

Cost of Achieving HbA1c Treatment Targets and Weight Loss Responses with Once-Weekly Semaglutide Versus Dulaglutide in the United States

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ABSTRACT

Introduction: The National Health and Nutrition Examination Surveys show that many people with type 2 diabetes (T2D) in the USA fail to achieve recommended treatment targets. In the SUSTAIN 7 randomized controlled trial, once-weekly semaglutide (0.5 and 1.0 mg) was superior to comparative doses of dulaglutide (0.75 and 1.5 mg) in reducing glycated hemoglobin (HbA1c) and body weight in people with T2D. The present study estimated the cost per patient achieving HbA1c treatment targets and weight loss responses with once-weekly semaglutide and dulaglutide in the USA.

Methods: Numbers needed to treat and annual cost per patient achieving HbA1c targets (including a triple composite endpoint of HbA1c < 7% without hypoglycemia and no weight gain) or weight loss responses were calculated on the basis of data from SUSTAIN 7 and

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the annual cost of treatment from a US health-care payer perspective.

Results: More patients reached HbA1c targets with once-weekly semaglutide than with dulaglutide, and once-weekly semaglutide showed lower costs of control for all modeled endpoints. The cost per patient achieving the triple composite endpoint was USD 11,916 with once-weekly semaglutide 1.0 mg and USD 15,204 with dulaglutide 1.5 mg, representing a 28% larger cost with dulaglutide 1.5 mg. The cost of reaching the target was 68% larger with dulaglutide 0.75 mg versus once-weekly semaglutide 0.5 mg. For each patient achieving an HbA1c < 7%, the cost would be 18% larger with dulaglutide 1.5 mg than with once-weekly semaglutide 1.0 mg.

Conclusions: The cost of bringing one patient to the triple composite endpoint of an HbA1c < 7% without hypoglycemia and no weight gain would be 28% and 68% higher with dulaglutide 1.5 mg relative to once-weekly semaglutide 1.0 mg and dulaglutide 0.75 mg relative to once-weekly semaglutide 0.5 mg, respectively. Once-weekly semaglutide therefore provides better value for money than dulaglutide for the treatment of people with T2D in the USA.

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Keywords: Costs and cost analysis; Diabetes mellitus, type 2; Glucagon-like peptides; United States

INTRODUCTION

An estimated 23.1 million people were living with a diagnosis of diabetes in the USA in 2015 comprising 7.2% of the US population, and 1.5 million new cases of diabetes (6.7 per 1000 population) were diagnosed among US adults aged 18 years or older in 2015 alone [1]. Type 2 diabetes (T2D) comprises approximately 95% of all diabetes, corresponding to 21.9 million people in the USA with diagnosed T2D [1]. The total direct medical costs incurred by patients with prediabetes or diabetes in the USA was estimated to be USD 312.2 billion per year and is expected to increase further to USD 472.0 billion by 2030 [2]. Including non-medical costs, these figures increase to USD 407.6 billion in 2015 and a projected USD 622 billion in 2030 [2]. Of these costs, Dall et al. estimated that 91.4% of expenditure was incurred in patients with T2D [3], and the majority of all diabetes-related expenditure is associated with treating complications of diabetes, with a 2012 study from the American Diabetes Association (ADA) reporting that medication costs accounted for 10.4% of all diabetes-attributable expenditure and just 6.0% of all expenditure in patients with diabetes [4].

Given the high economic burden of treating diabetes complications and the negative effects on patient quality of life, reducing the incidence of complications is beneficial from both the healthcare payer and patient perspectives. Data from large-scale studies such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, conducted across 77 clinical centers in the USA and Canada, and the United Kingdom Prospective Diabetes Study (UKPDS) have shown that improvements in glycemic control reduce the risk of micro- and macrovascular complications in people with T2D [5–7]. The progressive nature of T2D typically necessitates a gradual intensification of treatment in order to achieve the goal of maintaining glycemic control. Since 2005, a number of new treatments have been approved for use in people with T2D, with the first glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1 RAs), dipeptidyl peptidase-4 (DPP-4)

inhibitors, and sodium–glucose cotransporter 2 (SGLT 2) inhibitors receiving approval from the US Food and Drug Administration (FDA) in 2005, 2006, and 2013, respectively [8–10].

