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ORIGINAL RESEARCH

The Short-Term Cost-Effectiveness of Once-Weekly Semaglutide Versus Once-Daily Sitagliptin and Once-Weekly Dulaglutide for the Treatment of Patients with Type 2 Diabetes: A Cost of Control Analysis in Spain

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ABSTRACT

Introduction: Once-weekly semaglutide has been associated with greater reductions in glycated hemoglobin (HbA1c) and body weight than sitagliptin and dulaglutide in the SUSTAIN 2 and 7 clinical trials, respectively. These trials also assessed the proportions of patients achieving treatment targets capturing glycemic control and avoidance of hypoglycemia and weight gain. This study assessed the cost of bringing patients with type 2 diabetes to three clinically relevant endpoints with semaglutide versus sitagliptin and dulaglutide in Spain.

Methods: The proportions of patients achieving endpoints of HbA1c < 7.0%, HbA1c < 7.0% without hypoglycemia and without weight gain, and a ≥ 1.0% HbA1c reduction with ≥ 5.0% weight loss were taken from SUSTAIN 2 and 7. Cost of control was calculated as the annual per patient cost of each medication, expressed in 2019 euros (EUR), divided by the proportion of patients achieving each endpoint.

Results: Based on SUSTAIN 2, cost of control was lower for sitagliptin for the HbA1c < 7.0% endpoint, results were comparable for the HbA1c < 7.0% without hypoglycemia and without weight gain endpoint, and both doses of semaglutide were associated with lower costs of control for the ≥ 1.0% HbA1c reduction with ≥ 5.0% weight loss endpoint. Based on SUSTAIN 7, both doses of semaglutide were associated with lower costs of control for all three endpoints.

Conclusion: Both doses of semaglutide were associated with comparable or lower costs of control versus sitagliptin when considering endpoints incorporating hypoglycemia and weight loss alongside glycemic control, and lower costs of control versus dulaglutide 1.5 mg for all endpoints in Spain.

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Keywords: Cost; Cost-effectiveness; Cost of control; Diabetes mellitus; Dulaglutide; GLP-1 receptor agonist; GLP-1 analogue; Semaglutide; Sitagliptin; Spain

Key Summary Points
Why carry out this study?
Optimizing care for patients with type 2 diabetes by achieving glycemic control targets, preventing weight gain, and avoiding hypoglycemic events can be achieved by using modern interventions, such as glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP4) inhibitors
Choosing interventions that can achieve these aims in a cost-effective manner is key for healthcare payers as the prevalence of type 2 diabetes continues to rise
The aim of the present study was to assess the short-term cost of control of bringing patients with type 2 diabetes to clinically relevant endpoints of glycated hemoglobin (HbA1c) $< 7.0\%$, HbA1c $< 7.0\%$ without hypoglycemia and without weight gain, and $\geq 1.0\%$ HbA1c reduction with $\geq 5.0\%$ weight loss with semaglutide 0.5 mg, semaglutide 1 mg, sitagliptin and dulaglutide in the Spanish setting based on the SUSTAIN 2 and SUSTAIN 7 randomized controlled trials
What was learned from this study?
Annual costs of control were marginally higher for semaglutide 0.5 mg and 1 mg versus sitagliptin for the endpoints of HbA1c $< 7.0\%$ and HbA1c $< 7.0\%$ without hypoglycemia and without weight gain, but substantially lower for the endpoint of a $\geq 1.0\%$ reduction in HbA1c with $\geq 5.0\%$ weight loss
Both doses of semaglutide were associated with lower costs of control for all endpoints versus dulaglutide

PLAIN LANGUAGE SUMMARY

Optimizing care for patients with type 2 diabetes by achieving glycemic control targets, preventing weight gain, and avoiding hypoglycemic events can be achieved by using modern interventions, such as GLP-1 receptor agonists and DPP4 inhibitors. Choosing interventions that can achieve these aims in a cost-effective manner is key for healthcare payers as the prevalence of type 2 diabetes continues to rise. The aim of the present study was to assess the short-term cost of control of bringing patients with type 2 diabetes to three clinically relevant endpoints with semaglutide 0.5 mg, semaglutide 1 mg, sitagliptin and dulaglutide in the Spanish setting based on the SUSTAIN 2 and SUSTAIN 7 randomized controlled trials.

