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ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness of Once-Weekly Semaglutide 1 mg versus Canagliflozin 300 mg in Patients with Type 2 Diabetes Mellitus in a Canadian Setting

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Abstract

Objective Our objective was to evaluate the long-term cost-effectiveness of once-weekly semaglutide 1 mg versus once-daily canagliflozin 300 mg in patients with type 2 diabetes mellitus (T2DM) uncontrolled with metformin from the healthcare payer and societal perspectives in Canada.

Methods Head-to-head data from the SUSTAIN 8 randomised trial (NCT03136484) were extrapolated over 40 years using economic simulation modelling. The cost-effectiveness of once-weekly semaglutide 1 mg versus canagliflozin 300 mg for treating T2DM was estimated using the Swedish Institute for Health Economics-Diabetes Cohort Model (IHE-DCM) and the Economic and Health Outcomes Model of T2DM (ECHO-T2DM). Unit costs and disutility weights capturing treatments and key macro- and microvascular complications were sourced from the literature to best match the Canadian setting. A probabilistic base-case simulation and sensitivity analyses were conducted.

Results Once-weekly semaglutide 1 mg was associated with reductions in macro- and microvascular complications, yielding incremental cost-effectiveness ratios (ICERs) of (Canadian dollars [CAD]) CAD16,392 and 18,098 per incremental quality-adjusted life-year (QALY) gained versus canagliflozin 300 mg for IHE-DCM and ECHO-T2DM, respectively, from a healthcare payer perspective. Accounting for productivity loss as well, ICERs were CAD14,127 and 13,188 per QALY gained for IHE-DCM and ECHO-T2DM, respectively, from a societal perspective. Sensitivity analyses confirmed that the base-case results were robust to changes in input parameters and assumptions used.

Conclusions At a willingness-to-pay threshold of CAD50,000 per QALY gained, once-weekly semaglutide 1 mg was cost-effective over 40 years versus once-daily canagliflozin 300 mg for the treatment of T2DM in patients failing to maintain glycemic control with metformin alone.

Key Points for Decision Makers

Model-based extrapolation of the SUSTAIN 8 trial demonstrated that, over a lifetime horizon, once-weekly semaglutide 1 mg was associated with reductions in macro- and microvascular complications and is likely to be cost-effective versus canagliflozin 300 mg at commonly used cost-effectiveness thresholds.

Once-weekly semaglutide 1 mg would provide good value for money versus canagliflozin 300 mg for the treatment of patients with type 2 diabetes mellitus uncontrolled with metformin, from both the healthcare payer and the societal perspectives in Canada.

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1 Introduction

Diabetes (of which about 90% is type 2 diabetes mellitus [T2DM] [6]) is a substantial health and economic burden worldwide, and the prevalence is rising [6]. In 2019, 2.8 million people lived with diabetes in Canada [6], and this number is projected to reach 3.3 million by 2045 [7]. T2DM is associated with a number of serious and life-threatening micro- and macrovascular complications, which in turn negatively affect patient health-related quality of life [8] and increase healthcare resource utilisation [9]. Total diabetes-related health expenditure in Canada was estimated at USD12.3 billion in 2019 [6]. The consequences of diabetes pose a significant challenge to patients, their families, and healthcare systems.

The Swedish Institute for Health Economics-Diabetes Cohort Model (IHE-DCM; a cohort-level model) [1] and the Economic and Health Outcomes Model of T2DM (ECHO-T2DM; a microsimulation model) [4] have been used to estimate cost-effectiveness for a number of therapeutic classes in a range of healthcare settings [11–15]. Both models use equations from the UK Prospective Diabetes Study (UKPDS) Outcome Models [16]. The UKPDS enrolled 5102 patients between 1977 and 1997, with a median follow-up of 17.6 years, to derive parametric proportional hazards models predicting absolute risks of diabetes complications and death and is widely used to set risk-prediction equations in the economic modelling of T2DM [16].

In the 52-week global SUSTAIN 8 randomised controlled trial, once-weekly semaglutide 1 mg demonstrated superiority to once-daily canagliflozin 300 mg in reducing glycated haemoglobin (HbA1c) (estimated treatment difference [ETD] −0.49% points, $p < 0.0001$) and bodyweight (ETD −1.06 kg, $p = 0.0029$) in patients with T2DM that was previously uncontrolled with metformin [17]. There are very few health economic evaluations for Canada specifically to support healthcare decision making on the choice between glucagon-like peptide-1 receptor agonists (GLP-1 RAs) or sodium–glucose co-transporter-2 (SGLT-2) inhibitors. The long-term cost-effectiveness of once-weekly semaglutide 1 mg compared with once-daily canagliflozin 300 mg in Canada has not previously been studied. The aim of this study was to estimate the cost-effectiveness of once-weekly semaglutide 1 mg versus once-daily canagliflozin 300 mg in patients with T2DM that was uncontrolled with metformin in Canada over a 40-year time horizon.

