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ORIGINAL RESEARCH ARTICLE

Semaglutide 2.4 mg versus Liraglutide 3 mg for the Treatment of Obesity in Greece: A Short-Term Cost-Effectiveness Analysis

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Abstract

Background Obesity is a global health issue with significant economic implications for health systems. Pharmacotherapy, including semaglutide 2.4 mg and liraglutide 3 mg, offers a treatment option for weight management; however, its cost-effectiveness requires evaluation. This study assesses the short-term cost-effectiveness of semaglutide 2.4 mg versus liraglutide 3 mg in achieving clinically relevant weight loss targets at 68 weeks in Greece.

Methods A short-term cost-effectiveness analysis was conducted from the perspective of the Greek third-party payer [National Organization for the Provision of Health Services (EOPYY)], comparing costs and outcomes for semaglutide 2.4 mg and liraglutide 3 mg over a 68-week horizon. Effectiveness was measured by the proportion of patients achieving weight loss targets of ≥ 5%, ≥ 10%, ≥ 15%, and ≥ 20%, using efficacy data from the STEP-8 head-to-head trial, a 68-week, randomized, double-blind study conducted in the USA, comparing semaglutide 2.4 mg versus liraglutide 3 mg in adults who were overweight or had obesity without diabetes. Only direct medical costs were included, reflecting the payer perspective, and no discounting was applied owing to the short time horizon. Deterministic and probabilistic sensitivity analyses assessed the results' robustness.

Results Semaglutide 2.4 mg had higher treatment costs (€3285.55) compared with liraglutide 3 mg (€2742.47) but demonstrated greater efficacy and a lower cost of control across all weight loss targets. The cost per patient achieving ≥ 5% weight loss was €3768.72 for semaglutide and €4718.66 for liraglutide, corresponding to a difference of €949.95 per patient. The cost difference widened at higher weight loss targets, with semaglutide showing differences of €6064.20 for ≥ 10% weight loss, €17,005.23 for ≥ 15%, and €37,296.00 for ≥ 20%. These findings were consistent across sensitivity analyses.

Conclusions Semaglutide 2.4 mg is likely to be a short-term, cost-effective treatment option for adults who are overweight or have obesity without diabetes in Greece.

1 Introduction

Obesity is a major global health issue with profound social and economic implications. Defined as the excessive accumulation of body fat, obesity is commonly assessed using body mass index (BMI), which is calculated by dividing a person's weight in kilograms by the square of their height in meters (kg/m^2) [1]. According to the World Health Organization, individuals with a BMI of 30 or higher are classified as obese [1]. Recent estimates indicate that 12.5% of the global population is obese, with this figure more than doubling since 1990 [1]. In Greece, the obesity rate is particularly concerning, with 27.98% of adults classified as obese and approximately 33.4% of children aged 4–12 years identified as overweight or obese [2, 3]. Recognizing the growing burden of childhood obesity, the Greek Ministry of Health has launched a national plan (2022–2026) to address this critical public health challenge [4].

Obesity is associated with significant morbidity and mortality, reduced quality of life (QoL), and decreased life expectancy. It is a well-established risk factor for numerous chronic diseases, including cardiovascular disease, endocrine disorders, musculoskeletal conditions, respiratory issues, gastrointestinal complications, and several types of cancer [5–8]. The Global Burden of Disease study attributes 5 million premature deaths annually to obesity, with high BMI accounting for 9% of all adult disability-adjusted life years (DALYs)—a metric representing years lost owing to illness, disability, or premature death [9, 10]. Obesity

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Key Points for Decision Makers

Semaglutide 2.4 mg demonstrated greater efficacy than liraglutide 3 mg for obesity management in Greece over 68 weeks, achieving lower costs of control across all weight loss targets (≥ 5%, ≥ 10%, ≥ 15%, and ≥ 20%).

While semaglutide 2.4 mg has higher drug acquisition costs compared with liraglutide 3 mg, its lower cost of control suggests it may represent a short-term, cost-effective option for achieving specific weight loss targets, with differences ranging from €949.95 per patient for a ≥ 5% weight loss target to €37,296.00 per patient for a ≥ 20% weight loss target.

The deterministic sensitivity analysis highlighted the robustness of semaglutide's cost-of-control results, with the proportion of patients achieving weight loss targets and the ex-factory price of liraglutide emerging as key drivers influencing the average cost of control (CoC) difference between medications.

Pricing scenario analyses indicated that, for liraglutide to match the average cost of control of semaglutide across all weight loss targets, its list price would need to decrease by over 77%. Furthermore, across 8100 simulated scenarios, semaglutide's average cost of control remained favorable in 94.23% of cases.

reduces life expectancy by 3–8 years, depending on BMI severity, and adversely impacts health-related quality of life (HRQoL), with higher BMI linked to declines across all domains of the 36-item Short Form Survey (SF-36), a widely used HRQoL instrument assessing both physical and mental health [11–15].