The proportions of patients achieving endpoints of HbA1c $< 7.0\%$, HbA1c $< 7.0\%$ without hypoglycemia and without weight gain, and a $\geq 1.0\%$ HbA1c reduction with $\geq 5.0\%$ weight loss were taken from SUSTAIN 2 and 7. Cost of control was calculated as the annual per patient cost of each medication divided by the proportion of patients achieving each endpoint.

Based on SUSTAIN 2, cost of control was lower for sitagliptin for the HbA1c $< 7.0\%$ endpoint, results were comparable for the HbA1c $< 7.0\%$ without hypoglycemia and without weight gain endpoint, and both doses of semaglutide were associated with lower costs of control for the $\geq 1.0\%$ HbA1c reduction with $\geq 5.0\%$ weight loss endpoint. Based on SUSTAIN 7, both doses of semaglutide were associated with lower costs of control for all three endpoints.

INTRODUCTION

Direct healthcare expenditure for type 2 diabetes in Spain exceeded EUR 9 billion in 2017 [1–3]. As healthcare payers are faced with increasingly limited budgets, choosing therapies that are cost-effective is becoming crucial. While it is well established that the majority of costs associated with diabetes are from long-term complications, economic constrains mean

that healthcare payers often set budgets where larger weight is given to short-term costs, such as medication acquisition costs.

A key treatment target for type 2 diabetes remains a glycated hemoglobin (HbA1c) of less than 7.0%, but latest guidelines recommend more individualized targets [4, 5]. Importantly, reductions in HbA1c > 0.9% have been associated with a reduced risk of microvascular complications. Furthermore, reductions in body weight have been associated with a reduced incidence of long-term complications, as well as short-term improvements in patients' quality of life [6–12]. Additional parameters such as avoidance of hypoglycemia or weight gain are therefore currently considered as relevant outcomes of diabetes therapies in both Spain-specific and Europe-wide guidance [4, 5].

Incretin therapies, including glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP4) inhibitors, represent modern treatments for type 2 diabetes that offer multifactorial benefits. The DPP4 inhibitor sitagliptin has been associated with improved glycemic control in patients with type 2 diabetes, while displaying weight neutrality and a low risk of hypoglycemia alongside good tolerability [5, 13]. GLP-1 receptor agonists have been associated with reductions in body weight and systolic blood pressure in addition to improved glycemic control, while displaying a low hypoglycemia risk [14–17]. Among GLP-1 receptor agonists, semaglutide has consistently displayed the greatest short-term efficacy, with greater reductions in HbA1c and body weight versus a variety of comparators (including DPP4 inhibitor sitagliptin and GLP-1 receptor agonist dulaglutide) throughout the SUSTAIN clinical trial program and several network meta-analyses (NMAs) [18–23]. In patients without established cardiovascular or chronic kidney disease, European Association for the Study of Diabetes (EASD) guidelines indicate that DPP4 inhibitors, GLP-1 receptor agonists or sodium/glucose cotransporter 2 (SGLT2) inhibitors as a second-line therapy following metformin failure where there is a compelling need to minimize hypoglycemia [5]. In patients with established cardiovascular disease, certain GLP-1 receptor agonists have been associated with a reduced risk of major cardiovascular events (MACE), with semaglutide, liraglutide, and dulaglutide displaying the most favorable profiles in SUSTAIN 6, LEADER, and REWIND, respectively [24–26]. Sitagliptin, conversely, has only been associated with no significant increase in the risk of MACE in TECOS [27]. Considering results from these trials, EASD guidelines specifically recommend GLP-1 receptor agonists as the first-line injectable therapy in patients with a high risk of cardiovascular events or seeking to minimize weight gain [5]. In the latter case, semaglutide could be viewed as the preferred treatment option with the best efficacy for weight loss alongside a reduced risk of cardiovascular disease.

In addition to the primary outcome measure of change in HbA1c in the SUSTAIN clinical trial program, these trials also assessed the proportions of patients achieving clinically relevant single and composite endpoints. Previous cost of control analyses for semaglutide have assessed the cost of bringing patients to these endpoints in the US, but to date no such studies have been published for the Spanish setting [28]. From the medications assessed in the SUSTAIN clinical trials, sitagliptin and dulaglutide represent the most relevant comparators for semaglutide for the treatment of type 2 diabetes in Spain.