On the basis of evidence from studies such as the ACCORD trial, the UKPDS and subsequent meta-analyses, the ADA recommends a glycated hemoglobin (HbA1c) target of < 7% in most patients, with a more stringent goal of 6.5% provided the patient does not experience significant hypoglycemia or other adverse effects of treatment [11]. In addition to maintaining tight glycemic control, the ADA guidelines also recommend reducing body weight (particularly in overweight or obese patients), minimizing the risk of hypoglycemia, and controlling blood pressure and serum lipid levels [12]. In considering these multifactorial treatment goals, the ADA notes that particular attention should be given to the likely effect of primary diabetes treatments on body weight and hypoglycemia [13].

The GLP-1 RAs are highly efficacious treatments offering glycemic control, reductions in body weight with a low risk of hypoglycemia. The ADA treatment guidelines recommend GLP-1 RAs as one option for dual therapy treatment in patients inadequately controlled with metformin alone within 3 months [13]. Once-weekly semaglutide is a novel GLP-1 analogue that is approved and marketed in the USA, the efficacy of which has been established in the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) trial program.

The aim of the present analysis was to evaluate the absolute and relative costs of bringing patients with T2D to various clinically relevant treatment targets suggested by ADA, covering glycemic control, weight loss, and hypoglycemia incidence, with once-weekly semaglutide relative to dulaglutide, based on the findings of the SUSTAIN 7 randomized controlled trial [14]. A cost of control modeling approach was selected on the basis of a previous analysis of liraglutide (a marketed GLP-1 RA) versus sitagliptin (a DPP-4 inhibitor) [15]. The approach of calculating the cost associated with bringing patients to a series of prespecified composite and single endpoints confers the benefit of balancing costs and effects in a

simple, transparent, and clinically relevant manner that is well suited to short-term evaluations of cost-effectiveness [15].

METHODS

Clinical Data

All of the clinical data driving the analysis were based on SUSTAIN 7, a 40-week randomized, open-label, active-controlled, parallel group, multicenter, multinational, four-armed, phase 3b trial comparing two dose levels of once-weekly semaglutide (0.5 and 1.0 mg) versus two dose levels of dulaglutide (0.75 and 1.5 mg) in subjects diagnosed with T2D inadequately controlled with metformin alone (Fig. 1) [14]. Of 1663 subjects evaluated for eligibility in the trial, 1201 patients were randomly assigned 1:1:1:1 to the four treatment arms, with 1199 patients ultimately receiving the study drug, 1129 patients completing the trial, and 1038 completing treatment. Mean HbA1c at baseline was 8.2% (66.4 mmol/mol) and mean body weight was 95.2 kg, corresponding to a mean body mass index of 33.5 kg/m² [14].

The primary endpoint was the change from baseline to week 40 in HbA1c, based on the full analysis and using data from the on-treatment without rescue observation period. The two principal comparisons were of once-weekly semaglutide 0.5 mg versus dulaglutide 0.75 mg

and once-weekly semaglutide 1.0 mg versus dulaglutide 1.5 mg. The confirmatory secondary endpoint was change from baseline to week 40 in body weight (kilograms). In brief, the once-weekly semaglutide doses were superior to the comparative dulaglutide doses in terms of glycemic control, based on a predetermined non-inferiority limit of 0.4% [14]. Treatment with once-weekly semaglutide also resulted in significantly greater weight loss than with dulaglutide with estimated treatment differences of – 2.26 and – 3.55 kg with once-weekly semaglutide 0.5 mg versus dulaglutide 0.75 mg and once-weekly semaglutide 1.0 mg versus dulaglutide 1.5 mg, respectively [14].