In addition to its health impact, obesity imposes a substantial economic burden. The World Obesity Atlas predicts global costs associated with overweight and obesity to rise from USD $2 trillion in 2020 to USD $4.32 trillion by 2035, representing nearly 3% of the global gross domestic product (GDP) [16]. In Greece, the economic impact of overweight and obesity was estimated at USD $4.33 billion in 2020, equivalent to 2.32% of the GDP, with more than 70% of these costs attributed to absenteeism, presenteeism, and premature mortality [16]. However, as indirect costs typically manifest over extended periods, they are excluded from this study, which adopts a short-term time horizon focusing on direct medical costs. This approach aligns with the perspective of the Greek third-party payer, the National Organization for the Provision of Health Services (EOPYY), which prioritizes pharmacy costs during negotiations with marketing authorization holders [the Ministry of Health (MoH)].

The management of obesity includes lifestyle modifications (diet and exercise) as the first-line approach, pharmacotherapy for cases where lifestyle changes are insufficient, and bariatric surgery for severe cases [17, 18]. Although lifestyle interventions are essential, they often fail to achieve long-term weight maintenance owing to physiological adaptations promoting weight regain such as reduced metabolic rate and increased appetite [19, 20]. Pharmacotherapy serves as a critical adjunct to support sustained weight loss, particularly for individuals with a BMI ≥ 30 or ≥ 27 with comorbidities, which sets the background for examining the cost-effectiveness of pharmacological options. Treatment guidelines recommend discontinuing pharmacotherapy if patients fail to achieve ≥ 5% weight loss within 3 months at maximum dosing, a criterion broadly applied across all anti-obesity drug therapies [20].

The Greek National Health System operates as a mixed healthcare system, combining elements of the Bismarck and Beveridge models, with EOPYY functioning as a monopsony that acts as the central purchaser of health services on behalf of the population [21]. In Greece, several European Medicines Agency (EMA)-approved medications for obesity, including phentermine, naltrexone-bupropion, and orlistat, are available but not reimbursed by EOPYY, requiring patients to purchase them out-of-pocket. The only reimbursed option is liraglutide 3 mg, making it a relevant comparator in this study. Semaglutide 2.4 mg, though not currently reimbursed, has shown significant efficacy in the STEP clinical trial program and represents a promising option for obesity management [22].

Resources are inherently finite in healthcare, requiring policymakers to allocate them efficiently across therapeutic categories. As the burden of obesity increases, pressure on healthcare budgets intensifies, necessitating the prioritization of treatments that are both clinically effective and cost-effective. Economic evaluation, defined as the comparative analysis of alternative courses of action in terms of both their costs and consequences, offers a robust framework for assessing new technologies [23]. The present study forms a cost-of-control analysis, a variant of cost-effectiveness analysis (CEA), which quantifies the cost of achieving specific clinically relevant targets within a short period [24, 25].

Short-term cost-effectiveness analyses assess clinical outcomes such as the proportion of patients achieving treatment targets over a 1–2-year timeframe. In this analysis, a 68-week horizon was chosen to align with available data from the STEP-8 clinical trial [22]. This approach complements traditional long-term cost-effectiveness analyses, which rely on modeling techniques to estimate the future benefits of sustained weight loss such as reductions in obesity-related complications and decreased mortality [26, 27].

Existing evidence consistently highlights the cost-effectiveness of semaglutide 2.4 mg for obesity management compared with no treatment, diet and exercise, and other anti-obesity medications, such as phentermine-topiramate, phentermine, naltrexone-bupropion, and liraglutide 3 mg in countries such as the USA, the UK, and Canada [28, 29]. However, limited research has explored the short-term cost-effectiveness of semaglutide 2.4 mg versus liraglutide 3 mg in European healthcare settings [30] where drug pricing mechanisms and reimbursement policies differ significantly. This study addresses this gap by leveraging head-to-head clinical trial data to evaluate the cost per patient achieving clinically relevant weight loss targets over 68 weeks in adults who are overweight or have obesity without diabetes, conducted from the perspective of the Greek third-party payer, EOPYY.

2 Methods

2.1 Type of Economic Evaluation

This study employed a cost-of-control analysis, a variant of CEA, to evaluate the short-term economic impact of semaglutide 2.4 mg versus liraglutide 3 mg in achieving predefined weight loss targets over 68 weeks. Unlike traditional CEA, which assesses long-term outcomes such as quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs) [26, 27], the cost-of-control approach focuses on specific clinical outcomes, such as the proportion of patients achieving weight-loss thresholds. This framework is particularly suited to short-term evaluations, addressing the needs of healthcare decision-makers managing constrained budgets [31].

The cost-of-control framework aligns closely with the clinical and economic priorities of managing obesity, particularly within this study, where EOPYY evaluates the direct medical costs required to achieve specific weight loss targets. By quantifying the financial resources necessary to meet weight loss goals over a 68-week horizon, this analysis provides decision-makers with practical, evidence-based insights to guide short-term policy decisions. Additionally, it is a valuable complement to traditional long-term cost-effectiveness analyses, which focus on broader, lifetime health outcomes.

2.2 Clinical Data

Clinical data were derived from the STEP-8 clinical trial, a randomized, open-label, 68-week, phase III trial conducted in the USA that compared the efficacy and safety of once-weekly semaglutide 2.4 mg and liraglutide 3 mg (both with diet and physical activity) in adults with BMI ≥ 30 or ≥ 27 with one or more weight-related comorbidities, without diabetes [22].