The aim of the present study was to provide relevant information for healthcare payers interested in treatments that target reductions in HbA1c while avoiding hypoglycemia and weight gain, through the assessment of the short-term costs of bringing patients with type 2 diabetes to three clinically relevant endpoints with semaglutide, sitagliptin, and dulaglutide in the Spanish setting.

METHODS

Modeling Approach

Short-term cost-effectiveness was assessed in terms of the cost per patient achieving each endpoint (cost of control), using a bespoke model built in Microsoft Excel (Microsoft Corporation, Redmond, WA) [28]. Four

interventions were evaluated: subcutaneous injectable once-weekly semaglutide 0.5 mg and 1 mg, orally administered once-daily sitagliptin 100 mg, and subcutaneous injectable once-weekly dulaglutide 1.5 mg. While the lower 0.75 mg dose of dulaglutide was also assessed in SUSTAIN 7, this is indicated only for monotherapy or in patients aged greater than 75 years by the European Medicines Agency (EMA), so this dose was not included in the present study [29]. Cost of control was calculated for three endpoints: HbA1c $< 7.0\%$, HbA1c $< 7.0\%$ without hypoglycemia and without weight gain, and a $\geq 1.0\%$ HbA1c reduction with $\geq 5.0\%$ weight loss. This approach allows the short-term cost-effectiveness of interventions to be evaluated in a simple, transparent, and clinically relevant manner. Analyses were performed over a 1-year time horizon, with no discounting applied.

The numbers of patients needed to treat to bring one patient to each of the three targets were calculated as the reciprocals of the proportions of patients achieving each target. Absolute cost of control was calculated by dividing the annual treatment cost of each medication by the proportions of patients achieving each target, while relative cost of control was calculated relative to semaglutide 1 mg, by dividing the absolute cost of control values for semaglutide 0.5 mg, sitagliptin, and dulaglutide by the value calculated for semaglutide 1 mg. The intervention with the lowest cost of control for a given endpoint can be considered the most cost-effective treatment option.

Clinical Data

Clinical data, in terms of the proportions of patients reaching each of the three endpoints included in the present analysis, were taken from the SUSTAIN 2 and SUSTAIN 7 clinical trials, for comparisons with sitagliptin and dulaglutide, respectively (Table 1) [18, 21, 30]. SUSTAIN 2 was a 56-week, randomized, double-blinded trial comparing semaglutide 0.5 mg and 1 mg with once-daily sitagliptin 100 mg in people with type 2 diabetes uncontrolled on metformin, pioglitazone, rosiglitazone, or combinations of either metformin and pioglitazone or metformin and rosiglitazone [18]. Concomitant medication use at baseline did not differ between the treatment arms, with 99.1% of participants receiving metformin and 5.1% of patients receiving a thiazolidinedione. SUSTAIN 7 was a 40-week, randomized, double-blinded trial comparing semaglutide 0.5 mg and 1 mg with once-weekly dulaglutide 0.75 mg and 1.5 mg in people with type 2 diabetes uncontrolled on metformin (100% of patients were receiving metformin with no patient receiving other concomitant diabetes medications at baseline) [21]. The proportions of patients achieving each endpoint were taken from the end of each trial. HbA1c was defined in percentage terms based on the National Glycohemoglobin Standardization Program approach. An HbA1c of 7% is equivalent to 53 mmol/mol, while a change in HbA1c of 1% is equivalent to a change of 10.9 mmol/mol. Hypoglycemia was defined as severe or blood glucose confirmed events, with a severe event defined based on the American Diabetes Association criteria of an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions, while a blood glucose confirmed event was defined as a plasma glucose measurement < 3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycemia.

Cost Data and Resource Use

Analyses were conducted from the perspective of a healthcare payer in Spain and costs were expressed in 2019 euros (EUR) [31]. Only medication acquisition costs were included, as sitagliptin is administered orally and needles are included in the semaglutide and dulaglutide packs (Table 2). It was assumed that patients would not require any self-monitoring of blood glucose (SMBG) testing, as the low levels of hypoglycemia associated with the included interventions were not expected to impact cost outcomes [18, 21].