Model

A cost of control model was developed in Microsoft Excel (Microsoft Corporation, Redmond, WA) to evaluate the numbers needed to treat (NNT), and the absolute and relative costs of bringing a single patient to each of the pre-specified composite and single endpoints in SUSTAIN 7, covering glycemic targets, body weight, and hypoglycemia outcomes: (1) HbA1c lower than 7.0% without hypoglycemia and no weight gain, (2) HbA1c reduction of 1.0% or greater with 3.0% or larger weight loss, (3) HbA1c of 6.5% or lower, (4) HbA1c lower than 7.0%, 5.0% or larger weight loss, and (5) 10.0% or larger weight loss (Tables 1, 2).

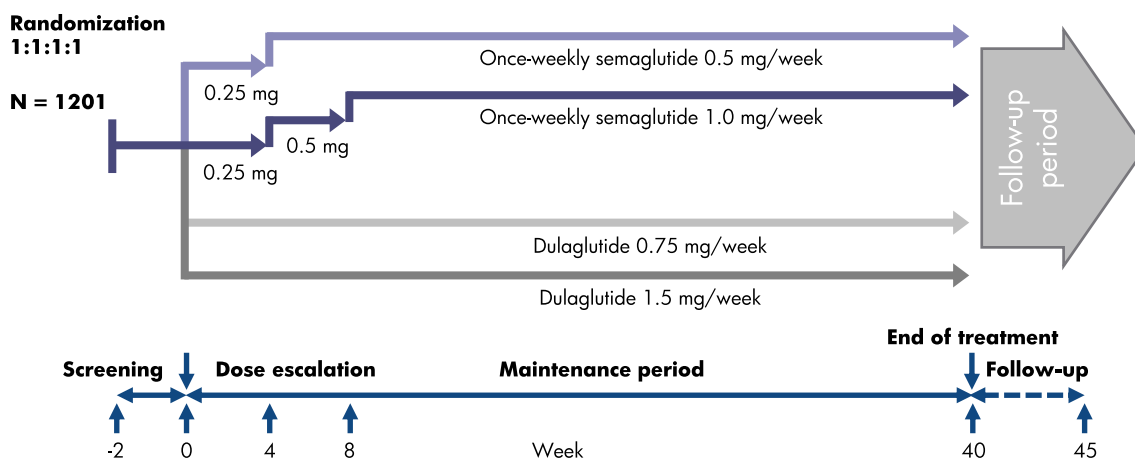


Fig. 1 Design of the SUSTAIN 7 randomized controlled trial

Table 1 Proportion of patients reaching target with once-weekly semaglutide 0.5 and 1.0 mg, and dulaglutide 0.75 and 1.5 mg, all in combination with metformin [14]

	Once-weekly semaglutide 0.5 mg (%)	Once-weekly semaglutide 1.0 mg (%)	Dulaglutide 0.75 mg (%)	Dulaglutide 1.5 mg (%)
HbA1c \leq 6.5%	49	67	34	47
HbA1c $<$ 7.0%	68	79	52	67
HbA1c $<$ 7.0% without hypoglycemia, and no weight gain	64	74	44	58
Weight loss \geq 5%	44	63	23	30
Weight loss \geq 10%	14	27	3	8
\geq 1.0% HbA1c reduction and \geq 3.0% weight loss	53	68	25	35

Table 2 Example cost of control calculation based on the proportion of patients achieving an HbA1c target of $<$ 7.0% without hypoglycemia and with no weight gain

	Once-weekly semaglutide 1.0 mg	Dulaglutide 1.5 mg	Interpretation
Annual drug cost (USD)	8818	8818	
Drug cost index	8818/8818 = 1.00	8818/8818 = 1.00	Once-weekly semaglutide 1.0 mg is at price parity with dulaglutide 1.5 mg
Drug efficacy (% of patients with HbA1c $<$ 7%, and no hypoglycemia or weight gain)	74%	58%	
Cost per patient achieving control (USD)	8818/ $74 \times 100 = 11,916$	8818/ $58 \times 100 = 15,204$	
Amount spent to achieve target relative to USD 1 spent on once-weekly semaglutide	11,916/ $11,916 = 1.00$	15,204/ $11,916 = 1.28$	For every USD 1 spent on bringing patients to target with once-weekly semaglutide 1.0 mg, USD 1.28 would have to be spent on dulaglutide 1.5 mg