The baseline characteristics of the STEP-8 participants were balanced across treatment groups. The mean age was 49 years; most participants were white (73.7%) and female (78.4%) [22]. The mean body weight was 104.5 kg, and the mean BMI was 37.5 kg/m^2 [22]. Most participants had up to two weight-related comorbidities at screening, with the most common being hypertension and dyslipidemia [22].

Efficacy outcomes included the proportion of patients achieving clinically meaningful weight-loss thresholds (≥ 5%, ≥ 10%, ≥ 15%, and ≥ 20%) and the mean percentage of weight loss from baseline. At 68 weeks, semaglutide 2.4 mg was associated with greater weight loss and a higher proportion of participants achieving all predefined weight-loss thresholds compared with liraglutide 3 mg ($p < 0.001$) [22]. The analysis did not include clinical data on improvements in obesity-related comorbidities, such as dyslipidemia or hypertension, as these benefits typically manifest over longer time horizons and fall outside the 68-week scope of this short-term cost-effectiveness analysis.

Adverse events, primarily gastrointestinal, which were predominantly mild to moderate in severity, were more frequent in the semaglutide versus the liraglutide group (84.1% versus 82.7%) but consistent with the known safety profile of glucagon-like peptide-1 receptor agonists [22]. The percentage of participants who discontinued treatment for any reason was 13.5% with semaglutide and 27.6% with liraglutide [22].

The STEP-8 reported mean weight change (%) from baseline to week 68, a figure used to calculate the cost per 1% weight reduction. The present cost of control analysis used observed proportions of patients reaching specific endpoints at 68 weeks (Table 1). The treatment policy estimand was employed by utilizing data from all randomized participants from the in-trial period irrespective of treatment adherence or rescue intervention initiation [22]. The decision to utilize efficacy data exclusively from the STEP-8 trial, rather than synthesizing evidence from other studies that compared liraglutide 3 mg and semaglutide 2.4 mg with placebo, was strategically decided to leverage the most direct and clinically relevant comparison between the two treatments.

2.3 Cost Data

The present analysis was conducted from the third-party payer's (EOPYY) perspective; hence, only direct medical costs were considered (Table 2). Indirect costs related to productivity losses, including absenteeism, presenteeism, or premature mortality, were not considered, given the analysis's short-term time horizon. Additionally, direct nonmedical costs associated with compliance roles, training, monitoring systems, administrative fees, and support

services were irrelevant to this study's scope, as they do not pertain to the direct pharmaceutical costs borne by payers.

Drug costs for semaglutide 2.4 mg and liraglutide 3 mg were accounted for over 68 weeks, on the basis of the retail prices of the medicines after subtracting the patients' co-payment (25%). Since semaglutide 2.4 mg is not currently priced in Greece, an analysis of available prices in Eurozone countries was conducted using official sources, as outlined by the Greek National Medicines Agency (EOF). According to Greek pricing regulations, the ex-factory price is derived from the average of the two different lowest ex-factory prices in Eurozone countries [32]. In the absence of a second Eurozone price beyond Germany, the wholesale price in Denmark (in euros), obtained from the Danish Medicines Agency, was used (Table 2). The list price of liraglutide 3 mg was retrieved from the most recently published drug price bulletin [33].

Both interventions were dosed according to the STEP-8 protocol. Liraglutide involved a 4-week titration period, starting at 0.6 mg per day in week 1 and increasing to 3 mg per day by week 4, followed by 64 weeks at the maintenance dose of 3 mg per day [22]. Semaglutide involved a 16-week titration period, starting at 0.25 mg per week in week 1 and increasing incrementally to 2.4 mg per week by week 16, followed by 52 weeks at the maintenance dose of 2.4 mg per week [22]. Liraglutide required daily injections, while semaglutide was administered weekly and did not require needles.

Costs related to blood glucose monitoring tools (e.g., test strips) were excluded, as resource use was assumed to be similar between treatments. Similarly, comorbidity-related costs (e.g., dyslipidemia and hypertension) were excluded, as their benefits often manifest over extended periods and fall outside this analysis's 68-week scope.

Table 1 Observed proportion [% (standard error)] of patients achieving weight-loss-treatment targets at 68 weeks (treatment policy estimand)

Weight loss targets	Semaglutide 2.4 mg	Liraglutide 3 mg
Weight loss ≥ 5%	87.18% (3.09%)	58.12% (4.56%)
Weight loss ≥ 10%	70.94% (4.20%)	25.64% (4.04%)
Weight loss ≥ 15%	55.56% (4.59%)	11.97% (3.00%)
Weight loss ≥ 20%	38.46% (4.50%)	5.98% (2.19%)
Body-weight change (%) from baseline	15.78	6.40

2.4 Cost-of-Control Calculations

The cost-effectiveness of semaglutide 2.4 mg versus liraglutide 3 mg was evaluated using a cost-of-control (CoC) model constructed in Microsoft Excel. Outcomes were assessed for four clinically relevant weight-loss endpoints: ≥ 5%, ≥ 10%, ≥ 15%, and ≥ 20% weight loss (Table 1). The CoC for each drug at each endpoint was calculated by dividing the total drug acquisition cost by the percentage of patients achieving each target at 68 weeks. This framework offers a transparent and clinically focused approach for examining short-term cost-effectiveness, particularly in obesity management [24, 25, 30].

