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ORIGINAL RESEARCH

Semaglutide 2.4 mg for Obese Patients with MASH: A Cost-Effectiveness Analysis from the Italian NHS Perspective

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Background and Objectives: Metabolic dysfunction–associated liver disease (MASLD) and its progression to steatohepatitis (MASH) are highly prevalent among obese patients, contributing substantially to healthcare costs. Semaglutide, a GLP-1 receptor agonist, has shown metabolic and hepatic benefits in this population. This study assessed the cost-effectiveness of Wegovy® (semaglutide 2.4 mg) versus no pharmacological treatment in obese patients with MASH ≤F3 without diabetes, from the perspective of the Italian National Health Service (NHS).

Materials and Methods: A cost-effectiveness analysis (CEA) was conducted using a Markov model developed in Microsoft Excel®, adopting the Italian NHS perspective over a 10-year horizon. In line with study perspective, the model included healthcare resource use and direct costs associated with the management of obesity with MASH (≤F3) and related complications (major obesity related complications and liver disease evolution). Since semaglutide 2.4 mg is not yet reimbursed in Italy, cost assumptions were applied. The target population was estimated from epidemiological data, and utility values were derived from international literature, reflecting the relationship between weight loss and improved quality of life. Costs and outcomes were discounted at 3% annually. Model robustness was tested through one-way deterministic sensitivity analyses (OWSAs).

Results: The base case estimated 782,920 obese adults in Italy with MASH ≤F3 without diabetes. The analysis yielded an incremental cost-effectiveness ratio (ICER) of €22,691 per QALY gained over 10 years, below the accepted Italian willingness-to-pay thresholds. OWSAs confirmed the robustness of results.

Conclusion: Semaglutide 2.4 mg is a cost-effective and sustainable option for treating obese patients with MASH ≤F3 in Italy, a subgroup at high risk of progressing to advanced liver disease. By improving both fibrosis and body weight, semaglutide may play a key role in reducing the long-term clinical and economic burden of MASLD.

Keywords: obesity, MASLD/MASH, semaglutide 2.4 mg, weight loss, fibrosis reduction, cost-effectiveness

Introduction

Obesity is among the fastest-growing public health challenges worldwide, and Italy is no exception to this trend. In 2021, approximately 10% of Italian adults were classified as obese, corresponding to more than 4 million individuals.[1] The condition and its related complications impose a considerable economic burden on the Italian National Health Service (NHS), with direct healthcare expenditures estimated at €7.89 billion annually.[2] Obesity is a multifactorial disorder that significantly increases the risk of multiple chronic diseases, including diabetes, cardiovascular disease (CVD), cancer, osteoarthritis, obstructive sleep apnea (OSA), chronic kidney disease (CKD), and depression.[3]

A further obesity-related condition, frequently underdiagnosed, is Metabolic Associated Steatotic Liver Disease (MASLD) and its progressive fibrotic evolution, Metabolic Associated Steatohepatitis (MASH). Epidemiological

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evidence indicates a prevalence of MASLD of 25.1% in the general population and up to 60% among individuals with obesity in Western Europe.[4]

MASLD is now recognized as a multisystem disease: in addition to being strongly associated with type 2 diabetes mellitus (T2DM), it substantially increases the risk of developing T2DM itself, CVD, CKD, and extrahepatic malignancies, particularly colorectal cancer. Importantly, MASLD also carries a high risk of liver-related complications, including progression to MASH, compensated (CC) and decompensated cirrhosis (DCC), and hepatocellular carcinoma (HCC). The incidence of these outcomes has been shown to exceed that observed for obesity-related comorbidities alone.[5]

Given the substantial clinical and economic burden of obesity, the development and implementation of effective therapeutic strategies are imperative to mitigate the incidence of obesity-related comorbidities.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been shown to induce clinically significative weight reduction in individuals with obesity and are currently widely used in high-income countries, primarily as out-of-pocket treatments. However, despite the meaningful social and economic implications of obesity, broad public reimbursement of these therapies is unlikely to be economically sustainable within the Italian healthcare system. A more viable approach may involve selective reimbursement strategies, prioritizing patients at the highest risk of developing obesity-related complications rather than those who already manifest them. Such a targeted policy could enhance both the clinical impact and the cost-effectiveness of GLP-1 RA therapy in the Italian context.