2 Methods

Given near parity in pricing for all GLP-1 RAs and SGLT-2 inhibitors in Canada [18], once-weekly semaglutide 1 mg and canagliflozin 300 mg were selected to establish a valid cost-effectiveness comparison between a GLP-1 RA and an SGLT-2 inhibitor using data from the robust head-to-head SUSTAIN 8 trial. A cost-effectiveness analysis was performed by modelling costs and clinical outcomes following the initiation of treatment with once-weekly semaglutide 1 mg or once-daily canagliflozin 300 mg in patients with T2DM inadequately controlled with daily metformin therapy from both healthcare payer and societal perspectives in Canada. A 40-year time horizon was simulated, which is long enough to cover the lifetime of most simulated patients. The Diabetes Modelling Input Checklist (Eighth Mount Hood Challenge) [19] and the Consolidated Health Economic Evaluation Reporting Standards checklist [20] were followed.

2.1 Model Overview

For practical reasons, model-based economic analysis is commonly performed using a single model. However, applying multiple models to a study problem permits a test of the structural assumptions and an additional assessment of the robustness of cost-effectiveness estimates, potentially strengthening conclusions and reducing decision-making uncertainty. For this reason, we used two validated economic models of T2DM in this study: IHE-DCM and ECHO-T2DM. The models are described in detail in Appendix A in the electronic supplementary material (ESM) and elsewhere in the literature [1–5, 21]. Briefly, both models define hypothetical patients using a host of demographic and clinical characteristics and capture the development of important macro- and microvascular complications and mortality; they support treatment-switching algorithms, probabilistic sensitivity analysis for treatment effects, risk coefficients, biomarker drifts, adverse events, unit costs, and quality-adjusted life-years (QALY) utility weights; and they have been internally validated (tested for internal consistency and accuracy), externally validated (tested for predictive accuracy against clinical trial data) [1, 4, 22], and recently cross-validated [10]. Schematic diagrams for the two models can be found in Figs. A1 and A2, respectively, in the ESM [10]. The model validity described using the Assessment of the Validation Status of Health-Economic decision modelling tool [23] is shown in Appendixes B and C in the ESM for IHE-DCM and ECHO-T2DM, respectively [10].

The most notable difference between the models is the approach: the cohort approach in IHE-DCM and the microsimulation approach in ECHO-T2DM [10]. Cohort models have traditionally been utilised for health economic analyses but do not account for between-patient variation during simulations, which could potentially produce biased cost-effectiveness estimates [10]. The limitations associated with cohort models are often weighed against their fast model runtime and being built

in a relatively user-friendly Microsoft Excel® platform. Microsimulation models such as ECHO-T2DM are better able to accommodate patient heterogeneity and can more accurately reflect individual clinical pathways and capture variation between patient characteristics at baseline [24, 25]. To achieve this, microsimulation models are often built using scientific programming languages, which generally makes this approach inaccessible (and hence not transparent) to non-programmers, compared with cohort models. That said, a recently published cross-validation demonstrated few and minor systematic differences in outputs between IHE-DCM and ECHO-T2DM, which suggests that the differences between modelling approaches have minimal impact on the final conclusions [10]. Results from more than one model are not required to reach a reasonable conclusion, but that conclusion could be strengthened if there is concordance between modelling methods.

Other important differences between IHE-DCM and ECHO-T2DM include how they model chronic kidney disease (CKD), end-stage renal disease, and estimated glomerular filtration rate (eGFR) progression, as well as rescue treatments such as insulin. Health states for kidney disease and foot ulcers also differ between these two models.

In the present analysis, treatment effects were applied as initial one-time changes in biomarker values, which evolved at user-defined rates. Treatment algorithms permitted the intensification of treatment when glycaemic goals were not met. Unit costs and disutility weights were applied based on health outcomes. This analysis was designed in accordance with the Canadian Agency for Drugs and Technologies in Health (CADTH) 2017 report for Economic Evaluation of Health Technologies in Canada, and future costs and QALYs were discounted at 1.5% annually [26].

2.2 Base-Case Analysis

The base-case simulation was probabilistic and sampled 1000 cohorts, with 1-year cycle length and half-cycle corrections. IHE-DCM is a cohort model with a single representative patient. Each cohort for the microsimulation ECHO-T2DM model comprised 2000 unique hypothetical patients created by drawing at random from distributions of initial patient characteristics. The UKPDS 82 risk equations [27] were used to project the development of macro- and microvascular complications and mortality for both models, in line with the CADTH 2017 report [26]. These risk equations were derived using data from the 20-year UKPDS trial with an additional 10 years of follow-up to estimate and project the long-term health outcomes of patients with diabetes [16].

2.3 Patients

SUSTAIN 8 was a 52-week, randomised, double-blind trial comparing the efficacy and safety of once-weekly semaglutide 1 mg versus canagliflozin 300 mg in patients with T2DM [17]. Patient demographic and clinical characteristics were sourced from the SUSTAIN 8 trial population (Table 1) [17]. In SUSTAIN 8, patients were recruited based on the following inclusion criteria: aged ≥ 18 years, diagnosed with T2DM, HbA1c levels of 7.0−10.5% (53−91 mmol/mol), on a stable daily dose of metformin (≥ 1500 mg or maximum tolerated dose) for ≥ 90 days, and an eGFR of ≥ 60 ml/min/1.73 m^2 [17].