Cost Data and Time Horizon

The analysis was conducted from the perspective of a private healthcare payer in the USA for 1 year, capturing expenditure on diabetes medication. No discounting was applied as no future costs were captured beyond the 1-year time horizon. The 1-year time horizon was selected

to align with a typical short-term forecasting period. The efficacy data were based on 40 weeks of follow-up data from the SUSTAIN 7 trial, and no extrapolation beyond the trial period was conducted, reducing uncertainty around the modeled outcomes. Drug prices for once-weekly semaglutide 0.5 and 1.0 mg, and dulaglutide 0.75 and 1.5 mg were based on the

Table 3 US drug prices in the base case analysis based on wholesale acquisition costs (WAC) in 2018 US dollars (January 2018)

Glucagon-like peptide 1 treatment	Pack contents (mg)	Pack price (USD)
Once-weekly semaglutide 0.5 mg	2	676.00
Once-weekly semaglutide 1.0 mg	4	676.00
Dulaglutide 0.75 mg	3	676.00
Dulaglutide 1.5 mg	6	676.00

2018 wholesale acquisition cost (WAC) prices from the Price-Rx database (Table 3). Adherence to both dulaglutide and once-weekly semaglutide was assumed to be 100%. No other costs were captured in the base case analysis; needles are included in the once-weekly GLP-1 packs, and self-monitoring of blood glucose (SMBG) test strip utilization was assumed to be the same regardless of the GLP-1 RA in use.

Effectiveness and Cost-Effectiveness Calculations

The NNT for one patient to reach each endpoint was calculated in absolute terms for each comparator (i.e., the reciprocal of the proportion of patients reaching each target). Cost of control calculations were similarly conducted by dividing the annual treatment cost by the proportion of patients reaching each target to give the absolute cost of control. The approach was conservative from the once-weekly semaglutide perspective, capturing a full year of treatment costs despite control being achieved after 40 weeks in SUSTAIN 7. In addition to the absolute cost of control calculations, relative costs of control were calculated by referencing the cost of control to once-weekly semaglutide 1.0 mg.

Sensitivity Analyses

A series of one-way sensitivity analyses were conducted around the base case, including varying the proportion of patients reaching each target by an approximation of the standard error (SE) derived using the following formula where n represents the number of patients in each arm of SUSTAIN 7 and p represents the proportion of patients reaching target:

$$\sqrt{\frac{1}{n}p(1-p)}. \quad (1)$$

Other one-way sensitivity analyses were conducted in which the costs of SMBG test strips and lancets were captured in an analysis assuming one test would be conducted per day.

Compliance with Ethics

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

Numbers Needed to Treat

The proportions of patients reaching each target were higher with once-weekly semaglutide than dulaglutide (Fig. 2). The high dose of once-weekly semaglutide and dulaglutide resulted in more patients reaching the target (and therefore a lower number needed to treat for one patient to reach the target) than the low dose of each intervention. Of all targets investigated, the most pronounced differences were in the $\geq 10\%$ weight loss endpoint, in which the numbers needed to treat with once-weekly semaglutide were 7.1 and 3.7 for the 0.5 and 1.0 mg doses, respectively, compared with 33.3 and 12.5 for the dulaglutide 0.75 and 1.5 mg doses, respectively.

