ORIGINAL RESEARCH

Management of Patients with Type 2 Diabetes with Once-Weekly Semaglutide Versus Dulaglutide, Exenatide ER, Liraglutide and Lixisenatide: A Cost-Effectiveness Analysis in the Danish Setting

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ABSTRACT

Introduction: Once-weekly semaglutide is a novel glucagon-like peptide-1 (GLP-1) analog for the treatment of type 2 diabetes (T2D) that has been associated with greater reductions in glycated hemoglobin (HbA1c) and body weight versus GLP-1 receptor agonists dulaglutide, exenatide extended-release (ER), liraglutide and lixisenatide in the SUSTAIN trial program and a network meta-analysis (NMA). The aim of the

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present study was to assess the long-term cost-effectiveness of semaglutide versus all available GLP-1 receptor agonists in Denmark, using a clinically orientated treatment approach.
Methods: Outcomes were projected over patient lifetimes using the IQVIA CORE Diabetes Model. Baseline characteristics and treatment effects were sourced from the corresponding SUSTAIN trials and the NMA. Patients were assumed to initiate GLP-1 receptor agonist therapy and subsequently treatment-intensify according to clinical treatment guidelines, with addition of basal insulin and switching to basal-bolus insulin occurring when HbA1c exceeded recommended targets. Patients were assumed to receive a GLP-1 receptor agonist plus basal insulin therapy once HbA1c levels reached 7.5% and a basal-bolus insulin regimen once HbA1c exceeded 8.0%. Costs were captured in 2017 Danish kroner (DKK), with future costs and outcomes discounted at 3% per annum.
Results: Primary analyses indicated that semaglutide 0.5 mg and 1 mg were associated with improvements in quality-adjusted life expectancy of 0.11 and 0.34 quality-adjusted life years, respectively, versus dulaglutide, achieved at cost savings of DKK 289 and DKK 13,416, respectively. Supporting analyses indicated that both doses of semaglutide were either cost-effective or dominant versus exenatide ER, liraglutide 1.2 mg and 1.8 mg and lixisenatide.

Conclusion: Semaglutide represents a cost-effective alternative to other GLP-1 receptor agonist therapies available in Denmark, demonstrating clinical benefits versus dulaglutide, exenatide ER, liraglutide and lixisenatide for the treatment of patients with T2D.

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PLAIN LANGUAGE SUMMARY

- As the prevalence and associated costs of diabetes increase, choosing cost-effective treatments is becoming ever more important.
- Studies have shown that early, multifactorial treatments that improve glycemic control and body weight reduce the risk of long-term diabetes-related complications.
- In the SUSTAIN clinical trial program, once-weekly semaglutide was associated with improved efficacy versus dulaglutide and exenatide extended-release (ER), while in a network meta-analysis, semaglutide was associated with improved efficacy versus liraglutide and lixisenatide in terms of greater HbA1c reductions and weight loss in patients with type 2 diabetes.
- The present analysis used a clinical treatment approach to assess the long-term cost-effectiveness of semaglutide versus all available GLP-1 receptor agonists for the treatment of patients with type 2 diabetes not achieving glycemic control on oral antidiabetic medications from a healthcare payer perspective in Denmark.
- Semaglutide 0.5 mg and 1 mg were associated with improved life expectancy and quality-adjusted life expectancy versus all comparators over the 50 years of the analysis. Semaglutide 0.5 mg was associated with delayed treatment intensification by between 1 and 4 years, reduced costs versus dulaglutide, liraglutide 1.8 mg and lixisenatide, and increased costs versus exenatide ER and liraglutide 1.2 mg, while semaglutide 1 mg was associated with delayed intensification by between 3 and 6 years and reduced costs versus all comparators over patient lifetimes.
- Both semaglutide doses therefore offer highly cost-effective alternatives to dulaglutide, exenatide ER, liraglutide and lixisenatide for the treatment of patients with type 2 diabetes in Denmark.

INTRODUCTION

Diabetes accounts for a substantial clinical and economic burden in Denmark, with 6.4% of the adult population living with diabetes in 2017 and diabetes-related direct and societal costs exceeding EUR 7.0 billion [1, 2]. Almost 60% of diabetes-related healthcare expenditure has been attributed to the 25% of patients who experience major diabetes-related complications, demonstrating the need for treatments that target the risk factors of these events [2]. Recent post hoc analysis of the Danish Steno-2 Study has suggested that intensive therapy targeting multiple short-term risk factors greatly increases life expectancy of patients with type 2 diabetes (T2D), without increasing the current level of expenditure seen with conventional therapy [3]. These findings correlate with several landmark studies, which have indicated that improvements in glycated hemoglobin (HbA1c), body weight, systolic blood pressure, plasma lipids and hypoglycemia risk are associated with a substantially reduced risk of long-term diabetes-related complications [4–14]. Early, multifactorial treatment that improves glycemic control while reducing body weight is therefore imperative to directly improve patients' quality of life while reducing costs for the healthcare payer [3, 10].

The Danish healthcare system provides healthcare for all Danish citizens and is based on the principles of free and equal access to healthcare for all. In Denmark, approximately 74% of patients with T2D are diagnosed, and among those 90% receive care within the last year of their diagnosis [15]. In newly diagnosed patients, only 30% of those receiving therapy in

primary care achieve an HbA1c level ≤ 7.0%, while 12% of patients have an HbA1c level ≥ 8.0% [16]. Moreover, results from a large Danish cohort study indicated that metformin monotherapy is often insufficient to maintain glycemic control, with 9678 out of 45,268 patients (21.4%) requiring treatment intensification with a second anti-diabetic therapy after 3 years, following a mean HbA1c level of 8.0% (64 mmol/mol) prior to intensification [17]. Additionally, patients with T2D often struggle to maintain a healthy body mass index (BMI), with approximately 80% of patients classified as either overweight (BMI 25.0–29.9 kg/m^2) or obese (BMI ≥ 30.0 kg/m^2) [18]. Novel, multifactorial treatments could therefore greatly benefit patients with T2D in Denmark.

Glucagon-like peptide-1 (GLP-1) receptor agonists are a class of multifactorial T2D medications that have been shown to improve numerous risk factors for diabetes-related complications, including glycemic control and body weight [19–22]. In addition, recent cardiovascular outcomes trials (CVOTs) have shown that long-acting human GLP-1 receptor agonists, including liraglutide, semaglutide, dulaglutide and albiglutide, are associated with improved cardiovascular outcomes in patients with T2D [23–26]. In Denmark, available GLP-1 receptor agonists include the once-weekly variants semaglutide, dulaglutide and exenatide extended-release (ER) and the once-daily variants liraglutide and lixisenatide. These therapies are recommended as a second-line therapy for patients with T2D with inadequate glycemic control (HbA1c > 7.0%) on metformin, particularly those with established cardiovascular disease, in line with the latest American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) guidelines [27, 28]. Additionally, ADA guidelines recommend considering dual therapy in patients with newly diagnosed type 2 diabetes with an HbA1c ≥ 1.5% above their glycemic target [29].

Once-weekly semaglutide is a novel GLP-1 analog that has been associated with improved glycemic control and weight loss versus all comparators throughout the SUSTAIN trial program, including dulaglutide 0.75 mg and 1.5 mg in the 40-week SUSTAIN 7 trial and exenatide ER in the 56-week SUSTAIN 3 trial [30–32]. In addition, a network meta-analysis (NMA) has shown that semaglutide is associated with similar benefits versus liraglutide 1.2 mg, liraglutide 1.8 mg and lixisenatide [33].