The annual cost of treatment with semaglutide 0.5 mg or 1 mg was estimated to be

Table 1 Proportions of patients achieving endpoints in SUSTAIN 2 and SUSTAIN 7

Endpoint	Semaglutide 0.5 mg	Semaglutide 1 mg	Sitagliptin 100 mg	Dulaglutide 1.5 mg
SUSTAIN 2, mean (standard error)				
HbA1c < 7.0%	69% (2.3%)	78% (2.0%)	36% (2.4%)	–
HbA1c < 7.0% without hypoglycemia and without weight gain	63% (2.4%)	74% (2.2%)	27% (2.2%)	–
≥ 1.0% HbA1c reduction with ≥ 5.0% weight loss	35% (2.4%)	54% (2.1%)	9% (0.8%)	–
SUSTAIN 7, mean (standard error)				
HbA1c < 7.0%	68% (2.7%)	79% (2.4%)	–	67% (2.7%)
HbA1c < 7.0% without hypoglycemia and without weight gain	64% (2.8%)	74% (2.5%)	–	58% (2.9%)
≥ 1.0% HbA1c reduction with ≥ 5.0% weight loss	38% (2.8%)	59% (2.6%)	–	23% (2.4%)

HbA1c glycated hemoglobin, *SUSTAIN 2* semaglutide 0.5 mg $n = 409$, semaglutide 1 mg $n = 409$, sitagliptin $n = 407$, *SUSTAIN 7* semaglutide 0.5 mg $n = 301$, semaglutide 1 mg $n = 300$, dulaglutide 1.5 mg $n = 299$

Table 2 Medication costs included in the base case analysis

Medication	Pack contents (mg)	Pack price (EUR)	Reference
Semaglutide 0.5 mg	2	86.28	[31]
Semaglutide 1 mg	4	86.28	
Sitagliptin 100 mg	2800	30.83	
Dulaglutide 1.5 mg	6	86.28	

EUR 2019 euros, *SMBG* self-monitoring of blood glucose

EUR 1126, versus EUR 402 for sitagliptin and EUR 1126 for dulaglutide 1.5 mg. Sitagliptin was therefore estimated to be 36% as costly as semaglutide, while dulaglutide and semaglutide were associated with equivalent costs.

Sensitivity Analyses

Sensitivity analyses were conducted around the clinical inputs, which increased and decreased the proportions of patients achieving targets by one standard error, to examine the impact of changes in the input parameters on the results. Additionally, a probabilistic sensitivity analysis (PSA) was conducted. In this PSA, the proportion of patients achieving each target with each intervention was sampled, and the cost of control calculated. This process was repeated 1000 times, with the mean cost of control for each endpoint with each intervention calculated across all 1000 iterations, as results were stable at this number of iterations.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with

human participants or animals performed by any of the authors.

RESULTS

Base Case Analysis

Number Needed to Treat

Based on SUSTAIN 2, the numbers of patients needed to treat to bring one patient to target were lowest for semaglutide compared with sitagliptin across all three endpoints (Table 3). For HbA1c < 7.0%, 1.45, 1.28, and 2.78 patients would need to be treated with semaglutide 0.5 mg, semaglutide 1 mg, and sitagliptin, respectively, for one patient to achieve target, while approximately 1.59, 1.35, and 3.70 patients would need to be treated with semaglutide 0.5 mg, semaglutide 1 mg, and sitagliptin, respectively, for one patient to achieve a target of HbA1c < 7.0% without hypoglycemia and without weight gain. For a ≥ 1.0% reduction in HbA1c with ≥ 5.0% weight loss, 2.86, 1.85, and 11.11 patients would need to be treated with semaglutide 0.5 mg, semaglutide 1 mg, and sitagliptin, respectively, for one patient to achieve target.