2.4 Treatment Algorithm

At simulation start, hypothetical patients were initiated on treatment with either once-weekly semaglutide 1 mg or once-daily canagliflozin 300 mg. Both models had a 1-year cycle length, so biomarker changes from baseline to week 52 from SUSTAIN 8 were used to inform initial treatment efficacy for each arm of the analysis. Following initial treatment efficacy, when HbA1c first exceeded the clinically relevant threshold selected for treatment intensification (8%), the initial treatments were discontinued and basal insulin initiated at 10 IU/day. Insulin dose was then titrated to a maximum dose of 60 IU/day as needed to maintain HbA1c under 8%, updated each cycle. Prandial insulin was added to the treatment regimen when the maximum basal insulin dose was reached and HbA1c again exceeded 8%, starting at 5 IU/day and titrated to a maximum dose of 200 IU/day as needed to maintain HbA1c under 8%.

2.5 Treatment Effects

Treatment effects and hypoglycaemic event rates of once-weekly semaglutide 1 mg and once-daily canagliflozin 300 mg were sourced from SUSTAIN 8 (Table 1) [17]. No adverse events other than hypoglycaemia were included in the analysis. As is common in cost-effectiveness analyses in Canada (and globally), changes from baseline were applied regardless of whether there was a statistically significant difference between treatment arms. HbA1c was assumed to drift upward at 0.14% annually to capture natural progression based on the results of the metformin arm of the ADOPT study, a 5-year study performed to assess glycaemic durability [28]. This is similar to the widely used HbA1c drift in the UKPDS trial (0.15% per year) [29]. Drifts for systolic blood pressure (0.3 mmHg per year) and lipids (triglycerides and low-density lipoprotein 0.03 mg/dL per year; high-density lipoprotein –0.03 mg/dL per year) were in line with those in the UKPDS trial [30]; no drift was assumed for body mass index (BMI). Treatment effects and

Table 1 Baseline characteristics and treatment effects from the SUSTAIN 8 trial

Baseline characteristics[a]		Mean (SD) or %
Demographics		
Age, years		56.6 (10.9)
Male, %		53.8
Ethnicity, %		
African American		6.1
American Indian		0.0[c]
Hispanic		37.2
Asian Indian		0.0
Risk factors and biomarkers		
Diabetes duration, years		7.4 (5.6)
Atrial fibrillation, %		1.9
Smoker, %		12.8
HbA1c, %		8.25 (1.0)
SBP, mmHg		130.35 (14.8)
Total cholesterol, mg/dL[b]		176.33 (41.4)
LDL, mg/dL[b]		97.68 (35.6)
HDL, mg/dL[b]		44.96 (11.0)
Triglycerides, mg/dL[b]		178.43 (117.3)
BMI, kg/m^2		32.3 (6.8)
Heart rate, bpm		74.1 (10.2)
White blood cell count, 1×106		7.07 (1.8)
eGFR, mL/min/1.73 m^2		97.43 (16.4)
History of complications, %		
Retinopathy		
BDR		8.3
Blindness in both eyes		0.0
PDR		0.6
ME		1.0
Neuropathy		
Symptomatic		11.3
Peripheral vascular disease		1.3
Diabetic foot ulcer		0.0[cd]
One lower-extremity amputation		0.1
Two or more lower-extremity amputations		0.0[cd]
Nephropathy		
Microalbuminuria		0.8
Macroalbuminuria		0.4
End-stage renal disease		0.0
Macrovascular complications		
Ischaemic heart disease		1.5
Congestive heart failure		0.0
Myocardial infarction		4.2
Stroke		0.0
Treatment effects[e] based on the SUSTAIN 8 trial (17)	OW semaglutide 1 mg, mean (SE)	Canagliflozin 300 mg, mean (SE)
HbA1c, %	−1.460 (0.060)	−0.980 (0.060)
SBP, mmHg	−3.520 (0.710)	−5.530 (0.710)
Total cholesterol, mg/dL[b]	−4.610 (1.780)	5.430 (1.770)

Table 1 (continued)

Treatment effects[e] based on the SUSTAIN 8 trial (17)	OW semaglutide 1 mg, mean (SE)	Canagliflozin 300 mg, mean (SE)
LDL, mg/dL[b]	−1.770 (1.630)	4.310 (1.540)
HDL, mg/dL[b]	1.590 (0.370)	3.680 (0.360)
Triglycerides, mg/dL[b]	−26.270 (3.920)	−17.860 (3.820)
BMI, kg/m^2	−1.900 (0.090)	−1.510 (0.090)
eGFR, mL/min/1.73 m^2	−2.190 (0.420)	−3.510 (0.420)
Non-severe hypoglycaemic events, per patient-year	0.065	0.015
Severe hypoglycaemic events, per patient-year	0.005	0

BDR background diabetic retinopathy, *BMI* body mass index, *bpm* beats per minute, *ECHO-T2DM* Economic and Health Outcomes Model-type 2 diabetes mellitus, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated haemoglobin, *HDL* high-density lipoprotein, *IHE-DCM* Swedish Institute of Health Economics-Diabetes Cohort Model, *LDL* low-density lipoprotein, *ME* macular oedema, *OW* once-weekly, *PDR* proliferative diabetic retinopathy, *SBP* systolic blood pressure, *SD* standard deviation, *SE* standard error

[a]Based on the SUSTAIN 8 trial population [17] and are reported as mean (SD) unless stated otherwise

[b]Converted from mg/dL to mmol/L by multiplying the mg/dL values with 0.0259 (total cholesterol, HDL, and LDL) and 0.0113 (triglycerides) in the IHE-DCM

[c]Assumed

[d]Not applicable in IHE-DCM

[e]Source data on file and treatment effects based on a 52-week treatment period

hypoglycaemic event rates for basal and prandial insulin were sourced from a systematic review [31].