The primary aim of the present analysis was to assess the long-term cost-effectiveness of semaglutide using a clinically relevant approach, with treatment intensification occurring at defined HbA1c thresholds. This recognized that glycemic control becomes increasingly difficult over the long term as T2D progresses. Previous long-term cost-effectiveness analyses of GLP-1 receptor agonists have focused on a more simplified treatment switching pattern with a fixed time period for each intervention before intensification to rescue therapy. Although this offers pertinent information for health technology assessments, such a treatment approach is less relevant from a clinical perspective. Primary analyses assessed the long-term cost-effectiveness of semaglutide 0.5 mg and 1 mg versus dulaglutide 1.5 mg for the treatment of patients with T2D not achieving glycemic control on metformin from a healthcare payer perspective in Denmark. Supporting analyses were also prepared to compare semaglutide 0.5 mg and 1 mg with the remaining GLP-1 receptor agonists available in Denmark, including exenatide ER, lixisenatide and liraglutide 1.2 mg and 1.8 mg.

METHODS

Model Overview

Analyses were performed using the IQVIA CORE Diabetes Model (version 9.0), a non-product specific diabetes policy analysis tool based on a series of inter-dependent sub-models that simulate short- and long-term diabetes-related complications, with projected outcomes validated against real-life data in 2004 and more recently in 2014 [34, 35]. The model projects outcomes for populations based on user inputs, including baseline cohort characteristics and history of complications; current and future diabetes management and concomitant medications; screening strategies; and changes in

physiological parameters over time [36]. Each of the 15 sub-models, which simulate angina, congestive heart failure, myocardial infarction, stroke, peripheral vascular disease, macular edema, cataract, retinopathy, nephropathy, neuropathy, foot ulcer and amputation, hypoglycemia, ketoacidosis, lactic acidosis and non-specific mortality, has a semi-Markov structure and uses time, state, time-in-state and diabetes type-dependent probabilities derived from published sources. Model outputs include life expectancy (measured in years), quality-adjusted life expectancy (measured in quality-adjusted life years [QALYs]), cumulative incidence and time to onset of diabetes-related complications, direct medical costs, and cost-effectiveness scatterplots and acceptability curves. Incremental cost-effectiveness ratios (ICERs), calculated as the incremental cost per unit of effectiveness gained by using the new intervention versus the comparator, can be used as a measure of cost-effectiveness where an intervention is associated with improved clinical outcomes at an increased cost.

All base case analyses were projected over patient lifetimes (up to 50 years) and utilized UK Prospective Diabetes Study (UKPDS) 68 risk equations, with background mortality based on Danish-specific life tables from the World Health Organization (WHO) [37]. This approach was chosen to capture all relevant long-term complications and costs and to assess the impact of each intervention on life expectancy and quality-adjusted life expectancy, in line with previous analyses of GLP-1 receptor agonists and the guidance on assessing the cost-effectiveness of interventions for diabetes [38–41]. All base case and sensitivity analyses were performed using a first-order Monte Carlo approach, with probabilistic sensitivity analyses performed separately using a second-order Monte Carlo approach. Clinical and cost outcomes were discounted at 3.0% annually, consistent with guidelines for health economic analyses in the Danish setting [42].

Clinical Data for the Primary Analysis

Clinical data, including baseline cohort characteristics and treatment effects, were sourced from SUSTAIN 7 for primary comparisons of semaglutide versus dulaglutide (Table 1 and Table S1). Data were obtained from pre-specified end points wherever possible, but to fulfill all of the data requirements for an analysis using the IQVIA CORE Diabetes Model, a number of post hoc analyses of the trial data were required. Pre-specified statistical analyses in SUSTAIN 7 assessed the statistical significance of differences in treatment effects between semaglutide 1 mg and dulaglutide 1.5 mg, but post hoc analyses were required to assess the statistical significance of differences in treatment effects between semaglutide 0.5 mg and dulaglutide 1.5 mg. While dulaglutide 0.75 mg was also assessed in SUSTAIN 7, this is indicated only for monotherapy or in patients aged > 75 years by the European Medicines Agency (EMA), so this dose was not included in the present study [43]. Treatment effects (both statistically and non-statistically significant differences, in line with ISPOR guidance) were applied in the first year of the analysis, while hypoglycemic event rates from SUSTAIN 7 were applied until patients treatment-intensified with the addition of basal insulin [44].

Clinical Data for the Supporting Analyses

Baseline cohort characteristics and treatment effects for supporting comparison of semaglutide 1 mg with exenatide ER were sourced from SUSTAIN 3 (Table 1 and Table S1). For supporting comparisons of semaglutide with exenatide ER, liraglutide and lixisenatide, treatment effect data were obtained from the NMA, with baseline patient characteristics based on the SUSTAIN 7 cohort (Table 1 and Table S1). Changes from baseline in HbA1c, systolic blood pressure and BMI (the outcomes included in the NMA that were applicable to an analysis using the IQVIA CORE Diabetes Model) versus placebo were applied in all treatment arms, with both statistically significant and non-statistically significant differences included. Where

Table 1 Treatment effects and adverse event rates applied in the analyses

Parameter	SUSTAIN 7			SUSTAIN 3		NMA				
	Semaglutide 0.5 mg	Semaglutide 1 mg	Dulaglutide 1.5 mg	Semaglutide 1 mg	Exenatide ER	Semaglutide 0.5 mg	Semaglutide 1 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Lixisenatide
Physiological parameters, means (standard errors)										
HbA1c (%)	− 1.51 (0.06)	− 1.78 (0.06)*	− 1.37 (0.06)	− 1.54 (0.06)*	− 0.92 (0.06)	− 1.23 (0.13)[¤,‡]	− 1.47 (0.12)[¤,†,‡]	− 0.87 (0.12)	− 1.11 (0.10)	− 0.56 (0.20)
Systolic blood pressure (mmHg)	− 2.44 (0.76)	− 4.88 (0.77)	− 2.86 (0.75)	− 4.60 (0.68)*	− 2.23 (0.70)	− 5.41 (1.55)	− 6.28 (1.52)[†,‡]	− 4.45 (1.39)	− 4.21 (1.36)	− 3.00 (1.93)
Diastolic blood pressure (mmHg)	− 0.57 (0.48)	− 2.05 (0.49)*	− 0.03 (0.47)	− 1.00 (0.45)	− 0.10 (0.46)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total cholesterol (mmol/l)	− 0.18 (0.04)	− 0.14 (0.05)	− 0.07 (0.05)	− 0.24 (0.04)	− 0.15 (0.05)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HDL cholesterol (mmol/l)	− 0.01 (0.01)*	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.00 (0.01)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LDL cholesterol (mmol/l)	− 0.08 (0.04)	− 0.01 (0.04)	0.02 (0.04)	− 0.12 (0.04)	− 0.09 (0.04)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Triglycerides (mmol/l)	− 0.16 (0.03)	− 0.25 (0.03)	− 0.19 (0.03)	− 0.28 (0.04)*	− 0.05 (0.04)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BMI (kg/m^2)	− 1.63 (0.10)*	− 2.33 (0.10)*	− 1.08 (0.10)	− 2.01 (0.10)*	− 0.65 (0.10)	− 0.86 (0.10)[¤,‡]	− 1.35 (0.10)[¤,†,‡]	− 0.64 (0.10)	− 0.73 (0.09)	− 0.32 (0.18)
Estimated glomerular filtration rate (ml/min/1.73 m^2)	− 2.42 (0.48)	− 2.80 (0.49)	− 3.51 (0.47)	− 5.83 (0.76)	− 5.27 (0.76)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hypoglycemia event rates, per 100 patient-years										
Non-severe hypoglycemia	1.28	2.60	1.26	9.66	11.27	0.00	0.00	0.00	0.00	0.00
Severe hypoglycemia	0.00	0.43	0.84	0.24	0.00	0.00	0.00	0.00	0.00	0.00
Proportion of non-severe events that are nocturnal	0.00	0.00	0.00	0.10	0.15	0.00	0.00	0.00	0.00	0.00

