COST-EFFECTIVENESS OF CANAGLIFLOZIN VERSUS SITAGLIPTIN WHEN ADDED TO METFORMIN AND SULFONYLUREA IN TYPE 2 DIABETES IN CANADA

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ABSTRACT

Background
Canagliflozin, an agent that inhibits sodium glucose co-transporter 2, is approved as add-on to metformin plus sulfonylurea for the treatment of type 2 diabetes in Canada. Canagliflozin offers greater glycemic control, as well as important additional benefits such as weight loss and blood pressure reductions, versus dipeptidyl peptidase-4 inhibitors such as sitagliptin.

Objective
This analysis evaluated the cost-effectiveness of canagliflozin 300 mg and canagliflozin 100 mg versus sitagliptin 100 mg in patients with type 2 diabetes inadequately controlled on metformin plus sulfonylurea from the perspective of the Canadian Agency for Drugs and Technologies in Health.

Methods
A 40-year cost-effectiveness analysis was performed using the validated Economic and Health Outcomes Model of Type 2 Diabetes Mellitus (ECHO-T2DM). Patient characteristics, treatment effects, and rates of hypoglycemia and adverse events were sourced from the canagliflozin clinical program. Canada-specific costs and utilities were applied. Sensitivity analyses were conducted using alternative values for key model inputs.

Results
Both canagliflozin 300 and 100 mg dominated sitagliptin 100 mg over 40 years, providing quality-adjusted life-year gains of 0.31 and 0.28, and cost offsets of $2,217 and $2,560, respectively. Both canagliflozin doses dominated sitagliptin in each of the sensitivity analyses.

Conclusions
Simulation results suggested that canagliflozin 300 and 100 mg provided better health outcomes and lower costs than sitagliptin 100 mg as a third-line therapy added-on to metformin and sulfonylurea in patients with type 2 diabetes in Canada.

Key Words: *Canagliflozin, cost-effectiveness analysis, sitagliptin, third-line therapy, type 2 diabetes*

In 2010, an estimated 6.4% of people ≥12 years of age were living with diabetes in Canada.[1] The majority (~90%) had type 2 diabetes mellitus (T2DM), which is characterized by chronic hyperglycemia, insulin resistance, and decreased β-cell function.[2] Inadequately controlled T2DM is associated with increased risks of debilitating micro- and macrovascular complications and an elevated risk of premature mortality.[2] Overall, diabetes management imposes a substantial economic burden to patients and payers, as annual health care costs in Canada are 3 to 4 times higher

for patients with diabetes compared to individuals without diabetes[3,4] and the total economic burden of diabetes in 2010 was estimated to be ~$12.2 billion (with direct costs accounting for 3.5% of public health care spending).[5]

The Canadian Diabetes Association (CDA) recommends maintaining glycated hemoglobin (HbA1c) <7.0% for most patients with T2DM to reduce the risk of complications, combined with a multifactorial therapeutic approach to control risk factors including weight, blood pressure (BP), and lipid levels.[6] However, despite the variety of available anti-hyperglycemic agents (AHAs) and anti-hypertensive and lipid-lowering medications, a recent survey of primary care physicians in Canada found that only ~50% of their patients with T2DM achieved HbA1c ≤7.0%, and only 13% achieved HbA1c ≤7.0%, low-density lipoprotein cholesterol (LDL-C) ≤77 mg/dL (2.0 mmol/L), and BP <130/80 mmHg, indicating a substantial unmet need.[7]

Lifestyle modifications, including improved diet and exercise, are the cornerstone of T2DM management. However, in order to meet glycemic targets, most patients require pharmacologic therapy with AHAs.[6] Metformin is the standard first-line pharmacologic therapy for T2DM, and initially provides adequate control for many patients. Given the progressive nature of T2DM however, AHA combination therapy is often required to reach HbA1c target levels over the long run. The CDA recommends that subsequent AHAs be individualized according to patient characteristics,[6] and the Canadian Agency for Drugs and Technologies in Health (CADTH) issued Optimal Use Reports to aid in the selection of efficacious and cost-effective second- and third-line therapies for patients with T2DM in Canada.[8,9] For example, CADTH considered the combination of metformin and sulfonylurea to be cost-effective for dual therapy,[8] and when additional glycemic control is needed, neutral protamine Hagedorn (NPH) insulin was found to be cost-effective for third-line therapy.[9] Because insulin is a poor option for many patients, CADTH designated dipeptidyl peptidase-4 (DPP-4) inhibitors as a cost-effective choice for third-line therapy in those patients[9]; they are currently the most commonly used product class for third-line therapy in Canada (with sitagliptin being the current market leader in this class).[10] DPP-4 inhibitors lower blood glucose by increasing incretin levels, thereby lowering glucagon secretion and increasing insulin secretion.[11] Compared with insulin, which is associated with weight gain and an increased risk of hypoglycemia, DPP-4 inhibitors have minimal or neutral effects on weight and a low inherent risk of hypoglycemia.[11]

A new type of AHA lowers glucose by inhibiting sodium glucose co-transporter 2 (SGLT2) and is available in Canada for the treatment of adults with T2DM. SGLT2 inhibition lowers plasma glucose levels in patients with T2DM by decreasing the renal threshold for glucose (RT_G), thereby increasing urinary glucose excretion (UGE) and leading to a mild osmotic diuresis and a net caloric loss.[12] Furthermore, there is an intrinsically low risk of hypoglycemia with SGLT2 inhibition since the lowered RT_G remains above the defined threshold for hypoglycemia (≥70 mg/dL [3.9 mmol/L]). As this mechanism of action works independently of insulin, it is complementary to other AHAs (including exogenous insulin).