2.6 Unit Costs

The payer perspective included the direct medical costs associated with anti-hyperglycaemic treatments, hypoglycaemia, and macro- and microvascular complications. The societal perspective included these direct medical costs in addition to the indirect costs of foregone labour market productivity (e.g. absenteeism from work due to retirement, illness, or premature mortality).

Costs of resource use (needles and test strips) and anti-hyperglycaemic treatments (Table A.1 in the ESM) were sourced in Canadian dollars (CAD) from Canadian list prices [32]. Annual treatment costs for once-weekly semaglutide 1 mg and once-daily canagliflozin 300 mg were CAD2542.71 and 1025.65, respectively. Costs for micro- and macrovascular complications and hypoglycaemic events in Canada were taken from the CADTH 2017 report [26] where possible. Costs for complications not available in the CADTH report were sourced from the literature and came from Canada or the USA [33–35] (Table A.2 and A.3 in the ESM). Indirect costs were calculated using the estimated annual salary multiplied by annual productivity loss (percentage of days absent from work). The estimated annual salary was calculated using the following equation: average hourly wage × average hours worked per week × 52 weeks × employment rate. Data for each component of annual salary were sourced from Statistics Canada [36] and are presented by sex and age group (Table A.4 in the ESM). Annual productivity loss, i.e. percentage of days absent from work due to diabetes-related complications (Table A.5 in the ESM), was based on a Danish registry study that included absence/sickness days, early retirement, and old-age pension [37], as suitable data for Canada could not be identified. All costs were inflation adjusted to year 2019 values using the national Canadian Consumer Price Index for healthcare [38].

2.7 Quality-Adjusted Life-Year Disutility Weights

QALYs were calculated by applying a baseline level of utility (i.e. QALYs for patients with T2DM without health-related complications) and subtracting decrements for elements that lead to a lower utility than at baseline. The complication-free utility value and disutility decrements for age, sex, and each 1 kg/m^2 increase were sourced from the CODE-2 study [39]. Disutility weights associated with macro- and microvascular complications were sourced from the CADTH 2017 report [26]. Several complications, including background diabetic retinopathy, proliferative diabetic retinopathy, macular oedema, gross proteinuria, CKD, peripheral vascular disease, diabetic foot ulcer, and symptomatic neuropathy, were missing from the CADTH report and supplemented with data from cross-sectional studies from Canada, the USA, Europe, and Australia (Table A.6 in the ESM) [39–42].

2.8 Sensitivity Analyses

Sensitivity analyses were conducted to assess study robustness and identify key outcome drivers. Specifically, the following scenarios were simulated:

- differences in treatment outcomes limited to HbA1c and BMI
- weighted average cost of canagliflozin, empagliflozin, and dapagliflozin for canagliflozin 300 mg
- HbA1c threshold for treatment intensification lowered to 7.5% (tighter glycaemic control)
- 25-year time horizon
- maximum insulin rescue dose of 200 IU (60 IU for basal insulin dose and 140 IU for prandial insulin dose)
- UKPDS 68 risk equations [43] were employed instead of UKPDS 82 [27]
- a 3.5% discount rate
- unit costs of complications increased by 25%
- unit costs of complications reduced by 25%
- 10% improved HbA1c effect for semaglutide versus canagliflozin
- 10% improved BMI effect for semaglutide versus canagliflozin
- 10% improved systolic blood pressure effect for semaglutide versus canagliflozin
- 10% improved lipid effect for semaglutide versus canagliflozin
- 10% worse HbA1c effect for semaglutide versus canagliflozin
- 10% worse BMI effect for semaglutide versus canagliflozin
- 10% worse systolic blood pressure effect for semaglutide versus canagliflozin
- 10% worse lipid effect for semaglutide versus canagliflozin

3 Results

3.1 Base-Case Analysis

3.1.1 Life Expectancy

The results of the base-case analysis are presented in Table 2. Predicted life expectancy was slightly longer with once-weekly semaglutide 1 mg for both models (0.05 and 0.09 years per patient for IHE-DCM and ECHO-T2DM, respectively), consistent with the limited differences in micro- and macrovascular complication rates (Table A.7 in the ESM).

3.1.2 Quality-Adjusted Life-Years

Mean quality-adjusted life expectancy favoured once-weekly semaglutide 1 mg for both models (0.34 and 0.38 QALYs gained per patient for IHE-DCM and ECHO-T2DM, respectively; Table 2). The QALY gains with once-weekly semaglutide 1 mg were primarily driven by the postponement of insulin therapy (and thus delays in insulin-related hypoglycaemia and weight gain) caused by greater HbA1c lowering, as well as by the direct effect of greater initial weight loss and lower subsequent insulin-related weight gain on disutility (Table A.8 in the ESM).