Based on SUSTAIN 7, the numbers of patients needed to treat to bring one patient to target were lowest for semaglutide compared with dulaglutide across all three endpoints (Table 3). For HbA1c < 7.0%, 1.47, 1.27, and 1.49 patients would need to be treated with semaglutide 0.5 mg, semaglutide 1 mg, and dulaglutide 1.5 mg, respectively, for one patient to achieve target. For HbA1c < 7.0% without hypoglycemia and without weight gain, 1.56, 1.35, and 1.72 patients would need to be treated with semaglutide 0.5 mg, semaglutide 1 mg, and dulaglutide 1.5 mg, respectively, for one patient to achieve target, while for a ≥ 1.0% reduction in HbA1c with ≥ 5.0% weight loss, 2.63, 1.69, and 4.35 patients would need to be treated with semaglutide 0.5 mg, semaglutide 1 mg, and dulaglutide 1.5 mg, respectively, for one patient to achieve target.

Cost of Control

Based on SUSTAIN 2, annual costs of control were marginally higher for semaglutide 0.5 mg and 1 mg versus sitagliptin for the endpoints of HbA1c < 7.0% (EUR 1631, EUR 1443, and EUR 1117, respectively) and HbA1c < 7.0% without hypoglycemia and without weight gain (EUR 1787, EUR 1521, and EUR 1490, respectively), but substantially lower for the endpoint of a ≥ 1.0% reduction in HbA1c with ≥ 5.0% weight loss (EUR 3216, EUR 2084, and EUR 4469, respectively) (Fig. 1). Relative cost of control analysis showed that sitagliptin was associated with a better efficacy-to-cost ratio for endpoints of HbA1c < 7.0% and HbA1c < 7.0% without hypoglycemia and without weight gain, but semaglutide 0.5 mg and 1 mg were associated with better efficacy-to-cost ratios for the endpoint of ≥ 1.0% reduction in HbA1c with ≥ 5.0% weight loss (Table 3).

Based on SUSTAIN 7, both doses of semaglutide were associated with lower costs of control for all endpoints versus dulaglutide (Fig. 1). For the single endpoint of HbA1c < 7.0%, costs of control were estimated to be EUR 1655 with semaglutide 0.5 mg, EUR 1425 with semaglutide 1 mg, and EUR 1680 with dulaglutide 1.5 mg. For the composite endpoint of HbA1c < 7.0% without hypoglycemia and without weight gain, semaglutide 0.5 mg, semaglutide 1 mg, and dulaglutide 1.5 mg were associated with costs of control of EUR 1759, EUR 1521, and EUR 1941, respectively. Costs of control for the composite endpoint of ≥ 1.0% reduction in HbA1c with ≥ 5.0% weight loss were estimated to be EUR 2962, EUR 1908, and EUR 4894 for semaglutide 0.5 mg, semaglutide 1 mg, and dulaglutide 1.5 mg, respectively. Evaluation of relative cost of control showed that semaglutide was associated with a better efficacy-to-cost ratio versus dulaglutide for all three endpoints (Table 3).

Sensitivity Analyses

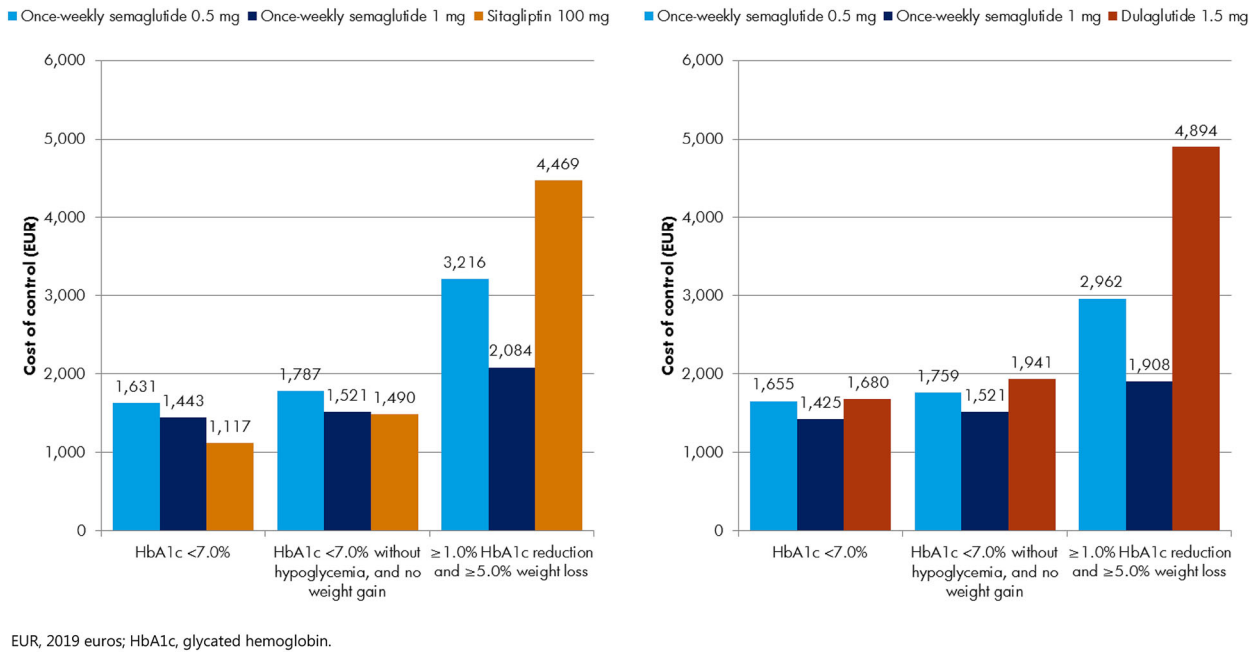
Sensitivity analyses, conducted around model inputs and assumptions, showed that the base case findings were robust to changes in these parameters, with cost of control results