Table 1 continued

Parameter	SUSTAIN 7			SUSTAIN 3		NMA				
	Semaglutide 0.5 mg	Semaglutide 1 mg	Dulaglutide 1.5 mg	Semaglutide 1 mg	Exenatide ER	Semaglutide 0.5 mg	Semaglutide 1 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Lixisenatide
Proportion of severe events that are nocturnal	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

BMI body mass index, *ER* extended-release, *HbA1c* glycated hemoglobin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

* Statistically significant difference at 95% confidence level versus dulaglutide 1.5 mg

§ Statistically significant difference at 95% confidence level versus exenatide ER

¤ Statistically significant difference at 95% confidence level versus liraglutide 1.2 mg

† Statistically significant difference at 95% confidence level versus liraglutide 1.8 mg

‡ Statistically significant difference at 95% confidence level versus lixisenatide

parameters were not included in the NMA, inputs were assumed to be 0 in all arms to ensure that these did not drive cost-effectiveness outcomes.

Treatment Effects, Biomarker Progression and Treatment Duration

Following application of the treatment effects in the first year of the analysis, HbA1c was modeled to increase by 0.14% per year, based on the metformin arm of the ADOPT study (as no data on long-term HbA1c changes with GLP-1 receptor agonists are available), and patients were assumed to receive semaglutide or comparator treatment until HbA1c reached 7.5% (Fig. 1) [45]. At this stage, treatment was intensified with addition of basal insulin and continuation of GLP-1 receptor agonist therapy (the most common intensification step from GLP-1 receptor agonists in Denmark), with the reduction in HbA1c based on an insulin-naïve population and derived from the "Core" multivariate equations estimated by Willis et al. [46]. HbA1c was subsequently modeled to follow the UKPDS progression equation until reaching 8.0%, after which patients discontinued GLP-1 receptor agonist therapy and intensified to basal-bolus insulin. HbA1c was modeled to drop according to the multivariate "Core" equations for an insulin-experienced population published by Willis et al. and then to progress according to the UKPDS equation, with patients remaining on basal-bolus insulin for the remainder of their lifetimes [46]. Using this approach, patients received semaglutide 0.5 mg, 1 mg and dulaglutide 1.5 mg for 7, 9 and 6 years, respectively, and once-weekly semaglutide 0.5 mg, 1 mg and dulaglutide 1.5 mg plus basal insulin for 3 years, before intensifying to basal-bolus insulin for the remainder of their lifetimes (Fig. 1). This approach was chosen to reflect common clinical practice, where, due to the progressive nature of T2D, glycemic control cannot be maintained indefinitely with one medication [27]. For the majority of patients, and particularly for those with high cardiovascular disease risk, for whom GLP-1 receptor agonists are recommended following
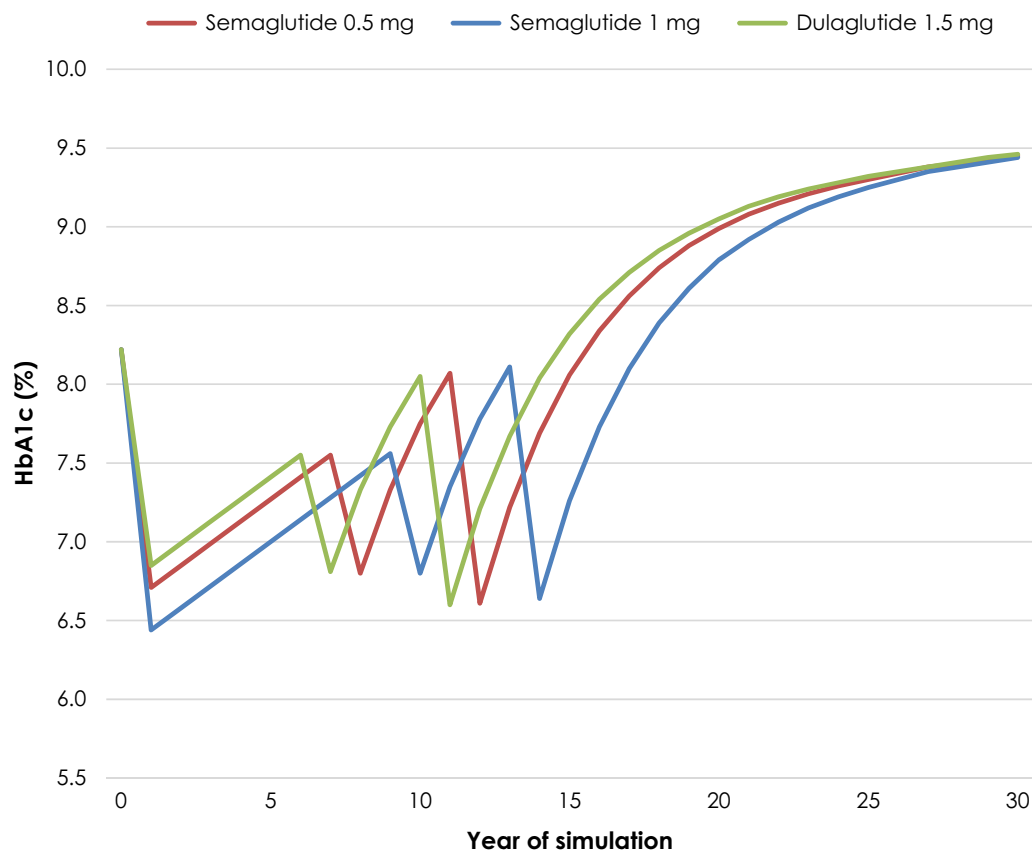
Fig. 1 HbA1c progression in the primary analysis based on SUSTAIN 7. *HbA1c* glycated hemoglobin. Curves for each medication continue to converge following year 30 until the end of the analysis (year 50). Changes in HbA1c for semaglutide 0.5 mg, 1 mg and dulaglutide 1.5 mg are − 0.75%, − 0.76% and − 0.74%, respectively, on first intensification and − 1.46%, − 1.47% and − 1.45%, respectively, on second intensification, based on the equations published by Willis et al. [46]. Intensification steps were delayed by 1 year with semaglutide 0.5 mg and by 3 years with semaglutide 1 mg

metformin failure, treatment intensification with the addition of basal insulin followed by basal-bolus insulin therapy is required to maintain good glycemic control over the long term [18, 27, 29]. Variations in initial treatment duration, including an analysis with GLP-1 receptor agonist therapy maintained for patient lifetimes, were explored in sensitivity analyses.

BMI progression was modeled to correlate with treatment switching patterns, taking into account the weight gain often observed in patients receiving basal insulin therapy (Fig. 2). Initial treatment effects with semaglutide or the comparator were maintained until basal insulin was added to the treatment regimen, where BMI was modeled to increase according to the

"Core" equations for an insulin-naïve population provided by Willis et al. [46]. BMI was maintained at this level until patients intensified to basal-bolus insulin therapy, after which BMI was further increased according to the equations for an insulin-experienced population, again published by Willis et al., with the differences between the treatment arms abolished [46].