Canagliflozin was the first agent in this class to be approved in Canada, and it is recommended by CADTH as an add-on to metformin plus sulfonylurea when insulin is not an option.[13] In Phase 3 studies, canagliflozin has demonstrated multiple benefits for the treatment of T2DM, including dose-dependent reductions in HbA1c, body weight, and systolic BP (SBP) when used in combination with various background AHAs.[14] Canagliflozin was associated with an increased incidence of adverse events (AEs) potentially related to the mechanism of SGLT2 inhibition, such as genital mycotic infections (e.g., yeast infections) and urinary tract infections.[14] However, it was generally well tolerated, as evidenced by the low rate of discontinuations attributable to AEs.[14]

The unique renal mechanism of glucose lowering with SGLT2 inhibition could provide renoprotection in patients with T2DM and is being evaluated in ongoing clinical trials.[15,16] Across studies, transient reductions in estimated

glomerular filtration rate (eGFR) were seen with canagliflozin shortly after treatment initiation that attenuated and stabilized near baseline levels with prolonged treatment; this effect was sustained over at least 2 years, the longest follow-up with canagliflozin to date.[15] Consistent with this finding from the canagliflozin clinical trial program is a recently reported finding on the SGLT2 inhibitor empagliflozin in the EMPA-REG OUTCOME trial, in which eGFR was observed to remain stable in T2DM patients treated with this SGLT2 inhibitor over the full 4 years of follow-up.[17] Longer-term studies of canagliflozin including the CANagliflozin cardioVascular Assessment Study renal endpoints (CANVAS-R; ClinicalTrials.gov identifier, NCT01989754) and the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE; NCT02065791) trials will formally evaluate the potential renoprotective effects of canagliflozin in patients with T2DM. While data from some clinical studies of DPP-4 inhibitors have signaled that this class may also exhibit renoprotective effects, there is no mechanistic explanation for this effect beyond glucose lowering.[18] Furthermore, there was no evidence for renoprotection with sitagliptin based on evidence from the Trial Evaluating Cardiovascular Outcomes Study (TECOS).[19]

Due to the growing burden of T2DM in Canada, strategies to better control the multiple risk factors of T2DM are needed, which could lead to lower long-term costs of managing T2DM and its complications. SGLT2 inhibitors, like canagliflozin, may be suitable alternatives for patients requiring third-line therapy in Canada due to their good glycemic control and low intrinsic risk of hypoglycemia, along with the added benefits of weight loss and BP reduction. However, the most recent CADTH Optimal Use Report for third-line therapy was released before SGLT2 inhibitors were available in Canada, so evaluation of the cost-effectiveness of canagliflozin in this line of therapy versus other AHAs was not included. CADTH is currently in the process of updating its Optimal Use Report for third-line therapy, in which SGLT2 inhibitors will be included, but it is yet to be published.[20] Given the chronic nature of T2DM, the benefits of treatment interventions are fully realized only over long time horizons. Few clinical trials have sufficiently long durations to capture the long-run consequences of T2DM intervention,[21,22] so economic computer modeling has become a widely used and accepted tool for generating economic evidence (e.g., expected long-term health outcomes and costs of alternative competing interventions).[21,22]

In this paper, we describe a cost-effectiveness evaluation investigating the use of canagliflozin versus sitagliptin in patients with T2DM inadequately controlled with metformin plus sulfonylurea from the perspective of CADTH in Canada.