Semaglutide is a GLP-1 RA currently approved for the treatment of both T2DM and obesity at once-weekly injectable doses of up to 2.4 mg. Clinical trials have demonstrated its efficacy in improving glycemic control, reducing cardiovascular risk, and inducing significant weight loss.[6–8] In particular, over a 68-week treatment horizon, obese patients receiving semaglutide experienced a mean weight reduction of 14.9% (–15.4 kg in the semaglutide group versus –2.6 kg in the placebo group).[9]

Beyond its metabolic effects, semaglutide has recently been shown to induce histological improvements in patients with MASH, promoting resolution of steatohepatitis without worsening of fibrosis (62.9% compared to 34.3% with placebo; estimated difference, 28.7%; 95% CI 21.1–36.2; P<0.001), and reducing liver fibrosis without worsening steatohepatitis (36.8% compared to 22.4% with placebo; estimated difference, 14.4%; 95% CI, 7.5–21.3; P<0.001).[10] Moreover, as previously discussed, semaglutide achieves a weight loss of approximately 15% in obese patients, rendering it a potentially suitable treatment option for individuals with concurrent obesity and MASLD/MASH.[9,10] Mechanistically, beyond weight reduction and improvement of insulin resistance, semaglutide exerts beneficial effects on cardiometabolic risk factors and mitigates hepatic lipotoxicity, thereby addressing the inflammatory pathways central to MASH progression up to stage 3 fibrosis.[10,11]

Given that MASLD and MASH are associated with a higher prevalence of cardiometabolic complications compared with obesity alone, and constitutes a major determinant of liver failure and cirrhosis, their identification among obese patients may represent a rational strategy to optimize patient selection for semaglutide therapy. Targeting this subgroup could maximize both clinical benefits and economic sustainability of the intervention.[12]

In particular, the analysis focused on patients with MASH ≤F3, as this subgroup is well represented in the ESSENCE trial population, represents the majority of obese patients with MASH, and corresponds to a clinically meaningful stage where early intervention may prevent progression to more advanced liver disease and its associated burden.[10,13]

The aim of the present study is to evaluate the cost-effectiveness of semaglutide 2.4 mg in the treatment of obese patients with MASH (≤F3) without diabetes from the perspective of the Italian National Health Service (NHS) over a 10-year time horizon.

Materials and Methods

Model Design

A cost-effectiveness analysis (CEA) was developed using a decision-analytic model constructed in Microsoft Excel®. The analysis was conducted from the perspective of the Italian NHS over a 10-year time horizon, considering healthcare resource use and direct costs associated with the management of obesity concomitant with MASH (≤F3) in MASLD patients without diabetes and its related complications in the Italian setting.

The target population was defined according to epidemiological prevalence data.

Efficacy inputs were derived from pivotal clinical trials of semaglutide 2.4 mg, including STEP 1, ESSENCE, and SELECT.[9,10,14] Specifically, the model evaluated the impact of semaglutide-induced reductions in body weight and fibrosis progression on the incidence of both major obesity-related complications and liver disease evolution. For major obesity-related complications, the relative risk reduction associated with a 15% body weight loss was drawn from a simulation study involving a hypothetical cohort of 100,000 Spanish adults with obesity, adapted to the Italian context.[15] The major obesity-related complications considered included dyslipidemia, hypertension, chronic kidney disease (CKD), type 2 diabetes mellitus (T2DM), osteoarthritis, atrial fibrillation (AF), unstable angina (UA)/acute myocardial infarction (AMI), heart failure (HF), asthma, and obstructive sleep apnea (OSA).[15,16]

For liver-specific complications, a Markov model structure was employed, consistent with our previous economic evaluations.[12,13]

Liver health states were: MASH without fibrosis (F0), fibrosis stages F1–F3, compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplantation (LT), first year post-transplant (yLT), post-transplant survival (PLT), and death. Three absorbing mortality states were incorporated: liver-related mortality (LRM), cardiovascular mortality (CVM), and background mortality (BM). A 1-year cycle length was applied, with patients transitioning through disease states until reaching an absorbing state.

Health state utility values were derived from published international literature, reflecting the correlation between weight loss and improvements in health-related quality of life (HRQoL).[17–19] Unit costs were obtained from Italian cost-of-illness studies, national tariffs, and published economic evaluations.[2,20–36]

Costs included both treatment-related expenses and the management of obesity and liver disease complications. Since the future reimbursed price of semaglutide 2.4 mg subcutaneous pen in Italy remains uncertain, cost assumptions were applied. Further methodological specifications on input definitions are reported in the following sections.

The model compared two cohorts: patients treated with semaglutide 2.4 mg versus those without pharmacological treatment. Costs and health outcomes were recorded over the 10-year horizon. Effectiveness was expressed in terms of Quality-Adjusted Life Years (QALYs). Outcomes included reductions in major obesity-related complications and liver-specific complications, improvements in HRQoL related to weight loss, and associated healthcare cost offsets. Notably, only weight-related improvements were considered for HRQoL estimation, whereas both weight and fibrosis effects were included in the economic evaluation, representing a conservative approach.