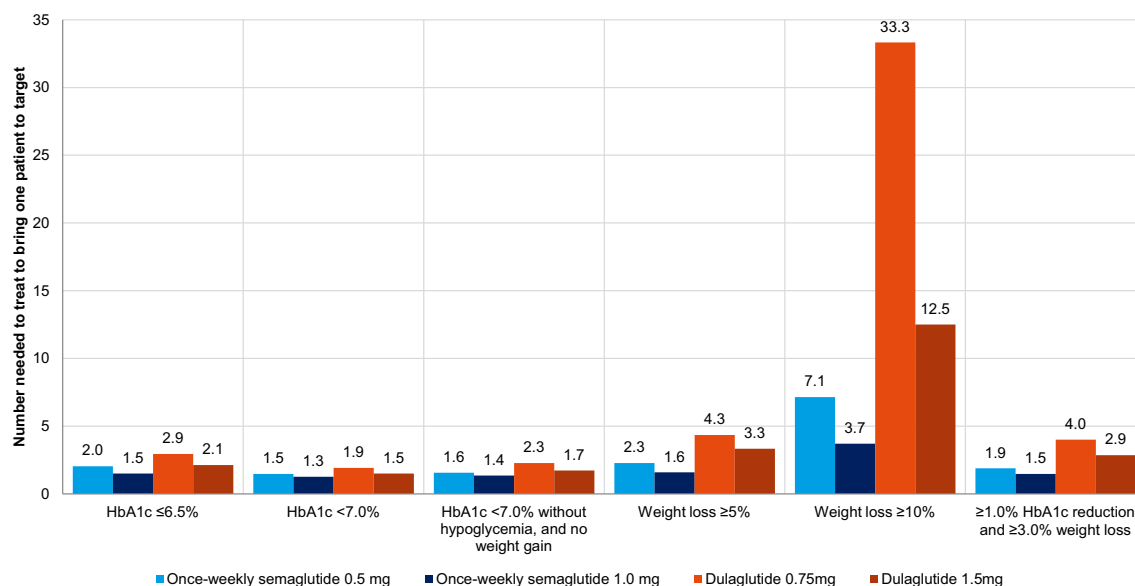


Fig. 2 Numbers needed to treat to bring one patient to target with once-weekly semaglutide 0.5 and 1.0 mg, and dulaglutide 0.75 and 1.5 mg. HbA1c, glycated hemoglobin

Cost of Control

The annual drug cost was USD 8818 per patient with both semaglutide doses and both dulaglutide doses owing to the weekly cost equivalence and the assumption of 100% adherence to all doses.

The absolute cost of control was calculated for each of once-weekly semaglutide and dulaglutide doses across the six clinical endpoints (Table 4). Costs of achieving control were universally lower with the once-weekly semaglutide vs dulaglutide, and the high dose of each GLP-1 RA uniformly resulted in lower costs of control than the low dose. For patients reaching the triple composite endpoint, the cost of control with once-weekly semaglutide 0.5 and 1.0 mg was USD 13,778 and USD 11,916, compared with USD 20,041 and 15,204 with dulaglutide 0.75 and 1.5 mg, respectively. This corresponds to an increased cost with dulaglutide 0.75 and 1.5 mg of USD 6263 and 3288, respectively. Relative costs of control were also calculated using once-weekly semaglutide 1.0 mg as the reference with an index of 100 (Fig. 3). The cost of bringing one patient to the triple composite endpoint was 16% higher with once-weekly semaglutide 0.5 mg, 28% higher

with dulaglutide 1.5 mg, and 68% higher with dulaglutide 0.75 mg.