3.1.3 Costs

Over the simulated time horizon, mean costs for anti-hyperglycaemic treatments were higher with once-weekly semaglutide 1 mg than with once-daily canagliflozin 300 mg for both models: CAD6737 (IHE-DCM) and CAD7932 (ECHO-T2DM) higher per patient (Table 2). The predicted savings in the cost of insulin therapy were CAD8501 (IHE-DCM) and CAD6501 (ECHO-T2DM), which offset approximately half of the higher acquisition cost of semaglutide versus canagliflozin. Additional cost offsets with once-weekly semaglutide 1 mg versus once-daily canagliflozin 300 mg were associated with managing hypoglycaemia (CAD219 in IHE-DCM, CAD229 in ECHO-T2DM) and treating diabetes-related complications, with the cost offset associated with avoided myocardial infarction, congestive heart failure, retinopathy, CKD, and lower-extremity disease (Table 2). Overall, mean direct costs for the once-weekly semaglutide 1 mg arm were higher than those for the once-daily canagliflozin 300 mg arm (CAD5512 [IHE-DCM] and CAD6808 [ECHO-T2DM] per patient, Table 2). Including indirect costs (costs associated with productivity loss) reduced these to CAD4750 (IHE-DCM) and CAD4961 (ECHO-T2DM) per patient (Table 2).

3.1.4 Incremental Cost-Effectiveness Ratios

Incremental costs coupled with QALY gains yielded incremental cost-effectiveness ratios (ICERs) for once-weekly semaglutide 1 mg versus canagliflozin 300 mg of CAD16,392 (IHE-DCM) and CAD18,098 (ECHO-T2DM) per QALY gained from a healthcare payer perspective, and CAD14,127 (IHE-DCM) and CAD13,188 (ECHO-T2DM) per QALY gained from a broader societal perspective (Table 2). Each of these estimated ICERs falls below the commonly used Canadian willingness-to-pay

Table 2 Results of the base-case analysis for once-weekly semaglutide 1 mg versus canagliflozin 300 mg in patients with T2DM

	IHE-DCM			ECHO-T2DM		
	Sema 1 mg	Cana 300 mg	Difference (sema 1 mg–cana 300 mg)	Sema 1 mg	Cana 300 mg	Difference (sema 1 mg–cana 300 mg)
Health gain						
Survival after 40 years, %	6.8	6.6	0.2	7.2	7.0	0.2
Life expectancy, years	18.50	18.45	0.05	17.48	17.39	0.09
Quality-adjusted life expectancy, QALYs	14.98	14.64	0.34	13.37	13.00	0.38
Direct costs, CAD						
Anti-hyperglycaemic treatment	47,095	40,358	6737	39,201	31,268	7932
Non-insulin	20,745	5507	15,238	20,638	6204	14,434
Insulin	26,350	34,851	−8501	18,563	25,064	−6501
Hypoglycaemia	984	1203	−219	1126	1355	−229
Macro- and microvascular complications						
Ischaemic heart disease	3459	3442	17	2661	2652	9
Myocardial infarction	6375	6387	−13	6769	6814	−45
Stroke	4913	4912	1	3675	3702	−27
Congestive heart failure	6052	6424	−372	4316	4577	−261
Retinopathy	1777	1916	−140	2523	2672	−149
Chronic kidney disease	4418	4673	− 255	1938	2153	− 215
Lower-extremity disease	22,594	22,839	− 245	23,661	23,868	− 207
Direct costs, CAD	97,666	92,155	5512	85,869	79,062	6808
Indirect costs, CAD	84,912	85,674	−762	162,535	164,381	−1,847
Total costs (direct and indirect costs), CAD	182,579	177,828	4750	248,404	243,443	4961
ICER based on direct costs, cost per QALY gained	16,392			18,098		
ICER based on total costs, cost per QALY gained	14,127			13,188		

CAD Canadian dollars, *cana* canagliflozin, *ECHO-T2DM* Economic and Health Outcomes Model of T2DM, *ICER* incremental cost-effectiveness ratio, *IHE-DCM* Swedish Institute of Health Economics-Diabetes Cohort Model, *QALY* quality-adjusted life-year, *sema* once-weekly semaglutide, *T2DM* type 2 diabetes mellitus

(WTP) threshold of CAD50,000 per QALY gained [44, 45].

3.1.5 Cost-Effectiveness Plane and Cost-Effectiveness Acceptability Curve

The cost-effectiveness plane scatter plots for 1000 iterations or cohorts in the base-case analysis indicated that semaglutide was a more effective treatment than canagliflozin and also had a higher cost, as illustrated by the majority of iterations falling in the 'northeast quadrant' in Fig. 1a. The cost-effectiveness acceptability curve showed that the likelihood of semaglutide being cost-effective relative to canagliflozin was sizeable for both models (96.3% [IHE-DCM] and 83.1% [ECHO-T2DM]) at a WTP threshold of CAD50,000 per QALY gained (Fig. 1b).

3.2 Sensitivity Analyses

The results of the sensitivity analyses are summarised in Fig. 2 and presented in more detail in Table A.9 in the ESM. In most scenarios, both IHE-DCM and ECHO-T2DM responded similarly to the changes in input parameter values. Even though once-weekly semaglutide 1 mg was associated with additional incremental costs across the sensitivity analyses, there were corresponding QALY gains of 0.25−0.46, yielding ICERs of CAD82−22,873 per QALY gained versus canagliflozin. The largest ICER was observed when a 10% worse HbA1c effect for semaglutide was assumed (Table A.9 in the ESM). The lowest mean incremental costs (CAD31 [IHE-DCM] and CAD1033 [ECHO-T2DM] per patient) and lowest ICERs (CAD82 [IHE-DCM] and CAD2635 [ECHO-T2DM] per QALY gained) were demonstrated when the HbA1c intensification threshold was tightened to 7.5% (Table A.9 in the ESM).

