously (sc), usually in the abdomen, thigh or upper arm, and gets absorbed in the bloodstream. The start dose is 0.6mg daily, increasing weekly by 0.6mg until the recommended maximum dose of 3.0mg is reached. For optimum WL efficiency in the management of obesity, lifestyle modifications, such as low-calorie diet and increased physical activity, are recommended, and were added to treatment with liraglutide or placebo in the SCALE studies (Apovian *et al.,* 2015; Bray *et al.,* 2016). Participants demographic and physical characteristics were evenly distributed between all treatment groups in these studies. Details of each study are displayed in Table 1. Additional endpoints, not related to weight loss, were changes in glycaemic control parameters, cardiometabolic biomarkers, vital signs (study 3), health-related quality of life (assessed via questionnaires) (study 2, 3, 4 and 5), and safety assessments.

Table 1: SCALE studies design, participant population, and clinical characteristics

STUDY DESIGN	PARTICIPANTS	INTERVENTION	BACKGROUND TREATMENT	PRIMARY ENDPOINTS
STUDY 1: **(Wadden *et al.*, 2013)** Randomised double-blind, placebo-controlled trial	Adults ≥18 yrs with BMI ≥30 or BMI ≥27 with comorbidities (N=422)	4–12-week LCD run-in period (1200-1400 kcal/day, incl. up to 3 liquid meal replacements) and weekly counselling with a nutritionist; pedometers were provided to encourage PA. Randomisation to liraglutide 3.0mg or placebo (after weight loss of ≥5% baseline BW) for 56 weeks, and a 12-week off-drug follow-up assessment. 1:1 ratio	Once ≥5% WL was achieved, participants were randomised to liraglutide or placebo with 500kcal/day deficit diet based on 24hr EE. Continued PA was recommended, and 17 counselling visits were provided.	% WC from randomisation to week 56 and to week 68. Proportion of individuals who maintained run-in ≥5% WL. Proportion who lost ≥5% BW after randomisation.
STUDY 2: **(Pi-Sunyer *et al.*, 2015)** Randomised, double-blind, controlled trial	Adults ≥18 yrs with a BMI ≥30 or BMI ≥27 with dyslipidaemia or hypertension (N= 3731)	56-week liraglutide 3.0mg daily SC injections or matched placebo (2:1 ratio). After 56 weeks, patients in liraglutide group w/o prediabetes were assigned to continued liraglutide or placebo for 12 weeks (patients in placebo group	Both groups received standardised counselling on lifestyle modification monthly (advice to reduce daily energy intake by 500kcal below individual requirements and increase PA to at least 150min/week). Pedometers and monthly 3-day food diaries were provided.	WC from baseline. Proportion of participants who lost ≥5% of their baseline BW. Proportion of participants who lost ≥10% of their baseline BW.

		continued receiving placebo).		
STUDY 3: **(Le Roux *et al.*, 2017)** Randomised double-blind, placebo-controlled trial	Adults ≥18 yrs with a BMI ≥30 or BMI ≥27 with dyslipidaemia and/ or hypertension and pre-diabetes (from STUDY 2) (N= 2254)	160-week either L 3.0mg daily SC injections or matched placebo, with RCD and increased PA, followed by a 12-week off-treatment follow-up period. (Main outcome: time to diabetes onset by 160 weeks) 2:1 ratio	Both groups received standardised counselling on lifestyle modification (advice to reduce daily energy intake by 500kcal below individual requirements and increase PA to at least 150min/week). Pedometers and 3-day food diaries were provided (every 2 months).	Proportion of individuals with T2D at week 160 and time to onset of T2D. Mean WL. Proportion of participants who lost ≥5% and ≥10% of their baseline BW.
STUDY 4: **(Wadden *et al.*, 2019)** Single-site, open-label, parallel group design randomised trial	Adults between 21 and 70 years; BMI between 30 and 55 (N= 150)	1 year trial with 21 IBT sessions (4 x weekly, then 10x every 2 weeks for 5 months, then 7 x monthly) 1:1:1 ratio	1 group was assigned to IBT alone, 1 group IBT-liraglutide, 1 group IBT-liraglutide combined with 1000/1200Kcal per day meal replacement diet, for 1 year.	Mean % reduction in baseline BW at week 24 and at week 52. % participants who lost ≥5%, ≥10% and ≥15% BW at week 52.
STUDY 5: **(Wadden *et al.*, 2020)** Randomised double-blind, placebo controlled multi-centre trial	Adults ≥18 yrs with a BMI ≥30 (N= 282)	56 weeks Liraglutide + IBT Or Placebo +IBT 1:1 ratio	1 group received liraglutide 3.0mg daily + IBT 1 group received placebo + IBT.	% change in BW from baseline to week 56 Proportion of participants who lost ≥5% baseline BW.

	Proportion who lost ≥4%* BW at week 16. Proportion who lost >10%, >15% baseline BW at week 56.

Abbreviations: BW: body weight; IBT: intensive behavioural therapy; L: liraglutide; LCD: low-calorie diet; N: number; PA: physical activity; R: randomisation; RCD: reduced-calorie diet; SC: subcutaneous; T2D: type 2 diabetes; WC: weight change; WL: weight loss.

(* The US label for liraglutide recommends treatment discontinuation if ≥4% loss of baseline body weight has not been achieved by week 16).

EFFICACY OUTCOMES

In the first SCALE study (Wadden *et al.,* 2013), participants lost a mean 6% body weight (BW) after a 12-week low-calorie diet; subjects who were then randomised to liraglutide lost an additional 6.2% (sd 7.3) of randomisation BW vs 0.2% (sd 7.0) for those in the placebo group, at week 56 (Table 2). Furthermore, 81.4% of liraglutide-treated participants maintained ≥5% run-in WL, compared to 48.9% of placebo-treated participants. 50.5% of participants in the liraglutide group lost ≥5% and 26.1 % lost >10% of their randomisation BW, compared to 21.8% and 6.3 % in the placebo group (P<0.0001) (Table 2). Participants in both groups regained weight in the 12-week off-drug follow-up; however, at week 68, the liraglutide group maintained 4.1% (sd 8.2) reduction in randomisation weight, whereas the placebo group gained 0.3% (sd 7.7) above randomisation weight, a significant statistical difference of 4.2% (95% class intervals -0.6 to -2.4; P<0.0001; Table 2).

In the second study (Pi-Sunyer *et al.,* 2015), both placebo and liraglutide groups received diet and exercise counselling. Around 92% of participants in the liraglutide group lost weight (change in BW: -8.0 ± 6.7%), compared to around 65% of participants in the placebo group (change in BW: -2.6 ± 5.7%) at week 56. Additionally, 63.2% of participants in the liraglutide group lost ≥5% BW and 33.1% lost >10% BW, compared to 27.1% and 10.6% in the placebo group (Table 2). Interestingly, liraglutide appeared to be less effective in participants with a BMI ≥40, than in those with a lower BMI.

In the third study (le Roux *et al.,* 2017), individuals from study 2 who had prediabetes at screening continued in the trial for a further 2 years and were assessed for WL achieved after 160 weeks, and time to onset of diabetes, in the liraglutide group compared to placebo. Individuals in the liraglutide group achieved -6.1% WL compared to -1.9% in the placebo group after 3 years. In addition, 49.6% of participants in the liraglutide group achieved ≥5% WL, 24.8% achieved >10% WL and 11.0% achieved >15% WL compared to 23.7%, 9.9% and 3.1% of participants in the placebo group, respectively. The 12-week off-treatment follow-up period will be assessed in chapter 4.4 on sustainability.

In study 4 (Wadden *et al.*, 2019), intensive behavioural therapy (IBT) combined with liraglutide showed better WL outcomes than IBT alone (11.5 ± 1.3% vs 6.1 ± 1.3%) at week 52; furthermore, the multicomponent group attained further weight loss compared to the IBT-liraglutide group at week 24 (12.2 ± 0.6% vs 10.1± 0.6%), but not significantly at week 52 (11.5 ± 1.3% vs 11.8 ± 1.3%) (Table 3).

In study 5 (Wadden *et al.*, 2020), in accordance with study 4, IBT combined with liraglutide showed greater WL than IBT and placebo after 56 weeks (7.5% vs 4.0%; estimated treatment difference [95% CI] -3.4% [-5.3% to -1.6%], P=0.0003) (Table 4).

These SCALE studies demonstrated an average WL efficacy of between 6% and 8.2% following treatment with liraglutide between 56 and 160 weeks (Table 2). Longer treatment period did not result in further increase in weight loss; however, IBT combined with liraglutide showed better WL outcomes than liraglutide alone.

Table 2: Outcomes for efficacy of liraglutide in SCALE trials

STUDIES	OUTCOME
SCALE Study 1 (Wadden *et al.*, 2013)	WL AT THE END OF LCD RUN-IN PERIOD: -6% of initial weight. ADDITIONAL WL FROM R TO WEEK 56: 6.2% with liraglutide 0.2% with placebo. % PARTICIPANTS WITH ≥5% WL FROM R TO WEEK 56: 50.5% on liraglutide 21.8% on placebo % PARTICIPANTS WITH ≥10% WL FROM R TO WEEK 56: 26.1% on liraglutide 6.3% on placebo % PARTICIPANTS WHO MAINTAINED RUN-IN WL AT WEEK 56: 81.4% on liraglutide 48.9% on placebo MAINTENANCE OF RANDOMISATION WL AT WEEK 68: Liraglutide group maintained 4.1% reduction of randomisation weight. Placebo group gained 0.3% above randomisation weight.
SCALE Study 2 (Pi-Sunyer *et al.*, 2015)	TOTAL WEIGHT LOSS AT WEEK 56: Liraglutide group: -8.0 ± 6.7% (observed means ±SD) Placebo group: -2.6 ± 5.7% (observed means ±SD) Estimated Treatment Difference L vs P (95% CI): -5.4 (-5.8 to-5.0) % PARTICIPANTS WITH ≥5% WEIGHT LOSS AT WEEK 56: Liraglutide group: 63.2% Placebo group: 27.1% % PARTICIPANTS WITH ≥10% WEIGHT LOSS AT WEEK 56: Liraglutide group: 33.1% Placebo group: 10.6%
SCALE Study 3 (le Roux *et al.*, 2017)	TOTAL WEIGHT LOSS AT WEEK 160: Liraglutide group: -6.1% Placebo group: -1.9% ≥5% WEIGHT LOSS AT WEEK 160: Liraglutide group: 49.6% Placebo group: 23.7% ≥10% WEIGHT LOSS AT WEEK 160: Liraglutide group: 24.8% Placebo group: 9.9% ≥15% WEIGHT LOSS AT WEEK 160: Liraglutide group: 11% Placebo group: 3.1% TIME TO ONSET OF DIABETES: 2.7x longer with liraglutide than with placebo (99 weeks vs 87 weeks).