Systolic blood pressure and serum lipids were assumed to follow the natural progression algorithms built into the IQVIA CORE Diabetes Model from the start of each analysis, based on the UKPDS or Framingham data (as described by Palmer et al.) [36]. Following the first treatment intensification with the addition of basal
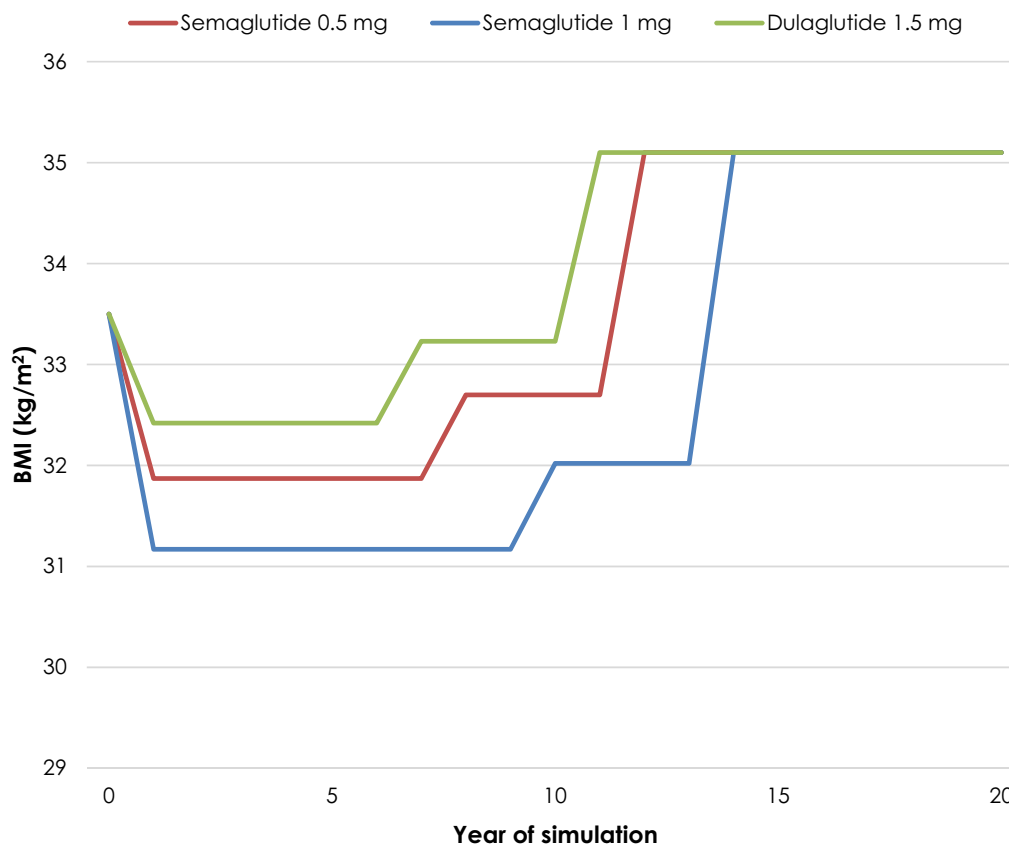
Fig. 2 BMI progression in the primary analysis based on SUSTAIN 7. *BMI* body mass index. Curves for each medication remain at the same level following year 20 until the end of the analysis (year 50). Changes in BMI for semaglutide 0.5 mg, 1 mg and dulaglutide 1.5 mg are + 0.83, + 0.85 and + 0.81 kg/m², respectively, on first intensification and + 2.40, + 3.08 and + 1.87 kg/m², respectively, on second intensification, based on the equations published by Willis et al. [46]. Intensification steps were delayed by 1 year with semaglutide 0.5 mg and by 3 years with semaglutide 1 mg

insulin, non-severe and severe hypoglycemic events were projected to increase to 10.615 and 0.258 events per patient per year, respectively, based on the Danish Hypoglycemia Assessment Tool study (as the multivariate regression results calculated by Willis et al. had a poor fit) [47]. These were applied in all arms and were maintained for the remainder of the analyses.

Costs and Utilities

Costs were estimated from a Danish healthcare payer perspective and expressed in 2017 Danish kroner (DKK). Pharmacy acquisition costs were sourced from the Danish Medicines Agency in March 2018 [48]. Diabetes medication resource use was based on the relevant clinical trials from which data were taken for each comparison.

Following addition of basal insulin to the treatment regimen, patients were assumed to receive the defined daily dose (DDD) of 40 IU, with the cost weighted to the market share of basal insulin in Denmark (to reflect current practice). Once patients intensified to basal-bolus insulin, patients were assumed to receive the DDDs of both basal insulin and bolus insulin (both 40 IU), with the cost again weighted to the market shares of basal and bolus insulin in Denmark. Costs were the same in all arms following the second intensification step. Resource use was used to calculate annual treatment costs for each arm (Table S2, Table S3 and Table S4).

Annual costs also captured concomitant medications, needle use and self-monitoring of blood glucose (SMBG) testing with GLP-1 receptor agonist and intensification treatments.

Costs of treating diabetes-related complications were based on a literature review updated in 2018, with prices inflated to 2017 DKK (Table S5). Utilities relating to quality of life were taken from a 2014 review by Beaudet et al., with the exception of those associated with hypoglycemia [49]. A diminishing approach for disutilities relating to non-severe hypoglycemic events was used, based on a 2014 publication by Lauridsen et al., while a disutility applied following severe events was sourced from a 2013 publication by Evans et al., both of which were published after the literature searches by Beaudet et al. had been completed [50, 51].

Sensitivity Analyses Conducted for the Primary Analysis

Projection of long-term outcomes from short-term data is associated with uncertainty. Therefore, to test the robustness of the primary analysis, several one-way deterministic sensitivity analyses and a probabilistic sensitivity analysis were conducted on key parameters and assumptions of the analyses.

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

Primary Base Case Analysis

Long-term projections, based on data from SUSTAIN 7, indicated that semaglutide 0.5 mg and 1 mg were associated with improvements in life expectancy of 0.04 and 0.15 years, respectively, and quality-adjusted life expectancy of 0.11 and 0.34 QALYs, respectively, versus dulaglutide (Table 2). Improvements in life expectancy and quality-adjusted life expectancy were a result of the multifactorial risk-reduction effects of semaglutide, delaying the time to treatment intensification and resulting in a delayed time to onset and reduced cumulative incidence of diabetes-relating complications in the long term.