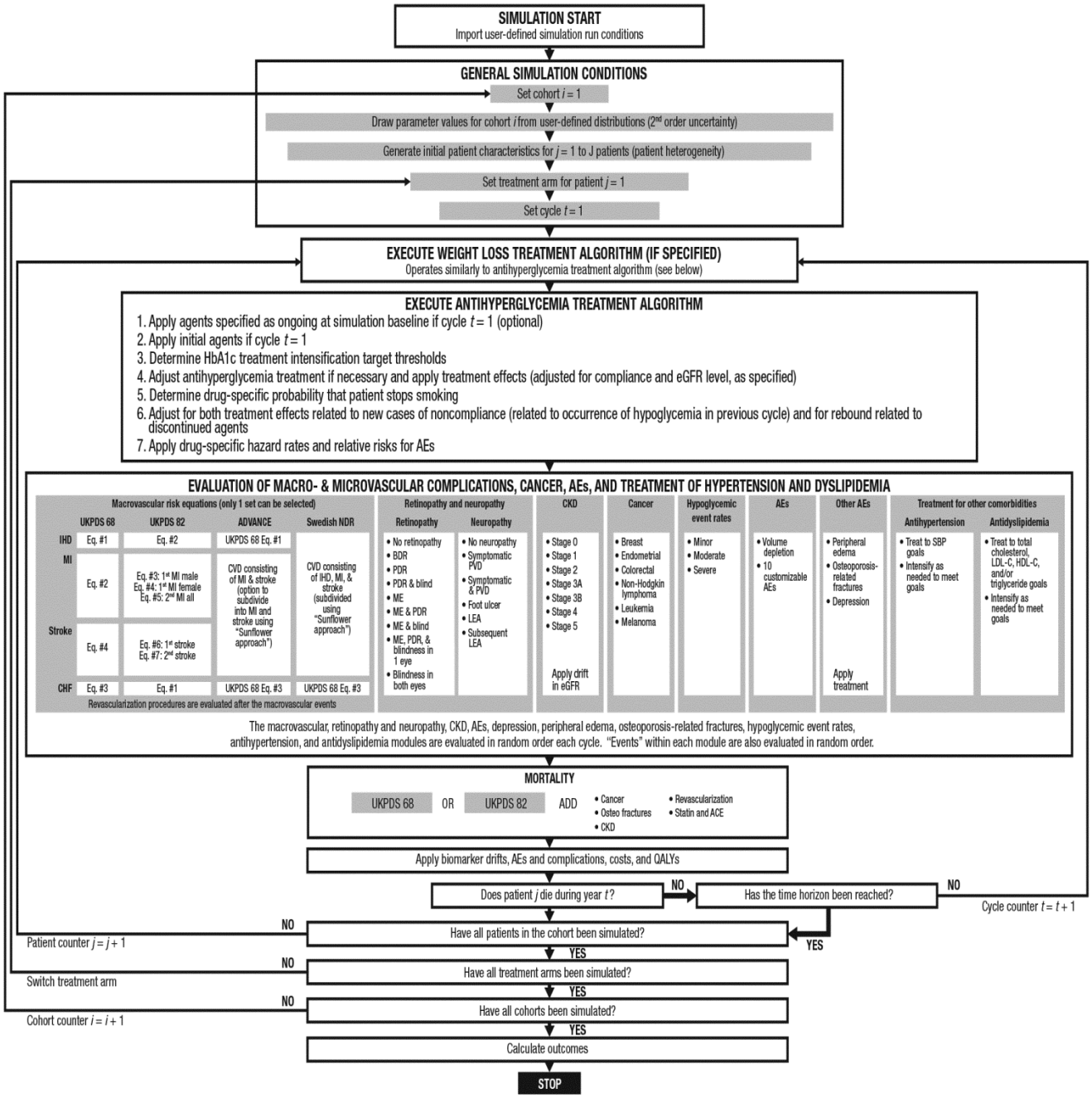
METHODS

Model Overview and Simulation Description

The Economic and Health Outcomes Model of T2DM (ECHO-T2DM) was used to perform the simulations. ECHO-T2DM is a stochastic, Markov-based, microsimulation model for estimating the cost-effectiveness of alternative treatments for T2DM. It has been reviewed by health technology assessment (HTA) agencies, including CADTH and Québec Institut National d'Excellence en Santé et en Services (INESSS) in Canada, the UK National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), and the National Centre for Pharmacoeconomics (NCPE) in Ireland. The analyses were performed in accordance with CADTH's guidelines for economic evaluations.[23] ECHO-T2DM has been externally validated[24,25] and has participated in the 3 most recent Mount Hood Challenges, in which diabetes modelers meet biennially and conduct cross-validation exercises.[21,26,27] The application of ECHO-T2DM to cost-effectiveness simulations using data from the canagliflozin program has been described previously.[28]

In ECHO-T2DM, health is captured with Markov health states reflective of T2DM, including micro- and macrovascular complications, hypoglycemia and treatment-related AEs, and mortality (Figure 1).[24]

FIG. 1 ECHO-T2DM model[28]



ACE, angiotensin-converting enzyme inhibitor; ADVANCE, Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation; AE, adverse event; BDR, background diabetic retinopathy; CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cardiovascular disease; ECHO-T2DM, Economic and Health Outcomes Model of Type 2 Diabetes Mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IHD, ischemic heart disease; LDL-C, low-density lipoprotein cholesterol; LEA, lower extremity amputation; ME, macular edema; MI, myocardial infarction; NDR, National Diabetes Registry; PDR, proliferative diabetic retinopathy; PVD, peripheral vascular disease; QALY, quality-adjusted life-year; SBP, systolic blood pressure; UKPDS, United Kingdom Prospective Diabetes Study. *Reprinted from Value in Health Regional Issues, Volume 8, Cheryl Neslusan, Anna Teschemaker, Pierre Johansen, Michael Willis, Atanacio Valencia-Mendoza, Andrea Puig, Cost-Effectiveness of Canagliflozin versus Sitagliptin as Add-on to Metformin in Patients with Type 2 Diabetes Mellitus in Mexico, Pages 8-19, Copyright 2015, with permission from Elsevier.*

The cycle length is 1 year and the time horizon is defined by the user. ECHO-T2DM accounts explicitly for both first-order uncertainty (due to patient-level variability) and second-order uncertainty (related to uncertainty regarding the true value of the underlying parameters). Cohorts of individual hypothetical patients with T2DM are generated based on initial patient demographics, biomarker values, and disease indicators observed in randomized controlled trials. Risk factor clustering of key biomarkers is supported (e.g., individuals who have higher body mass index [BMI] values tend to have less favorable cholesterol values).[29] Biomarker values are updated annually to reflect changes associated with treatments and any underlying deterioration in the biomarkers over time.[30]

The hypothetical patients are assigned risks for micro- and macrovascular complications and for mortality that are individualized to patient characteristics using risk functions. Transition probabilities for microvascular health states are sourced from previous modeling efforts in this area and reflect differences in HbA1c levels and/or duration of T2DM.[31-33] ECHO-T2DM supports multiple sets of macrovascular and mortality event risk prediction equations; in this analysis, risk functions from the United Kingdom Prospective Diabetes Study (UKPDS 82) were used.[34] Specifically, the UKPDS 82 risk equations include the 4 macrovascular complications included in ECHO-T2DM (including second events for myocardial infarction [MI] and stroke and separate risks for first MI events for males and females) and 4 unique mortality risk equations (the one used at each time point depending on whether an individual patient has a prior history of diabetes-related complications and has experienced an event during the current cycle). The risks are tailored to each patient's current health history (including age, gender, disease duration, biomarker values, and micro- and macrovascular health history) at each point in time.

A treatment algorithm based on treatment thresholds was used to simulate AHA treatment over time; AHAs can be added or changed to maintain HbA1c target values and/or avoid AEs (including an option for contraindication, which can result in discontinuation). Treatment algorithms for medical management of hypertension and dyslipidemia can be applied where treatment can be intensified when BP and lipid targets are not met. Deterioration of patient biomarker values are accounted for via specification of annualized measures of deterioration in biomarkers over time (i.e., "drifts"; HbA1c, 0.14%; SBP, 0.3 mmHg; lipids, 0.3 mg/dL), which are updated within each cycle.[30,35] Natural deterioration of eGFR over time occurs in line with the validated Centers for Disease Control and Prevention (CDC) Model of Chronic Kidney Disease (CKD).[33] Specifically, eGFR declines by 1.1, 4.1, 2.8, and 5.2 mL/min/1.73 m^2 per cycle in patients with eGFR >60 mL/min/1.73 m^2 and normoalbuminuria, eGFR >60 mL/min/1.73 m^2 and albuminuria, eGFR <60 mL/min/1.73 m^2 and normoalbuminuria, and eGFR <60 mL/min/1.73 m^2 and albuminuria, respectively.[33,36]

ECHO-T2DM can accommodate parameterizing up to 3 different levels of severity for hypoglycemic events. In the present application, severe and non-severe symptomatic hypoglycemic episodes were modeled, where severe was defined as episodes requiring the assistance of another individual or resulting in seizure or loss of consciousness and non-severe symptomatic was defined as symptoms accompanied by a glucose reading ≤70 mg/dL (3.9 mmol/L) that were not considered to be severe. AEs potentially associated with the SGLT2 mechanism of action (e.g., genital mycotic infections [e.g., yeast infections],[37] urinary tract infections[38]) were also included explicitly.