Abbreviations: L: liraglutide; LCD: low-calorie diet; P: placebo; R: randomisation; WL: weight loss.

Table 3: Results of SCALE study 4 (Wadden *et al.*, 2019)

	IBT alone	IBT+ LIRAGLUTIDE	MULTICOMPONENT
WL at week 24	-5.4 ± 0.6%	-10.1 ± 0.6%	-12.2 ± 0.6%
WL at week 52	-6.1 ± 1.3%	-11.5 ± 1.3%	-11.8 ± 1.3%
≥5% WL at week 24 *	46%	78%	82%
≥5% WL at week 52 *	44%	70%	74%
≥10% WL at week 24 *	20%	46%	60%
≥10% WL at week 52 *	26%	46%	52%
≥15% WL at week 24 *	6%	20%	32%
≥15% WL at week 52 *	12%	28%	36%

Abbreviations: IBT: intensive behaviour therapy; WL: weight loss.
*Results show percentages of participants who achieved specified weight loss. (Percentages are cumulative.) Values shown are estimated marginal means (± standard error of the mean) for the intention-to-treat population (N=150).

Table 4: Results of SCALE study 5 (Wadden *et al.*, 2020)

	IBT + PLACEBO	IBT+ LIRAGLUTIDE
WL at week 56	-4.0%	-7.5%
≥5% WL at week 56 *	38.8%	61.5%
≥10% WL at week 56 *	19.8%	30.5%
≥15% WL at week 56 *	8.9%	18.1%

Abbreviations: IBT: intensive behaviour therapy; WL: weight loss.
*Results show percentages of participants who achieved specified weight loss. (Percentages are cumulative.)

SAFETY OUTCOMES OF SCALE STUDIES

Adverse events (AE) were experienced on average across the first 3 studies by 89% of participants in the liraglutide group, versus 80% of participants in the placebo group (Table 5). These events were mostly GI related (nausea, constipation, diarrhoea and vomiting), mild to moderate, transient, and mainly happened during dose escalation. However, on average across the first 3 studies, 9.3% participants in the liraglutide group versus 5% in the placebo group withdrew due to adverse events.

In the first study (Wadden *et al.,* 2013), about 25% participants in the liraglutide group reported nausea in the first 4 weeks of treatment, decreasing to <10% at week 10 and <3% subsequently. Of the 8.5% participants who withdrew from the liraglutide group due to serious AE, 44.4% withdrew within the first 4 weeks of the trial during dose escalation.

In the second study (Pi-Sunyer *et al.,* 2015), AE occurred in 80.3% of patients in the liraglutide group vs 63.3% in the placebo group; serious events occurred in 6.2% and 5.0% of patients respectively (Table 5). Additionally, 6.4% patients in the liraglutide withdrew from the trial due to GI events compared to 0.7% in the placebo group (Table 5). In concurrence with the first SCALE study, nausea and vomiting occurred primarily in the first 4 to 8 weeks of liraglutide treatment. Patients in the liraglutide group also reported more gallbladder-related events (2.5%), cholelithiasis (0.8%) and cholecystitis (0.5%) than in the placebo group (1%, 0.4% and 0% respectively).

In study 3 (le Roux *et al.*, 2017), GI disorders were the most common side-effects in the liraglutide group and were mostly mild to moderate (93%). GI AE caused withdrawal in 8% of participants in the liraglutide group vs 2% in the placebo group (Table 5). 41% reported nausea, 25% diarrhoea, 22% constipation and 20% vomiting in the liraglutide group, compared to 17%, 14%, 11% and 5% respectively in the placebo group. Regarding the length of the trial, the safety profile over 3 years was in line with that observed over the initial 56-week period. Additionally, the retention rate was 53% in the liraglutide group and 45% in the placebo group over the 3-year trial.

In study 4 (Wadden *et al.*, 2019), all AE were reported more frequently with liraglutide than placebo (Table 5). Nausea occurred in 36% of participants in IBT-liraglutide group, 26% in the multicomponent group, and 8% in the placebo group. Constipation occurred in 30%, 34% and 2% of participants in the IBT-liraglutide, multicomponent and placebo groups respectively. Diarrhoea occurred in 12%, 14% and 4% respectively, and vomiting in 12%, 10% and 6% respectively.

In study 5 (Wadden *et al.*, 2020), similarly to the previous SCALE studies, GI events were the most frequent AE in both groups, with higher rates in the liraglutide-IBT group than the placebo-IBT (71% vs 49%). Nausea occurred in the first 4 to 8 weeks of treatment predominantly, and in 47.9% of the liraglutide-IBT group compared to 17.9% in the placebo-IBT group.

Table 5: Adverse events (AE) experienced in the SCALE studies

STUDIES	ALL ADVERSE EVENTS (AE)	GI EVENTS	SERIOUS AE	AE LEADING TO WITHDRAWAL
SCALE Study 1 (Wadden *et al.,* 2013)	L= 91.5% P= 88.6%	L= 74% P= 45%	N/A	L= 8.5% (61% GI events; 33% serious event) P=8.5% (28% T2D onset; 33% serious event)
SCALE Study 2 (Pi-Sunyer *et al.,* 2015)	L= 80.3% P= 63.3%	N/A	L= 6.2% P= 5.0%	L= 6.4% (GI events) P= 0.7% (GI events)
SCALE Study 3 (le Roux *et al.*, 2017)	L= 95% P= 89%	N/A	L= 15% P= 13%	L= 13% (8% GI) P= 6% (2% GI)
SCALE Study 4 (Wadden *et al.*, 2019)	IBT= 60% L-IBT= 90% MULTI= 94%	N/A	IBT= 4% L-IBT= 0% MULTI= 6%	N/A
SCALE Study 5 (Wadden *et al.*, 2020)	L-IBT= 95.8% P-IBT= 88.6%	L-IBT= 71% P-IBT= 49%	L-IBT= 4.2% P-IBT= 1.4%	L-IBT= 8.5% P-IBT= 4.3%

Results show the proportion of participants in analysis set having experienced adverse events.

Abbreviations: AE: adverse events; GI: gastrointestinal; L: liraglutide; L-IBT: liraglutide-intensive behaviour therapy; MULTI: multicomponent; N/A: not available; P: placebo; P-IBT: placebo-intensive behaviour therapy.

STEP STUDIES

The aim of the Semaglutide Treatment Effect in People with obesity (STEP) trials was to explore the efficacy of semaglutide weekly 2.4mg subcutaneous injections for weight loss in adults with overweight or obesity. This chapter will analyse the STEP 1, 3, 4, 5 and 8 trials, as they focused on adults with overweight or obesity without T2D (Table 6). The STEP 1 trial extension (Wilding *et al.,* 2022), which investigated weight regain after withdrawal of semaglutide, will be reviewed in the chapter on sustainability of weight loss (chapter 4.4).

STEP 1 and STEP 3 were 68-week double-blind trials comparing the efficacy of semaglutide vs placebo, both with lifestyle intervention consisting of individual counselling sessions to help participants adhere to a reduced-calorie diet and increased physical activity (diet and PA were recorded daily by participants and reviewed during counselling sessions) (Table 6).

STEP 4 had a similar design apart from all participants received semaglutide for 20 weeks and were then randomised to continued semaglutide or switch to placebo for 48 weeks. Results from this study will be further evaluated in chapter 4.4 on sustainability.

STEP 5 was a 104-week trial assessing the long-term weight loss efficacy and safety of semaglutide vs placebo, both with behavioural intervention.

STEP 8 aimed to compare the efficacy and safety of 68-week treatment with semaglutide compared to liraglutide and placebo, all combined with diet and PA.

Semaglutide is a similar peptide to liraglutide but has high albumin binding and GLP-1R potency which results in a more convenient once-weekly administration, instead of the burdensome daily liraglutide injections (Knudsen and Lau, 2019). Semaglutide has shown to reduce hunger and calorie intake, and to increase feelings of satiety (Friedrichsen *et al.,* 2021; Singh and Singh, 2020). Semaglutide is administered subcutaneously, once weekly, usually in the abdomen, thigh or upper arm, and gets absorbed in the bloodstream. In the STEP trials, treatment with semaglutide started with an initial dose of 0.25mg weekly for 4 weeks, followed by increases to 0.5 mg, 1 mg, and 1.7 mg over the following 12 weeks, culminating in a maintenance dose of 2.4 mg weekly after 16 weeks. If participants were unable to tolerate a dose during the escalation phase, dose increase could be postponed by 4 weeks, and if the maintenance dose was not well tolerated, a reduction to 1.7mg for up to 4 weeks was recommended before reinstating the dose to 2.4mg. Discontinuation was advised if issues persisted.

Overall, all participants in these studies had similar demographic and baseline characteristics. Details of each study are displayed in Table 6. Secondary endpoints not linked to weight loss were change from baseline in systolic blood pressure (STEP 1,3,4,5, 8), physical functioning score (assessed via questionnaires) (STEP 1,3,4), and safety assessments.