Semaglutide 0.5 mg and 1 mg were associated with cost savings of DKK 289 and DKK 13,416 per patient, respectively, versus dulaglutide over the lifetime course of the

Table 2 Long-term cost-effectiveness outcomes from the primary analysis based on SUSTAIN 7

Health outcomes	Semaglutide 0.5 mg	Dulaglutide 1.5 mg	Difference
Discounted life expectancy (years)	14.27 (0.19)	14.24 (0.20)	+ 0.03
Discounted quality-adjusted life expectancy (QALYs)	9.19 (0.12)	9.08 (0.12)	+ 0.11
Discounted direct costs (DKK)	415,200 (10,048)	415,489 (9722)	− 289
ICER for semaglutide 0.5 mg versus dulaglutide 1.5 mg	Semaglutide 0.5 mg dominant		
Health outcomes	**Semaglutide 1 mg**	**Dulaglutide 1.5 mg**	**Difference**
Discounted life expectancy (years)	14.39 (0.20)	14.24 (0.20)	+ 0.15
Discounted quality-adjusted life expectancy (QALYs)	9.41 (0.12)	9.08 (0.12)	+ 0.34
Discounted direct costs (DKK)	402,073 (9719)	415,489 (9722)	− 13,416
ICER for semaglutide 1 mg versus dulaglutide 1.5 mg	Semaglutide 1 mg dominant		

Values are means (standard deviations)

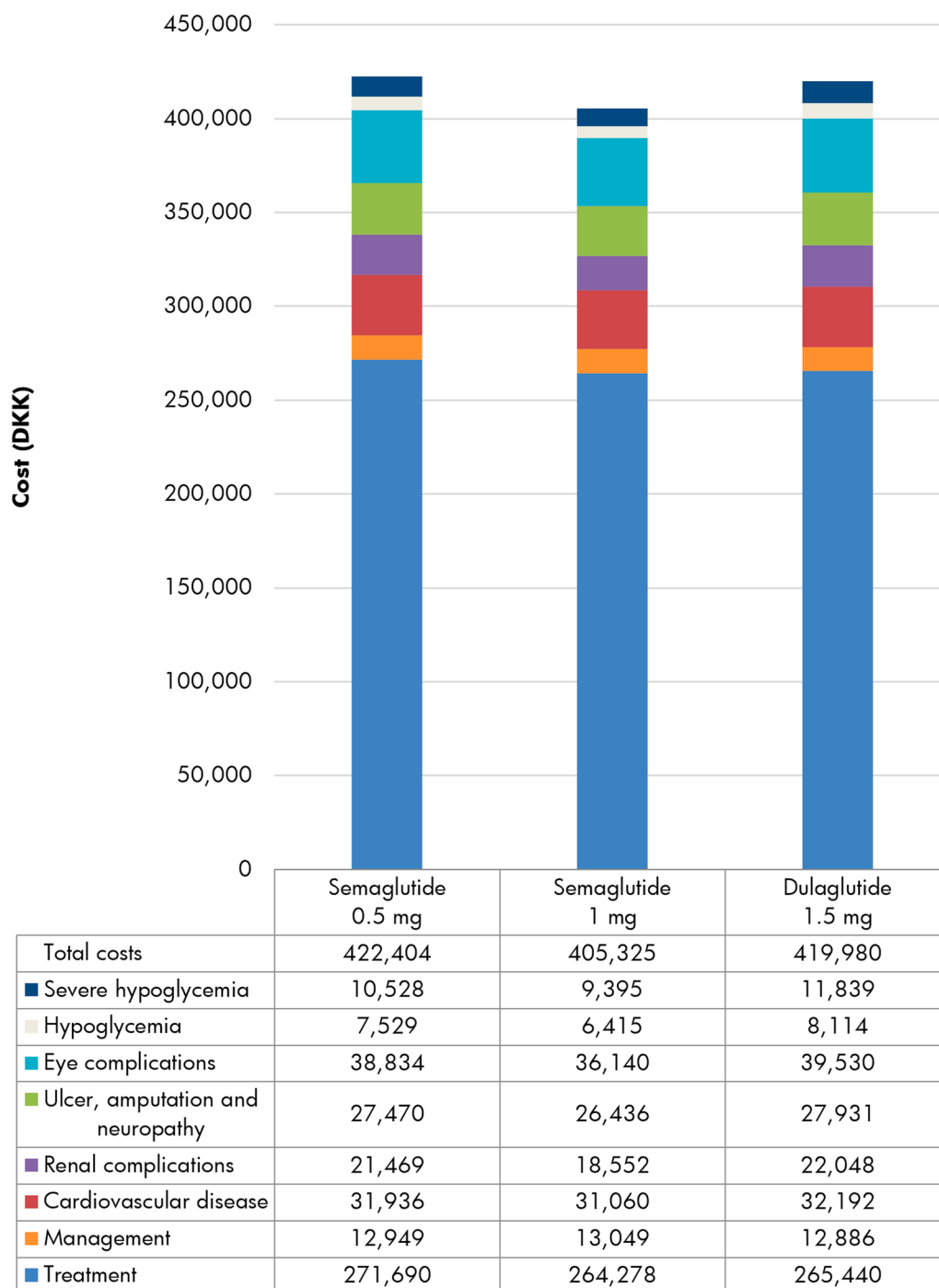*DKK* 2017 Danish kroner, *ICER* incremental cost-effectiveness ratio, *QALYs* quality-adjusted life years

	Semaglutide 0.5 mg	Semaglutide 1 mg	Dulaglutide 1.5 mg
Total costs	422,404	405,325	419,980
■ Severe hypoglycemia	10,528	9,395	11,839
▪ Hypoglycemia	7,529	6,415	8,114
■ Eye complications	38,834	36,140	39,530
■ Ulcer, amputation and neuropathy	27,470	26,436	27,931
■ Renal complications	21,469	18,552	22,048
■ Cardiovascular disease	31,936	31,060	32,192
■ Management	12,949	13,049	12,886
■ Treatment	271,690	264,278	265,440

Fig. 3 Discounted direct costs over patient lifetimes in the primary analysis based on SUSTAIN 7. *DKK* 2017 Danish kroner

analysis (Fig. 3). This was primarily due to improved glycemic control with semaglutide, delaying the first intensification step to the costlier treatment combination of a GLP-1 receptor agonist plus basal insulin (Table S2). Further cost savings were achieved through avoidance of diabetes-related complications, most notably severe hypoglycemia (mean cost

savings of DKK 2719 per patient with semaglutide 0.5 mg and DKK 6158 per patient with semaglutide 1 mg). With clinical benefits achieved at cost savings, both semaglutide 0.5 mg and 1 mg were considered dominant versus dulaglutide.

Sensitivity Analyses

Sensitivity analyses, conducted for the primary comparisons of semaglutide 0.5 mg and 1 mg versus dulaglutide, showed that the results of the base case analysis were robust to changes in the input parameters and assumptions used (Table 3 and Table S6). Shortening the time horizon to 10 and 20 years resulted in reduced incremental clinical benefits for semaglutide, but the 1 mg dose remained cost saving and dominant versus dulaglutide, while the 0.5 mg dose was associated with increased costs and ICERs of DKK 12,793 and DKK 24,490 per QALY gained, respectively.

Maintaining GLP-1 therapy for patient lifetimes led to increased clinical benefits for both doses of semaglutide, with the 1 mg dose remaining cost saving and dominant but the 0.5 mg dose associated with slight cost increases and an ICER of DKK 6264 per QALY gained.

Including only statistically significant treatment effects between the treatment arms led to only slightly reduced clinical benefits and cost savings for semaglutide 1 mg, and it remained dominant versus dulaglutide, while semaglutide 0.5 mg was associated with reduced clinical benefits and increased incremental costs, yielding an ICER of DKK 683,944 per QALY gained. This was driven by treatment switching occurring simultaneously, as HbA1c progression was equal in both treatment arms.

