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Cost Effectiveness Evaluation of Canagliflozin in Combination with Metformin in the Treatment of Type 2 Diabetes Mellitus in Poland

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BACKGROUND

- Type 2 diabetes mellitus (T2DM) generally occurs in people older than 40 years; the incidence increases with age, with more than 10% of people over 65 years having T2DM. In recent years, T2DM more often arises at a younger age due to an increasingly obese society, poor childhood dietary habits, and sedentary lifestyles [1–3].
- T2DM is a major public health problem and affects 10 million people in Europe (4% of the total population). Based on World Health Organization (WHO) estimates, by 2030, the number of people with diabetes could be over 350 million throughout the world [4]. Estimated prevalence of T2DM in Poland is about 6.5% [5].
- Canagliflozin (CANA) is a novel, oral antihyperglycaemic agent (AHA) with sodium glucose co-transporter 2 (SGLT2) inhibition developed for the treatment of adults with T2DM [6, 7]; CANA was approved for use in the European Union in November 2013.
  - By inhibiting SGLT2, CANA reduces renal glucose reabsorption and increases urinary glucose excretion, thereby lowering blood glucose [8–10]; this independent of pancreatic ß cell function mechanism of action makes it complementary to other AHAs, including insulin.
- In Phase 3 studies, CANA:
  - Provided improved glycaemic control and body weight and blood pressure reductions. Was generally well tolerated, with an increased incidence of adverse events (AEs) related to the mechanism of action (eg, genital mycotic infections, urinary tract infections, AEs related to osmotic diuresis), but a low inherent risk of hypoglycaemia, such that discontinuation due to AEs was low and generally similar in the CANA and non-CANA patients [6, 7].
- Proven in CANA clinical trials - weight loss and blood pressure reduction, is not associated with SITA nor GLIM.

OBJECTIVE

The objective of the analysis was to assess cost-effectiveness of canagliflozin (Invokana®) as add-on to metformin (MET) compared to sitagliptin (SITA) and maximally tolerated glimepiride (GLIM) in treatment of T2DM in adult patients. The analysis was conducted in Polish setting from a public payer perspective.

METHODS

Scope of the analysis and its methodology is based on Polish guidelines on health technology assessment (HTA).

The IMS CORE Diabetes Model (*www.core-diabetes.com*) was used to evaluate cost-effectiveness of canagliflozin. The CORE Model is a validated [11] and widely used tool allowing to simulate diabetes progression in lifetime horizon. It implements Markov model using series of interconnected sub-models representing diabetes complications.

The model offers the possibility to implement country-specific and intervention-specific data. Polish data on costs of drugs and treatment for T2DM related complications and all cause (i.e. non-T2DM-related) mortality rates were applied into the model. Clinical effectiveness data were sourced from two head to head randomized clinical trials (RCTs) comparing canagliflozin to the analyzed interventions in patients inadequately controlled on maximally tolerated metformin. [6, 7] The effectiveness of interventions was measured by change in HbA1c, BMI, systolic blood pressure (SBP), lipids level and hypoglycemic event rates. Utilities data were obtained from a systematic review of published literature on quality of life of patients with diabetes and its complications, which was conducted according to Polish HTA guidelines. Costs of drugs and treatment of diabetes complications were calculated using data from Polish National Health Fund (NHF) and Ministry of Health (MoH).

A lifetime horizon was adopted, so that the impact of long-term complications of T2DM could be assessed. Outcomes were discounted according to Polish HTA guidelines (costs were discounted at 5% and health effects with 3.5%).

It was assumed that patients are treated with canagliflozin, sitagliptin or glimepiride for 5 years and later switch to NPH + MET + SU (neutral protamine Hagedorn insulin + metformin + sulfonylurea) therapy, which is then continued lifetime. Treatment with NPH in the following line is in agreement with Polish guidelines of T2DM treatment.

The main outcomes of the analysis were costs and QALYs (quality-adjusted life years). Costs were reported in Polish złoty (PLN, 1 EUR = 4.10 PLN). Based on the costs and QALY results, incremental cost-utility ratio (ICUR) was calculated and compared to the cost-effectiveness threshold, which is 111,381 PLN/QALY in Poland (2014).

In order to measure uncertainty of obtained results, probabilistic sensitivity analysis (PSA) and a series of one-way sensitivity analyses were conducted.

DATA

Baseline characteristics

Baseline characteristics were sourced from RCTs for canagliflozin [6, 7] and Polish observational studies [12–14]. The parameters included in the analysis are presented in **Table 1**.