Table 6: STEP 1, STEP 1-extension, STEP 3, 4, 5 and 8 trials

NAME	DESIGN	POPULATION	INTERVENTION	BACKGROUND TREATMENT	PRIMARY ENDPOINT
STEP 1 WM (Wilding *et al.*, 2021)	Randomised, double-blind placebo-controlled trial.	Adults without diabetes, with a BMI ≥30 or BMI ≥27 with ≥1 comorbidity. (N= 1961)	68 weeks 2.4mg sc semaglutide 1/week or placebo. 2:1 ratio	Lifestyle intervention, RCD (500 kcal/day deficit relative to EEE) and increased physical activity (150 min/week).	% change in BW ≥5% WL (Secondary endpoints: ≥10% WL, ≥15% WL).
STEP 1 TRIAL EXTEN-SION (Wilding *et al.*, 2022)	Blinded follow-up of participants from STEP 1 trial after withdrawal from treatment and lifestyle intervention.	N= 228 from semaglutide arm N= 99 from placebo arm. (Total N= 327)	52 weeks no treatment administered. Visits at weeks 68, 75, 80, 104 and 120 to record body measurements, vital signs and laboratory assessments.	None.	Change in BW and cardio-metabolic factors. Consistency of 68-week semaglutide vs placebo.
STEP 3 WM+IBT (Wadden *et al.*, 2021)	Randomised double-blind parallel group.	Adults without diabetes, with a BMI ≥30 or BMI ≥27 with ≥1 comorbidity. (N= 611)	68 weeks 2.4mg sc semaglutide weekly or placebo. 2:1 ratio	IBT, LCD (1000-1200 kcal/day meal replacement for 1st 8 weeks post-random, then a hypocaloric diet (1200-1800 kcal/day) of conventional food for the last 68 weeks, +100 min/week PA at randomisation, increasing by 25 min every 4 weeks, to reach 200 min/ week, + 30 individual IBT visits with a registered dietitian.	% change in BW ≥5% WL (Secondary endpoints: ≥10% WL, ≥15% WL).
STEP 4 SWM	Randomised double-blind phase 3a	Adults without diabetes, with a	20-week run-in dose-escalated 2.4mg sc	Lifestyle intervention RCD (500 kcal/day	% change in BW from R to week 68.

(Rubino *et al.*, 2021)	withdrawal study.	BMI ≥30 or BMI ≥27 with ≥1 comorbidity. (N= 902 enrolled/ 803 randomised)	semaglutide, followed by 48 weeks continued sc semaglutide or placebo. 2:1 ratio	deficit relative to EEE) and increased PA (150 min/ week).	
STEP 5 **2YR WM** **(Garvey *et al.*, 2022)**	Randomised double-blind placebo-controlled multinational trial.	Adults without diabetes, with a BMI ≥30 or BMI ≥27 with ≥1 comorbidity. (N= 304)	104-week 2.4mg sc semaglutide 1/week or placebo. 1:1 ratio	Lifestyle intervention RCD (500 kcal/day deficit relative to EEE) and increased PA (150 min/ week).	% change in BW, and ≥5% WL, from baseline to week 104. (Secondary endpoints: ≥10% WL ≥15% WL ≥20%WL.
STEP 8 **S vs L** **(Rubino *et al.*, 2022)**	Randomised open-label treatment vs placebo.	Adults without diabetes, with a BMI ≥30 or BMI ≥27 with ≥1 comorbidity. (N= 338)	68 weeks 2.4mg sc semaglutide 1/week or matching placebo or daily 3mg sc liraglutide or matching placebo. 3:1:3:1 ratio	Lifestyle intervention RCD (500 kcal/day deficit relative to EEE) and increased PA (150 min/ week).	% change in BW. (Secondary endpoints: ≥10% WL ≥15% WL ≥20% WL).

Abbreviations: BMI: body mass index; BW: body weight; EEE: estimated energy expenditure; IBT: intensive behavioural therapy; L: liraglutide; N: number; PA: physical activity; R: randomisation; RCD: reduced-calorie diet; S: semaglutide; sc: subcutaneous; SWM: sustained weight management; WL: weight loss; WM: weight management.

EFFICACY OUTCOMES

In STEP 1, after 68 weeks, the mean BW change for participants in the semaglutide group was -14.9% compared to -2.4% in the placebo group (estimated treatment difference: -12.4 percentage points (95% confidence interval [CI], -13.4 to -11.5; P<0.001) (Table 7). Moreover, 86.4% of participants in the semaglutide group achieved ≥5% WL compared to 31.5% in the placebo group; 69.1% achieved ≥10% WL vs 12.0% in the placebo group, and 50.5% achieved ≥15% WL vs 4.9% in the placebo group.

STEP 1 trial extension followed 327 participants from STEP 1 trial for 52 weeks off-treatment. Net BW loss from week 0 to week 120 was 5.6% (sd 8.9%) for the semaglutide participants and 0.1% (SD: 5.8%) for the placebo participants (Table 7). (The results for sustainability of WL from this study are analysed in chapter 4.4.)

STEP 3 trial included an 8-week low-calorie diet at the start of the trial and intensive behavioural therapy for the whole 68 weeks of the trial, which resulted in an estimated mean body weight change of -16.0% for the semaglutide group compared to -5.7% for the placebo group (difference,10.3 percentage points [95%CI, -12.0 to -8.6]; *P*<.001) (Table 7).

In STEP 4, a 20-week run-in treatment with semaglutide resulted in a mean -10.6% BW change; however, participants who switched to placebo after 20-week treatment with semaglutide gained 6.9% BW, despite lifestyle intervention, compared to participants who remained in the semaglutide group, who lost an additional 7.9% BW from randomisation (Table 7).

STEP 5 trial resulted in a mean weight loss of -15.2% following 102 weeks treatment with semaglutide, versus -2.6% with placebo. 77.1% of participants in the semaglutide group achieved ≥5% weight loss compared to 34.4% in the placebo group (Table 7).

STEP 8 trial demonstrated better WL outcomes for semaglutide (-15.8%) vs liraglutide (-6.4%) (difference, -9.4 percentage points [95% CI, -12.0 to -6.8]; *P*<.001), both higher than placebo (-1.9%) (Table 7).

The results from STEP 1, 3,4 and 8 trials show an average weight loss efficacy of between 14.9 % (STEP 1) and 17.4% (STEP 4) following treatment with semaglutide for 68 weeks.

Overall, across STEP 1, 3, 4 and 8 trials, 86%-89% of participants in the semaglutide treatment arms achieved ≥5% weight loss, 69%-79% achieved ≥10% weight loss, 51%-64% achieved ≥15% weight loss, and 32%-40% achieved ≥20% weight loss (Table 8).

Table 7: Results of primary endpoints from STEP trials

STUDIES	PRIMARY OUTCOMES: BODY WEIGHT CHANGES
STEP 1 (Wilding *et al.*, 2021)	Treatment policy estimand: S= -14.9% BW P= -2.4% BW (Estimated treatment difference: -12.4 percentage point) Trial product estimand: S= -16.9% P= -2.4% (Estimated treatment difference: -14.4 percentage point)
STEP 1 EXT. (Wilding *et al.*, 2022)	Weight regain: S= 11.6 percentage points P= 1.9 percentage points Net mean BW loss over the full 120 weeks: S= -5.6% P= 0.1% % participants with ≥5% BW change at week 120: S= 48.2% P= 22.6%
STEP 3 (Wadden *et al.*, 2021)	S= -16% BW P= -5.7% BW
STEP 4 (Rubino *et al.*, 2021)	Baseline to week 20= -10.6% BW S= -7.9% BW change from week 20 P= +6.9% BW change from week 20 S= -17.4% BW change (week 0 to week 68) P= -5% BW change (week 0 to week 68)
STEP 5 (Garvey *et al.*, 2022)	S= -15.2% BW P= -2.6% BW
STEP 8 (Rubino *et al.*, 2022)	S= -15.8% BW L= -6.4% BW P= -1.9% BW

Abbreviations: BW: body weight; P: placebo; S: semaglutide.

(Treatment policy estimand shows the effect regardless of treatment discontinuation or rescue intervention. Trial product estimand shows the effect if the drug or placebo was taken as intended.)

Table 8: Results of secondary endpoints

STUDY	≥5% WL	≥10% WL	≥15% WL	≥20% WL
STEP 1 (Wilding *et al.*, 2021)	S= 86.4% P= 31.5%	S= 69.1% P= 12%	S= 50.5% P= 4.9%	S= 32% P= 1.7%
STEP 1 EXT (Wilding *et al.*, 2022)	S= 48.2% P= 22.6%			
STEP 3 (Wadden *et al.*, 2021)	S= 86.6% P= 47.6%	S= 75.3% P= 27%	S= 55.8% P= 13.2%	S= 35.7% P= 3.7%
STEP 4 (Rubino *et al.*, 2021) (week 0 to week 68)	S= 88.7% P= 47.6% (from week 20)	S= 79% P= 20.4% (from week 20)	S=63.7% P= 9.2% (from week 20)	S=39.6% P = 4.8% (from week 20)
STEP 5 (Garvey *et al.*, 2022)	S= 77.1% P= 34.4%	S= 61.8% P= 13.3%	S= 52.1% P= 7%	S= 36.1% P= 2.3%
STEP 8 (Rubino *et al.*, 2022)	S= 87.2% L= 58.1% P= 29.5%	S= 70.9% L= 25.6% P= 15.4%	S= 55.6% L= 12% P= 6.4%	S= 38.5% L= 6% P= 2.6%

Abbreviations: WL: weight loss; P; placebo; S; semaglutide.

SAFETY OUTCOMES

Adverse events were experienced by between 81.3% (STEP 4) and 96.1% (STEP 5) of participants in the semaglutide groups, comparably to the placebo groups (between 75% (STEP 4) and 96.1% (STEP 3) of participants). These AE were mostly gastrointestinal events, transient, and of mild to moderate severity. However, withdrawal from trial due to GI AE occurred in between 0.8% (STEP 8) and 4.5% (STEP 1) of participants in the semaglutide groups, compared to between 0% (STEP 3) and 1.2% (STEP 8) of participants in the placebo groups. Rates of overall adverse events in STEP 8 were similar between the semaglutide and liraglutide groups, but discontinuation due to AE was higher in the liraglutide group (12.6% vs 3.2%).