Costs were assigned individually for each patient based on treatment, micro- and macrovascular complications, severe hypoglycemic events, and AEs experienced during the simulation (i.e., according to individual patient histories). Patient preferences for health states were captured similarly using quality-adjusted life-year (QALY) disutility weights (i.e., decrements in quality of life). Model outcomes include life-years (LYs) and QALYs; cost and cost-effectiveness metrics; biomarker evolution curves; cumulative incidences for each type of health outcome; and relative risk

reductions (RRRs) in micro- and macrovascular events.

Model Inputs

In the base case, a total of 1,000 cohorts each consisting of 2,000 hypothetical individuals with T2DM (i.e., 2 million unique patients) were randomly generated and simulated over 40 years. Two treatment comparisons were simulated (both as add-on to metformin plus sulfonylurea):

1) Canagliflozin 300 mg versus sitagliptin 100 mg
2) Canagliflozin 100 mg versus sitagliptin 100 mg

For the comparison of canagliflozin 300 mg and sitagliptin 100 mg, patient characteristics were sourced from the 52-week, head-to-head trial of canagliflozin versus sitagliptin as add-on to metformin plus sulfonylurea (Table 1).[39]

TABLE 1 Key Baseline Patient Characteristics

Characteristic*	CANA 300 mg vs SITA 100 mg† Total (N = 755)	CANA 100 mg vs SITA 100 mg‡ Total (N = 1,224)
Sociodemographic characteristics		
Age, y	56.7 (9.5)	56.6 (9.4)
Male, %	55.9	54.0
Duration of T2DM, y	9.6 (6.2)	9.6 (6.2)
Current smoker, %	10.6	11.4
Biomarkers		
HbA1c, %	8.1 (0.9)	8.1 (0.9)
Total cholesterol, mg/dL	178.7 (42.6)	182.0 (44.6)
LDL-C, mg/dL	98.8 (36.9)	100.4 (37.5)
HDL-C, mg/dL	45.7 (11.8)	45.3 (11.5)
Triglycerides, mg/dL	175.4 (119.6)	183.5 (124.0)
SBP, mmHg	130.7 (13.6)	130.6 (13.5)
BMI, kg/m^2	31.6 (6.9)	32.2 (6.8)
Complications/comorbidities		
PVD, %	0.7	0.6
Microalbuminuria, %	1.2	1.2
Macroalbuminuria, %	1.1	0.7
Macular edema, %	0	0
Proliferative diabetic retinopathy, %	0	0
Background diabetic retinopathy, %	10.2	9.2
Symptomatic neuropathy, %	0.4	0.3

BMI, body mass index; CANA, canagliflozin; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metformin; PVD, peripheral vascular disease; SBP, systolic blood pressure; SD, standard deviation; SITA, sitagliptin; SU, sulfonylurea; T2DM, type 2 diabetes mellitus. Data are mean (SD) unless otherwise indicated.
†Data sourced from the 52-week, head-to-head study of CANA 300 mg versus SITA 100 mg as add-on to MET + SU.[39]
‡Data sourced from a pooled analysis of the 2 CANA add-on to MET + SU studies.[39,40]

For the comparison of canagliflozin 100 mg versus sitagliptin 100 mg, patient characteristics were sourced from a pooled analysis of the head-to-head study versus sitagliptin and a 52-week, placebo-controlled trial as add-on to metformin plus sulfonylurea (Table 1).[39,40] Treatment effects, hypoglycemia rates, and AE rates for canagliflozin 300 mg and sitagliptin

100 mg were sourced from the head-to-head study of canagliflozin versus sitagliptin as add-on to metformin plus sulfonylurea.[38] In the absence of similar head-to-head data comparing canagliflozin 100 mg and sitagliptin 100 mg and given the similar study design and baseline characteristics between the 2 trials that investigated canagliflozin as add-on to metformin plus sulfonylurea,[39,40] the comparison was performed using treatment effects, hypoglycemia rates, and AE rates from the placebo-controlled study for canagliflozin 100 mg and from the active-controlled study for sitagliptin 100 mg.

Treatment effects were applied for each patient in the first year of the simulation (Table 2). In the base case, eGFR was assumed to remain stable (i.e., no deterioration over time) for as long as patients continued on canagliflozin; the CDC Model of CKD drift in eGFR was applied for patients who discontinued canagliflozin (and initiated rescue therapy) and for patients assigned to sitagliptin in all scenarios.[33] The impact of eGFR stabilization with canagliflozin was explored via a sensitivity analysis where eGFR drifted downward in accordance with the CDC model of CKD.

TABLE 2 Clinical Inputs for CANA 300 and 100 mg and SITA 100 mg

Treatment effects, mean change from baseline	**CANA 300 mg***	**CANA 100 mg†**	**SITA 100 mg***
HbA1c, %	–1.03	–0.74	–0.66
Total cholesterol, mg/dL	9.79	1.73	1.03
LDL-C, mg/dL	6.25	0.29	0.38
HDL-C, mg/dL	2.88	2.62	–0.47
Triglycerides, mg/dL	2.26	3.33	5.65
SBP, mmHg	–5.06	–3.66	0.85
BMI, kg/m^2	–0.82	–0.73	0.06
AEs, events per patient-year of exposure			
Severe hypoglycemia	0.075	0.0080	0.053
Non-severe symptomatic hypoglycemia	1.899	1.136	1.486
Male genital mycotic infection	0.112	0.095	0.063
Female genital mycotic infection	0.188	0.391	0.056
Lower UTI	0.058	0.116	0.077
Upper UTI	0	0.008	0.007
Discontinuation rate associated with AEs in the first year, %	5.6	7.0	3.7

AE, adverse event; BMI, body mass index; CANA, canagliflozin; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metformin; SBP, systolic blood pressure; SITA, sitagliptin; SU, sulfonylurea; UTI, urinary tract infection. *Data sourced from the 52-week, head-to-head add-on to MET + SU study for CANA 300 mg and SITA 100 mg.[39]