To further contextualize the results, the number needed to treat (NNT) was calculated to compare the relative efficacy of semaglutide with liraglutide. The NNT represents the number of patients who must be treated with semaglutide instead of liraglutide to achieve one additional patient meeting a specific weight loss target [35]. NNT values were computed for each weight-loss threshold using the formula: 1/(proportion of patients achieving each target) [35]. These NNT results were integrated into the CoC model to estimate the cost per patient achieving each weight loss target. The latter was calculated by multiplying the NNT for each target by the total treatment cost, offering a dual measure of efficacy and cost-effectiveness.

As is standard for economic evaluations with short-term time horizons, no discounting was applied in this analysis,

Table 2 Drug and consumable acquisition payer costs

Medications	Retail price (€)	Co-payment	Payer's cost (€)	Payer's cost per day (€)	Reference
Semaglutide 0.25 mg × 4 doses	166.54	25%	124.91	4.46	Average of the list prices of Germany and Denmark
Semaglutide 0.50 mg × 4 doses	166.54	25%	124.91	4.46	
Semaglutide 1 mg × 4 doses	166.54	25%	124.91	4.46	
Semaglutide 1.7 mg × 4 doses	229.28	25%	171.96	6.14	
Semaglutide 2.4 mg × 4 doses	280.91	25%	210.68	7.52	
Liraglutide 18 mg × 5 pens	233.66	25%	175.25	5.84	Ministerial Decree 40977 (09/24/2024) [33]
Consumable costs	**Reimbursed price (€)**	**Co-payment**	**Payer's cost (€)**	**Payer's cost/needle (€)**	
NovoFine 32G 0.23/0.25 × 6 mm × 100 units	9.18	0%	9.18	0.092	Government Gazette (FEK B' 4045/17-11-2017) [34]

which spans 68 weeks and includes a 52-week maintenance period [23]. The short-term nature of the study negates the need for discounting, aligning with accepted practices in health economics.

Additionally, the relative CoC of the two medications was examined. Relative efficacy was calculated as the ratio of the percentage of patients achieving each weight loss target with liraglutide 3 mg to the corresponding percentage for semaglutide 2.4 mg, as reported in the STEP-8 trial. Similarly, the relative cost was derived by dividing the drug acquisition cost of liraglutide 3 mg by the cost of semaglutide 2.4 mg. These results were presented as relative CoC outcomes, expressed as the cost and efficacy of liraglutide relative to semaglutide (Supplementary File).

The outcomes were visualized on a cost-efficacy plane, where relative efficacy was plotted on the horizontal axis and relative cost on the vertical axis (Supplementary File). Semaglutide 2.4 mg served as the reference point (relative efficacy and cost set at 100%) and was represented by the equality line. Data points above the equality line indicate a worse cost-to-efficacy ratio for liraglutide, reflecting higher costs for equivalent efficacy or lower efficacy for equivalent costs. Conversely, points below the line represent a better cost-to-efficacy ratio for liraglutide, reflecting lower costs for equivalent efficacy or higher efficacy for the equivalent cost.

2.5 Sensitivity Analyses

To evaluate the robustness of the base case results, a deterministic sensitivity analysis (DSA) was conducted by varying key input parameters by ±20% (Supplementary File). These parameters included the two lowest list prices of semaglutide stock keeping units (SKUs) (derived from Eurozone countries) and the list price of liraglutide to account for potential pricing fluctuations. Clinical efficacy inputs, such as the proportions of patients achieving weight-loss thresholds (≥ 5%, ≥10%, ≥ 15%, and ≥ 20%) and the average percentage weight loss per drug as reported in the STEP-8 trial, were also varied. Additionally, the impact of potential deviations in adherence or dosing protocols was assessed by altering the maintenance dosing schedules for semaglutide (2.4 mg weekly) and liraglutide (3 mg daily).

A price scenario analysis was conducted to simulate potential price reductions for liraglutide (ranging from 1 to 90% of its original value) following the introduction of generics. This analysis evaluated whether such reductions could shift the average cost of control (CoC) across all weight loss targets, favoring liraglutide. Furthermore, a two-way scenario analysis examined the impact of simultaneous price reductions (1–90%) for semaglutide and liraglutide on the average CoC difference across all weight loss targets (Supplementary File). Across 8100 simulated scenarios, the analysis identified the pricing conditions under which liraglutide's CoC could become favorable compared with semaglutide.

Lastly, a probabilistic sensitivity analysis (PSA) was performed using a second-order Monte Carlo simulation, incorporating the standard errors of the proportions of patients achieving the examined weight-loss endpoints. The NORMIV function was employed to simulate these proportions, which was consistent with established practices for modeling clinical outcomes. As Briggs, Claxton, and Schulpher highlighted, the normal distribution is particularly suitable for PSA when sample sizes are sufficiently large to satisfy the normality assumption under the central limit theorem [36]. This approach allows for structured incorporation of uncertainty around mean estimates, which are normally distributed owing to extensive data aggregation, ensuring the simulated results are statistically robust [36].