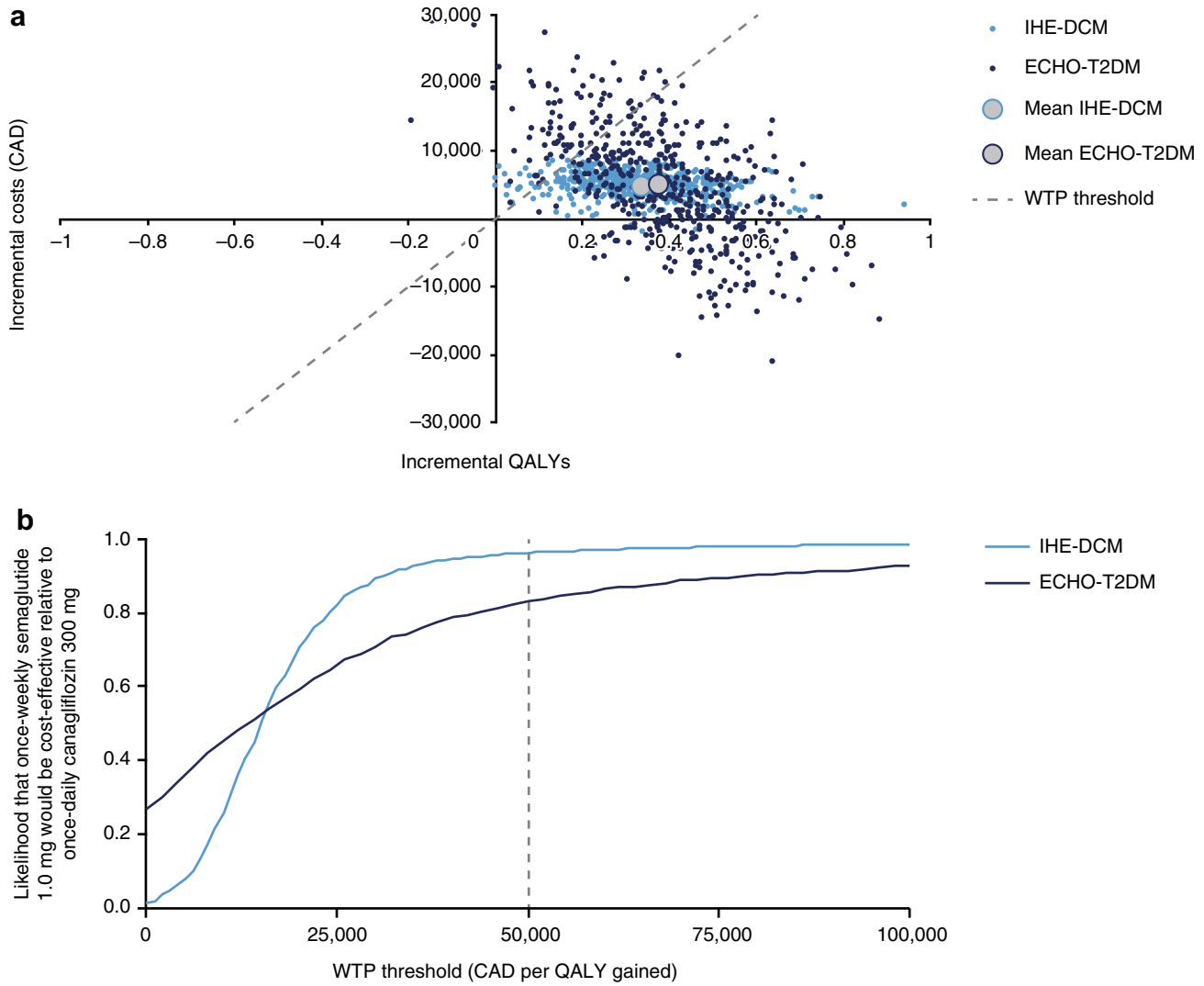

Fig. 1 **a** Cost-effectiveness plane and **b** cost-effectiveness acceptability curve from IHE-DCM and ECHO-T2DM. The *dashed line* is the commonly accepted WTP threshold of $CAD50,000 per QALY gained in Canada. *CAD* Canadian dollars, *ECHO-T2DM* Economic and Health Outcomes Model of Type 2 Diabetes Mellitus, *IHE-DCM* Swedish Institute of Health Economics-Diabetes Cohort Model, *QALY* quality-adjusted life-year, *WTP* willingness to pay