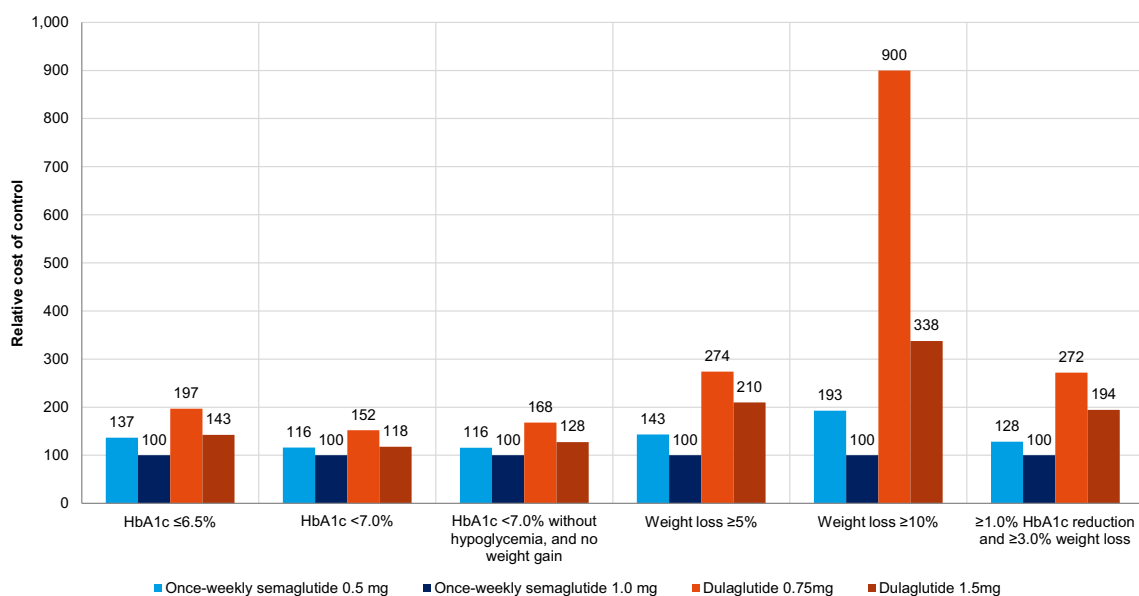
The costs associated with bringing patients to an HbA1c target below 7.0% were lower than the cost of bringing patients to 6.5% or lower. The cost of bringing one patient to an HbA1c target lower than 7.0% was USD 3990 lower with once-weekly semaglutide 0.5 mg than dulaglutide 0.75 mg, and USD 1999 lower with once-weekly semaglutide 1.0 mg than dulaglutide 1.5 mg. The corresponding cost of bringing patients to 6.5% or lower were reduced by USD 7940 with once-weekly semaglutide 0.5 mg relative to dulaglutide 0.75 mg (USD 17,996 versus USD 25,936; Table 4) and by USD 5601 with once-weekly semaglutide 1.0 mg relative to dulaglutide 1.5 mg (USD 13,161 versus USD 18,762; Table 4).

Costs savings with once-weekly semaglutide were more pronounced with the weight loss endpoints, with cost reductions of USD 18,299 and USD 15,397 associated with using the low and high doses of once-weekly semaglutide relative to the comparative doses of dulaglutide for weight loss $\geq 5\%$, and cost reductions of USD 230,952 and USD 77,567 associated with using the low and high doses of once-weekly

Table 4 Absolute annual cost of control outcomes with once-weekly semaglutide 0.5 and 1.0 mg, and dulaglutide 0.75 and 1.5 mg in 2018 US dollars

Endpoint	Once-weekly semaglutide 0.5 mg (USD)	Once-weekly semaglutide 1.0 mg (USD)	Dulaglutide 0.75 mg (USD)	Dulaglutide 1.5 mg (USD)
HbA1c < 7.0% without hypoglycemia, and no weight gain	13,778	11,916	20,041	15,204
HbA1c < 6.5%	17,996	13,161	25,936	18,762
HbA1c < 7.0%	12,968	11,162	16,958	13,161
Weight loss \geq 5%	20,041	13,997	38,340	29,394
Weight loss \geq 10%	62,987	32,660	293,939	110,227
\geq 1.0% HbA1c reduction and \geq 3.0% weight loss	16,638	12,968	35,273	25,195

HbA1c glycated hemoglobin

**Fig. 3** Relative cost of control with once-weekly semaglutide 0.5 mg, dulaglutide 0.75 mg, and dulaglutide 1.5 mg versus once-weekly semaglutide 1.0 mg (index = 100). HbA1c, glycated hemoglobin

semaglutide relative to the comparative doses of dulaglutide for weight loss \geq 10%.