†Data from the 52-week, placebo-controlled add-on to MET + SU study for CANA 100 mg.[40]

TABLE 3 Event-year and State Costs and QALY Utility Weight Inputs

Clinical Event	Event-year cost,* $	State, annualized cost, $	Disutility weight
Patient characteristics			
Age (per 10 years)	NA	NA	–0.0235[61]
Female	NA	NA	–0.093[61]
Duration of T2DM (per 10 years)	NA	NA	–0.0163[61]
Macrovascular			
IHD	5,950	3,436	–0.024[9,62]
MI	19,012	2,973	–0.012[9,62]
CHF	17,392	4,876	–0.018[9,62]
Stroke	25,896	3,593	–0.04[9,62]
PVD	1,490	532	–0.063[63]
Microvascular			
Microalbuminuria	77	12	0[32]
Macroalbuminuria	67	22	–0.048[32]
eGFR 30-59 mL/min/1.73 m^2	NA	NA	–0.05[33]
eGFR 15-29 mL/min/1.73 m^2	NA	NA	–0.07[33]
eGFR <15 mL/min/1.73 m^2	0	0	–0.175[32]
ESRD	25,774	25,774	–0.088[9,64,†]
Macular edema	376	342	NA
Proliferative diabetic retinopathy	526	50	0[32]
Background diabetic nephropathy	82	82	NA
Any blindness	3,181	2,267	–0.0498[9]
Symptomatic neuropathy	4,426	4,426	–0.084[32]
Diabetic foot ulcer	13,370	0	–0.2[63]
Lower extremity amputation	40,179	5,502	–0.28[9,64]
Symptomatic neuropathy and PVD	5,916	4,958	–0.085[32]
Hypoglycemia			
Non-severe symptomatic hypoglycemic event	0	NA	–0.000004767[9]
Severe hypoglycemic event	2,031	NA	–0.01[9]
Overweight/obesity			
For each 1 kg/m^2 over BMI 25 kg/m^2	NA	NA	–0.0061[32]
AEs			
Lower UTI (male and female)	41.67	NA	–0.00123[55]
Upper UTI (male and female)	339.54	NA	–0.00729[55]
Genital mycotic infection (male and female)	38.35	NA	–0.0046[55]

AE, adverse event; BMI, body mass index; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IHD, ischemic heart disease; MI, myocardial infarction; NA, not applicable; PVD, peripheral vascular disease; QALY, quality-adjusted life-year; T2DM, type 2 diabetes mellitus; UTI, urinary tract infection. *Event-year costs are associated with management of the acute episode and any subsequent care in the first year.
†Note that ESRD occurs simultaneously with eGFR <15 mL/min/1.73 m^2 in the model, resulting in an overall disutility weight of –0.263.

In this case, treatment with canagliflozin 300 mg was discontinued when eGFR fell below 60 mL/min/1.73 m^2 and canagliflozin 100 mg was discontinued when eGFR fell below 45 mL/min/1.73 m^2 as per the label.[41] Note that when simulated eGFR fell below 60 mL/min/1.73 m^2 for patients who received canagliflozin 100 mg, hazard ratios from the pooled canagliflozin trial data for patients with moderate renal impairment (eGFR ≥45 and <60 mL/min/1.73 m^2)[42,43] were used to adjust the treatment effects for HbA1c, weight, and SBP.

Rescue therapy was applied as follows: when HbA1c first exceeded 8.0%, basal insulin (10 IU/day NPH) was added and titrated as needed to maintain HbA1c ≤8.0%, up to a maximum dose of 60 IU/day; after NPH reached the maximum dose, prandial insulin (insulin glulisine) was added as needed to maintain glycemic control, starting at a dose of 5 IU/day and titrated up to a maximum dose of 200 IU/day. Treatment effects and rates of hypoglycemia associated with the use of basal and prandial insulin were sourced from the literature.[44-46] Anti-hypertension and anti-dyslipidemia treatment algorithms were also applied based on meeting SBP and LDL-C targets recommended by the CDA Clinical Practice Guidelines.[6] Treatment for hypertension was initiated with an angiotensin-converting enzyme inhibitor (ramipril 5 mg) to maintain SBP <130 mmHg, followed by a calcium channel blocker (amlodipine 5 mg) if additional SBP control was needed. Treatment for dyslipidemia was initiated using atorvastatin 10 mg to maintain LDL-C ≤77 mg/dL (2.0 mmol/L), which could be intensified to 20 mg if additional LDL-C control was needed.

This analysis was conducted from the perspective of a Canadian provincial ministry of health and Canada's federal plans, and Canada-specific costs were applied (Table 3).[9,47-51] The unit price for sitagliptin 100 mg was $2.62 per day based on the lowest public list price in Canada (Quebec).[52] The price for both canagliflozin doses was based on the lowest list price in Canada (Quebec; $2.62 per day).[52] Other drug costs were obtained from the Ontario Public Drug Program (2013) or the Quebec public plan (2013).[52,53] Costs were inflated as necessary to 2013 Canadian dollars using the health care component of the Consumer Price Index. Costs and health outcomes (i.e., QALYs) were discounted at 5% per CADTH guidelines.[23]

QALY disutility weights relevant to Canada (primarily sourced from the CADTH third-line therapy report[9]) were applied to baseline utilities for each applicable year and were assumed to be additive when patients experienced more than 1 event in a cycle (Table 3). For example, a 50-year-old male with 10 years of T2DM duration and a history of ischemic heart disease (IHD) who is experiencing an MI during the current cycle (but has no other disutility-causing conditions) is applied a QALY weight of 1.027 (the intercept) minus 0.00235 for each year of age (i.e., 0.00235 × 50 years = 0.1175), 0.00163 for each year of T2DM duration (i.e., 0.00163 × 10 years = 0.0163), 0.024 for IHD history, and 0.012 for experiencing an MI, yielding a total of 0.8572 QALYs for that cycle. In the absence of Canada-specific disutility weights, values were sourced from the literature.[32,40,54] Disutility weights for AEs potentially associated with SGLT2 inhibition were obtained from a time trade-off study.[55]

Outcomes

Economic outcomes of this analysis included mean LYs, QALYs, and survival; incremental cost-effectiveness ratios (ICERs); and scatterplots of the cost-effectiveness planes. Patient outcomes, such as cumulative incidence rates for each type of micro- and macrovascular outcome, AE event rates, and RRRs for the micro- and macrovascular complications, were also calculated and are presented to facilitate interpretation of the primary results.