Exploration of alternative treatment switching approaches, with a set period of 3 or 5 years for GLP-1 receptor agonist treatment followed by intensification to basal insulin (aligned with a recent cost-effectiveness analysis of semaglutide published in the UK setting), resulted in reduced clinical benefits and increased incremental costs for semaglutide 0.5 mg and 1 mg, yielding ICERs of DKK 68,414 and DKK 30,408 per QALY gained, respectively, when treatment switching occurred after 3 years, and DKK 96,326 and DKK 31,721 per QALY gained, respectively, when treatment switching occurred after 5 years [52]. There were only minor changes to the overall results when altering HbA1c thresholds for treatment switching, changing costs by ± 25% or using alternative BMI and hypoglycemia disutilities versus dulaglutide [51, 53, 54].

Clinical outcomes from the PSA were similar to those from the base case analysis, but semaglutide 0.5 mg and 1 mg were associated with increased incremental costs and reduced cost savings, respectively, with greater variance shown around the mean outcomes (Fig. 4). Semaglutide 0.5 mg and 1 mg were associated with increased quality-adjusted life expectancy of 0.10 and 0.30 QALYs, respectively, versus dulaglutide. Mean costs were DKK 3668 higher with semaglutide 0.5 mg but DKK 6718 lower with semaglutide 1 mg versus dulaglutide over patient lifetimes. Semaglutide 0.5 mg was therefore associated with an ICER of DKK 37,197 per QALY gained, while semaglutide 1 mg was dominant versus dulaglutide in the PSA. At a willingness-to-pay threshold of DKK 250,000 per QALY gained (a representative value based on GBP 20,000 in the UK), the probabilities of once-weekly semaglutide 0.5 mg and 1 mg being considered cost-effective were 58.8% and 79.2%, respectively, versus dulaglutide 1.5 mg (Fig. 5).

Supporting Analyses

In the supporting analysis based on SUSTAIN 3, semaglutide 1 mg was projected to improve life expectancy by 0.24 years, and quality-adjusted life expectancy by 0.47 QALYs, versus exenatide ER (Table 4). Clinical benefits were achieved at a cost saving from a healthcare payer perspective, with semaglutide 1 mg costing DKK 18,088 less over a patient's lifetime than exenatide ER. Clinical benefits and cost savings were a result of a reduced incidence and delayed time to onset of diabetes-related complications.

In the supporting analyses based on the NMA, semaglutide 0.5 mg and 1 mg were associated with clinical benefits versus all

Table 3 Sensitivity analyses results for semaglutide 1 mg versus dulaglutide 1.5 mg based on SUSTAIN 7

Analysis	Discounted quality-adjusted life expectancy (QALYs)			Discounted direct costs (DKK)			ICER (DKK per QALY gained)
	Semaglutide 1 mg	Dulaglutide 1.5 mg	Difference	Semaglutide 1 mg	Dulaglutide 1.5 mg	Difference	
Base case	9.41	9.08	+ 0.34	402,073	415,489	− 13,416	Semaglutide dominant
20-year time horizon	8.17	7.88	+ 0.28	295,697	306,919	− 11,222	Semaglutide dominant
10-year time horizon	5.48	5.28	+ 0.20	152,959	167,743	− 14,785	Semaglutide dominant
Statistically significant differences only	9.40	9.08	+ 0.32	403,334	415,489	− 12,156	Semaglutide dominant
First treatment intensification at HbA1c ≥ 7.0% and second intensification at HbA1c ≥ 7.5%	9.16	8.88	+ 0.28	427,307	438,257	− 10,950	Semaglutide dominant
First treatment intensification at HbA1c ≥ 8.0% and second intensification at HbA1c ≥ 8.5%	9.59	9.24	+ 0.34	383,083	390,248	− 7165	Semaglutide dominant
Treatment intensification at 3 years	9.65	9.54	+ 0.11	386,173	382,932	+ 3242	30,408
Treatment intensification at 5 years	9.72	9.60	+ 0.12	375,320	371,568	+ 3753	31,721
GLP-1 receptor agonist treatment continued for patient lifetimes	9.45	9.08	+ 0.37	476,223	502,717	− 26,494	Semaglutide dominant
Cost of complications + 25%	9.41	9.08	+ 0.34	436,659	454,138	− 17,479	Semaglutide dominant

Table 3 continued

Analysis	Discounted quality-adjusted life expectancy (QALYs)			Discounted direct costs (DKK)			ICER (DKK per QALY gained)
	Semaglutide 1 mg	Dulaglutide 1.5 mg	Difference	Semaglutide 1 mg	Dulaglutide 1.5 mg	Difference	
Cost of complications − 25%	9.41	9.08	+ 0.34	367,496	376,849	− 9353	Semaglutide dominant
All costs + 25%	9.41	9.08	+ 0.34	499,312	516,115	− 16,803	Semaglutide dominant
All costs − 25%	9.41	9.08	+ 0.34	304,842	314,872	− 10,030	Semaglutide dominant
Lee et al. BMI disutility applied	8.96	8.57	+ 0.40	402,073	415,489	− 13,416	Semaglutide dominant
Evans et al. hypoglycemia disutilities applied	9.30	8.94	+ 0.37	402,073	415,489	− 13,416	Semaglutide dominant
Currie et al. hypoglycemia disutilities applied	9.49	9.17	+ 0.32	402,073	415,489	− 13,416	Semaglutide dominant

BMI body mass index, *DKK* 2017 Danish kroner, *HbA1c* glycated hemoglobin, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life year

comparators (Table 5). Over patient lifetimes, semaglutide 0.5 mg was associated with higher costs of DKK 3218 versus exenatide ER and DKK 1518 versus liraglutide 1.2 mg, but cost savings of DKK 30,970 versus liraglutide 1.8 mg and DKK 16,961 versus lixisenatide. This yielded ICERs of DKK 17,024 and DKK 7390 per QALY gained for semaglutide 0.5 mg versus exenatide ER and liraglutide 1.2 mg, respectively, while it was considered dominant versus liraglutide 1.8 mg and lixisenatide. Semaglutide 1 mg was associated with cost savings of DKK 11,884, DKK 13,583, DKK 46,071 and DKK 32,063 versus exenatide ER, liraglutide 1.2 mg, liraglutide 1.8 mg and lixisenatide, respectively, and was therefore considered dominant versus all comparators.