The PSA calculated the CoC for each intervention on the basis of the sampled proportions, repeating the process 1000 times. The results included the mean CoC for each intervention and the corresponding 95% confidence intervals constructed using the percentile method to reflect the variability in outcomes.

3 Results

3.1 Treatment Medication Costs

Semaglutide treatment included a 16-week induction period, during which four packs of semaglutide (0.25 mg, 0.50 mg, 1 mg, and 1.7 mg) were utilized, amounting to a total cost of €546.68 (€124.91 × 3 + €171.96). Following this, patients received a maintenance dose of 2.4 mg weekly for 52 weeks, requiring 13 packs, calculated as (2.4 mg/week × 52 weeks)/(2.4 mg/dose × 4 doses per pack of 2.4 mg). The payer cost per pack of semaglutide 2.4 mg was €210.68, yielding a total maintenance cost of €2738.87. The total treatment cost for semaglutide over 68 weeks was estimated at €3285.55.

The induction period spanned 4 weeks for liraglutide, with daily doses progressively increasing from 0.6 mg in week 1 to 2.4 mg in week 4. This corresponded to a total of 42 mg of liraglutide [(0.6 mg + 1.2 mg + 1.8 mg + 2.4 mg) × 7 days], with a payer cost per mg of €1.95 (€175.25/90 mg), resulting in a total induction cost of €81.78. The maintenance phase involved 3 mg daily for 64 weeks, amounting to 1344 mg (3 mg/day × 7 days/week × 64 weeks), with a total maintenance cost of €2616.99. Additionally, liraglutide required 476 needles (68 weeks × 7 days/week) at €0.09 per needle, resulting in an additional consumable cost of €43.70.

The total treatment cost of semaglutide was estimated at €3285.55, while the total treatment cost of liraglutide was €2742.47, including needle costs, which accounted for €43.70 (1.59%). Semaglutide's total treatment cost was 19.80% (€543.07) higher than liraglutide 3 mg (Supplementary File).

3.2 The Number Needed to Treat

Based on the STEP-8 trial data, the NNT for semaglutide 2.4 mg was consistently lower across all weight loss targets: 1.15 for ≥ 5% weight loss, 1.41 for ≥ 10%, 1.80 for ≥ 15%, and 2.60 for ≥ 20%. In comparison, the corresponding NNT values for liraglutide 3 mg were 1.72, 3.90, 8.36, and 16.71, respectively (Supplementary File).

3.3 Cost of Control

The cost of control (CoC) was consistently lower for semaglutide 2.4 mg compared with liraglutide 3 mg across all examined weight loss targets (Fig. 1). For the ≥ 5% weight loss target, semaglutide 2.4 mg demonstrated a cost difference of €949.95 compared with liraglutide 3 mg. This difference increased at higher weight loss targets, amounting to €6064.20 for the ≥ 10% target and €17,005.23 for the ≥ 15% target (Table 3). The largest CoC difference was observed in the ≥ 20% weight loss target, where semaglutide 2.4 mg demonstrated a €37,296.00 lower cost than liraglutide 3 mg.

Additionally, the STEP-8 trial reported the average weight loss at 68 weeks relative to baseline weight. The average cost per 1% weight reduction was €207.95 for semaglutide 2.4 mg, compared with €428.51 for liraglutide 3 mg. These results suggest that semaglutide 2.4 mg offers a cost-effective option for achieving meaningful weight-loss outcomes in a short-term timeframe.

3.4 Relative Cost of Control

Semaglutide 2.4 mg demonstrated a favorable cost-to-efficacy ratio across all examined weight loss targets compared with liraglutide 3 mg (Supplementary File). Although semaglutide 2.4 mg was 19.80% more costly than liraglutide 3 mg, liraglutide exhibited notably lower efficacy, with reductions of 66.67%, 36.14%, 21.54%, and 15.56% for achieving weight loss targets of ≥ 5%, ≥ 10%, ≥ 15%, and ≥ 20%, respectively (Supplementary File). Consequently, liraglutide's relative cost-to-efficacy ratio declined as higher weight loss targets were evaluated, with all points lying above the equality line, indicating higher cost for the same or lower efficacy (Supplementary File).

3.5 Sensitivity Analysis

The deterministic sensitivity analysis (DSA) confirmed the robustness of the base case results, consistently demonstrating semaglutide's lower cost of control over liraglutide across all weight loss targets (Supplementary File). At the ≥ 5% weight loss target, the cost-of-control (CoC) difference ranged from €−2129.61 to €−163.50, favoring semaglutide in all scenarios. The most influential parameter was the proportion of patients achieving the weight loss target for semaglutide and liraglutide.