Table 3 Number of patients needed to treat to bring one patient to target and cost of control results relative to semaglutide 1 mg

Endpoint	Semaglutide 0.5 mg	Semaglutide 1 mg	Sitagliptin 100 mg	Dulaglutide 1.5 mg
Number need to treat				
SUSTAIN 2				
HbA1c < 7.0%	1.45	1.28	2.78	–
HbA1c < 7.0% without hypoglycemia and without weight gain	1.59	1.35	3.70	–
≥ 1.0% HbA1c reduction with ≥ 5.0% weight loss	2.86	1.85	11.11	–
SUSTAIN 7				
HbA1c < 7.0%	1.47	1.27	–	1.49
HbA1c < 7.0% without hypoglycemia and without weight gain	1.56	1.35	–	1.72
≥ 1.0% HbA1c reduction with ≥ 5.0% weight loss	2.63	1.69	–	4.35
Cost of control relative to semaglutide 1 mg				
SUSTAIN 2				
HbA1c < 7.0%	113	100	77	–
HbA1c < 7.0% without hypoglycemia and without weight gain	117	100	98	–
≥ 1.0% HbA1c reduction with ≥ 5.0% weight loss	154	100	214	–
SUSTAIN 7				
HbA1c < 7.0%	116	100	–	118
HbA1c < 7.0% without hypoglycemia and without weight gain	116	100	–	128
≥ 1.0% HbA1c reduction with ≥ 5.0% weight loss	155	100	–	257

HbA1c glycated hemoglobin

remaining similar to the base case analyses in all scenarios (Table 4). Decreasing the proportions of patients achieving each endpoint by one standard error yielded higher cost of control values for all interventions. For SUSTAIN 2, cost of control was estimated to be EUR 1687, 1482, and 1196 for semaglutide 0.5 mg, semaglutide 1 mg, and sitagliptin, respectively, for HbA1c < 7.0%; EUR 1857, 1567, and 1622, respectively, for HbA1c < 7.0% without hypoglycemia and without weight gain; and EUR 3448, 2184, and 5305, respectively, for ≥ 1.0% reduction in HbA1c with ≥ 5.0% weight loss. For SUSTAIN 7, semaglutide 0.5 mg,



EUR, 2019 euros; HbA1c, glycated hemoglobin.

Fig. 1 Absolute cost of control based on SUSTAIN 2 and SUSTAIN 7. EUR 2019 euros, HbA1c glycated hemoglobin

semaglutide 1 mg, and dulaglutide 1.5 mg were associated with cost of control values of EUR 1723, 1468, and 1751, respectively, for HbA1c < 7.0%; EUR 1838, 1575, and 2041, respectively, for HbA1c < 7.0% without hypoglycemia and without weight gain; and EUR 3197, 2004, and 5473, respectively, for ≥ 1.0% reduction in HbA1c with ≥ 5.0% weight loss.