DISCUSSION

Recent studies have emphasized the importance of early, intensive glycemic control to reduce the risk of long-term complications, thereby drastically increasing patients' quality of life and life expectancy while minimizing healthcare payer expenditure [3, 9, 10]. Moreover, multifactorial treatments that target improvements in blood pressure, cholesterol level and body weight, as well as HbA1c, have been shown to reduce the risk of death, myocardial infarction and stroke in patients with T2D [55]. Semaglutide represents a novel treatment option in the class of GLP-1 receptor agonists and has been associated with greater reductions in HbA1c and body weight throughout the SUSTAIN clinical trial program and several
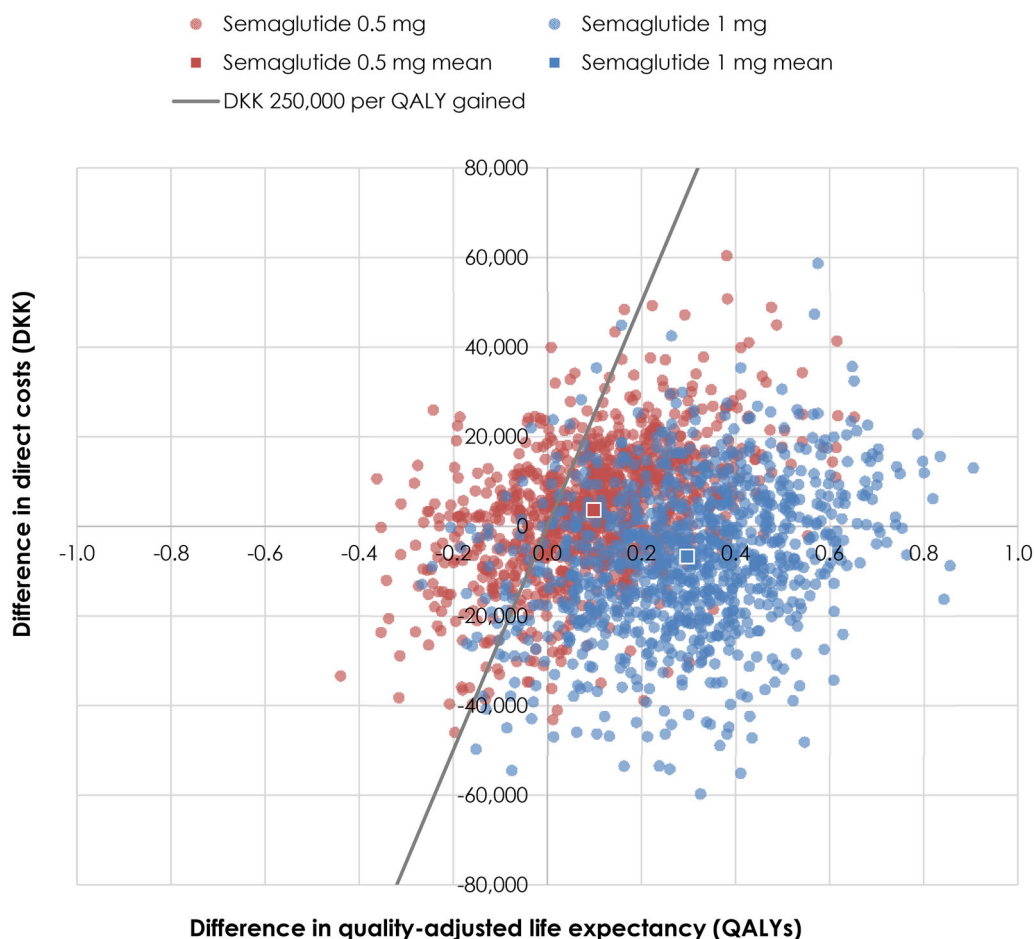
Fig. 4 Probabilistic sensitivity analysis scatterplot for the primary analysis versus dulaglutide, based on SUSTAIN 7. *DKK* 2017 Danish kroner, *QALYs* quality-adjusted life years

NMAs versus medications used throughout the T2D treatment algorithm [30, 32, 33]. The present analysis exemplifies the legacy effect of these short-term improvements, translating to a substantial benefit over patient lifetimes in terms of life expectancy and quality-adjusted life expectancy. Moreover, the greater clinical efficacy of semaglutide 1 mg led to delayed intensification with basal and bolus insulins by 3 years compared with dulaglutide. While there is no officially recognized willingness-to-pay threshold in Denmark, an estimate can be based on the threshold of between GBP 20,000 and 30,000 per QALY gained set by the National Institute for Health and Care Excellence (NICE) in the UK. Based on a representative threshold of DKK 250,000 per QALY gained, semaglutide 0.5 mg and 1 mg were found to be dominant

versus dulaglutide 1.5 mg for the treatment of patients with T2D with inadequate glycemic control on metformin. Supporting analyses showed that semaglutide 0.5 mg was cost-effective, and semaglutide 1 mg was dominant, versus exenatide ER and liraglutide 1.2 mg, while both doses of semaglutide were dominant versus liraglutide 1.8 mg and lixisenatide. The consistently higher effectiveness associated with the 1 mg dose of semaglutide highlights the need for patients to receive early and aggressive treatment to stem the risk of long-term complications, and patients should ideally be up-titrated as soon as possible provided they do not experience any serious treatment-related adverse events.

Previous long-term cost-effectiveness analyses of semaglutide have reported similar
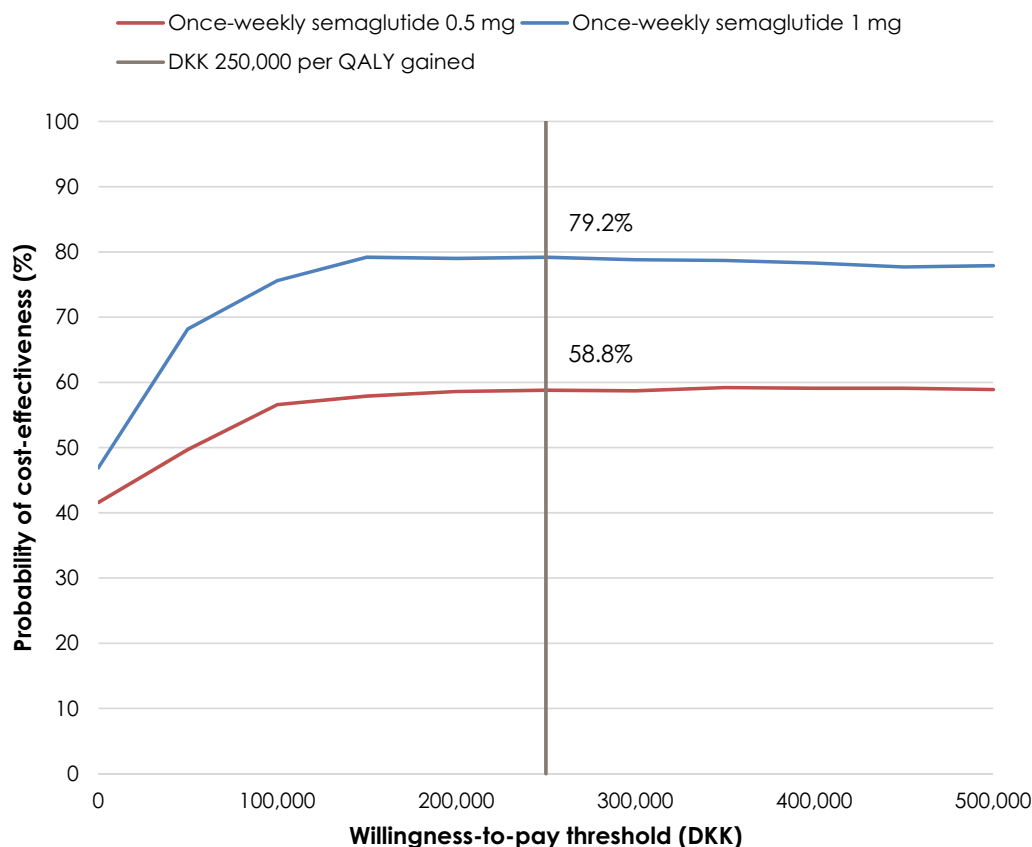
Fig. 5 Cost-effectiveness acceptability curve for the primary analysis versus dulaglutide, based on SUSTAIN 7. *DKK* 2017 Danish kroner, *QALY* quality-adjusted life year

outcomes to this study, but these used distinct periods of GLP-1 receptor agonist treatment before simultaneous treatment intensification to basal insulin therapy in all arms [52, 56, 57]. While this approach allows a more direct comparison of any two interventions, this treatment progression is less representative of real-world practice, where patients with T2D have tailored treatment regimens and would continue to receive a given treatment as long as they remain within glycemic target. Additionally, analyses performed with fixed 3- or 5-year periods of initial treatment, such as the sensitivity analyses conducted for this study, yielded lower health outcomes and increased incremental costs for semaglutide compared with the base case analysis, highlighting the importance of a clinically oriented modeling approach in capturing all relevant clinical and economic benefits. The present study is among the first to use such an approach for GLP-1 receptor agonists,

which recognizes the progressive nature of T2D and the difficulty of maintaining glycemic control in the long term. Moreover, the use of the multivariate prediction equations published by Willis et al., which provide estimates of changes in HbA1c and BMI when basal and basal-bolus insulin therapies are initiated, represents a key strength of the present analysis [46]. As the equations are based on a review of the published literature, the subsequent calculated treatment effects are informed by data from a variety of sources, allowing the present study to avoid the use of specific treatment effects designed to artificially improve modeling outcomes.