Sensitivity Analyses

One-way sensitivity analyses were conducted to explore the robustness of the base case results with respect to the choice of discount rate, time horizon, HbA1c treatment intensification threshold, disutility associated with weight gain, and eGFR drift as follows:

- Discount rate: reduced discount rate of 0% (SA1) or 3% (SA2)
- Time horizon: shorter time horizon of 10 years (SA3) or 5 years (SA4)

- eGFR drift: apply the eGFR drift from the CDC Model of CKD[33] to canagliflozin (SA5)
- Alternative treatment thresholds: HbA1c treatment intensification threshold at HbA1c of 7.0% (SA6) or 9.0% (SA7)
- Weight-related disutility assumptions: assume disutility due to BMI increase from CADTH report (–0.001950135[9]; SA8) or 0 (SA9)

For each of these analyses, 1,000 cohorts of 1,000 hypothetical patients (i.e., 1 million unique patients) were generated and simulated.

RESULTS

Base Case Analyses

The differences in the product profiles of canagliflozin 300 and 100 mg and sitagliptin 100 mg translated into differences in health outcomes and patient costs over 40 years (Table 4). For the canagliflozin 300 mg comparison, canagliflozin-treated patients experienced 0.23 more LYs and 0.31 more QALYs than sitagliptin-treated patients, with total health-related costs that were $2,217 lower ($44,680 vs $46,897). At the end of the simulation (40 years), 8.5% of patients in the canagliflozin 300 mg group and 5.2% of patients in the sitagliptin 100 mg were still alive (difference of 3.3 percentage points).

TABLE 4 Base Case Results: Costs of Complications and AEs, Average Costs, and Benefits per Person Over 40 Years

	CANA 300 mg	SITA 100 mg	Difference	CANA 100 mg	SITA 100 mg	Difference
Costs, $						
Macrovascular						
MI	4,160	4,265	–104	4,360	4,465	–105
IHD	2,559	2,674	–115	2,769	2,899	–130
CHF	2,606	2,770	–164	2,732	2,879	–147
Stroke	1,878	1,980	–101	1,977	2,063	–86
Microvascular						
Retinopathy	944	939	5	945	904	40
Nephropathy	85	1,396	–1,311	101	1,350	–1,249
Neuropathy	9,465	9,390	75	9,638	9,422	216
AHA						
Oral agents	13,542	13,491	51	13,411	13,570	–160
Insulin	5,803	6,668	–865	6,969	6,886	83
Prescription treatment						
Hypoglycemia	1,676	1,234	443	344	1,248	–904
AEs	107	94	13	155	95	60
Hypertension	687	917	–230	715	918	–202
Dyslipidemia	1,167	1,080	87	1,130	1,109	21
Total costs, $	44,680	46,897	–2,217	45,247	47,807	–2,560
Health indicators						
LYs	11.99	11.76	0.23	12.04	11.83	0.21
QALYs	8.65	8.35	0.31	8.64	8.37	0.28
Survival,* %	8.5%	5.2%	3.3%	8.6%	5.5%	3.1%
Cost per QALY, $			Dominating			Dominating

AE, adverse event; AHA, antihyperglycemic agent; CANA, canagliflozin; CHF, congestive heart failure; IHD, ischemic heart disease; LY, life-year; MI, myocardial infarction; QALY, quality-adjusted life year; SITA, sitagliptin. *Percent alive at simulation end.

TABLE 5 Base Case Results: Cumulative Incidences and RRRs of Key Micro- and Macrovascular Events Over 40 Years

Cumulative incidence, %	CANA 300 mg	SITA 100 mg	RRR	CANA 100 mg	SITA 100 mg	RRR
Macrovascular events						
MI	17.6	18.7	6.1	18.4	19.6	5.9
IHD	16.8	18.1	7.2	16.7	18.2	8.0
CHF	11.3	12.8	11.2	11.9	13.3	10.1
Stroke	7.1	7.8	8.3	7.3	7.9	7.2
PVD	44.8	43.6	–2.9	44.9	43.6	–3.1
Microvascular events						
Microalbuminuria	6.6	16.9	61.3	6.4	16.3	60.5
Macroalbuminuria	1.8	12.0	85.0	1.5	11.3	86.4
ESRD	0.6	11.3	94.6	0.8	10.8	93.0
Macular edema	36.7	36.7	–0.1	37.5	36.4	–2.9
Proliferative diabetic retinopathy	2.5	2.5	–2.7	2.5	2.4	–7.6
Background diabetic retinopathy	57.0	57.5	0.9	58.1	57.2	–1.6
Blindness						
One eye	2.3	2.2	–5.0	2.3	2.1	–9.8
Both eyes	2.2	2.1	–6.6	2.2	2.0	–11.0
Symptomatic neuropathy	35.9	34.6	–3.8	36.0	34.6	–4.2
Diabetic foot ulcer	30.1	28.7	–5.1	30.3	28.7	–5.4
Lower extremity amputation	19.7	18.5	–6.5	19.8	18.5	–7.0

CANA, canagliflozin; CHF, congestive heart failure; ESRD, end-stage renal disease; IHD, ischemic heart disease; MI, myocardial infarction; PVD, peripheral vascular disease; RRR, relative risk reduction; SITA, sitagliptin.

