Poster PDB109

Cost Effectiveness Evaluation of Canagliflozin in Combination with Metformin and Sulfonylurea in Comparison to NPH Insulin 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 [11, 12]; 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 [6–8]; 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 [9, 10].

OBJECTIVE

The objective of the analysis was to assess cost-effectiveness of canagliflozin (Invokana®) as add-on to metformin (MET) and sulfonylurea (SU) compared to NPH insulin 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 randomized clinical trials (RCTs) comparing canagliflozin or NPH insulin to other interventions. The effectiveness of interventions was measured by change in HbA1c, BMI, systolic blood pressure (SBP), lipids levels 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 or NPH insulin for 5 years and later switch to premixed insulin + MET + SU therapy, which is then continued lifetime. Treatment with premixed insulin 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 zloty (PLN, 1 EUR = 4.10 PLN). Based on the cost 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 series of one-way sensitivity analyses were conducted.

DATA

Baseline characteristics

Baseline characteristic were sourced from RCTs for canagliflozin [9, 10] and Polish observational studies [12–14]. The values used in the analysis are presented in **Table 1**.

Table 1. Baseline characteristics of patients in CANA clinical trials

Parameter	Value	
	CANA 100 vs NPH	CANA 300 vs NPH
Age [years]	56.7	
Sex [male]	51.4%	
Duration of T2DM [years]	9.6	
BMI [kg/m2] (baseline)	33.3	32.0
HbA1c [%] (baseline)	8.1	8.1
SBP [mm Hg] (baseline)	130.4	131.1
TC [mg/dl]	182.1	
HDL [mg/dl]	45.4	
LDL [mg/dl]	100.8	
TRIG [mg/dl]	182.7	

All data was obtained as a result of a pooled analysis of RCTs for CANA [9, 10]
SBP – systolic blood pressure, HDL – high density lipoprotein, LDL – low density lipoprotein, TRIG – triglycerides, TC – total cholesterol
Final levels – after 26 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 and NPH insulin were searched. As no head-to-head trial comparing canagliflozin with NPH insulin were identified, mixed treatment comparison analysis was conducted (following Polish HTA guidelines). Two RCTs assessing effectiveness of canagliflozin in triple therapy were identified [2, 3]. Due to lack of trials assessing effectiveness of NPH insulin fulfilling review's inclusion criteria, it was assumed that the effectiveness of NPH insulin is comparable to effectiveness of insulin glargine [15].

The methodology of calculations for treatment effects focused on relative efficacy measures, therefore we conducted following analysis steps:

- calculating mean level of HbA1c/BMI/SBP reported at the end of RCTs (follow-up of 26 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 (as final values reported in trials already including changes of these parameters are used);
- change of HbA1c/BMI/SBP for NPH was set as the mean difference between interventions obtained from mixed treatment comparison analyses.

The clinical effects applied in calculations are summarized in **Table 2**. Change of HbA1c, BMI and SBP parameters 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 were modified.

Table 2. Key efficacy and safety parameters based on Polish MTC analysis

Parameter	CANA 100 vs NPH	CANA 300 vs NPH
Baseline values in the CORE model		
HbA1c (%)	7.3	7.0
BMI (kg/m^2)	32.6	31.1
SBP (mm Hg)	125.5	125.4
Relative efficacy – Mean Difference [95% credible interval] [a]		
HbA1c change (%)	0.1 [-0.2; 0.5]	-0.1 [-0.4; 0.2]
BMI change (kg/m^2)	-3.5 [-5.5; -1.5]	-4.2 [-6.4; -2.1]
SBP change (mm Hg)	-4.2 [-9.0; 0.7]	-3.6 [-8.4; 1.3]
Major hypoglycemia (per 100 patient-years)	CANA 100: 0.6 NPH: 2.4	CANA 300: 0.6 NPH: 2.4
Minor hypoglycemia (per 100 patient-years)	CANA 100: 269.8 NPH: 475.0	CANA 300: 269.8 NPH: 475.0

a) calculated from trial data, negative values indicate that canagliflozin is more efficacious than NPH insulin
MTC – mixed treatment comparison

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		0.785
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**) [16]. 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 100 + MET + SU vs NPH + MET +SU

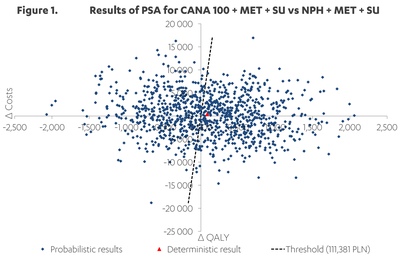
The estimated difference in QALYs between CANA 100 + MET + SU and NPH + MET + SU is equal to 0.084 QALYs. The difference in costs is equal to 378 PLN. Incremental cost-utility ratio is equal to 4,477 PLN/QALY. The detailed results are presented in **Table 4**.