For the ≥ 10% weight loss target, the CoC difference ranged from €−8738.11 to €−4281.60, with semaglutide maintaining its advantage. Key drivers of variability

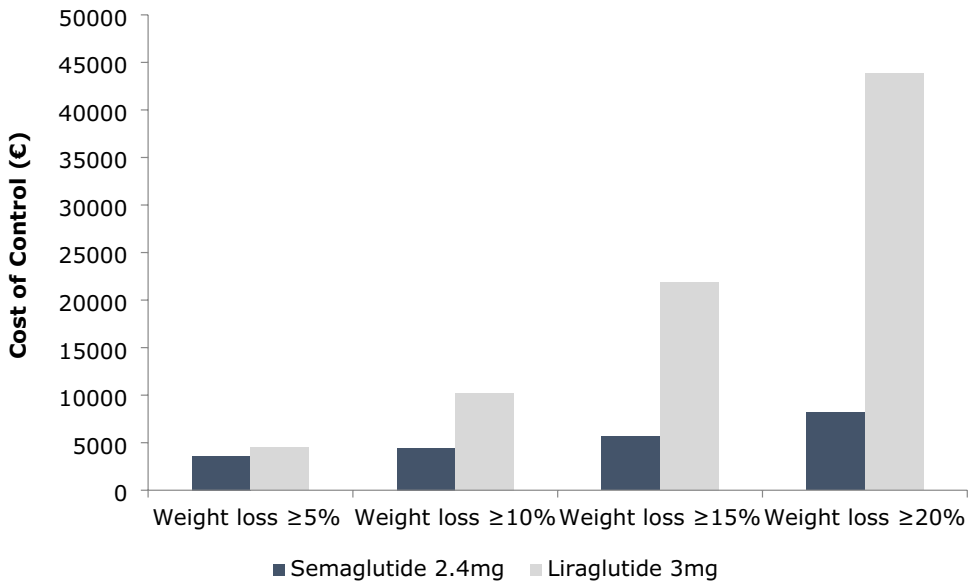

Fig. 1 Cost of control figures of semaglutide 2.4 mg versus liraglutide 3 mg based on STEP 8

Table 3 Base case cost of control figures between semaglutide 2.4 mg and liraglutide 3 mg

Weight loss targets	Semaglutide 2.4 mg (€)	Liraglutide 3 mg (€)	Difference (€)
Weight loss ≥ 5%	3768.72	4718.66	−949.95
Weight loss ≥ 10%	4631.43	10,695.63	−6064.20
Weight loss ≥ 15%	5913.99	22,919.21	−17,005.23
Weight loss ≥ 20%	8542.42	45,838.42	−37,296.00
The average cost for 1% weight loss	207.95	428.51	−220.56

included the proportion of patients achieving the weight loss target with liraglutide and the ex-factory price of liraglutide 3 mg. Similar patterns were observed at the ≥ 15% weight loss target, where the CoC difference ranged from €−22,735.02 to €−13,185.35, driven primarily by liraglutide's efficacy and ex-factory price.

At the ≥ 20% weight loss target, the CoC difference ranged from €−48,755.61 to €−29,656.27, with liraglutide's efficacy and ex-factory price remaining the most impactful parameters. For the 1% weight loss target, the CoC difference ranged from €−327.69 to €−149.14, influenced mainly by the average weight loss achieved with liraglutide and its ex-factory price.

Additionally, a scenario analysis was performed to assess the impact of potential price reductions for semaglutide and liraglutide on the average CoC difference across all weight loss targets (Supplementary File). The findings indicated that liraglutide's list price must be reduced by approximately 77.23% for the average CoC difference across all weight loss targets to favor liraglutide (be positive). A two-way price scenario analysis further revealed that, across 8100 simulated pricing scenarios, semaglutide remained economically advantageous in 94.23% of cases. Notably, scenarios most favorable to liraglutide required at least 78% price reductions, whereas semaglutide's price reductions were capped at 36%.

The probabilistic sensitivity analysis (PSA) assessed the impact of uncertainty in clinical efficacy parameters on the cost-of-control outcomes (Table 4). The PSA results aligned closely with the deterministic analysis, consistently showing that semaglutide 2.4 mg was associated with a lower cost of control compared with liraglutide 3 mg across all four weight loss targets (Table 4).

Across 1000 PSA iterations, semaglutide 2.4 mg was associated with a lower cost of control versus liraglutide 3 mg for all weight loss targets (the difference in control cost was negative.

4 Discussion

The findings of this study highlight the clinical and economic value of semaglutide 2.4 mg compared with liraglutide 3 mg for achieving meaningful weight loss targets in adults who are overweight or have obesity without diabetes in Greece. By demonstrating a lower CoC for semaglutide across all weight loss targets, this study provides actionable evidence to support healthcare decision-making. In the Greek healthcare context, where the economic burden of obesity continues to escalate rapidly, these findings highlight that semaglutide 2.4 mg has the potential to serve as an additional reimbursed obesity pharmacotherapy, as it demonstrates both clinical and economic merits for achieving weight loss targets. However, it should be noted that, despite its lower cost of control compared with liraglutide, semaglutide incurs higher overall treatment costs and thus cannot be considered cost-saving. Moreover, the absence of an established cost-effectiveness threshold for weight loss targets complicates the evaluation of whether its increased efficacy fully justifies the higher costs of semaglutide.