No safety outcomes were recorded in the STEP-1 trial extension due to the nature of the trial.

No new safety concerns were raised following these trials. The incidence of cholelithiasis was in line with the evidence between rapid weight loss and increased risk of gallstone disease, and with reports of gallbladder disorders linked to GLP-1RAs (He *et al.,* 2025; Stokes and Lammert, 2021).

SURMOUNT STUDIES

The aim of the SURMOUNT trials was to evaluate the efficacy and safety of tirzepatide, a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist, alongside diet and exercise, in chronic weight management (CWM) in adults with overweight or obesity (le Roux *et al.,* 2023). This chapter will focus on SURMOUNT-1, 3 and 4, multi-centred, randomised, double-blind, parallel, placebo-controlled trials, involving adults with obesity or overweight with at least 1 weight-related complication, without diabetes (Aronne *et al.,* 2024; Jastreboff *et al.,* 2022; Wadden *et al.,* 2023). Tirzepatide is a single molecule which activates the receptors for the incretin hormones GLP-1 and GIP, found in the brain, and regulate appetite (Nauck and D 'Alessio, 2022). Studies of tirzepatide demonstrated its potential to decrease food intake and modulate fat utilisation, as well as improvements in obesity-related conditions such as obstructive sleep apnoea (OSA), heart failure with preserved ejection fraction (HFpEF) and non-alcoholic steatohepatitis (NASH) (Liarakos and Koliaki, 2023; Sidrak, Kalra and Kalhan, 2024). Tirzepatide was approved by the FDA in 2022 as Mounjaro for the treatment of obesity (Syed, 2022). In the SURMOUNT trials, dosage started with 2.5mg subcutaneous (sc) injection (or matching placebo) once weekly for 4 weeks, and increased every 4 weeks by 2.5mg, until assigned dose or maximum tolerated dose (MTD) was reached (5mg, 10mg or 15mg).

SURMOUNT-1trial aimed to compare the efficacy of tirzepatide weekly doses of either 5mg, 10mg or 15mg, versus placebo, for 72 weeks. In addition, participants received regular professional lifestyle counselling sessions on adhering to the recommended guidelines for PA and adhering to a balanced diet with a 500kcal deficit per day; Fitbit activity trackers and food and exercise logs were provided as an optional extra help to encourage self-monitoring and behavioural change (le Roux *et al.,* 2023).

SURMOUNT-3 trial aimed to assess the effect of a weekly dose of MTD tirzepatide (10mg or 15mg) for 72 weeks on weight reduction following a 12-week intensive lifestyle intervention, compared to placebo. Secondary outcomes included the proportion of participants in each group who maintained ≥80% lead-in WL.

SURMOUNT-4 trial aimed to assess the effect of continued treatment with tirzepatide vs placebo on maintaining weight reduction achieved during a 36-week open-label lead-in period of weekly maximum tolerated dose (10mg or 15mg) of tirzepatide.

Key secondary endpoints from SURMOUNT studies included ≥10%, ≥15% and ≥20% weight reduction. In addition, a subgroup of participants in SURMOUNT-1 trial underwent dual-energy x-ray absorptiometry (DEXA) and were assessed for percentage change in total body-fat mass from baseline to end of trial.

Secondary endpoints not relating to weight loss achievement included systolic blood pressure, fasting insulin and lipid levels, and physical function score (assessed via questionnaires) (SURMOUNT-1), and safety assessment. An exploratory end point of ≥25% body weight reduction was added in SURMOUNT-3 and 4.

Demographics were evenly distributed across each group in each study. Details of each study are displayed in Table 10.

Table 10: SURMOUNT 1, 3 and 4 trials

STUDY	DESIGN	POPULA-TION	INTER-VENTION	BACK-GROUND TREATMENT	PRIMARY ENDPOINT
SURMOUNT-1 **(Jastreboff *et al.*, 2022)**	Multi-centred, randomised, double-blind, parallel, placebo-controlled trial.	Adults without diabetes, with a BMI ≥30 or BMI ≥27 with ≥1 comorbidity. (N=2539)	72-week 5mg, 10mg or 15 mg sc T or placebo (incl. a 20-week dose-escalation period). Ratio1:1:1:1	Lifestyle counselling sessions RCD + increased PA (150 min/ week).	% WC from baseline to week 72. ≥5% WL at week 72 (Secondary endpoints: ≥10% WL ≥15% WL ≥20% WL at week 72).
SURMOUNT-3 **(Wadden *et al.*, 2023)**	Multi-centred, randomised, double-blind, parallel, placebo-controlled trial.	Adults without diabetes, with a BMI ≥30 or BMI ≥27 with ≥1 comorbidity. (N=806)	12-week lead-in intensive lifestyle intervention (579 achieved ≥5% WL and were randomised to 72-week T MTD or placebo). 1:1 ratio	RCD (1200~1500 kcal/day) + ≥150mins PA / week + ≥14 BC sessions over 6 months.	% WC from R to week 72. Proportion of individuals who achieved an additional ≥5% WL.
SURMOUNT-4 **(Aronne *et al.*, 2024)**	Multi-centred, randomised, double-blind, parallel, placebo-controlled trial.	Adults without diabetes, with a BMI ≥30 or BMI ≥27 with ≥1 comorbidity. (N=783)	36-week-lead-in 10mg or 15mg tirzepatide, followed by 52-week either continued tirzepatide or switch to placebo. (1:1 ratio)	RCD (500 kcal/day deficit) + ≥150mins PA / week.	% WC from week 36 to week 88 (Secondary endpoint: Proportion of individuals who maintained ≥80% lead-in WL).

Abbreviations: BC: behavioural counselling; BMI: body-mass index; MTD: maximum treatment dose; N: number; PA: physical activity; R: randomisation; RCD: reduced-calorie diet; sc: subcutaneous; T: tirzepatide; WC: weight change; WL: weight loss.

EFFICACY OUTCOMES

In SURMOUNT-1, participants who took higher doses of tirzepatide showed greater results for weight loss efficacy after 72 weeks: from 15% WL with 5mg, to 19.5% with 10 mg, and 20.5% with 15mg (Table 11). Similarly, the percentage of participants achieving weight loss of ≥5%, ≥10%, ≥15% and ≥20% were higher in the 15mg group than in the 5mg and 10mg groups (Table 11). All 3 tirzepatide doses were superior to placebo. The estimated treatment differences relative to placebo were -11.9 percentage points (95% CI, -13.4 to -10.4) for 5mg, -16.4 percentage points (95% CI, -17.9 to -14.8) for 10mg, and -17.8 percentage points (95% CI, -19.3 to -16.3) for 15mg.

In SURMOUNT-3, participants who lost ≥5% baseline BW after 12-week intensive lifestyle intervention were randomised to tirzepatide maximum tolerated dose (MTD) (10 or 15mg) or placebo for 72 weeks. Comparably to SURMOUNT-1, participants in the tirzepatide MTD group achieved higher rates of weight loss than in the placebo group (Table 11): -18.4% vs +2.5% from randomisation to week 72, an estimated treatment difference of -20.8 percentage points (95% CI -23.2, -18.5; $P < 0.001$) for tirzepatide relative to placebo. Moreover, 94% of participants in the tirzepatide group maintained ≥80% lead-in WL compared to 43.8% in the placebo group. Over the whole 84-week trial, the total weight change in the tirzepatide group was -24.3% vs -4.5% in the placebo group.

In SURMOUNT-4, participants lost a mean -20.9% BW in the 36-week lead-in period with tirzepatide MTD (10 or 15mg), followed by a further -5.5% WL for those continuing tirzepatide vs 14% weight gain for those receiving placebo for 52 weeks (difference, -19.4% [95% CI, -21.2% to -17.7%]; $P < 0.001$; Table 7). Additionally, 89.5% participants who continued receiving tirzepatide maintained ≥80% lead-in WL compared to 16.6% in the placebo group. Over the whole 88-week trial, participants who carried on with tirzepatide lost 25.3% compared to 9.9% of those randomised to placebo.

Overall, tirzepatide MTD 10mg or 15mg resulted in weight loss of between 18.4% (SURMOUNT-3) and 25.3% (SURMOUNT-4).

Across all trials, 89%-97.3% participants achieved ≥5% WL; 78%-92.1% achieved ≥10% WL; 67%-84.1% achieved ≥15% WL, and 50%-69.5% achieved ≥25% WL with 10mg or 15 mg MTD tirzepatide.

Table 11: Results of SURMOUNT trials (primary end points)

STUDIES	OUTCOME
SURMOUNT -1 (Jastreboff *et al.*, 2022)	MEAN % BW CHANGE FROM BASELINE TO WEEK 72: Tirzepatide 5mg= -15% Tirzepatide 10mg= -19.5% Tirzepatide 15mg= -20.9% Placebo= -3.1% % PARTICIPANTS WHO ACHIEVED ≥5% WL AT WEEK 72: Tirzepatide 5mg= 85% Tirzepatide 10mg= 89% Tirzepatide 15mg= 91% Placebo= 35%
SURMOUNT -3 (Wadden *et al.*, 2023	MEAN % BW CHANGE FROM RANDOMISATION TO WEEK 72: Tirzepatide MTD (10 or 15mg) = -18.4% Placebo= 2.5% PARTICIPANTS WHO LOST ≥5% BW: Tirzepatide MTD= 87.5% Placebo= 16.5% PARTICIPANTS WHO MAINTAINED ≥80% LEAD-IN WL: Tirzepatide MTD= 94% Placebo= 43.8% TOTAL WEIGHT CHANGE FROM WEEK 0 TO WEEK 84: Tirzepatide MTD= -24.3% Placebo= -4.5%
SURMOUNT -4 (Aronne *et al.*, 2024)	36-WEEK LEAD-IN PERIOD MEAN % WEIGHT CHANGE: -20.9% MEAN % WEIGHT CHANGE FROM WEEK 36 TO WEEK 88: Tirzepatide= -5.5% Placebo= 14.0% % PARTICIPANTS WHO MAINTAINED ≥80% LEAD-IN WL: Tirzepatide= 89.5% Placebo= 16.6% OVERALL WEIGHT REDUCTION AT WEEK 88: Tirzepatide= 25.3% Placebo= 9.9%

Abbreviations: MTD: maximum tolerated dose: WL: weight loss.