Increasing the proportions of patients achieving each endpoint by one standard error led to the converse effect, with lower cost of control values for all interventions. For SUSTAIN 2, cost of control for reaching the endpoint of HbA1c < 7.0% was estimated to be EUR 1579, 1406, and 1048 for semaglutide 0.5 mg, semaglutide 1 mg, and sitagliptin, respectively; application of HbA1c < 7.0% without hypoglycemia and without weight gain yielded cost of control values of EUR 1721, 1478, and 1377, respectively; and cost of control was estimated to be EUR 3013, 1993, and 3860, respectively, for ≥ 1.0% reduction in HbA1c with ≥ 5.0% weight loss. For SUSTAIN 7, cost of control for semaglutide 0.5 mg, semaglutide 1 mg, and dulaglutide 1.5 mg was estimated to be EUR 1592, 1384, and 1614, respectively, for HbA1c < 7.0%; EUR 1686, 1471, and 1850, respectively, for HbA1c < 7.0% without hypoglycemia and without weight gain; and EUR 2759, 1820, and 4425, respectively, for ≥ 1.0% reduction in HbA1c with ≥ 5.0% weight loss.

PSA, performed with sampling around the input data, resulted in comparable mean outcomes to the base case analysis (Table 4). Based on SUSTAIN 2, mean costs of control were EUR 1635, 1445, and 1123 for semaglutide 0.5 mg, semaglutide 1 mg, and sitagliptin, respectively, for a target of HbA1c < 7.0%; EUR 1791, 1522, and 1495, respectively, for a target of HbA1c < 7.0% without hypoglycemia and without weight gain; and EUR 3217, 2088, and 4589, respectively, for a ≥ 1.0% reduction in HbA1c with ≥ 5.0% weight loss. Based on SUSTAIN 7, mean costs of control for semaglutide 0.5 mg, semaglutide 1 mg, and dulaglutide 1.5 mg were EUR 1659, 1425, and 1683, respectively, for a target of HbA1c < 7.0%; EUR 1764, 1523, and 1945, respectively, for a target of HbA1c < 7.0% without hypoglycemia and without weight gain; and EUR 2980, 1913, and 4967, respectively, for a ≥ 1.0% reduction in HbA1c with ≥ 5.0% weight loss.

Table 4 Sensitivity analysis results

Analysis	Costs of control for SUSTAIN 2 (EUR)			Costs of control for SUSTAIN 7 (EUR)		
	Semaglutide 0.5 mg	Semaglutide 1 mg	Sitagliptin 100 mg	Semaglutide 0.5 mg	Semaglutide 1 mg	Dulaglutide 1.5 mg
HbA1c < 7.0%						
Base case	1631	1443	1117	1655	1425	1680
Proportion of patients reaching target minus one standard error	1687	1482	1196	1723	1468	1751
Proportion of patients reaching target plus one standard error	1579	1406	1048	1592	1384	1614
PSA	1635	1445	1123	1659	1425	1683
HbA1c < 7.0% without hypoglycemia and without weight gain						
Base case	1787	1521	1490	1759	1521	1941
Proportion of patients reaching target minus one standard error	1857	1567	1622	1838	1575	2041
Proportion of patients reaching target plus one standard error	1721	1478	1377	1686	1471	1850
PSA	1791	1522	1495	1764	1523	1945
≥ 1.0% HbA1c reduction with ≥ 5.0% weight loss						
Base case	3216	2084	4469	2962	1908	4894
Proportion of patients reaching target minus one standard error	3448	2184	5305	3197	2004	5473
Proportion of patients reaching target plus one standard error	3013	1993	3860	2759	1820	4425
PSA	3217	2088	4589	2980	1913	4967

EUR 2019 euros, *HbA1c* glycated hemoglobin, *PSA* probabilistic sensitivity analysis

DISCUSSION

The present analysis indicated that costs of control were highly dependent on the desired treatment target. Based on data from SUSTAIN 2, sitagliptin was associated with a lower cost of control when considering only glycemic control (HbA1c < 7.0%), but modern treatment targets for type 2 diabetes often incorporate additional clinically relevant parameters, as these have been shown to also reduce the risk of long-term complications