Table 1. Baseline characteristics of patients in CANA clinical trials

Parameter	Value	
	CANA 100 vs SITA/ GLIM	CANA 300 vs SITA/ GLIM
Age [years]	55.8	
Sex [male]	51.4%	
Duration of T2DM [years]	6.6	
BMI [kg/m^2] (baseline)	31.6	31.3
HbA1c [%] (baseline)	7.9	7.8
SBP [mm Hg] (baseline)	128.7	129.2
TC [mg/dl]	187.6	
HDL [mg/dl]	46.3	
LDL [mg/dl]	106.5	
TRIG [mg/dl]	182.7	

All data was obtained as a result of a pooled analysis of RCTs for CANA [6, 7]
SBP – systolic blood pressure, HDL – high density lipoprotein, LDL – low density lipoprotein, TRIG – triglycerides, TC – total cholesterol
Final levels – after 52 weeks of follow-up

Efficacy and safety

According to Polish HTA guidelines, a systematic literature review was conducted in which data on comparative efficacy and safety of canagliflozin, sitagliptin and glimepiride were searched. Two head-to-head RCTs assessing effectiveness of canagliflozin in dual therapy were identified [6, 7].

The methodology of calculations, adopted for Polish cost-effectiveness analysis, included:

- calculating mean level of HbA1c/BMI/SBP reported at the end of RCTs (follow-up of 52 weeks) for CANA 100 and CANA 300 arm; these outcomes were applied as baseline levels of HbA1c/BMI/SBP in the modeling (**Table 1**);
- change of HbA1c/BMI/SBP for CANA 100 and CANA 300 arm was set to zero (a final value reported in trials already includes changes of these parameters);
- change of HbA1c/BMI/SBP for SITA/GLIM was set as the mean difference between interventions.

The clinical effects applied in calculations are summarized in **Table 2**. Change of HbA1c, BMI and SBP level is assumed to take place in the first cycle, BMI is conservatively assumed to return to the baseline level after 5 years (at the moment of treatment switch). No additional efficacy in terms of other clinical endpoints associated with switch of treatment was assumed, excepting hypoglycemic event rates. Clinical trials demonstrated statistical superiority of CANA 300 to comparators in lowering HbA1c, BMI and SBP [6,7] and statistical superiority of CANA 100 to comparators in lowering BMI and SBP [6,7].

Table 2. Key efficacy and safety parameters used in the simulations

Parameter	CANA 100 vs SITA	CANA 300 vs SITA	CANA 100 vs GLIM	CANA 300 vs GLIM
Baseline values in the CORE model				
HbA1c (%)	7.1	6.9	7.1	6.9
BMI (kg/m^2)	30.3	29.9	30.3	29.9
SBP (mm Hg)	125.7	124.8	125.7	124.8
Relative efficacy – Mean Difference [95% CI] [a]				
HbA1c change (%)	0.00 [-0.12; 0.12]	-0.15 [-0.27; -0.03]	-0.01 [-0.11;0.09]	-0.12 [-0.22;-0.02]
BMI change (kg/m^2)	-0.8	-0.9	-1.6 [-1.7; -1.4]	-1.7 [-1.9; -1.6]
SBP change (mm Hg)	-2.8 [-4.5 -1.3]	-4.0 [-5.6; -2.4]	-3.5 [-4.9; -2.1]	-4.8 [-6.2; -3.4]
Minor hypoglycemia [b] (per 100 patient-years)	No data	No data	CANA 100: 14 GLIM: 150	CANA 300: 7 GLIM: 150

a) calculated from trial data, negative values indicate that canagliflozin is more efficacious than comparator;
b) documented hypoglycemia (<=39 mmol/l or severe) – no data for severe hypoglycemia was available

Costs and utilities

Costs of AHAs and complications were calculated from public payer perspective based on NHF and MoH data. Complications in the CORE model include cardiovascular, renal, retinopathies and other vision problems, neuropathies, hypoglycemia, diabetic foot ulcers and amputations (**Table 3**).

Table 3. Costs and utilities of selected complications of diabetes

Complication	Cost [PLN]	Utility
	First year / Following years	First year / Following years
T2DM	0	0.785
Myocardial infarction	12,679 / 2,708	-0.055 [a] / 0.730
Angina pectoris	819	0.695
Heart failure	6,701	0.677
Stroke	12,712 / 438	-0.164 [a] / 0.621
Hemodialysis	71,532 / 69,922	0.610
Peritoneal dialysis	86,935 / 84,325	0.610
Renal transplantation	60,127 / 13,456	0.785
Severe hypoglycemia	114	-0.012 [a]
Mild hypoglycemia	0	-0.004 [a]
Amputation (no prosthesis)	8,919	-0.280 [a] / 0.505
Amputation (prosthesis)	13,166	

a) decrease in utility

Utilities of health states were established based on systematic review of published literature (**Table 3**). [15]. The decrease of utility associated with BMI above 25 kg/m^2 was conservatively assumed at level of -0.0061 per unit BMI above 25.

RESULTS

CANA + MET vs SITA + MET

The estimated difference in QALY between CANA 100 + MET / CANA 300 + MET and SITA + MET is equal to 0.060 QALY and 0.093 QALY, respectively. The difference in costs is equal to -2,811 PLN for CANA 100 and 4,163 for CANA 300. CANA 100 dominates SITA + MET and for CANA 300 + MET incremental cost-utility ratio is equal to 45,008 PLN/QALY. The detailed results are presented in **Table 4**.