Table 4. Results of deterministic analysis – CANA 100 vs NPH

Category	CANA 100 + MET + SU	NPH + MET + SU	Difference
QALY	6.189	6.104	0.084
Costs	39,751	39,373	378
ICUR	-	-	**4,477**

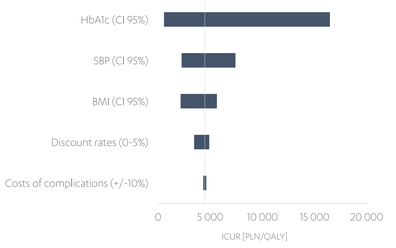
Modeling indicates that treatment with CANA 100 versus NPH insulin is highly cost-effective, as the ICUR level is far below cost-effectiveness threshold in Poland. The scatterplot that depicts the incremental costs and QALYs from each of the 1000 cohorts is presented in **Figure 1**.

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



One-way sensitivity analyses showed the greatest impact of HbA1c level on final results, however, extreme values of this parameter still suggest that canagliflozin is cost-effective versus NPH insulin (**Figure 2**).

Figure 2. Results of one-way sensitivity analysis CANA 100 + MET + SU vs NPH + MET + SU



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

CANA 300 + MET + SU vs NPH + MET + SU

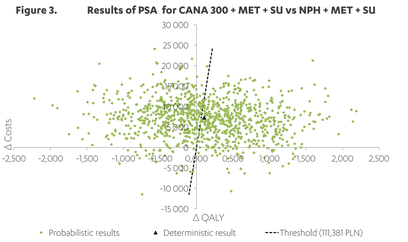
The estimated difference in QALYs between CANA 300 + MET + SU and NPH + MET + SU is equal to 0.106 QALYs. The difference in costs is equal to 7,299 PLN. Incremental cost-utility ratio is equal to 69,081 PLN/QALY. The detailed results are presented in **Table 5.**

Table 5. Results of deterministic analysis – CANA 300 vs NPH

Category	CANA 300 + MET + SU	NPH + MET + SU	Difference
QALY	6.310	6.204	0.106
Costs	46,322	39,023	7,299
ICUR	-	-	**69,081**

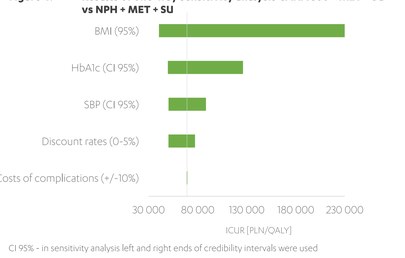
Modeling indicates that treatment with CANA 300 versus NPH insulin is cost-effective as the ICUR is below defined Polish cost-effectiveness threshold. The scatterplot that depicts the incremental costs and QALYs from each of the 1000 cohorts is presented on **Figure 3**. The majority of the points lie in the northern quadrants indicating a positive difference in QALYs.

Figure 3. Results of PSA for CANA 300 + MET + SU vs NPH + MET + SU



One-way sensitivity analyses showed the greatest impact of BMI on final results. Only in the extreme case of using a value for BMI or HbA1c set to the left end of 95% credibility interval resulted in ICURs higher than the threshold. Other scenarios confirm cost-effectiveness of canagliflozin (**Figure 4**).

Figure 4. Results of one-way sensitivity analysis CANA 300 + MET + SU vs NPH + MET + SU



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

CONCLUSIONS

Favorable clinical outcomes for canagliflozin (specifically weight loss and lower hypoglycemic events rates) translate into health benefit gains and into cost-effectiveness of CANA 100 and CANA 300 vs NPH in the long-term. These analyses suggests that treatment algorithms with the use of CANA 100 and CANA 300 in comparison to NPH insulin as an add-on in patients needing additional HbA1c control with background MET plus SU therapy will result in a more efficient allocation of resources in the Polish setting. For both comparisons base-case ICURs are below the cost-effectiveness threshold in Poland.

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