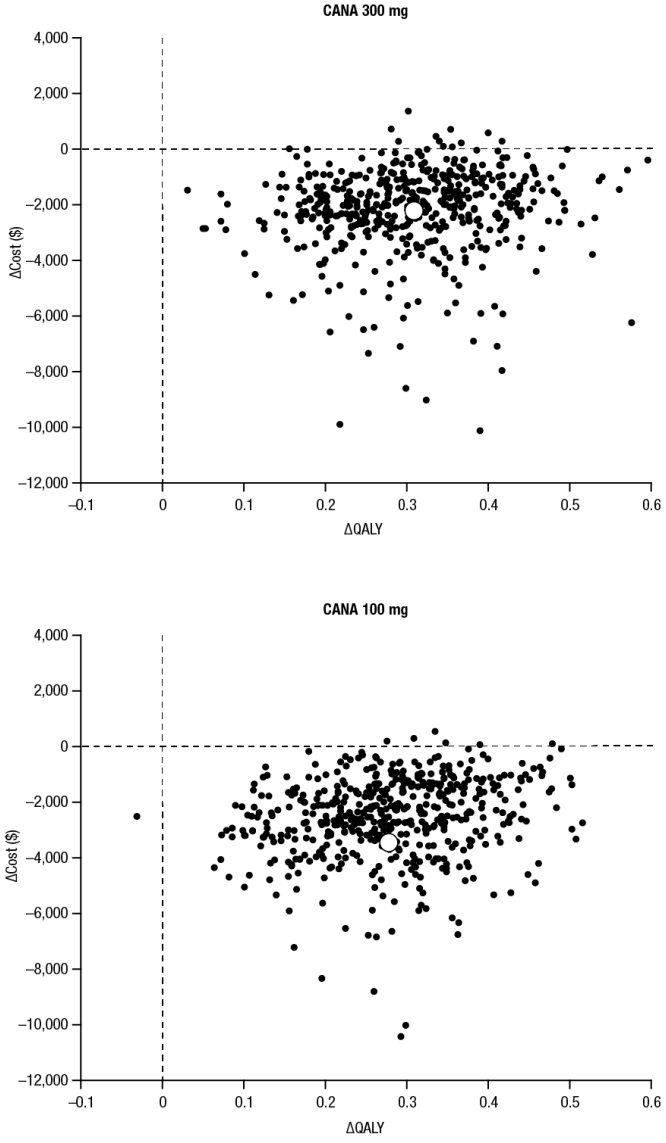
The largest sources of cost offsets were associated with nephropathy (related to stabilization of eGFR) and with insulin rescue medication (the need for which was postponed given better initial HbA1c lowering). The results were generally similar for the canagliflozin 100 mg comparison, with LY and QALY gains of 0.21 and 0.28, respectively, and cost savings of $2,560 relative to sitagliptin. In addition, 8.6% of patients in the canagliflozin 100 mg group and 5.5% of patients in the sitagliptin 100 mg group were surviving at the end of the simulation (difference of 3.1 percentage points), which is consistent with the results seen with canagliflozin 300 mg. Nephropathy was the largest source of cost offsets for this comparison as well. This combination of lower costs and better outcomes is commonly referred to as "dominant."

Cumulative incidences and RRRs of key micro- and macrovascular events with canagliflozin versus sitagliptin are presented in Table 5. Macrovascular event rates were generally lower with both canagliflozin doses than with sitagliptin. There were sizable decreases in microalbuminuria, macroalbuminuria, and ESRD, which were largely attributable to simulated differences in eGFR deterioration between canagliflozin and sitagliptin. The improved weight

profile was associated with 0.047 and 0.037 lower QALY disutility (i.e., yielding higher utility) related to excess weight for canagliflozin 300 and 100 mg, respectively.

The cost-effectiveness planes illustrated in Figure 2 indicate a high degree of certainty that both canagliflozin doses were associated with cost savings and improved quality of life versus sitagliptin 100 mg, as most cohort replications were located in the southeast quadrant (i.e., lower costs and greater QALYs). Both canagliflozin 300 and 100 mg have near 100% likelihoods of being cost-effective versus sitagliptin at all willingness-to-pay thresholds.

FIG. 2 Cost-effectiveness planes* for CANA 300 and 100 mg versus SITA 100 mg.



CANA, canagliflozin; SITA, sitagliptin; QALY, quality-adjusted life-year.
*Larger white circles represent the mean value across cohorts.

TABLE 6 Sensitivity Analysis Results: Costs and QALY Differences and ICERs for CANA 300 and 100 mg Versus SITA 100 mg

	CANA 300 mg			CANA 100 mg		
	Cost difference vs SITA, $	**QALY difference vs SITA***	**ICER, $/QALY**	**Cost difference vs SITA, $**	**QALY difference vs SITA***	**ICER, $/QALY**
Base case	–2,217	0.31	Dominating	–2,560	0.28	Dominating
Discount rate						
SA1: Discount rate at 0%	–4,399	0.94	Dominating	–4,689	0.85	Dominating
SA2: Discount rate at 3%	–2,876	0.47	Dominating	–3,212	0.42	Dominating
Time horizon						
SA3: 10-year time horizon	–897	0.06	Dominating	–1,249	0.05	Dominating
SA4: 5-year time horizon	–406	0.03	Dominating	–712	0.02	Dominating
eGFR drift						
SA5: Normal eGFR drift for CANA	–2,870	0.08	Dominating	–2,594	0.06	Dominating
Alternative treatment thresholds						
SA6: 7.0% HbA1c intensification trigger	–2,265	0.31	Dominating	–2,698	0.27	Dominating
SA7: 9.0% HbA1c intensification trigger	–2,161	0.31	Dominating	–2,457	0.27	Dominating
Weight-related disutility assumptions						
SA8: Assume alternative BMI disutility (–0.001950135)[9]	–2,302	0.27	Dominating	–2,535	0.25	Dominating
SA9: Assume alternative BMI disutility (0)	–2,302	0.26	Dominating	–2,535	0.24	Dominating

BMI, body mass index; CANA, canagliflozin; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SITA, sitagliptin; SA, sensitivity analysis.
*QALY differences are rounded to 2 decimal places.