The lowest cost of bringing a single patient to a target was USD 11,162 to bring one patient to an HbA1c value less than 7.0% with once-weekly semaglutide 1.0 mg; the corresponding cost with

dulaglutide 1.5 mg was USD 13,161 corresponding to an increased cost of 18% with dulaglutide 1.5 mg. The highest cost of a single patient achieving response was associated with the 10.0% or larger weight loss endpoint, which would cost USD 293,939 with dulaglutide 0.75 mg.

Table 5 One-way sensitivity analysis results showing absolute annual cost of control outcomes with once-weekly semaglutide 0.5 and 1.0 mg, and dulaglutide 0.75 and 1.5 mg in 2018 US dollars

Endpoint	Once-weekly semaglutide 0.5 mg (USD)	Once-weekly semaglutide 1.0 mg (USD)	Dulaglutide 0.75 mg (USD)	Dulaglutide 1.5 mg (USD)
HbA1c \leq 6.5%	17,996	13,161	25,936	18,762
Proportion reaching target + 1 SE; - 1 SE	16,997-19,121	12,649-13,717	24,002-28,209	17,677-19,990
Including daily SMBG tests	18,965	13,870	27,331	19,772
HbA1c < 7.0%	12,968	11,162	16,958	13,161
Proportion reaching target + 1 SE; - 1 SE	12,475-13,502	10,840-11,505	16,065-17,956	12,648-13,718
Including daily SMBG tests	13,666	11,763	17,870	13,870
HbA1c < 7.0% without hypoglycemia, and no weight gain	13,778	11,916	20,041	15,204
Proportion reaching target + 1 SE; - 1 SE	13,207-14,401	11,522-12,339	18,814-21,440	14,491-15,991
Including daily SMBG tests	14,520	12,558	21,120	16,022
Weight loss \geq 5%	20,041	13,997	38,340	29,394
Proportion reaching target + 1 SE; - 1 SE	18,818-21,435	13,404-14,645	34,671-42,877	27,008-32,242
Including daily SMBG tests	21,120	14,750	40,403	30,975
Weight loss \geq 10%	62,987	32,660	293,939	110,227
Proportion reaching target + 1 SE; - 1 SE	55,114-73,485	29,828-36,086	221,199-437,960	92,154-137,118
Including daily SMBG tests	66,376	34,417	309,755	116,158
\geq 1.0% HbA1c reduction and \geq 3.0% weight loss	16,638	12,968	35,273	25,195
Proportion reaching target + 1 SE; - 1 SE	15,781-17,593	12,474-13,503	32,061-39,199	23,354-27,350
Including daily SMBG tests	17,533	13,666	37,171	26,550

Sensitivity Analyses

One-way sensitivity analyses showed that, when decreasing the proportion of patients reaching target by one SE with once-weekly semaglutide and simultaneously increasing the proportion of patients reaching target with the

comparative dose of dulaglutide by one SE, the cost of control for once-weekly semaglutide was still lower in every comparison with dulaglutide (Table 5). Analyses in which once-daily SMBG testing was included in the analysis increased the absolute cost of control of reaching all targets, but did not change any of the relative

outcomes. Thus, the sensitivity analyses supported the conclusions from the estimated cost analysis.

DISCUSSION

The present study used the SUSTAIN 7 findings from 1201 patients with T2D to compare the cost of bringing a patient to each of six predefined clinical endpoints in the trial with once-weekly semaglutide 0.5 and 1.0 mg relative to dulaglutide 0.75 and 1.5 mg. Once-weekly semaglutide was superior to dulaglutide in reduction of HbA1c and body weight at 40 weeks. The modeling analysis showed that bringing patients to a series of clinically relevant endpoints investigated in SUSTAIN 7 would result in cost savings with once-weekly semaglutide relative to dulaglutide.