This study makes a novel contribution to literature by being the first to evaluate the short-term cost-effectiveness of semaglutide 2.4 mg versus liraglutide 3 mg using head-to-head data from the STEP-8 trial. Unlike previous studies that relied on short-term indirect comparisons or long-term modelled projections [26, 27, 30], this analysis draws on direct efficacy data, allowing for a robust assessment of the two treatments' relative economic and clinical value. Explicitly, prior research, such as the work by Azuri et al., examined cost per 1% weight loss using data from different trials (e.g., STEP 1 and SCALE) and applied adjustments

Table 4 Probabilistic cost of control figures between semaglutide 2.4 mg and liraglutide 3 mg

Treatment target	Mean cost of control (95% CI) semaglutide 2.4 mg (€)	Mean cost of control (95% CI) liraglutide 3 mg (€)	Difference mean cost of control (95% CI) (€)
Weight loss ≥ 5%	3770.81 (3534.41–4044.38)	4742.50 (4110.18–5592.49)	−971.69 (1804.60 to −274.77)
Weight loss ≥ 10%	4645.65 (4156.05–5190.25)	10,983.84 (8230.15–15,548.01)	−6338.19 (11,175.88 to −3581.56)
Weight loss ≥ 15%	5964.35 (5142.73–7059.27)	24,689.64 (15,326.81–47,581.23)	−18,725.28 (41,616.17 to −9213.65)
Weight loss ≥ 20%	8646.76 (6987.34–10,906.07)	58,495.89 (27,367.88–155,486.85)	−49,849.14 (146,171.02 to −18,382.82)

to account for heterogeneity in study populations and follow-up durations [30]. While valuable, these approaches carried inherent limitations owing to their reliance on indirect evidence and cross-trial assumptions [30]. In contrast, this study's head-to-head trial data ensure reliability and clinical relevance, whilst the examination of additional clinically meaningful weight loss targets, including the proportion of patients achieving ≥ 5%, ≥ 10%, ≥ 15%, and ≥ 20% weight loss, offers a more comprehensive and holistic perspective compared with previous research.

The cost-of-control methodology further distinguishes this study from traditional economic evaluations, such as cost-effectiveness or cost–utility analyses, focusing on broader outcomes such as QALYs or DALYs. By linking costs directly to predefined clinical outcomes, the CoC approach offers a more targeted framework for addressing the short-term priorities of healthcare payers. This methodology aligns well with the immediate policy needs in Greece, where resources are constrained, and there is an urgent need to manage the rising clinical and economic burden of obesity.

This study highlights the importance of evidence-based reimbursement decisions grounded in robust comparative analyses for policymakers. Assessing the inclusion of semaglutide as an additional anti-obesity medication in the reimbursement list can expand patient treatment options, potentially yielding better clinical outcomes at a higher yet acceptable cost. The findings also emphasize the need for integrating similar analyses into health technology assessment processes to inform net pricing negotiations and ensure sustainable pharmaceutical expenditures across therapeutic categories.

Despite its strength, the present analysis carries limitations that must be acknowledged. The focus on short-term outcomes excludes the potential long-term benefits of sustained weight loss, such as reductions in obesity-related comorbidities, reductions in mortality, benefits in HRQoL and increases in quality-adjusted life expectancy. The analysis assumes maximum dosing per the trial protocol without accounting for real-world adherence patterns or dose modifications due to tolerability issues. However, this limitation was tackled in the deterministic sensitivity analysis, in which the different maintenance doses of semaglutide and liraglutide were altered to assess their impact on the cost of control outcomes. Also, while the STEP-8 trial reported higher discontinuation rates for liraglutide than semaglutide, costs associated with managing adverse events were not included. The reason was that, according to the STEP-8 trial, these adverse events were predominantly mild, with insignificant incremental costs from the payer's perspective. Also, a limitation of the present analysis is that while the probabilistic sensitivity analysis (PSA) accounted for variability in clinical efficacy using standard errors directly derived from the STEP-8 trial, a similar approach could not be applied to costs owing to the unavailability of standard error data for drug acquisition costs. A PSA for costs was not conducted to ensure methodological consistency and avoid introducing potential bias or misrepresentation through arbitrary assumptions (e.g., 20%) that would directly affect the alpha and beta parameters of the gamma distribution [36].

Furthermore, focusing on semaglutide 2.4 mg and liraglutide 3 mg excludes other anti-obesity medications, such as the recently authorized tirzepatide, which could offer alternative perspectives. This decision was driven by the lack of a published network meta-analysis (NMA) examining semaglutide and other drugs and the fact that liraglutide 3 mg is currently the only reimbursed obesity pharmacotherapy in Greece. Therefore, the third-party payer would be predominantly interested in comparing a potentially reimbursed pharmaceutical product (semaglutide) with the standard of care (liraglutide) and examining whether the new medicine is cost-effective and hence meets the requirements for reimbursement. Also, only direct medical costs relevant to the third-party payer of Greece were considered (pharmaceuticals and consumables). In contrast, other direct nonmedical costs were not considered, such as staff salaries for compliance roles, training, monitoring systems, administration fees, and support services costs.