Results were expressed as the Incremental Cost-Effectiveness Ratio (ICER), defined as the incremental cost per QALY gained. Specifically, the relationship between incremental costs and benefits between semaglutide 2.4 mg and the no treatment arm allowed to calculate the ICER for the base case scenario, measured as $\Delta€/\Delta QALY$, considering as target population patients with obesity and concomitant MASH (≤F3), in MASLD patients without diabetes.

Cost-effectiveness was assessed against the willingness-to-pay (WTP) threshold of €33,004 per QALY, corresponding to the average acceptability value (ICER) recently published for Italy, based on data reported in 48 price negotiation procedures submitted to the Italian Medicines Agency (AIFA).[37]

A 3% annual discount rate was applied to both costs and outcomes.

Uncertainty was explored through a deterministic one-way sensitivity analysis (OWSA), assessing the robustness of the results to variations in key input parameters and model assumptions. The analysis adhered to international methodological standards and was reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[38]

Model design is briefly described in Figure 1.

Population

The target population was defined using a prevalence-based model. We considered the Italian population aged between 18 and 75 (43,230,246 at January 2025),[39] and applied the prevalence of obesity, equal to 10%.[1] The prevalences of MASLD and progressive disease, MASH, in the obese population, 75% and 34% respectively, obtained from the international literature, were applied to this population.[5]

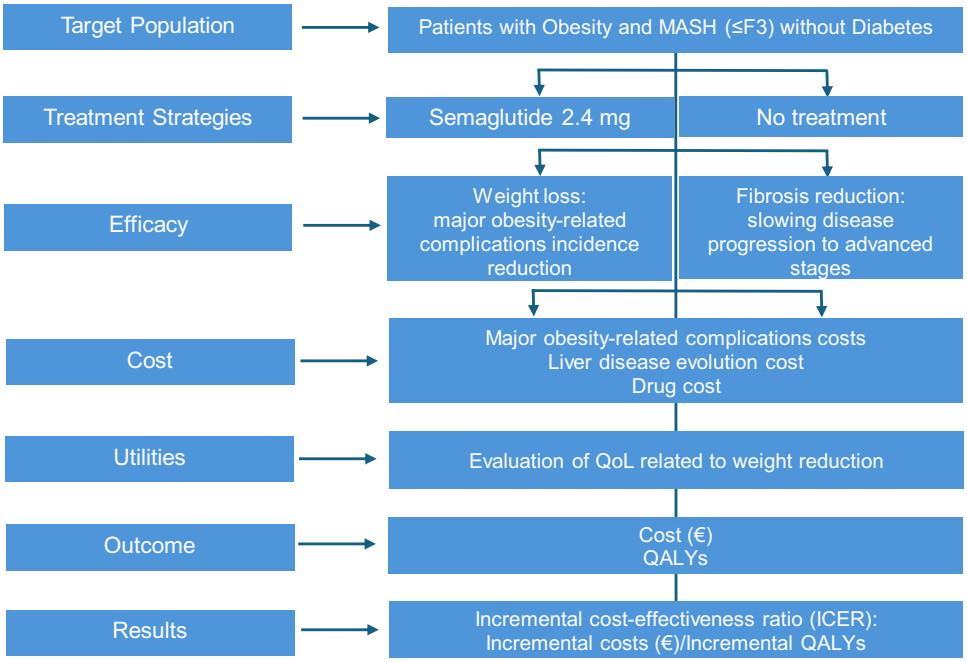

Figure 1 Model design flowchart.
Abbreviations: MASH, Metabolic Associated Steatohepatitis; QoL, quality of life; QALYs, quality-adjusted life year; ICER, incremental Cost-Effectiveness Ratio.

To appropriately evaluate the therapeutic impact of semaglutide 2.4 mg on body weight reduction and fibrosis progression, the analysis focused on obese patients with fibrosis (F0–F3), who account for approximately 92% of the obese population with MASH.[40]

Finally, the percentage of patients with diabetes was excluded from this population.[41]

Obese patients with MASH (≤F3) without diabetes represent the target population for the base case scenario.

Figure S1 shows the population flow used to define the target population.

Efficacy Data

The efficacy data informing model development were derived from clinical trials specifically evaluating semaglutide 2.4 mg, which provided robust evidence on its therapeutic impact in terms of weight reduction and metabolic outcomes.[9,10,14]

Specifically, the STEP 1 trial provided a mean reduction in body weight of −14.9% in the semaglutide 2.4 mg group compared with −2.4% for placebo (95% confidence interval [CI], −13.4 to −11.5; P<0.001) at 68 weeks. These findings provided the necessary evidence to assess the impact of weight reduction on the long-term incidence of major obesity-related complications. On this basis, and following appropriate numerical adjustment, we applied to our target population the estimates reported in the literature for a 15% weight loss in a cohort of 100,000 obese individuals in Spain, which projected a reduction in the incidence of major obesity-related comorbidities over a 10-year horizon.[15]

Given the increased risk of cardiovascular complications in patients with obesity and MASLD, a correction factor was applied to the incidence data reported in the Spanish cohort of obese patients. This adjustment was based on incidence rates and risk ratios available in the literature.[42,43]

The estimation of risk reduction incorporated the specific data reported in the SELECT trial for semaglutide 2.4 mg. Relative risk reductions of major obesity-related comorbidities in patients treated with semaglutide 2.4 mg, as result of a 15% weight reduction, are reported in Table S1.