Table 12: Results of secondary end points (SURMOUNT trials)

STUDIES	≥5% WL	≥10% WL	≥15% WL	≥20% WL	≥25% WL
SURMOUNT -1	5mg= 85% 10mg= 89% 15mg= 91% P= 35%	5mg= 69% 10mg= 78% 15mg= 84% P= 19%	5mg= 48% 10mg= 67% 15mg= 71% P= 9%	5mg= 30% 10mg= 50% 15mg= 57% P= 3%	N/A
SURMOUNT -3	T= 87.5% P= 16.5%	T= 76.7% P= 8.9%	T= 65.4% P= 4.2%	T= 44.7% P= 2.2%	T= 28.7% P= 1.2%
SURMOUNT -4	T= 97.3% P= 70.3%	T= 92.1% P= 46.2%	T= 84.1% P= 25.9%	T= 69.5% P= 12.6%	T= 54.5% P= 5.0%

Abbreviations: P: placebo; T: tirzepatide; WL: weight loss.

CHANGE IN BODY COMPOSITION IN SURMOUNT-1 DEXA SUBGROUP

In the subgroup of participants who underwent DEXA, the mean reduction in total body fat mass was 33.9% with tirzepatide vs 8.2% with placebo (estimated treatment difference -25.7 percentage points (95% CI, -31.4 to -20.0)). Additionally, the total fat mass to total lean mass ratio decreased from 0.93 at baseline to 0.70 at week 72 with tirzepatide compared to 0.95 to 0.88 with placebo.

SAFETY OUTCOMES

Over the 3 SURMOUNT studies, adverse events (AE) were experienced by between 60.3% and 87.1% in the tirzepatide group compared to 55.8%-76.7% in the placebo group (Table 13).

In SURMOUNT-1, GI events (nausea, diarrhoea, and constipation) were the most frequently reported AE and were higher in the tirzepatide group than in the placebo group. They occurred mainly during the dose-escalation period, and were transient and mild to moderate. 4.3% of participants in the 5mg tirzepatide group discontinued trial due to serious AE, compared with 7.1% in the 10mg group, 6.2% in the 15mg, and 2.6% in the placebo group (Table 13).

In SURMOUNT-3, 87.1% of participants in the tirzepatide group vs 76.7% of participants in the placebo group reported AE (Table 13). Comparably to SURMOUNT-1, the most frequently reported events were GI related, mild to moderate and mostly during dose-escalation. AE leading to treatment withdrawal occurred in 10.5% of participants in the tirzepatide group vs 2.1% in the placebo group (Table 13).

In SURMOUNT-4, 81.0% of participants reported at least 1 AE during the tirzepatide lead-in period (Table 13). Nausea was reported by 35.5% of participants, diarrhoea by 21.1%, constipation by 20.7% and vomiting by 16.3% of participants during the 36-week lead-in period. 7.0% of participants discontinued treatment during the lead-in period due to an AE (mainly GI). Overall, 2.0% reported serious AE during the lead-in period compared to 3.0% in the double-blind period.

Table 13: Adverse events (AE) experienced in the SURMOUNT trials

STUDIES	ALL ADVERSE EVENTS (AE)	GI EVENTS (NAUSEA)	SERIOUS AE	AE LEADING TO WITHDRAWAL
SURMOUNT -1	T5mg= 81% T10mg= 81.8% T15mg= 78.9% P= 72%		T5mg= 6.3% T10mg= 6.9% T15mg= 5.1% P= 6.8%	T5mg= 4.3% T10mg= 7.1% T15mg= 6.2% P= 2.6%
SURMOUNT -3	T= 87.1% P= 76.7%	T= 8.4% P= 1.4%	T= 5.9% P= 4.8%	T= 10.5% P= 2.1%
SURMOUNT -4	T= 60.3%** P= 55.8%**	T= 8.1% P= 1.2%	T= 3%** P= 3%**	T= 1.8%** P= 0.9%**

(** After randomisation)

SUSTAINABILITY OF WEIGHT LOSS: EVIDENCE FROM 4 STUDIES

SCALE STUDY 3 (le Roux *et al.,* 2017)

Participants were followed for an additional 12 weeks post-trial after treatment cessation at week 160. During these 12 weeks, a mean weight regain of 1.9% was observed in the participants from the liraglutide group who entered the follow-up period. Despite this, participants in the liraglutide group achieved greater weight loss at week 172 compared to those in the placebo group. Additionally, blood pressure increased in both groups post-treatment.

STEP 1- Trial extension (Wilding *et al.,* 2022)

After treatment withdrawal, participants in both semaglutide and placebo arms regained weight: a mean 11.6 percentage points (SD: 7.7) vs 1.9 percentage points (SD: 4.8) respectively. The net mean BW loss from week 0 to week 120 was 5.6% (SD: 8.9%) in the semaglutide arm, vs 0.1% (SD: 5.8%) in the placebo arm. 48.2% of participants in the semaglutide arm achieved ≥5% WL at week 120 compared to 22.6% in the placebo arm. The greater the weight loss from week 0 to week 68, the greater the weight regain from week 68 to week 120; however, net weight losses were still greater in those participants. Mean systolic and diastolic BP reverted to baseline by week 120 in both groups.

STEP 4 (Rubino *et al.,* 2021)

20-week open-label run-in treatment with semaglutide; 89% were randomised 2:1 to continued semaglutide or switch to placebo, alongside lifestyle intervention in both groups (mean WL: 10.6%). Mean body weight change from randomisation to 48 weeks was –7.9% with semaglutide vs +6.9% with placebo (difference, -14.8 [95% CI, -16.0 to -13.5] percentage points; $P<.001$). Those randomised to semaglutide sustained weight loss achieved at randomisation, compared to those assigned to placebo, who gradually regained weight. Weight loss for participants in the semaglutide group continued until reaching a plateau at week 60 to 68. In addition, improvements in systolic blood pressure remained stable with continued semaglutide but reversed significantly with placebo (difference, -3.9 mm Hg [95% CI, -5.8 to –0.2 mm Hg]; $P<.001$). Continued semaglutide led to further reductions in haemoglobin A1c and fasting plasma glucose, and improvements in lipid profile, compared to placebo. Additionally, the physical and mental scores considerably improved with semaglutide compared to placebo.

SURMOUNT-4 (Aronne *et al.*, 2024)

Following a 36-week open-label lead-in period treatment with tirzepatide MTD (10 or 15mg) (mean WL: 20.9%), 670 participants were randomised to a double-blind trial of continued tirzepatide or switch to placebo for 52 weeks. Participants who continued with tirzepatide carried on losing weight (-5.5%) whereas participants who switched to placebo regained weight (14%) (difference, -19.4% [95% CI, -21.2% to -17.7%]; $P<.001$). Additionally, improvements in cardiometabolic risk factors were reversed in participants in the placebo group.

These results indicate homogeneity between these 3 trials relating to the evidence of weight regain following discontinuation of the GLP-1 RAs liraglutide, semaglutide and tirzepatide. Furthermore, health improvements achieved with GLP1-RAs treatment during the trials reversed or reverted to baseline after withdrawal. This leads to the conclusion that continued treatment is needed to maintain weight loss and other health benefits achieved during treatment.

The next chapter will assess the strengths and limitations of each study.

CRITICAL APPRAISAL OF THE STUDIES

SCALE STUDIES

Table 14: Strengths and limitations

STUDY	STRENGTHS	LIMITATIONS	ACKOWLEDGEMENTS
SCALE Study 1 (Wadden *et al.*, 2013)	High retention rates (70.0% with liraglutide and 69.5% with placebo). Inclusion of lifestyle intervention. High rate of maintenance of 5% WL with liraglutide.	Difficulty in establishing the exact impact of liraglutide on CVD and metabolic risk factors due to the effects of the LCD on these markers during the run-in period. Selection of participants was based on successful 5% WL in the LCD run-in period, which could have influenced the high rate of WL in this trial.	Trial funded by Novo Nordisk.
SCALE Study 2 (Pi-Sunyer *et al.*, 2015)	Large sample. High retention rates. Inclusion of lifestyle intervention.	Use of last-observation-carried-forward imputation in the pre-specified primary analysis (however, the use of alternative imputation methods to take into consideration the dropout rates confirmed the strength of the primary analyses).	Trial funded by Novo Nordisk.
SCALE Study 3 (le Roux *et al.*, 2017)	Large sample size. Length of trial.	Missing data from participants who withdrew prior to the end of trial, which can have an impact on the interpretation of the results.	Trial funded by Novo Nordisk.
SCALE Study 4 (Wadden *et al.*, 2019)	High retention rates. Participant commitment to the trial.	Short trial duration. Lack of participants aged ≥ 65. The trial was not conducted in a primary care setting. The absence of a usual-care group.	Trial funded by Novo Nordisk.
SCALE Study 5 (Wadden *et al.*, 2020)	Large sample size. Study design. High retention rate (96%).	Short trial duration. Challenge in assessing the specific level of IBT required to achieve clinically meaningful weight loss alongside liraglutide.	Trial funded by Novo Nordisk.