Additionally, only list prices were considered, excluding clawback, confidential discounts, or volume-based rebates that may influence drug costs. This limitation, though, was adequately tackled in the scenario analysis in which the list prices of liraglutide and semaglutide were simultaneously altered to assess whether the CoC results significantly altered. The one-way scenario analysis revealed that significant price reductions for liraglutide (> 77%) would be required to make its average CoC across all weight loss targets comparable to semaglutide. The two-way scenario analysis demonstrated that, in 8100 potential pricing scenarios, liraglutide's cost of control remained economically disadvantageous at 94.23% of cases. This highlights the robustness of the base case results, even in the face of potential list pricing shifts.

Finally, the analysis did not account for indirect costs, such as productivity losses, premature mortality, absenteeism and presenteeism, and early retirement costs, which could further enhance the perceived value of semaglutide. Future research should prioritize conducting long-term cost-effectiveness analyses incorporating all relevant comparators and adopting a societal perspective to comprehensively capture both direct and indirect costs and the long-term benefits of sustained weight loss. Additionally, as trial-based data are subject to uncertainty surrounding baseline clinical and demographic characteristics, Greek-specific real-world data should be captured to validate the economic results of the present analysis. For example, the cost of control (CoC) of

semaglutide versus liraglutide should be examined across different subgroups, such as patients who are overweight or have obesity with complications and diabetes, as STEP-8 focused on individuals without diabetes. Since both medications are also authorized for treating diabetes and obesity, it would be valuable to explore the CoC for additional dual or triple endpoints that encapsulate both obesity and diabetes outcomes. This would provide a more comprehensive understanding of their clinical and economic potential across varied patient populations. Such an analysis would address a significant gap, as individuals with diabetes often have distinct clinical and economic considerations that may influence treatment efficacy, adherence, and cost-effectiveness.

From a policy perspective, the present study's findings provide crucial insights into the value of semaglutide as an additional obesity pharmacotherapy in Greece. Semaglutide's lower cost of control than liraglutide offers an economic argument for its potential inclusion in the list of reimbursed medicinal products. However, given that obesity is a chronic, complex, and multifactorial disease, pharmacotherapy should be viewed as one component of the broader framework of multi-disciplinary actions, including lifestyle modifications, behavioral counseling, nutritional support, physical activity interventions, and, when necessary, surgical treatments. Policymakers must weigh the clinical benefits and cost implications of reimbursing semaglutide versus other available therapies, ensuring that any decisions are adequately justified, especially within constrained healthcare budgets. Given the scarcity of health resources, prioritizing the most cost-effective treatments is crucial, as every euro allocated to a specific drug carries an opportunity cost, limiting investment in other critical healthcare interventions.

Given the high prevalence of obesity and the correspondingly sizeable eligible population for anti-obesity pharmacotherapy, coupled with the high drug acquisition costs of new anti-obesity medications, policymakers face a critical challenge in ensuring the sustainability of healthcare budgets. To address this, decision-makers should consider implementing outcome-based agreements that align payment with the clinical effectiveness of treatments [37]. Such agreements enable healthcare systems to pay for the most efficacious therapies while ensuring that truly innovative medications are rewarded for their added value [37]. By linking reimbursement to real-world outcomes, outcome-based agreements can foster a more efficient allocation of resources, mitigate financial risks associated with large eligible populations, and incentivize the rewarding of genuinely innovative treatments.

Finally, a multi-stakeholder approach is essential for effectively addressing the growing obesity epidemic, necessitating collaboration between policymakers, third-party payers, medical associations, patient advocacy groups, pharmaceutical companies, public health experts, health economists, and academic institutions. Strengthening the national obesity task force could provide a structured platform for stakeholders to share insights, align objectives, and develop comprehensive, evidence-based strategies and policies. Such initiatives would ensure that diverse perspectives are considered, fostering innovative solutions and coordinated efforts to tackle obesity holistically.

5 Conclusions

This study found that semaglutide 2.4 mg demonstrated a lower cost of control than liraglutide 3 mg across all examined weight loss targets in adults who are overweight or have obesity without diabetes in Greece. While no established willingness-to-pay threshold exists for weight loss outcomes at 68 weeks, semaglutide's lower cost of control and higher efficacy versus liraglutide suggest it is likely to be a cost-effective treatment option.

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Declarations

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Contributions Panagiotis Papantoniou and Nikolaos Maniadakis have made equal and substantial contributions to this study, from its conceptualization and design to the meticulous analysis of data and its meaningful interpretation and revision.

Conflicts of Interest Professor Maniadakis and Dr. Papantoniou have no conflicts of interest directly relevant to the content of this article.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability The data analysis for this study was conducted using Microsoft Excel. The cost-of-control model is available as an electronic supplementary material.

Data Availability The data supporting the findings of this study are derived from publicly available sources and referenced within the manuscript. Clinical efficacy data were sourced from the STEP-8 trial, while cost inputs were obtained from the official drug price list published by the Greek Ministry of Health and government Gazette, as detailed in the references. For any further information or data queries, please contact the corresponding author.

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