For each major obesity-related complication, annual incidence rates were estimated for the two comparator populations: patients receiving semaglutide 2.4 mg, achieving an average body weight reduction of 15%, and untreated patients, for which weight stability was assumed. A half-cycle correction was applied to account for the timing of event

occurrence, assuming events were distributed at the midpoint of each annual cycle. Subsequently, the 10-year cumulative incidence was projected, and the corresponding economic evaluation was conducted.

The ESSENCE RCT was adopted to evaluate semaglutide 2.4 mg effects on liver fibrosis.[10]

In this study, reduction in liver fibrosis without worsening of steatohepatitis was observed in 36.8% of patients treated with semaglutide and in 22.4% of those receiving placebo, corresponding to an estimated absolute difference of 14.4% (95% CI, 7.5–21.3; P<0.001). Treatment effect was incorporated into the Markov model by adjusting the transition probabilities between fibrosis stages (≤F3). Table S2 reports the transition probabilities modified based on treatment effects, while Table S3 presents the original transition probability matrix adopted for the analysis.

The model was then used to estimate the impact of fibrosis regression on slowing disease progression to more advanced stages over a 10-year horizon. Again, a half-cycle correction was applied, assuming that transitions between health states occurred at the midpoint of each cycle. For the economic evaluation, costs associated with each health state were allocated proportionally: the cost of the baseline state was applied to the first half of the cycle, and the cost of the subsequent state to the second half.

In the base case analysis, the economic model incorporated the absolute efficacy values for semaglutide 2.4 mg as reported in clinical trials. Sensitivity analyses were conducted to assess the robustness of the results by examining the impact of treatment effects relative to placebo.

Utilities Data

The relationship between weight reduction and health-related quality of life was derived from the decrease in BMI observed in the STEP 1 trial, corresponding to a mean reduction of 5.54 points.[9] Utility values associated with BMI change were estimated using EQ-5D data, based on evidence reported in the international literature.[17–19] Specifically, a utility gain of 0.09 was applied for patients without diabetes and 0.11 for incident diabetic patients treated with semaglutide 2.4 mg.[17–19] As the STEP 1 outcomes were reported at week 68, while the economic evaluation adopted a 10-year horizon, an implementation rule was applied whereby 80% of patients were assumed to achieve the target weight reduction in year 1, with full achievement by year 2. The weight reduction, and consequently the associated utility gains, were assumed to be maintained throughout the remaining time horizon.

Cost Data

The cost analysis was conducted from the perspective of the Italian NHS and therefore including only direct healthcare costs. Resource utilization categories comprised major obesity-related complications, liver disease evolution states, and pharmacological treatment with semaglutide 2.4 mg. Unit cost assignment for major obesity-related complications and costs of liver disease evolution states was based on published literature and national tariffs, with costs expressed either as average annual cost per event or per-unit cost, depending on the type of data (healthcare service or incident disease cost).[2,20–36]

As semaglutide 2.4 mg is not reimbursed by the Italian Medices Agency (AIFA), the ex-factory price used is hypothetical as cost assumptions were considered and alternative cost scenarios were incorporated into the model. For the base case analysis, the ex-factory price per pack for the non-reimbursed product was applied, corresponding to €230.24.

The ex-factory price was calculated from the publicly available retail price (€380), obtained from the Gallery® Farmadati database.[44] The annual treatment cost was calculated according to the recommended dosing regimen and applied consistently across cycles.

Scenario analyses were conducted to test the impact of alternative drug pricing hypotheses, assuming potential ex-factory price discounts of 15%, 30%, and 45%, respectively, while deterministic sensitivity analyses further explored the robustness of cost inputs.

The main unit costs included in the model are summarized in Table S4. Table S5 presents the price assumptions for semaglutide 2.4 mg.

Sensitivity Analysis

A deterministic one-way sensitivity analysis (OWSA) was conducted to assess the robustness of the base case results with respect to the key model inputs and structural assumptions. Parameter uncertainty was addressed by varying each

input around its base case value within plausible ranges, and the resulting impact on model outcomes was visualized through a tornado diagram to highlight the most influential drivers.

Scenario analyses were performed to benchmark alternative assumptions against the base case estimates, using the 10-year ICER as reference metrics.