[10–12]. When these factors were considered in the endpoint of HbA1c < 7.0% without hypoglycemia and without weight gain, semaglutide 1 mg and sitagliptin were associated with comparable costs of control, while combination of these factors in the endpoint of ≥ 1.0% reduction in HbA1c with ≥ 5.0% weight loss led to both doses of semaglutide being associated with lower costs of control versus sitagliptin. Based on data from SUSTAIN 7, semaglutide yielded the lowest cost of control values for all three endpoints versus dulaglutide 1.5 mg. These short-term efficacy benefits are likely to confer long-term benefits in terms of fewer diabetes-related complications, as shown throughout the published literature [6–12]. These results also correlate with the latest EASD guidelines, which indicate semaglutide as the preferred GLP-1 receptor agonist in patients seeking to avoid weight gain [5]. The interventions included in this analysis differ in terms of glucose-lowering potential. The increased efficacy of semaglutide, particularly the 1 mg dose, compared with sitagliptin and dulaglutide 1.5 mg was the key driver of lower cost of control outcomes in the present analysis.

The captured costs, time horizon, and perspective should be considered when interpreting the findings of the present analysis. Only medication acquisition costs were included in the analysis—the costs of diabetes-related complications were not included, as these would not be expected to differ over the 1-year time horizon, and neither micro- nor macrovascular complications were assessed in SUSTAIN 2 or SUSTAIN 7. Moreover, the proportions of patients achieving the included endpoints from the two trials were taken from different time periods (56 weeks for SUSTAIN 2 and 40 weeks for SUSTAIN 7) and this should be considered when comparing the two sets of results, especially given the combination of these clinical data with annual treatment costs. However, intra-trial comparisons of semaglutide and the comparator used clinical data collected at the same time point, meaning any drawbacks of this approach should be equally prevalent in both treatment arms for these comparisons. Additionally, the present analysis is designed to complement, not replace, conventional long-term analyses, and demonstration of the short-term benefits of an intervention with clinically relevant endpoints offers additional pertinent information for healthcare payers considering short-term budgets. The approach used in the present analysis has also been previously demonstrated throughout the published literature [28, 32, 33]. Furthermore, how well the randomized controlled trial cohorts reflect the Spanish population with type 2 diabetes also needs to be considered. The SUSTAIN 2 and SUSTAIN 7 trials enrolled 6% and 5% of the total study participants in Spain. The patients enrolled in Spain were similar to those enrolled in other countries, and therefore it is likely that the clinical trials used to inform the present analysis are representative of the appropriate population in Spain.

To date, there is no evidence to inform indirect costs, such as lost workplace productivity, associated with semaglutide, sitagliptin, and dulaglutide in Spain. Therefore these costs were not included in the present analysis. As these costs become available, future analyses should look to capture these costs.

A further limitation was the threshold-based binary classifiers of glycemic control in both the single and composite endpoints. Whilst the threshold of 7% was based on the current EASD treatment guidelines and is therefore clinically relevant, glycemic control improvements observed in patients not reaching target (or not meeting or exceeding a 1.0% reduction) were not captured in the analysis. However, given the larger proportions of patients reaching target with semaglutide, and the lower HbA1c levels achieved relative to the other agents, this assumption is likely to be conservative from the semaglutide perspective [18–21].

Short-term analyses also offer several advantages over their long-term counterparts, primarily in their simplicity, transparency, and ease of interpretation, with outcomes that are easily explainable to both patients and healthcare professionals. Moreover, these analyses can be easily updated if new clinical data become available, or if medication prices change, and no long-term projections of short-term data are required (in contrast to typical long-term

diabetes modeling) avoiding the uncertainty associated with data extrapolation.

CONCLUSIONS

Based on data from SUSTAIN 2, sitagliptin was associated with a lower cost of control when considering solely glycemic control, but semaglutide 1 mg was associated with comparable or lower costs of control versus sitagliptin when considering composite endpoints incorporating avoidance of hypoglycemia and weight loss alongside glycemic control, and semaglutide 0.5 mg was associated with lower costs of control when considering the endpoint of $\geq$ 1.0% reduction in HbA1c with $\geq$ 5.0% weight loss. Based on data from SUSTAIN 7, semaglutide 0.5 mg and 1 mg were associated with lower costs of control compared with dulaglutide for both single endpoints capturing glycemic control and composite endpoints incorporating hypoglycemia risk and weight loss in Spain.

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