4 Discussion

Economic analysis using two different simulation models yielded ICERs for once-weekly semaglutide 1 mg versus canagliflozin 300 mg for patients with T2DM uncontrolled with metformin in Canada that were well below the commonly accepted Canadian WTP threshold of CAD50,000. This demonstrates that the additional cost of once-weekly semaglutide 1 mg is justified by the health benefits gained in comparison with once-daily canagliflozin 300 mg. These favourable ICERs with once-weekly semaglutide 1 mg were found despite small differences in predicted life expectancy in the two arms. This limited treatment difference is a well-known consequence of simulating treat-to-target algorithms, as treatment intensification limits between-arm differences in biomarkers over time. Health benefits with once-weekly semaglutide 1 mg were largely driven by better HbA1c lowering and greater weight loss versus canagliflozin. In addition to the direct effects, the indirect effect related to delaying rescue insulin therapy (and its associated weight gain) compounded the effect. Moreover, the delay in starting insulin was sufficient to offset the lower costs of managing hypoglycaemic events for patients treated with canagliflozin (vs. semaglutide) and led to overall higher costs associated with hypoglycaemia in the canagliflozin arm. Additional benefits with once-weekly semaglutide 1 mg were observed through reductions in both diabetes-related complications and productivity loss for the working-age subpopulation.

Although literature comparing the cost-effectiveness of GLP-1 RAs and SGLT-2 inhibitors is limited, a previous

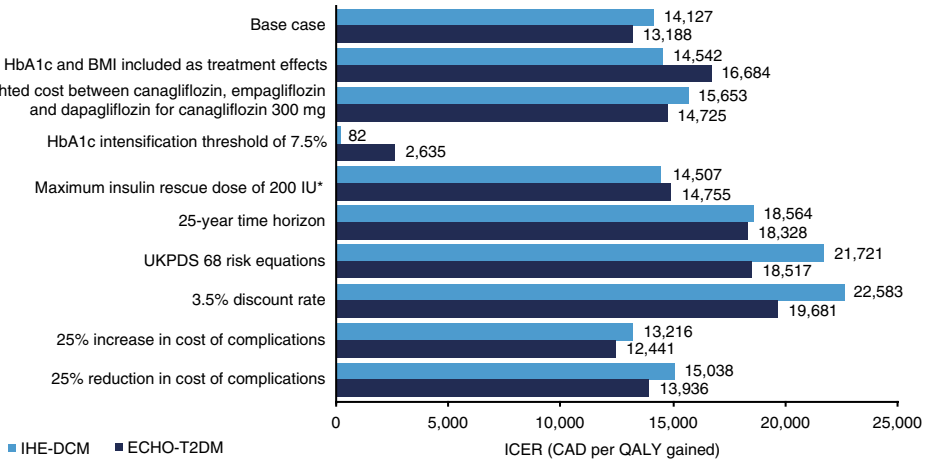

Fig. 2 Results of the sensitivity analyses comparing once-weekly semaglutide 1 mg with canagliflozin 300 mg in patients with type 2 diabetes mellitus. *Maximum basal insulin dose of 60 IU and maximum prandial insulin dose of 140 IU. *BMI* body mass index, *CAD* Canadian dollars, *ECHO-T2DM* Economic and Health Outcomes Model of T2DM, *HbA1c* glycated haemoglobin, *ICER* incremental cost-effectiveness ratio, *IHE-DCM* Swedish Institute of Health Economics-Diabetes Cohort Model, *QALY* quality-adjusted life-year, *UKPDS* UK Prospective Diabetes Study

post hoc analysis of the PIONEER 2 trial found oral semaglutide to be cost-effective compared with empagliflozin over 40 years in patients with T2DM uncontrolled with metformin in Canada [46]. Further studies comparing the cost-effectiveness of GLP-1 RAs and SGLT-2 inhibitors in other countries showed similar findings to ours [47–50].

The likelihood of once-weekly semaglutide 1 mg being cost-effective relative to once-daily canagliflozin 300 mg was high at a WTP threshold of CAD50,000 per QALY gained, suggesting that the base-case findings are robust. There was greater uncertainty in the ECHO-T2DM results than with the IHE-DCM (as shown by the distribution of points on the cost-effectiveness plane scatterplots), which can primarily be attributed to the better ability of microsimulation models to accommodate patient heterogeneity. Robustness of the base-case analysis was also suggested by the results of the sensitivity analyses, which were relatively insensitive to individual changes in the input parameters and assumptions used; the sensitivity analyses were uniformly favourable for once-weekly semaglutide 1 mg. In these sensitivity analyses, the ICER was smallest when a strict glycaemic goal of 7.5% rather than 8.0% was simulated, demonstrating the importance of HbA1c as a driver of between-treatment differences.

Both once-weekly semaglutide 1 mg and once-daily canagliflozin 300 mg are currently recommended by Diabetes Canada as second-line therapies for the treatment of T2DM [51] and reimbursed by public and private healthcare payers in most Canadian provinces. The present study aimed to examine the cost-effectiveness of semaglutide injection versus an SGLT-2 inhibitor in the Canadian setting.

A key strength of the present study was the use of two different validated economic models (IHE-DCM and ECHO-T2DM), which used two different modelling approaches (cohort and microsimulation), both of which yielded ICERs suggesting that once-weekly semaglutide 1 mg is a cost-effective alternative to canagliflozin 300 mg. Given the well-known challenges and uncertainties associated with simulating diabetes [52], the use of two different models could reduce decision-making uncertainty [10]. The cohort-modelling approach produced survival, QALY, and unit cost predictions that were generally higher in absolute value than did the microsimulation approach, but the between-arm incremental differences that are the foundation of cost-effectiveness metrics were similar. An additional strength includes the use of head-to-head clinical trial data for treatment effects from the 52-week SUSTAIN 8 clinical trial, rather than the results of an indirect comparison. Lastly, both payer and societal perspectives were considered in this manuscript, as the former includes costs associated with interventions, medications, and inpatient and outpatient services, whereas the latter further considers costs to society arising from productivity reduction.