Price scenarios for semaglutide 2.4 mg were explored by adjusting the base case annual ex-factory price to simulate potential price negotiations, applying annual price reductions of 15%, 30%, and 45%, respectively.

The impact of potential generic entry was also evaluated by modelling three alternative timings of market availability (year 5, year 7, and year 9 of the time horizon).

Furthermore, an alternative efficacy assumption was tested by applying treatment effects expressed as incremental differences compared to placebo, derived from the ESSENCE trial, in place of absolute efficacy estimates for semaglutide 2.4 mg. Finally, the robustness of model results was examined through ±20% variations applied to key clinical and economic parameters, including fibrosis regression rates, body weight loss, health-state utilities, unit costs of major obese-related comorbidities and liver disease evolution states, and the discount rate for costs and outcomes.

Results

Based on the epidemiological evidence and published reviewed literature, the base case analysis estimated a target population of 782,920 obese adults in Italy with MASH ≤F3 without diabetes. The clinical, economic, and health-related quality of life outcomes associated with semaglutide 2.4 mg, compared with no treatment, are reported below. Treatment with semaglutide 2.4 mg was associated with a mean body weight reduction of –14.9%, which in turn resulted in a substantial decrease in the incidence of major obesity-related complications, Table S6. This effect translated into projected cost savings of €213,662,133 at the base case 10-year time horizon, Table 1 and Table S7.

In addition, applying the 36.8% reduction in liver fibrosis without worsening of steatohepatitis observed with semaglutide 2.4 mg to the transition probabilities of fibrosis stages (≤F3) resulted in savings of €269,577,974, Table 1. This outcome was attributable to delayed progression towards more advanced and costly stages of disease, Table S8.

The pharmacological treatment costs were estimated at €1,565,127,948, based on the ex-factory price per pack adopted in the model, under the assumption of continuous treatment and full adherence in the base case scenario.

Within the base case population and base case horizon, weight reduction was associated with an overall gain of 47,680 QALYs.

A summary of the economic outcomes and QALYs for the base case time horizon is reported in Table 1.

The cost-effectiveness analysis yielded an incremental cost-effectiveness ratio (ICER) of €22,691 per QALY gained for the base case target population at the 10-year horizon, below the Italian WTP threshold, Table 1.[37]

Table 1 Cost-Effectiveness Results for Base Case Scenario (10-Year Time Horizon)

Results	Δ vs No Treatment	ICER
Costs		
Major obesity-related complications	-€ 213,662,133	€ 22,691
Liver disease evolution	-€ 269,577,974	
Semaglutide 2.4 mg treatment	€ 1,565,127,948	
Effectiveness		
QALYs	47,680	

Notes: Δ, Delta, indicates the difference between semaglutide 2.4 mg and the no treatment scenario.
Abbreviations: ICER, incremental Cost-Effectiveness Ratio; QALYs, quality-adjusted life year.

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Table 2 One-Way Sensitivity Analysis Results for Base Case Time Horizon (10-Year)

Scenarios	ICER Results
Base case	€ 22,691
Annual drug cost - 15%	€ 17,767
Annual drug cost - 30%	€ 12,843
Annual drug cost - 45%	€ 7,919
Generic entry in year 9	€ 6,278
Generic entry in year 7	€ 6,278
Generic entry in year 5	€ 6,278
Fibrosis reduction versus placebo	€ 25,365
Fibrosis reduction −20%	€ 23,547
Fibrosis reduction +20%	€ 21,831
Weight loss - 20%	€ 23,387
Weight loss + 20%	€ 22,121
Utilities - 20%	€ 28,363
Utilities + 20%	€ 18,909
Comorbidity costs - 20%	€ 23,587
Comorbidity costs + 20%	€ 21,794
Liver disease evolution state costs - 20%	€ 23,821
Liver disease evolution state costs + 20%	€ 21,560
Discount rate (costs) - 20%	€ 24,056
Discount rate (costs) + 20%	€ 21,410
Discount rate (outcomes) - 20%	€ 21,403
Discount rate (outcomes) + 20%	€ 24,047

One-way sensitivity analyses (OWSAs) supported the robustness of these findings. Across the time horizon, the ICER was most sensitive to changes in the price of semaglutide, and in the utility values associated with body weight reduction, as well as to the potential impact of generic entry, Table 2.

Notably, in all simulated scenarios, ICERs were below the WTP threshold in Italy, including under the most conservative assumptions Table 2 and Figure 2.

Discussion

Our cost-effectiveness analysis modelled the potential impact of semaglutide 2.4 mg subcutaneous pen adoption in obese and MASLD patients with MASH (≤F3) without diabetes in Italy.