Sensitivity Analyses

Results from the sensitivity analyses were robust and support the findings from the base case analysis, with canagliflozin 300 and 100 mg dominating sitagliptin 100 mg in each scenario (Table 6). Not surprisingly, with lower discount rates of 0% or 3%, canagliflozin 300 and 100 mg dominated sitagliptin 100 mg as future cost offsets and QALY gains were no longer down-weighted. Given the chronic nature of T2DM treatment, larger cost offsets and QALY gains with both canagliflozin doses versus sitagliptin 100 mg were estimated over the longer base case time horizon of 40 years versus the shorter time frames considered in sensitivity analyses; however, even in periods as short as 5 and 10 years, canagliflozin dominated sitagliptin, though the magnitude of the cost savings and QALY gains were naturally smaller. Canagliflozin 300 and 100 mg dominated sitagliptin 100 mg in the simulations that assumed that eGFR drifted down over time with canagliflozin. Canagliflozin 300 and 100 mg also continued to dominate sitagliptin 100 mg in the sensitivity analyses that varied the treatment intensification thresholds, including the higher HbA1c threshold of 9.0% (which may be more reflective of the glycemic control of many actual Canadian T2DM patients).[7] Consistent with the base case, canagliflozin dominated sitagliptin across a range of weight-related disutility values.

DISCUSSION

In this economic evaluation, canagliflozin 300 and 100 mg dominated sitagliptin 100 mg as add-on to metformin plus sulfonylurea, providing more QALYs at a lower cost, from the perspective of CADTH in the Canadian setting. In the base case sets of simulations, QALY gains with both canagliflozin doses were largely composed of a decreased incidence of CKD, improved longevity, and canagliflozin-related initial weight loss. Approximately half of the cost savings associated with the use of canagliflozin 300 and 100 mg relative to sitagliptin 100 mg in third-line therapy were due to reductions in the costs of treating nephropathy, consistent with the assumption that renal function does not deteriorate while on canagliflozin treatment. Other important sources of cost savings include reduction in macrovascular complications (both doses), insulin rescue therapy (300 mg dose), hypoglycemia (100 mg dose), and hypertension medication (both doses). Scatterplots of the incremental costs and QALYs for canagliflozin 300 and 100 mg versus sitagliptin 100 mg indicate a high degree of certainty, as most cohort replications were associated with lower costs and increased QALYs; results indicated a high likelihood of canagliflozin being cost-effective relative to sitagliptin.

Because CKD is a serious complication of T2DM, the base case assumption that renal function does not deteriorate while on canagliflozin treatment was an important driver of the associated cost offsets and QALY gains, though removing this assumption did not reverse canagliflozin "dominance" for either dose, as demonstrated in the sensitivity analysis. This assumption is supported by recent evidence from a long-term outcomes trial with the SGLT2 inhibitor empagliflozin, which found stable eGFR over 4 years of treatment (i.e., the full study period)[17] and is consistent with results from the longest available canagliflozin trial data to date (2 years).[56] Of note, the initial decline in eGFR with agents that inhibit SGLT2 is transient and, as such, no renal damage (glomerular or tubular) is expected to occur.[15] Additionally, indirect evidence from clinical trials of canagliflozin indicates that treatment may confer renoprotection not only due to favorable efficacy in terms of HbA1c lowering, weight loss, and BP reductions, but fundamentally via its mechanism of action.[15] The CANVAS-R and CREDENCE trials were designed to explicitly evaluate the long-term impact of canagliflozin on renal outcomes.

Findings from sensitivity analyses support the robustness of the base case; canagliflozin 300 and 100 mg dominated sitagliptin 100 mg in each of the sensitivity analyses. Weight change generally appears to be a key driver of uncertainty in health economic models, and weight management can improve clinical outcomes related to T2DM; however, previous HTA assessments have raised concerns about the use of overly optimistic weight-related disutility values. In the base case, we applied a conservative weight-related disutility from a population of

patients with T2DM.[32] Canagliflozin continued to dominate sitagliptin when a very small weight-related disutility value from the CADTH Optimal Use Report was used, the original source of which was based on a group of people without T2DM (from the NICE obesity guidelines).[57,58] Even in the scenario where no decrement in utility from weight gain was assumed, canagliflozin dominated sitagliptin. Findings from the base case were also robust in the sensitivity analyses that varied other model parameters, including discount rate, time horizon, and HbA1c treatment intensification threshold.

This analysis derived key modeling parameters from robust clinical trial data, including a head-to-head study of canagliflozin 300 mg versus sitagliptin 100 mg and a placebo-controlled study that included canagliflozin 100 mg.[39,40] In addition, the results of these simulations were tailored to the Canadian health care system by using Canadian costs and Canadian-relevant disutility estimates where possible. However, as with all long-term economic evaluations in T2DM and owing to the absence of long-term clinical evidence for alternative T2DM treatments, a key caveat for this analysis is the use of short-term clinical data (i.e., HbA1c, BP, and lipid changes) to predict the occurrence of complications over time. The importance of this caveat for the finding that both canagliflozin doses dominate sitagliptin 100 mg in third-line therapy is minimized via the use of a well-validated model. In addition, ECHO-T2DM was explicitly tailored to reflect some of the unique aspects of SGLT2 inhibition, including side effects potentially related to this mechanism of action. However, conventional macrovascular and mortality risk equations, such as UKPDS 82, were not estimated using patients taking SGLT2 inhibitors.[34] Recent findings from the EMPA-REG cardiovascular outcomes trial found that the SGLT2 inhibitor empagliflozin significantly reduced cardiovascular mortality, all-cause mortality, and hospitalization for heart failure.[59] Therefore, use of conventional risk equations may underestimate cardiovascular risk reductions associated with SGLT2 inhibitors,[60] resulting in a conservative estimate of cost-effectiveness for canagliflozin versus sitagliptin in these simulations.

CONCLUSIONS

These economic simulations suggest that canagliflozin is associated with lower costs and more LYs and QALYs than sitagliptin in patients inadequately controlled with metformin plus sulfonylurea in the Canadian setting, with key drivers of these results being better glucose, weight, and SBP control, as well as delayed progression of CKD. As such, canagliflozin is likely to provide good "value for money," with lower costs and better health outcomes, compared with sitagliptin, when used in third-line therapy with metformin and sulfonylurea in Canada.

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Conflict of Interest

This analysis was sponsored by Janssen Inc. and was based on data from studies supported by Janssen Research & Development, LLC. S.S. and K.Y. are employees of Janssen Inc. C.N. and A.T. are employees of Janssen Global Services, LLC. P.J. and M.W. are employees of the Swedish Institute for Health Economics, which has provided consulting services for Janssen Global Services, LLC.

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