Alternative treatment options for patients with T2D with inadequate glycemic control on metformin in Denmark not assessed in the present study include dipeptidyl peptidase-4 (DPP-4) inhibitors, SGLT-2 inhibitors, sulfonylureas, thiazolidinediones and basal insulin

Table 4 Long-term cost-effectiveness outcomes from the supporting analyses based on SUSTAIN 3

Health outcomes	Semaglutide 1 mg	Exenatide ER	Difference
Discounted life expectancy (years)	14.79 (0.18)	14.55 (0.20)	+ 0.24
Discounted quality-adjusted life expectancy (QALYs)	9.46 (0.12)	8.98 (0.12)	+ 0.47
Discounted direct costs (DKK)	461,487 (10,962)	479,575 (11,829)	− 18,088
ICER for semaglutide 1 mg versus exenatide ER	Semaglutide 1 mg dominant		

Values are means (standard deviations)

DKK 2017 Danish kroner, *ER* extended-release, *ICER* incremental cost-effectiveness ratio, *QALYs* quality-adjusted life years

therapy [58]. Semaglutide has been shown to improve short-term clinical outcomes of HbA1c and body weight versus DPP-4 inhibitor sitagliptin in SUSTAIN 2, basal insulin glargine U100 in SUSTAIN 4 and SGLT-2 inhibitor empagliflozin in an NMA [59–61]. Moreover, treatment with sulfonylureas or thiazolidinediones is often associated with weight gain, contrasting with the weight loss associated with semaglutide therapy [58]. Considering that greater reductions in HbA1c are associated with a delayed time to treatment intensification in the present analysis, treatment with semaglutide is likely to result in a delayed time to intensification versus all currently available second-line therapies, yielding both clinical benefits for patients and cost savings for the healthcare payer. However, further analyses are required before the long-term benefits versus all second-line comparators are fully elucidated. Nonetheless, among current GLP-1 receptor agonists, a once-weekly injection of

semaglutide provides clear benefits over the once-daily injectables liraglutide and lixisenatide, while improving patient outcomes versus existing once-weekly variants dulaglutide and exenatide ER.

One aspect of care the present analyses were unable to incorporate was the additional short-term cardiovascular benefits GLP-1 receptor agonists offer. Recent evidence has suggested that GLP-1 receptor agonists as a class are potentially beneficial for patients at risk of cardiovascular disease, with semaglutide, liraglutide and albiglutide demonstrating significant benefits versus placebo in SUSTAIN 6, LEADER and HARMONY Outcomes, respectively, while lixisenatide and exenatide ER have displayed cardiovascular safety versus placebo in ELIXA and EXSCEL, respectively [23, 24, 26, 62, 63]. Current guidelines for the treatment of T2D in Denmark recommend treatment with SGLT-2 inhibitors or GLP-1 receptor agonists for patients with established cardiovascular disease. However, considering that most patients with T2D eventually develop micro- and macrovascular disease, and that 22% of newly diagnosed patients in Denmark have existing macrovascular disease, a sensitivity analysis was included to explore patients remaining on GLP-1 receptor agonist therapy for their lifetimes, which confirmed that semaglutide improved health outcomes for patients while minimizing costs for the healthcare payer [16, 58]. Given the results of SUSTAIN 6 and the clinical benefits displayed in this analysis, semaglutide is considered a valuable second-line treatment option for patients with T2D [58, 64].

The use of data from an NMA for supporting analyses could be seen as a potential limitation of the study. However, these analyses aimed to compare both doses of semaglutide with the most relevant comparators in Denmark, namely all available GLP-1 receptor agonists. Additionally, the NMA data were shown to be robust through the two comparisons of semaglutide 1 mg with exenatide ER, one of which used data from the head-to-head SUSTAIN 3 trial and one that used data from the NMA, which both yielded similar outcomes. Moreover, the use of methodologically guided evidence synthesis such as this is becoming increasingly central to

Table 5 Long-term cost-effectiveness outcomes from the supporting analyses based on the NMA

Health outcomes	Semaglutide 0.5 mg	Semaglutide 1 mg	Exenatide ER	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Lixisenatide
Discounted life expectancy (years)	14.16 (0.21)	14.26 (0.19)	14.07 (0.21)	14.04 (0.20)	14.12 (0.20)	13.98 (0.19)
Discounted quality-adjusted life expectancy (QALYs)	8.94 (0.13)	9.14 (0.12)	8.75 (0.13)	8.73 (0.12)	8.80 (0.12)	8.55 (0.12)
Discounted direct costs (DKK)	431,248 (10,024)	416,147 (9771)	428,031 (10,687)	429,730 (9883)	462,218 (10,721)	448,210 (11,094)
ICER for semaglutide 0.5 mg (DKK per QALY gained)	–	–	17,024	7390	Semaglutide 0.5 mg dominant	Semaglutide 0.5 mg dominant
ICER for semaglutide 1 mg (DKK per QALY gained)	–	–	Semaglutide 1 mg dominant	Semaglutide 1 mg dominant	Semaglutide 1 mg dominant	Semaglutide 1 mg dominant

Values are means (standard deviations)

DKK 2017 Danish kroner, *ER* extended-release, *ICER* incremental cost-effectiveness ratio, *QALYs* quality-adjusted life years

decision making and accepted by health technology assessment agencies worldwide [65, 66].

Modeling HbA1c increases during the first phase of the analyses based on data from the metformin arm of ADOPT could also be seen as a drawback [45]. However, patients were at a similar stage in the T2D treatment algorithm to patients receiving GLP-1 receptor agonists in Denmark. The data from ADOPT could therefore be argued to be applicable to patients receiving GLP-1 receptor agonists. Indeed, the progression of HbA1c observed in SUSTAIN 6, where patients received semaglutide, correlates with the increases seen in ADOPT, adding credence to this assumption [24, 47].

A further limitation is the use of short-term data to project long-term outcomes. However, this remains one of the essential tenets of health economic modeling and arguably one of the best available options to inform decision making in the absence of long-term clinical trial data [38]. Additionally, projecting outcomes over patient lifetimes is recommended in guidelines for economic evaluation of interventions for patients with diabetes mellitus [38]. While there is always an element of clinical doubt around the accuracy of such an approach, every effort was made in the present analysis to minimize this, primarily by using a model of diabetes that has been extensively published and validated against real-life data both on first publication and recently following a series of model updates, in addition to extensive sensitivity analyses that test the robustness of the base case findings [34, 35].

CONCLUSIONS

Semaglutide represents a highly cost-effective treatment option within the class of GLP-1 receptor agonists available in Denmark, with the present analyses demonstrating clinical benefits versus dulaglutide, exenatide ER, liraglutide 1.2 mg and 1.8 mg and lixisenatide for the treatment of patients with T2D.

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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.

Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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