The modelling framework aimed to translate the primary clinical benefits demonstrated in the STEP 1, ESSENCE, and SELECT trials, namely, weight reduction, improvement in liver fibrosis status and cardiovascular risk reduction, into health-economic outcomes, by linking these effects to reductions in comorbidities and improvements in quality of life among obese patients with MASH.

The results highlighted the cost-effectiveness of semaglutide 2.4 mg in the target population, from the perspective of the Italian NHS and over a 10-year time horizon, with an ICER of €22,691 per QALY gained.

Semaglutide 2.4 mg is not currently reimbursed by the Italian NHS; for this reason, ex-factory price assumptions were incorporated to explore potential future sustainability, considering both the substantial therapeutic value of the drug and the significant disease burden of the target population.

In the base case, the ex-factory price per pack of the non-reimbursed product was estimated from the retail price.[44] Although this represents the current applicable price, it is expected that a discount will be negotiated in case of reimbursement.

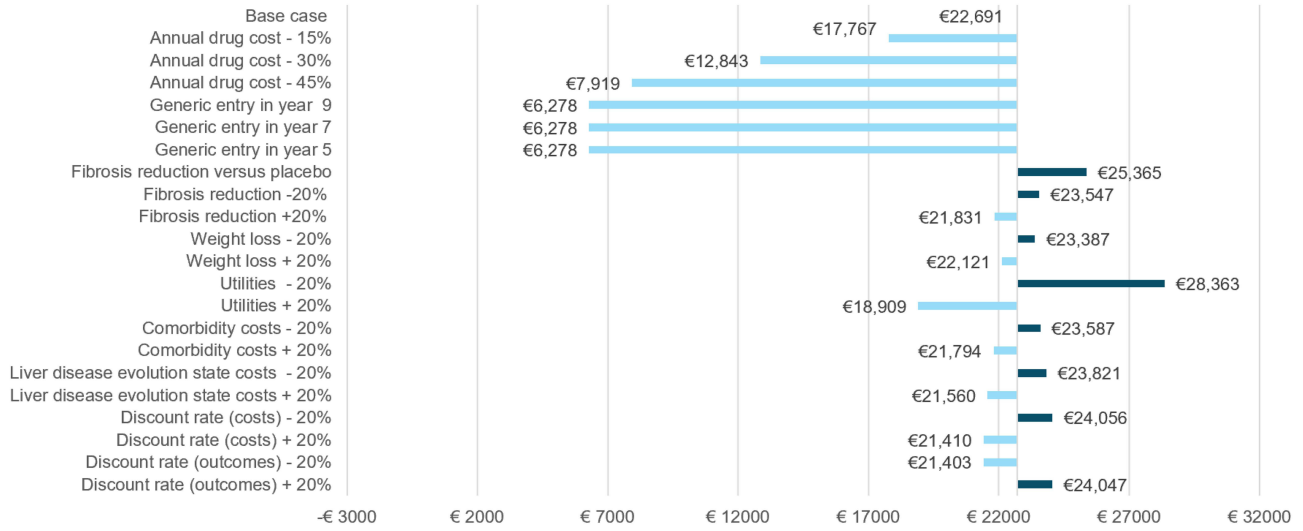

Figure 2 Tornado diagram for one-way sensitivity analysis results. Deterministic one-way sensitivity analysis (OWSA) results based on the 10-year base-case ICER (€22,691) are presented in the tornado diagram, which illustrates the impact of varying key model inputs and assumptions within predefined ranges on cost-effectiveness outcomes. Drug acquisition cost emerged as a key driver of uncertainty. Scenario analyses exploring the timing of generic entry showed a substantial impact on the results. Variations in utility values also affected the results, although to a lesser extent. In contrast, ±20% variations in comorbidity costs, liver disease costs, and discount rates for both costs and outcomes had only a marginal influence on the results.

Accordingly, scenario analyses were developed for semaglutide 2.4 mg, incorporating realistic ex-factory prices reflecting some possible negotiation outcomes. These scenarios yielded progressively more favorable ICERs, remaining well below the willingness-to-pay threshold, with the lowest ICER (€7,919) observed under a 45% price reduction.

These findings suggest that, within the target population considered, semaglutide would likely represent a cost-effective therapeutic option under real-world reimbursement conditions, as already indicated by the base case analysis and simulation scenarios.

Over the 10-year horizon, economic outcomes were primarily influenced by cost offsets from reduced major obesity-related complications and slower progression of liver disease due to fibrosis improvement, despite higher drug acquisition costs. Gains in quality of life associated with weight reduction also played a major role, resulting in a cumulative increase of 47,680 QALYs.

The estimated ICER proved to be robust in deterministic sensitivity analysis, with cost-effectiveness maintained across all scenarios for base case time horizon. The annual cost of semaglutide and the utility estimates associated with weight reduction emerged as the main drivers of the model. Moreover, the assessment of future price reductions related to genericization highlighted the potential for markedly favorable ICERs over time.