STEP STUDIES

Table 15: Strengths and limitations

STUDY	STRENGTHS	LIMITATIONS	ACKNOWLEDGMENTS
STEP 1 (Wilding *et al.*, 2021)	Large sample size. High rates of adherence to treatment and completion of trial. Inclusion of DXA assessment.	Low inclusion rate of men and ethnic minorities. Short trial length. Low sample of participants selected for DXA assessment.	Trial funded by Novo Nordisk.
STEP 1-EXT (Wilding *et al.*, 2021)	Pragmatic design which simulates a real-world setting. Multinational settings. High rates of trial completion.	Small sample size Selection of sites which could create bias (however, further analysis show that the extension sample was representative of the overall population included in STEP 1). The potential use of AOM during the extension trial. Exploratory nature of the analyses.	Trial funded by Novo Nordisk.
STEP 3 (Wadden *et al.*, 2021)	Design. Sample size.	Challenge in determining the relative benefits of IBT and initial LCD combined with semaglutide.	Trial funded by Novo Nordisk.
STEP 4 (Rubino *et al.*, 2021)	Blinded, withdrawal design. Large sample size. High rates of treatment regimen and trial completion.	Lack of flexibility in the run-in period (only participants who tolerated the strict dose titration schedule were included). Lack of assessment of lifestyle intervention adherence.	Trial funded by Novo Nordisk.
STEP 5 (Garvey *et al.*, 2022)	High rates of adherence to treatment and completion of trial. Trial length.	Low inclusion rate of men and ethnic minorities.	Trial funded by Novo Nordisk.
STEP 8 (Rubino *et al.*, 2022)	Comparison between semaglutide and liraglutide. Double-bind design of the placebo groups and treatment groups.	Different responses to low tolerance of maintenance dose between liraglutide and semaglutide. Treatment dose differences meant participants knew which drug group they were in.	Trial funded by Novo Nordisk.

SURMOUNT STUDIES

Table 16: Strengths and limitations

STUDY	STRENGTHS	LIMITATIONS	ACKNOWLEDGEMENTS
SURMOUNT-1 (Jastreboff *et al.*, 2022)	Large sample size. Duration of treatment. High completion rate (90% across the tirzepatide groups, 86% overall) despite the Covid-19 pandemic.	Potential misrepresentation of the general population with obesity (participants in this trial might have had a greater commitment to weight-management efforts). Only 5.5% patients had overweight.	Trial funded by Eli Lilly.
SURMOUNT-3 (Wadden *et al.*, 2023)	Large sample. High rate of men and Hispanic ethnicity compared to previous trials. Trial length. Flexibility of the titration phase.	Geographical restrictions. Most participants were white. Those who failed to lose 5% BW in the intensive lifestyle intervention were excluded from the trial.	Trial funded by Eli Lilly.
SURMOUNT-4 (Aronne *et al.*, 2023)	Large sample. Randomised withdrawal design.	Fixed treatment dose after randomisation. Lack of evaluation of the effects of IBT on weight loss maintenance. Participants who tolerated the initial treatment might misrepresent the general population.	Trial funded by Eli Lilly.

Overall, the strengths of this narrative review include the comparison of 3 types of GLP-1RAs, the large number of studies included and their design and recentness. Limitations include the short time frame in which the research was conducted, which could have led to some studies being omitted, the lack of diversity in participant demographics across all studies, and the potential bias of the studies included due to funding by the drug companies supplying the treatments.

The next chapter will evaluate practical implications and areas for future research.

PRACTICAL IMPLICATIONS AND AREAS FOR FUTURE RESEARCH

The main findings from this research demonstrate the strong potential of liraglutide, semaglutide and tirzepatide, alongside lifestyle behaviour counselling, for weight management in adults with overweight or obesity without diabetes. Furthermore, their safety profile were generally favourable, with the most reported adverse events being GI related, transient, mild-to moderate, and mainly occurring during dose-escalation period. However, results of the studies on weight loss maintenance following treatment withdrawal showed immediate weight regain and reversal of health benefits achieved during the trials.

These findings highlight the need for a multi-faceted approach to weight management in primary care settings, with the inclusion of regular behavioural therapy alongside medical treatment. Achieving the best health outcomes for patients requires health prescribers to work with dietitians who can support patients throughout their weight loss journey by encouraging them to adhere to a healthier lifestyle with a structured protocol. Additionally, following patients in a primary care setting should enable health care providers to adapt the treatment to the patient according to their response and tolerance to the drugs.

Educating professionals and patients on the side-effects expected with such treatments is also necessary and advice on suitable dietary modifications (increasing fibre and water intake for example) as well as reducing treatment dose in case of severe adverse events, should be provided. Raising awareness on the effect of rapid weight loss on gallbladder is also key to support patients.

Further studies are required to assess the efficacy and safety of GLP1-RAs in populations with obesity and other health conditions, on medication (possible drug interactions), younger populations, and individuals with eating disorders. Additionally, trials in primary care settings would be more reflective of real-life response to treatment compared to clinical settings, as well as including patients who struggle to lose weight with lifestyle behaviour modifications. Moreover, the potential reasons for participants' lack of response to treatment need investigating.

Future research to improve the average efficacy and tolerability of AOM, while reducing adverse events, would be valuable, together with improvements in drug administration, such as longer-acting, oral approaches rather than daily or weekly subcutaneous injections, would be advantageous for both patients and subscribers. Trials assessing the effects of switching from one treatment to another would be beneficial. Identifying issues with weight loss maintenance, and preservation of muscle and bone mass following weight loss while on treatment, are areas worthy of investigation.

CONCLUSION

Weight loss (WL) is essential for the management of obesity. Lifestyle behaviour changes alongside liraglutide, semaglutide or tirzepatide have shown promising results after reviewing their efficacy, safety and sustainability across 14 studies on adult participants with obesity or overweight and associated comorbidities, without diabetes.

In the SCALE studies appraised in this review, liraglutide 3.0mg once-daily subcutaneous injection led to 6%-8.2% weight loss, an overall estimated placebo subtracted efficacy of -4.8%. In the first 3 studies, 50%-63.5% of participants achieved ≥5% WL, and 25% to 33% % achieved ≥10% WL. In study 4 and 5, IBT combined with liraglutide led to greater numbers of participants achieving ≥5% WL (70% and 61.5% respectively, ≥10% WL (46% and 30.5%), and ≥15% WL (28% and 18.1%). Furthermore, more participants in the multicomponent group (IBT+ liraglutide + 1000-to-1200kcal meal replacement diet for 12 weeks) in study 4 lost ≥5% BW (74%), ≥10% BW (52%) and ≥15% BW (36%) compared to IBT+ liraglutide.

In the STEP studies appraised in this review, semaglutide 2.4mg once-weekly subcutaneous injection led to 14.9%-17.4% WL, an overall estimated placebo subtracted efficacy of -11%. Additionally, 86%-89% of participants in the semaglutide treatment arms achieved ≥5% WL, 69%-79% achieved ≥10% WL, 51%-64% achieved ≥15% WL, and 32%-40% achieved ≥20% WL.

In the SURMOUNT studies appraised in this review, tirzepatide 10-15mg once-weekly subcutaneous injection led to 18.4%-25.3% WL, an overall estimated placebo subtracted efficacy of -18.6%. Additionally, across all trials, 89%-97.3% participants achieved ≥5% WL; 78%-92.1% achieved ≥10% WL; 67%-84.1% achieved ≥15% WL, and 50%-69.5% achieved ≥25% WL. Tirzepatide MTD 10-15mg led to greater WL than 5mg.

Semaglutide achieved better WL outcomes than liraglutide overall, but less than tirzepatide. Studies including IBT showed increased WL outcomes. An added benefit of all 3 GLP-1RAs was reductions in glycaemic variables and cardiometabolic risk factors, and improvements in health-related quality of life.

In respect of safety outcomes, similar numbers of participants in treatment and placebo groups experienced adverse events. Most events in the treatment groups were GI related, transient, mild to moderate in severity and occurred during dose escalation. Overall, withdrawal due to AE occurred in around 9% with liraglutide vs 4.9% with placebo, 5% with semaglutide vs 3% with placebo, and 6% of participants with tirzepatide vs 2% with placebo, which shows a high tolerance to the adverse effects.

Regarding the sustainability of WL, discontinuation of treatment led to weight regain in all trial groups, therefore, to conclude, the literature reviewed shows that the management of obesity should not only focus on weight loss but also on the prevention and improvement of obesity-related disorders, quality of life, physical fitness and mental and social wellbeing of

the patients. Obesity is a chronic disease which requires a long-term, personalised, multi-disciplinary comprehensive intervention.

REFERENCE LIST

Apovian, C.M., Aronne, L.J., Bessesen, D.H., McDonnell, M.E., Murad, M.H., Pagotto, U., Ryan, D.H. and Still, C.D. (2015) 'Pharmacological management of obesity: an endocrine Society clinical practice guideline', *The Journal of Clinical Endocrinology & Metabolism,* 100(2), pp. 342–362.

Ard, J., Fitch, A., Fruh, S. and Herman, L. (2021) 'Weight loss and maintenance related to the mechanism of action of glucagon-like peptide 1 receptor agonists', *Advances in Therapy,* 38(6), pp. 2821–2839.

Aronne, L.J., Sattar, N., Horn, D.B., Bays, H.E., Wharton, S., Lin, W., Ahmad, N.N., Zhang, S., Liao, R. and Bunck, M.C. (2024) 'Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial', *Jama,* 331(1), pp. 38–48.

Bettge, K., Kahle, M., Abd El Aziz, M.S., Meier, J.J. and Nauck, M.A. (2017) 'Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: a systematic analysis of published clinical trials', *Diabetes, Obesity and Metabolism,* 19(3), pp. 336–347.

Blackman, A., Foster, G.D., Zammit, G., Rosenberg, R., Aronne, L., Wadden, T., Claudius, B., Jensen, C.B. and Mignot, E. (2016) 'Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnoea: the SCALE Sleep Apnoea randomized clinical trial', *International journal of obesity,* 40(8), pp. 1310–1319.

Blüher, M. (2019) 'Obesity: global epidemiology and pathogenesis', *Nature Reviews Endocrinology,* 15(5), pp. 288–298.

Bray, G.A., Frühbeck, G., Ryan, D.H. and Wilding, J.P. (2016) 'Management of obesity', *The Lancet,* 387(10031), pp. 1947–1956.