Table 4. Results of deterministic analysis – CANA vs SITA

Category	CANA 100 + MET	SITA + MET	Difference	CANA 300 + MET	SITA + MET	Difference
QALY	6.667	6.607	0.060	6.726	6.634	0.093
Costs	39,258	42,069	-2,811	46,091	41,928	4,163
ICUR	-	-	CANA dominates	-	-	**45,008**

Modeling indicates that regimens with canagliflozin versus those with SITA are costs-saving for CANA 100 and cost-effective for CANA 300. The scatterplots that depict the incremental costs and QALYs from each of the 1000 cohorts are presented on **Figure 1** and **Figure 2**.

Figure 1. Results of PSA for CANA 100 + MET vs SITA + MET

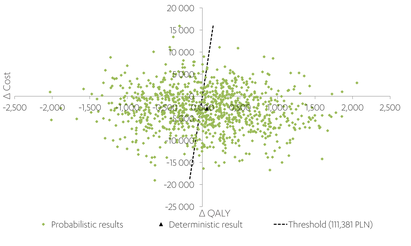
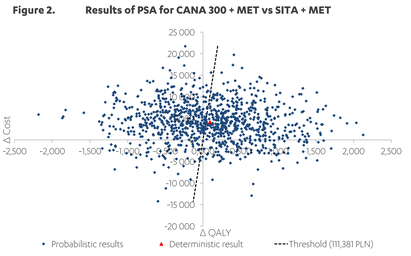
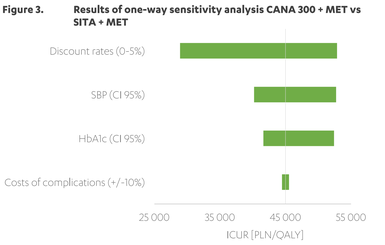


Figure 2. Results of PSA for CANA 300 + MET vs SITA + MET



One-way sensitivity analyses showed the greatest impact of discount rates on final results for CANA 300, however, extreme values of this parameter still suggest that canagliflozin is cost-effective versus SITA (**Figure 3**). For CANA 100 one-way sensitivity analyses indicate that SITA is dominated by CANA 100.

Figure 3. Results of one-way sensitivity analysis CANA 300 + MET vs SITA + MET



CI 95% - in sensitivity analysis left and right ends of confidence intervals were used

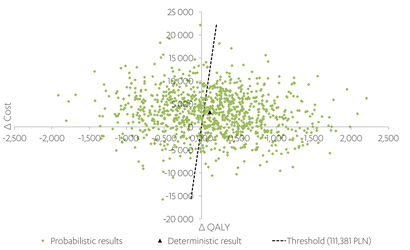
CANA + MET vs GLIM + MET

The estimated difference in QALYs between CANA 100 + MET / CANA 300 + MET and GLIM + MET is equal to 0.112 QALY and 0.140 QALY, respectively. The difference in costs is equal to 3,184 PLN for CANA 100 and 10,235 for CANA 300. Incremental cost-utility ratio for CANA 100 is equal to 28,454 PLN/QALY and for CANA 300 + MET 73,102 PLN/QALY. The detailed results are presented in **Table 5**.

Table 5. Results of deterministic analysis – CANA vs GLIM

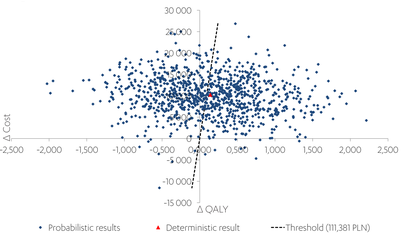
Category	CANA 100 + MET	GLIM + MET	Difference	CANA 300 + MET	GLIM + MET	Difference
QALY	6.665	6.553	0.112	6.725	6.585	0.140
Costs-	39,258	36,074	3,184	46,108	35,873	10,235
ICUR	-	-	**28,454**	-	-	**73,102**

Figure 4. Results of PSA for CANA 100 + MET vs GLIM + MET



Modeling indicates that treatment with CANA 100 or CANA 300 versus maximally tolerated GLIM are cost-effective in Polish reimbursement setting. The scatterplots that depict the incremental costs and QALYs from each of the 1000 cohorts are presented on **Figure 4** and **Figure 5**.

Figure 5. Results of PSA for CANA 300 + MET vs GLIM + MET



One-way sensitivity analyses showed the greatest impact of discount rates on final results, however, extreme values of this parameter still imply cost-effectiveness of canagliflozin (**Figure 6**).

Figure 6. Results of one-way sensitivity analysis CANA + MET vs GLIM + MET

CI 95% - in sensitivity analysis left and right ends of confidence intervals were used

CONCLUSIONS

Favorable clinical outcomes for canagliflozin (specifically HbA1c, BMI and SBP reductions) translate into long-term health benefit gains and into cost-effectiveness of CANA 100 and CANA 300 vs GLIM/SITA. The analysis indicates higher effectiveness of treatment algorithms with the use of CANA 100 and CANA 300 in comparison to SITA and GLIM as an add-on therapy in patients inadequately controlled with MET. In the comparison with sitagliptin, CANA 100 was the dominant therapy. For all comparisons ICURs are below the cost-effectiveness threshold in Poland.

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