Limitations of the present study should also be acknowledged. First, as with many long-term health economic analyses of treatments for T2DM, the use of short-term data to project outcomes over patient lifetimes is naturally associated with uncertainty, although this approach generally represents the best available option for decision making in the absence of long-term clinical data. Second, both models projected health outcomes based on probabilities

derived primarily from the effects of reducing HbA1c, and no adverse events other than hypoglycaemia were included in this analysis. Thereby, differences in the incidence of congestive heart failure, stroke, and CKD may not accurately reflect the benefits of either treatment, as these benefits may occur independently of HbA1c lowering and weight loss [53–56]. However, it was not appropriate to apply clinical data for cardiovascular outcomes in our simulations, as our population of interest differs from the populations of cardiovascular outcome trials, which typically consist of patients with diabetes at high risk of cardiovascular outcomes. Third, the treatment algorithm applied in the model may not be reflective of routine clinical care; specifically, treatment intensifications would not necessarily result in discontinuation of previous therapies, and second-line therapies as recommended by the Canadian guidelines may be used simultaneously rather than independently. The clinical data to inform this are unfortunately not captured within SUSTAIN 8. A further complexity of real-world practice—differences in acceptability of and adherence to the two therapies—were not included in our model. However, the patient-reported outcome from SUSTAIN 8 showed that patients were more satisfied with once-weekly semaglutide 1 mg than with canagliflozin 300 mg, and there were no differences in overall health-related quality of life between the two treatments [17]. Fourth, we assumed that the treatment effects did not rebound following discontinuation of initial therapies. As a result, the treatment with greater efficacy had slightly better health economic outcomes. The magnitude of rebound is presumably somewhere between zero and the treatment effects observed in the clinical trials, but the exact number is unknown. Finally, the disutility weights assumed for hypoglycaemic events differ from the CADTH recommended disutility weights [57], as values from a Canada-specific study [41] were used. The potential importance of appropriately incorporating the effects of hypoglycaemia has been illustrated by Lovato et al. [58], who demonstrated that failure to do so may result in misleading predictions.

The present analysis is the first to evaluate the cost-effectiveness of once-weekly semaglutide 1 mg versus daily canagliflozin 300 mg in a Canadian setting. These findings complement the clinical evidence, contribute to current evidence of the economic value of GLP-1 RAs and SGLT-2 inhibitors, and provide insights to assist decision makers in choosing between the two treatments based on their value for money.

5 Conclusion

These economic simulations demonstrate that, at a WTP threshold of CAD50,000 per QALY gained, once-weekly semaglutide 1 mg is likely to be cost-effective (i.e. represent good value for money) compared with daily canagliflozin 300 mg for the treatment of patients with T2DM uncontrolled with metformin, from both healthcare payer and societal perspectives in Canada.

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Declarations

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Conflicts of interest SS has received continuing medical education honoraria from Novo Nordisk, Boehringer Ingelheim, Lilly, Sanofi, Janssen, AstraZeneca, Medtronic, Tandem, Abbott, Dexcom, CCRN, CPD Network, and MD Briefcase; participated in advisory boards for Novo Nordisk, Boehringer Ingelheim, Lilly, Sanofi, Janssen, AstraZeneca, and Abbott; and received research support from Sanofi, AstraZeneca, and Novo Nordisk. AL is an employee of Novo Nordisk Canada Inc. PB is an employee and shareholder of Novo Nordisk Canada Inc. AF and AN are employees of, and MW is an employee, minority owner, and unpaid director of the Swedish Institute for Health Economics, which provides consulting services for governmental bodies, academic institutions, and commercial life science enterprises, including Novo Nordisk A/S. The Swedish Institute for Health Economics owns the ECHO-T2DM and IHE-DCM, used in this analysis. The Swedish Institute for Health Economics is owned principally by the non-profit Bengt Jönsson Foundation for Health Economic Research. NM is an employee of Novo Nordisk A/S.

Availability of data and material The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability The IHE-DCM [1] and the ECHO-T2DM are described in detail in Appendix A in the ESM and elsewhere in the literature [1–5].

Author contribution statement
SS is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. All authors confirm that they meet the International Committee of Medical Journal Editors uniform requirements for authorship and that they have contributed to the critical analysis and interpretation of the data and drafting and/or critically revising the article and share the final responsibility for the content of the manuscript and the decision to submit it for publication.

Ethics approval The SUSTAIN 8 trial was performed in compliance with the International Conference on Harmonisation Good Clinical

Practice Guidelines and the Declaration of Helsinki. Prior to trial initiation, the protocol, the consent form, and the patient information sheet were reviewed and approved according to local regulations by appropriate health authorities and by an independent ethics committee/institutional review board.

Consent for participation All patients provided written informed consent for trial participation.

Consent for publication All patients provided written informed consent for publication of their data.

Human studies and subjects This article does not contain any new studies with human or animal subjects performed by any of the authors.

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