Burcelin, R. and Gourdy, P. (2017) 'Harnessing glucagon-like peptide-1 receptor agonists for the pharmacological treatment of overweight and obesity', *Obesity Reviews,* 18(1), pp. 86–98.

Chakhtoura, M., Haber, R., Ghezzawi, M., Rhayem, C., Tcheroyan, R. and Mantzoros, C.S. (2023) 'Pharmacotherapy of obesity: an update on the available medications and drugs under investigation', *EClinicalMedicine,* 58.

Cercato, C. and Fonseca, F.A. (2019) 'Cardiovascular risk and obesity', *Diabetology & metabolic syndrome,* 11, pp. 1–15.

Cerillo, J.L. and Parmar, M. (2024) 'Liraglutide'*StatPearls [Internet]* StatPearls Publishing.

Cornell, S. (2020) 'A review of GLP-1 receptor agonists in type 2 diabetes: a focus on the mechanism of action of once-weekly agents', *Journal of clinical pharmacy and therapeutics,* 45, pp. 17–27.

Davies, M.J., Bergenstal, R., Bode, B., Kushner, R.F., Lewin, A., Skjøth, T.V., Andreasen, A.H., Jensen, C.B., DeFronzo, R.A. and NN8022-1922 Study Group (2015) 'Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial', *Jama,* 314(7), pp. 687–699.

Dodangeh, S. and Hasani-Ranjbar, S. (2024) 'Old and new anti-obesity drugs', *Journal of Diabetes & Metabolic Disorders,* 24(1), pp. 16.

Drucker, D.J. (2018) 'Mechanisms of action and therapeutic application of glucagon-like peptide-1', *Cell metabolism,* 27(4), pp. 740–756.

FDA (2023) *FDA Approves New Medication for Chronic Weight Management.* Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-medication-chronic-weight-management (Accessed: 25 January 2025).

FDA (2022) *FDA requests the withdrawal of the weight-loss drug Belviq, Belviq XR (lorcaserin) from the market.* Available at: https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market#:%7E:text=On%20February%2013%2C%202020%20FDA,an%20increased%20occurrence%20of%20cancer (Accessed: 25 January 2025).

Friedrichsen, M., Breitschaft, A., Tadayon, S., Wizert, A. and Skovgaard, D. (2021) 'The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity', *Diabetes, Obesity and Metabolism,* 23(3), pp. 754–762.

Garvey, W.T., Batterham, R.L., Bhatta, M., Buscemi, S., Christensen, L.N., Frias, J.P., Jódar, E., Kandler, K., Rigas, G. and Wadden, T.A. (2022) 'Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial', *Nature medicine,* 28(10), pp. 2083–2091.

Garvey, W.T., Mechanick, J.I., Brett, E.M., Garber, A.J., Hurley, D.L., Jastreboff, A.M., Nadolsky, K., Pessah-Pollack, R. and Plodkowski, R. (2016) 'American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity', *Endocrine Practice,* 22, pp. 1–203.

Greenhalgh, T., Thorne, S. and Malterud, K. (2018) 'Time to challenge the spurious hierarchy of systematic over narrative reviews?', *European journal of clinical investigation,* 48(6).

Grunvald, E., Shah, R., Hernaez, R., Chandar, A.K., Pickett-Blakely, O., Teigen, L.M., Harindhanavudhi, T., Sultan, S., Singh, S. and Davitkov, P. (2022) 'AGA clinical practice guideline on pharmacological interventions for adults with obesity', *Gastroenterology,* 163(5), pp. 1198–1225.

Haase, C.L., Eriksen, K.T., Lopes, S., Satylganova, A., Schnecke, V. and McEwan, P. (2021) 'Body mass index and risk of obesity-related conditions in a cohort of 2.9 million people: Evidence from a UK primary care database', *Obesity science & practice,* 7(2), pp. 137–147.

Haththotuwa, R.N., Wijeyaratne, C.N. and Senarath, U. (2020) 'Worldwide epidemic of obesity *'Obesity and obstetrics* Elsevier, pp. 3–8.

He, L., Li, J., Cheng, X., Luo, L. and Huang, Y. (2025) 'Association between GLP-1 RAs and DPP-4 inhibitors with biliary disorders: pharmacovigilance analysis', *Frontiers in Pharmacology,* 16, pp. 1509561.

Heymsfield, S. B. (2024). Advances in body composition: a 100-year journey. *International Journal of Obesity*, 1–5.

Heymsfield, S.B. and Wadden, T.A. (2017) 'Mechanisms, pathophysiology, and management of obesity', *New England Journal of Medicine,* 376(3), pp. 254–266.

Holst, J.J. (2019) 'From the incretin concept and the discovery of GLP-1 to today's diabetes therapy', *Frontiers in endocrinology,* 10, pp. 260.

Holst, J.J. (2024) 'GLP-1 physiology in obesity and development of incretin-based drugs for chronic weight management', *Nature Metabolism,* 6(10), pp. 1866–1885.

Javaid, A., Baviriseaty, S., Javaid, R., Zirikly, A., Kukreja, H., Kim, C.H., Blaha, M.J., Blumenthal, R.S., Martin, S.S. and Marvel, F.A. (2024) 'Trends in glucagon-like peptide-1 receptor agonist social media posts using artificial intelligence', *JACC: Advances,* 3(9_Part_2), pp. 101182.

Jastreboff, A.M., Kotz, C.M., Kahan, S., Kelly, A.S. and Heymsfield, S.B. (2019) 'Obesity as a disease: the obesity society 2018 position statement', *Obesity,* 27(1), pp. 7–9.

Jastreboff, A.M., Aronne, L.J., Ahmad, N.N., Wharton, S., Connery, L., Alves, B., Kiyosue, A., Zhang, S., Liu, B. and Bunck, M.C. (2022) 'Tirzepatide once weekly for the treatment of obesity', *New England Journal of Medicine,* 387(3), pp. 205–216.

Kaplan, L.M., Apovian, C.M., Ard, J.D., Allison, D.B., Aronne, L.J., Batterham, R.L., Busetto, L., Dicker, D., Horn, D.B. and Kelly, A.S. (2024) 'Assessing the state of obesity care: Quality, access, guidelines, and standards', *Obesity Science & Practice,* 10(4), pp. e765.

Khan, S.S., Ning, H., Wilkins, J.T., Allen, N., Carnethon, M., Berry, J.D., Sweis, R.N. and Lloyd-Jones, D.M. (2018) 'Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity', *JAMA cardiology,* 3(4), pp. 280–28.

Knudsen, L.B. and Lau, J. (2019) 'The discovery and development of liraglutide and semaglutide', *Frontiers in endocrinology,* 10, pp. 155.

Kuriyan, R. (2018). Body composition techniques. *Indian Journal of Medical Research, 148*(5), 648–658.

Latif, W., Lambrinos, K.J. and Rodriguez, R. (2021) 'Compare and contrast the glucagon-like peptide-1 receptor agonists (GLP1RAs)'.

Le Roux, C.W., Astrup, A., Fujioka, K., Greenway, F., Lau, D.C., Van Gaal, L., Ortiz, R.V., Wilding, J.P., Skjøth, T.V. and Manning, L.S. (2017) '3 years of liraglutide versus placebo for

type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial', *The Lancet,* 389(10077), pp. 1399–1409.

le Roux, C.W., Zhang, S., Aronne, L.J., Kushner, R.F., Chao, A.M., Machineni, S., Dunn, J., Chigutsa, F.B., Ahmad, N.N. and Bunck, M.C. (2023) 'Tirzepatide for the treatment of obesity: Rationale and design of the SURMOUNT clinical development program', *Obesity,* 31(1), pp. 96–110.

Liarakos, A.L. and Koliaki, C. (2023) 'Novel dual incretin receptor agonists in the spectrum of metabolic diseases with a focus on tirzepatide: real game-changers or great expectations? A narrative review', *Biomedicines,* 11(7), pp. 1875.

Maciejewski, M.L., Arterburn, D.E., Van Scoyoc, L., Smith, V.A., Yancy, W.S., Weidenbacher, H.J., Livingston, E.H. and Olsen, M.K. (2016) 'Bariatric surgery and long-term durability of weight loss', *JAMA surgery,* 151(11), pp. 1046–1055.

MacLean, P.S., Wing, R.R., Davidson, T., Epstein, L., Goodpaster, B., Hall, K.D., Levin, B.E., Perri, M.G., Rolls, B.J. and Rosenbaum, M. (2015) 'NIH working group report: innovative research to improve maintenance of weight loss', *Obesity,* 23(1), pp. 7–15.

Magkos, F., Fraterrigo, G., Yoshino, J., Luecking, C., Kirbach, K., Kelly, S.C., de Las Fuentes, L., He, S., Okunade, A.L. and Patterson, B.W. (2016) 'Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity', *Cell metabolism,* 23(4), pp. 591–601.

Mechanick, J. I., Butsch, W. S., Christensen, S. M., Hamdy, O., Li, Z., Prado, C. M., & Heymsfield, S. B. (2025). Strategies for minimizing muscle loss during use of incretin-mimetic drugs for treatment of obesity. *Obesity Reviews, 26*(1), e13841.

Mechanick, J.I., Hurley, D.L. and Garvey, W.T. (2017) 'Adiposity-based chronic disease as a new diagnostic term: the American Association of Clinical Endocrinologists and American College of Endocrinology position statement', *Endocrine Practice,* 23(3), pp. 372–378.

Montesi, L., El Ghoch, M., Brodosi, L., Calugi, S., Marchesini, G. and Dalle Grave, R. (2016) 'Long-term weight loss maintenance for obesity: a multidisciplinary approach', *Diabetes, metabolic syndrome and obesity: targets and therapy*, pp. 37–46.