The analysis serves as a comparative tool for payers interested in a short-term time horizon; longer time horizons or stakeholders that require comparisons to be drawn with other antihyperglycemic agents would be better addressed by an analysis in which the cost per quality-adjusted life year (QALY) gained were calculated. This is due to the presentation of all cost of control endpoints in natural units (e.g., the cost of reducing HbA1c to < 7.0% in one patient) for which no willingness-to-pay thresholds are established. In increasing the transparency of the analysis, this approach simultaneously limits the generalizability and comparability of the findings in the context of other economic analyses of antihyperglycemic agents. As with previous cost of control analyses, the present analysis is intended to provide complementary information to assist decision-makers with shorter time horizons [16]. It is worth noting that “absolute” NNTs were selected to avoid the introduction of multiple pairwise comparisons across the four doses included in the analysis that would have arisen with the use of relative NNT values calculated as the reciprocal of the absolute risk reduction. Adopting the former approach avoids the need to present negative NNTs or numbers needed to harm (NNH) for certain comparisons.

When considering the importance of the findings, the clinical relevance of the prespecified endpoints should first be considered. HbA1c targets of $\leq 6.5\%$ and $< 7.0\%$ are considered clinically relevant by the American Association of Clinical Endocrinologists (AACE) and the ADA, who use the targets as the centerpiece of their respective treatment guidelines for T2D [17], while a weight loss of 5% or more improves metabolic and cardiovascular risk factors [18]. The clinical basis for the benefits of once-weekly semaglutide over dulaglutide may arise from its lower molecular weight relative to dulaglutide (4 kDa relative to 63 kDa), facilitating uptake in the brain and resulting in appetite regulation effects and clinically relevant weight loss [19, 20].

Given the lower HbA1c values achieved with once-weekly semaglutide, the analysis is likely to be highly conservative from the longer-term perspective of a payer covering both the initial drug costs and subsequent treatment of diabetes complications; the short time horizon of the present analysis reduces the likelihood that any significant differences in complication incidence would be observed. As with all modeling analyses, there are a number of caveats and limitations of the present study that should be acknowledged and considered when interpreting the results. Firstly, the captured costs and the payer perspective should be taken into account. The analysis only captured the drug costs based on wholesale acquisition costs (WAC); costs of SMBG tests were not captured, nor were any interactions with healthcare professionals, or costs associated with onset or ongoing treatment of diabetes complications. Sensitivity analyses were conducted in which once-daily SMBG test costs were captured, showing no substantive changes in outcomes from the base case analysis. The use of WAC prices for the drug costs may not reflect the costs ultimately borne by the healthcare payer as a result of privately negotiated discounts, manufacturer rebates, or patient co-pay to offset the cost of the drug. Work has recently been published on presenting budget impact calculations over ranges of discount or rebate scenarios for two comparators, which could be integrated into future cost of control analyses to

present cost of control scenarios in which different discounts or rebates are secured for each comparator [21]. The present analysis has illustrated the short-term costs of bringing patients to various treatment targets and weight loss responses with once-weekly semaglutide relative to dulaglutide in patients with type 2 diabetes in the US setting. Further research would be required to complement the present analysis with an evaluation of the relative cost-effectiveness of the two interventions over longer time horizons.

CONCLUSIONS

The cost of bringing one patient to the triple composite endpoint of an HbA1c < 7% without hypoglycemia and no weight gain would be 28% and 68% higher with dulaglutide 1.5 mg relative to once-weekly semaglutide 1.0 mg and dulaglutide 0.75 mg relative to once-weekly semaglutide 0.5 mg, respectively. Once-weekly semaglutide therefore provides better value for money than dulaglutide for the treatment of people with T2D in the USA.

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Compliance with Ethics Guidelines. This article does not contain any new studies of human or animal subjects performed by any of the authors.

Data Availability. All data generated or analyzed during this study are included in this published article.

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