The main strengths of this analysis lie in both the originality of its focus and the robustness of the clinical evidence for semaglutide 2.4 mg, derived from the STEP 1, ESSENCE, and SELECT trials.[9,10,14] These trials served as the primary data source, ensuring that the model was anchored in clinically validated outcomes, thereby enhancing its reliability and translational relevance.

To the best of our knowledge, this is the first cost-effectiveness evaluation of semaglutide 2.4 mg specifically targeting obese patients with MASH (≤F3) and without diabetes in Italy. While several economic assessments of semaglutide have been conducted in populations with obesity or obesity and cardiovascular disease, none have addressed the subgroup of patients with obesity and MASH, without diabetes. Existing studies, performed in diverse healthcare settings such as the United States, United Kingdom, Portugal, and Canada, adopted varying perspectives, time horizons, comparators, and WTP thresholds, but consistently reported broadly favorable results.[45–48]

Focusing on patients with multiple comorbidities, particular attention has been given in the literature to patients with obesity and cardiovascular disease without diabetes, consistent with the SELECT trial population. For this group, cost-effectiveness outcomes appear highly sensitive to both product pricing and the specific WTP thresholds applied across national contexts, with positive results in the United States and less favorable outcomes in jurisdictions with more

stringent thresholds or higher price assumptions.[48–51] In such contexts, cost-effectiveness was generally achieved when scenarios assumed reductions in drug cost or targeted high-risk subgroups.[49–51]

By focusing on obese patients with MASH in Italy, our analysis contributes to filling an important evidence gap. Within the context of the Italian NHS and a WTP threshold of approximately €33,000 per QALY, our findings indicate that semaglutide 2.4 mg represents a cost-effective intervention for a population characterized by a substantial disease burden, thereby providing evidence to support reimbursement decision-making and prioritization strategies.

The economic evaluation shares the typical limitations of Markov model–based simulation studies that rely on published evidence and modelling assumptions. In the absence of real-world data from Italy on the target population and the long-term evolution of hepatic and extrahepatic complications, we drew upon evidence from the international literature. Specifically, transition probabilities for the progression of liver disease were derived from Younossi et al (2019),[52] consistent with the approach adopted in our previous analysis.[13] Estimates of cardiovascular event incidence in the obese population, as well as events reduction achievable with a 15% weight loss, were obtained from Ballesteros et al,[15] applying a correction factor to account for the co-occurrence of obesity and MASLD in the population under study.

In the simulation study of Ballesteros et al the potential health-economic impact of weight loss has been investigated, involving a hypothetical cohort of 100,000 Spanish adults with obesity (BMI 30–50 kg/m^2).[15] The analysis estimated cost savings derived from the reduced incidence of 10 obesity-related comorbidities when comparing a stable-weight cohort to a cohort achieving a sustained body weight reduction of 10–25% (average: 15%) over a 10-year time horizon.[15,16] The model projected total savings of approximately €105 million, primarily attributable to risk reductions for obstructive sleep apnea (–56.4%), T2DM (–39.2%), asthma (–20.2%), hypertension (–18.7%), osteoarthritis (–16%), and chronic kidney disease (–13%). Notably, the model did not account for MASLD and its progressive form, MASH, which constitutes additional drivers of clinical and economic benefit. Our study was specifically designed to address this gap by focusing on these conditions.

Utility data specific to the Italian context were not available, and therefore a targeted literature search was undertaken to identify appropriate inputs. Among the different approaches reported, we adopted the correlation between BMI reduction and improvements in health-related quality of life, as measured through the EQ-5D questionnaire. This methodology, while one of several possible options, is supported by evidence showing that the magnitude of weight reduction associated with semaglutide is comparable to that observed in the early years following bariatric surgery in a similar patient population.[53] Given the central role of this parameter as a key driver of the model, its influence was tested in sensitivity analyses.

The impact of using relative efficacy data (semaglutide versus placebo) on fibrosis reduction, rather than the absolute values applied in the base case scenario, was also explored. In addition, the effect of varying weight loss outcomes by ±20% was tested, with the lower bound consistent with the relative efficacy of semaglutide versus placebo. Both sensitivity analyses confirmed the cost-effectiveness of semaglutide, reporting favourable ICER values.

Consistent with the study perspective, only direct healthcare costs were included in the model. However, given the substantial societal burden of obesity, largely driven by absenteeism and productivity losses related to the clinical condition and its complications, future evaluations adopting a broader perspective may provide a more comprehensive assessment of value.

Moreover, while the model incorporated the effects of major comorbidities associated with obesity, it did not capture the full spectrum of potential health consequences. Conditions such as atopic dermatitis, gastroesophageal reflux disease (GERD), urinary incontinence, whose association with obesity is well documented,[54] were not included.