Moore, P.W., Malone, K., VanValkenburg, D., Rando, L.L., Williams, B.C., Matejowsky, H.G., Ahmadzadeh, S., Shekoohi, S., Cornett, E.M. and Kaye, A.D. (2023) 'GLP-1 agonists for weight loss: pharmacology and clinical implications', *Advances in Therapy,* 40(3), pp. 723–742.

Müller, T.D., Blüher, M., Tschöp, M.H. and DiMarchi, R.D. (2022) 'Anti-obesity drug discovery: advances and challenges', *Nature reviews. Drug discovery,* 21(3), pp. 201–223. Doi: 10.1038/s41573-021-00337-8.

Müller, M.J., Braun, W., Enderle, J. and Bosy-Westphal, A. (2016) 'Beyond BMI: conceptual issues related to overweight and obese patients', *Obesity facts,* 9(3), pp. 193–205.

Müller, T.D., Finan, B., Clemmensen, C., DiMarchi, R.D. and Tschöp, M.H. (2017) 'The new biology and pharmacology of glucagon', *Physiological Reviews,* 97(2), pp. 721–766.

Neagu, M., & Neagu, A. (2025). A Decade of Progress in Ultrasound Assessments of Subcutaneous and Total Body Fat: A Scoping Review. *Life, 15*(2), 236.

Neeland, I. J., Linge, J., & Birkenfeld, A. L. (2024). Changes in lean body mass with glucagon-like peptide-1-based therapies and mitigation strategies. *Diabetes, Obesity and Metabolism, 26*, 16–27.

NHS (2023). *Obesity.* Available at: https://www.nhs.uk/conditions/obesity/ (Accessed: 25 January 2025).

NICE (2025) *Overweight and obesity management*. Available at: https://www.nice.org.uk/guidance/ng246/chapter/Identifying-and-assessing-overweight-obesity-and-central-adiposity (Accessed: 25 January 2025).

O'Neil, P.M., Birkenfeld, A.L., McGowan, B., Mosenzon, O., Pedersen, S.D., Wharton, S., Carson, C.G., Jepsen, C.H., Kabisch, M. and Wilding, J.P. (2018) 'Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial', *The Lancet,* 392(10148), pp. 637–649.

Pi-Sunyer, X., Astrup, A., Fujioka, K., Greenway, F., Halpern, A., Krempf, M., Lau, D.C., Le Roux, C.W., Violante Ortiz, R. and Jensen, C.B. (2015) 'A randomized, controlled trial of 3.0 mg of liraglutide in weight management', *New England Journal of Medicine,* 373(1), pp. 11–22.

Pratley, R.E., Kang, J., Trautmann, M.E., Hompesch, M., Han, O., Stewart, J., Sorli, C.H., Jacob, S. and Yoon, K. (2019) 'Body weight management and safety with efpeglenatide in adults without diabetes: a phase II randomized study', *Diabetes, Obesity and Metabolism,* 21(11), pp. 2429–2439.

Ruban, A., Stoenchev, K., Ashrafian, H. and Teare, J. (2019) 'Current treatments for obesity', *Clinical Medicine,* 19(3), pp. 205–212.

Rubino, D., Abrahamsson, N., Davies, M., Hesse, D., Greenway, F.L., Jensen, C., Lingvay, I., Mosenzon, O., Rosenstock, J. and Rubio, M.A. (2021) 'Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial', *Jama,* 325(14), pp. 1414–1425.

Rubino, F., Cummings, D. E., Eckel, R. H., Cohen, R. V., Wilding, J. P., Brown, W. A., Stanford, F. C., Batterham, R. L., Farooqi, I. S., & Farpour-Lambert, N. J. (2025) Definition and diagnostic criteria of clinical obesity. *The Lancet Diabetes & Endocrinology.*

Rubino, D.M., Greenway, F.L., Khalid, U., O'Neil, P.M., Rosenstock, J., Sørrig, R., Wadden, T.A., Wizert, A., Garvey, W.T. and Arauz-Pacheco, C. (2022) 'Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial', *Jama,* 327(2), pp. 138–150.

Ryan, D.H. and Yockey, S.R. (2017) 'Weight loss and improvement in comorbidity: differences at 5%, 10%, 15%, and over', *Current obesity reports,* 6, pp. 187–194.

Samms, R.J., Coghlan, M.P. and Sloop, K.W. (2020) 'How may GIP enhance the therapeutic efficacy of GLP-1?', *Trends in Endocrinology & Metabolism,* 31(6), pp. 410–421.

Sarma, S., Sockalingam, S. and Dash, S. (2021) 'Obesity as a multisystem disease: Trends in obesity rates and obesity-related complications', *Diabetes, Obesity and Metabolism,* 23, pp. 3–16.

Sidrak, W.R., Kalra, S. and Kalhan, A. (2024) 'Approved and emerging hormone-based anti-obesity medications: A review article', *Indian Journal of Endocrinology and Metabolism,* 28(5), pp. 445–460.

Singh, A.K. and Singh, R. (2020) 'Pharmacotherapy in obesity: a systematic review and meta-analysis of randomized controlled trials of anti-obesity drugs', *Expert review of clinical pharmacology,* 13(1), pp. 53–64.

Smits, M.M. and Van Raalte, D.H. (2021) 'Safety of semaglutide', *Frontiers in endocrinology,* 12, pp. 645563.

Sombra, L.R.S., Anastasopoulou, C. (2021) *Pharmacologic therapy for obesity.* StatPearls Internet. Treasure Island: StatPearls. Available at: https://www.ncbi.nlm.nih.gov/books/NBK562269/ (Accessed: 23 January 2025).

Stokes, C.S. and Lammert, F. (2021) 'Excess body weight and gallstone disease', *Visceral medicine,* 37(4), pp. 254–260.

Sukhera, J. (2022a). Narrative Reviews: Flexible, Rigorous, and Practical. *Journal of Graduate Medical Education, 14*(4), 414–417. 10.4300/JGME-D-22-00480.1

Sukhera, J. (2022b). Narrative reviews in medical education: key steps for researchers. *Journal of Graduate Medical Education, 14*(4), 418–419.

Syed, Y.Y. (2022) 'Tirzepatide: first approval', *Drugs,* 82(11), pp. 1213–1220.

Tchang, B.G., Aras, M., Kumar, R.B. and Aronne, L.J. (2024) 'Pharmacologic treatment of overweight and obesity in adults'. Available at: https://www.ncbi.nlm.nih.gov/sites/books/NBK279038/(Accessed: 23 January 2025).

Theilade, S., Christensen, M.B., Vilsbøll, T. and Knop, F.K. (2021) 'An overview of obesity mechanisms in humans: Endocrine regulation of food intake, eating behaviour and common determinants of body weight', *Diabetes, Obesity and Metabolism,* 23, pp. 17–35.

The Obesity Society (2022) *Consensus Statement on Obesity.* Available at: https://www.obesity.org/ (Accessed: 23 January 2025).

Tolvanen, L., Christenson, A., Surkan, P.J. and Lagerros, Y.T. (2022) 'Patients' experiences of weight regain after bariatric surgery', *Obesity Surgery,* 32(5), pp. 1498–1507.

Ussher, J.R. and Drucker, D.J. (2023) 'Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action', *Nature Reviews Cardiology,* 20(7), pp. 463–474.

Wadden, T.A., Bailey, T.S., Billings, L.K., Davies, M., Frias, J.P., Koroleva, A., Lingvay, I., O'Neil, P.M., Rubino, D.M. and Skovgaard, D. (2021) 'Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial', *Jama,* 325(14), pp. 1403–1413.

Wadden, T.A., Chao, A.M., Machineni, S., Kushner, R., Ard, J., Srivastava, G., Halpern, B., Zhang, S., Chen, J. and Bunck, M.C. (2023) 'Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial', *Nature medicine,* 29(11), pp. 2909–2918.

Wadden, T.A., Hollander, P., Klein, S., Niswender, K., Woo, V., Hale, P.M. and Aronne, L. (2013) 'Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study', *International journal of obesity,* 37(11), pp. 1443–1451.

Wadden, T.A., Tronieri, J.S., Sugimoto, D., Lund, M.T., Auerbach, P., Jensen, C. and Rubino, D. (2020) 'Liraglutide 3.0 mg and intensive behavioral therapy (IBT) for obesity in primary care: the SCALE IBT randomized controlled trial', *Obesity,* 28(3), pp. 529–536.

Wadden, T.A., Walsh, O.A., Berkowitz, R.I., Chao, A.M., Alamuddin, N., Gruber, K., Leonard, S., Mugler, K., Bakizada, Z. and Tronieri, J.S. (2019) 'Intensive behavioral therapy for obesity combined with liraglutide 3.0 mg: a randomized controlled trial', *Obesity,* 27(1), pp. 75–86.

Watanabe, J.H., Kwon, J., Nan, B. and Reikes, A. (2024) 'Trends in glucagon-like peptide 1 receptor agonist use, 2014 to 2022', *Journal of the American Pharmacists Association,* 64(1), pp. 133–138.

WHO (2024) *Obesity and overweight.* Available at: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. (Accessed: 25 September 2024).

Wilding, J.P., Batterham, R.L., Calanna, S., Davies, M., Van Gaal, L.F., Lingvay, I., McGowan, B.M., Rosenstock, J., Tran, M.T. and Wadden, T.A. (2021) 'Once-weekly semaglutide in adults with overweight or obesity', *New England Journal of Medicine,* 384(11), pp. 989–1002.

World Obesity (2023). *World Obesity Atlas 2023.* Available at: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2023. (Accessed: 25 September 2024).

Yang, M., Liu, S. and Zhang, C. (2022) *The related metabolic diseases and treatments of obesity.* MDPI, pp. 1616.

Zheng, Z., Zong, Y., Ma, Y., Tian, Y., Pang, Y., Zhang, C. and Gao, J. (2024) 'Glucagon-like peptide-1 receptor: mechanisms and advances in therapy', *Signal Transduction and Targeted Therapy,* 9(1), pp. 234.

Zushin, P.H. and Wu, J.C. (2024) 'Evaluating the benefits of the early use of GLP-1 receptor agonists', *The Lancet*.