Furthermore, the model assumes a constant prevalence of obesity in Italy across the time horizon; this simplifying assumption may lead to an underestimation of the future burden, given the upward trajectory in obesity rates documented in recent years, as highlighted in the Obesity Barometer Report 2025.[55]

In this analysis utility values were applied exclusively to body weight reduction, rather than to different stages of liver disease progression, further reinforcing the conservative nature of the approach.

For the comparator, the analysis adopted a “no treatment” scenario to mirror the effects reported in clinical trials of semaglutide 2.4 mg. Nonetheless, it should be noted that alternative treatment options, both pharmacological and

surgical, are available. Future economic evaluations should therefore expand the comparison framework to incorporate these alternatives.

Furthermore, the results are based on assumptions of high treatment adherence and sustained weight loss over time, in line with evidence from pivotal clinical trials, in which treatment discontinuation observed within study cohorts is nonetheless considered, thereby at least partially reflecting the effects of non-complete adherence. These assumptions are also consistent with standard modelling practice in the absence of real-world data.

The effects on weight reduction and fibrosis regression are reported in clinical studies over time horizons shorter than that adopted in the present economic evaluation; accordingly, treatment efficacy was assumed to be sustained over the entire cost-effectiveness analysis time horizon. This assumption was adopted to inform projections of the product's long-term modelled outcomes; however, it warrants further validation through simulation analyses based on real-world evidence and/or long-term outcomes derived from treatment registries.

In this regard, future real-world evidence generation and registry-based studies will be crucial to assess the durability of treatment effects and to corroborate the model assumptions in routine clinical practice, thereby strengthening the translational relevance of the findings.

Despite potential limitations, the robustness of our analysis is confirmed by the results of the OWSA and our model and assumption can be generalized to other healthcare settings, although healthcare costs and WTP threshold differs across countries.

Patients with concomitant diabetes were excluded, in order to isolate the specific impact of obesity and MASH. Nonetheless, exploratory simulations conducted on a hypothetical cohort including individuals with diabetes also confirmed the cost-effectiveness of the intervention, yielding favourable ICER values.

Finally, our analysis highlighted the cost-effectiveness of treatment with semaglutide 2.4 mg in patients with obesity and MASH ≤F3 in Italy, focusing on a subgroup of patients at high risk of rapidly progressing to more advanced stages of liver disease and characterized by a significant disease burden.

The healthcare sustainability of semaglutide 2.4 mg for the treatment of early stages of liver disease in obese patients is essential in the case of a chronic and worsening condition with extensive multisystem metabolic involvement, such as MASLD. The availability of treatments like semaglutide 2.4 mg, capable of reducing both fibrosis and body weight, represents a key tool for the long-term management of disease burden and associated costs.

In parallel, the establishment and implementation of standardized and cost-effective screening and diagnostic strategies are crucial to enable timely treatment initiation in patients at higher risk of progression to more advanced liver disease. Such measures are essential not only to optimize clinical outcomes, but also to mitigate the long-term economic impact of the disease on healthcare systems.

Conclusions

This analysis demonstrates that semaglutide 2.4 mg represents a cost-effective intervention for obese patients with MASH (≤F3) without diabetes within the Italian healthcare setting, generating substantial health gains and remaining below the commonly accepted willingness-to-pay threshold, reporting an ICER equal to € 22,691 per QALY gained for the basecase scenario.

The model suggests that clinical benefits observed in randomized trials, namely weight reduction and improvement in fibrosis, translate into meaningful long-term economic value, primarily through the reduction of obesity-related complications and the slowing of liver disease progression.

These findings are further strengthened under plausible real-world pricing scenarios, where negotiated discounts markedly improve cost-effectiveness outcomes. Despite higher upfront drug costs, the intervention is associated with significant quality-of-life improvements and downstream cost offsets, supporting its potential sustainability within the Italian NHS.

This study meaningfully advances the field by providing decision-relevant evidence that may inform reimbursement prioritization and policy discussions for obesity treatments linked to liver disease improvement. The novelty of the study lies in the targeted population selection and the integration of fibrosis regression effects, offering a novel and context-specific perspective within the Italian healthcare context.

Overall, semaglutide 2.4 mg emerges as a valuable therapeutic option in a high-burden population at risk of disease progression. Future research incorporating real-world evidence, broader comparators, and context-specific longitudinal data will be essential to further validate these findings and refine estimates of long-term value.

In parallel, the integration of effective pharmacological treatments with early screening and risk stratification strategies will be critical to optimize both clinical outcomes and healthcare resource allocation in MASLD and and its progressive fibrotic evolution MASH.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. Further inquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

For the development of this study, it was not necessary to proceed with the request for ethical approval and consent to participate, and previously published and validated literature sources were adopted.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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