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- ОПРЕДЕЛЕНИЕ ПОРОГА «ГОТОВНОСТИ ПЛАТИТЬ» ПРИ ОДОБРЕНИИ МЕДИЦИНСКИХ ТЕХНОЛОГИЙ В УСЛОВИЯХ РОССИЙСКОГО ЗДРАВООХРАНЕНИЯ, РАССЧИТАННОГО НА ОСНОВЕ ПАРИТЕТА ПОКУПАТЕЛЬНОЙ СПОСОБНОСТИ
- ОРИГИНАЛЬНЫЕ РОССИЙСКИЕ ФАРМАКОЭКОНОМИЧЕСКИЕ ИССЛЕДОВАНИЯ

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PHARMACOECONOMIC STUDY OF CANAGLIFLOZIN (INVOCANA) THERAPY AS A PART OF COMBINED THERAPY FOR PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Study purpose: *to determine whether canagliflozin is a pharmacoeconomically justified option to be included into therapy for patients with insufficient glycemic control and treated with metformin either as monotherapy administered in the maximum tolerated dose or as a part of a combined therapy with sulfonylurea derivatives taking into account the conditions existing in the Russian Federation.*

Materials and methods: *the retrospective modelling was performed according to the standard pharmacoeconomic methods, such as cost-effectiveness analysis, budget impact analysis and sensitivity analysis. In order to forecast the long-term impact of the therapies being compared on the results of the cost-effectiveness analysis regarding the QALYs, as well as direct and indirect expenses, the Markov modelling for a period of 20 years was performed. The following options were compared: a combined therapy comprising metformin and inhibitors of the sodium-glucose co-transporter (SGLT2) (canagliflozin), the dipeptidyl peptidase 4 inhibitors (iDPP-4) (sitagliptin, vildagliptin), sulfonylurea derivatives (glimepiride). In addition we performed the comparative analysis of triple combinations including canagliflozin or sitagliptin combined with metformin or glimepiride.*

Study results: *in the cost-effectiveness analysis the CER was 528 862 roubles, 531 556 roubles, 560 025 roubles, 544 528 roubles and 572 645 roubles for the combined therapy with metformin and Invokana 100 mg per day, Invokana 300 mg per day, Januvia, Galvus and Amaryl, respectively. For triple combinations comprising metformin and glimepiride the CER amounted at 556 436 roubles and 648 268 roubles for Invokana and Januvia accordingly.*

Conclusion: *the use of canagliflozin (Invokana) as combined with metformin or with both metformin and glimepiride improves glycemic control, contributes to the patient´s blood pressure and body weight control, which indirectly (according to the results of modelling) helps to reduce the frequency of the type 2 diabetes mellitus complications and, consequently, the related costs. Because of this, the lowest CER level is associated with Invokana therapy as compared to the iDPP-4 and glimepiride in similar combinations.*

Key words: *type 2 diabetes mellitus, QALY, CER, cost-effectiveness analysis, canagliflozin, iDPP-4, metformin, glimepiride.*

Introduction

"The world is facing a growing diabetes epidemic of potentially devastating proportions, which can paralyze the healthcare authorities worldwide", said Robert Beaglehole, the Director of the WHO Department of Chronic Disease and Health Promotion, which is becoming more relevant year by year, as new epidemiological data and forecasts are being developed.

According to the new data published by the WHO, every year diabetes mellitus (DM) kills 4,9 million persons. This figure is three times higher than the earlier indexes. In 2000 around 175 million patients with diabetes were registered, while in 2014 this number reached 387 million. By 2030 this number will grow up to 592 million. According to the report published by the WHO and the International Diabetes Federation (IDF), the impact is felt most severely in developing countries [3]. Thus, the State register of patients with DM says that by 2014 in the Russian Federation over 3,96 million patients were treated, and over 3,2 million of them were patients with type 2 DM [25]; still, according to the epidemiological studies, the real number of patients with type 2 DM in this country exceeds 6,7 million [4].

Up to 90% of cases are those of type 2 DM. These patients have an increased risk of cardiovascular diseases, blindness, amputations and renal failure. The treatment of such cases obstructs the functioning of the healthcare authorities. According to the Ministry of Healthcare, today in Russia about 15% of the healthcare budget is assigned for the diabetes control. Of these expenses, over 80% account for the diabetes complications. So, if the action is not taken now, tomorrow these expenses will be considerably higher [1,4,5]. The International Diabetes Federation estimates that in 2014 the treatment of one patient with type 2 diabetes in the Russian Federation cost 1 120 US dollars [2].

The elaboration of a new therapeutic approach for patients with type 2 DM is nowadays one of the most relevant challenges of the modern medicine.

The type 2 DM therapeutic approach shall be aimed to improve glycemic control and B cell performance, as well as to reduce the intensity of other disorders associated with type 2 DM (for example, obesity, hypertension). The modern treatment regimen is expected not only to provide effective therapy, but also to prevent successfully and to control the disease progression and the related complications risk. Thus, the modern DM control strategy might help to reduce the estimated long-term expenses for the national healthcare systems [5-6].

The mentioned facts clearly show the importance of a pharmacoeconomic analysis of type 2 DM drug therapy as a tool, which helps to enhance the efficiency of pharmaceutical assistance aimed to minimize the risk of complications and to improve the quality of life.

The emergence of a promising class of medicinal products (MP), sodium–glucose co-transporter 2 (SGLT2) inhibitors, which inhibit the renal glucose reabsorption from the patient´s primary urine, requires certain revision to

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be made so that these MP could be included into type 2 DM management guidelines. This study is a clinical and economic evaluation of the use of Invokana (canagliflozin), which is a sodium–glucose co-transporter 2 (SGLT2) inhibitor, as a part of a combined therapy of type 2 DM.

Materials and methods

Model structure description

The retrospective study was performed according to the standard pharmacoeconomic methods, such as cost-effectiveness analysis, budget impact analysis and sensitivity analysis.

The time horizon of the modelling was 20 years with the discount rate of 3%. We used the Microsoft Excel software in order to build a Transition matrix of the Markov model, necessary to make a forecast regarding the impact of the compared therapy methods on the disease progression in a long-term perspective.

The Markov model cycle duration was of one year. The efficacy starting points of the compared treatment regimens were assigned by using the data of randomized clinical trials (RCT). Thus, the performance evaluation of the compared treatment regimens was made taking into account the reduction of glycated hemoglobin A1c (HbA1c) levels, systolic blood pressure (sBP) and the patient´s weight. The secondary efficacy points comprised the frequency of microvascular and macrovascular complications of type 2 DM. They were estimated basing on the data regarding changes in HbA1c and sBP, as well as the information regarding the impact of changes in these indexes on the risk of complications mentioned in the UKPDS (The United Kingdom Prospective Diabetes Study). The integral index QALY was used as the effectiveness endpoints, as it shows the number of additional years of life taking into account its quality during the full modelling period and the impact of the type 2 DM complications, their consequences and body weight changes. The correlation structure of the endpoints of the Markov model is shown in fig. 1.

Comparator drugs

In most cases, the pharmaceutical treatment of type 2 DM is recommended to be started with metformin as monotherapy [1,2,3]. If the glycemic control is insufficient in patients, who are treated with metformin in the maximum tolerated dose, the Russian practice (as well as that of the Western countries) often supposes that sulfonylurea derivatives are to be added. The latter are quite attractive when it comes to their price, still, they produce several negative effects, such as an elevated hypoglycemia risk, body weight increase, though it was already excessive, negative impact on the functional β-cells reserve. According to the modern algorithms [1], as a double therapy is applied, instead of the sulfonylurea derivatives it is recommended to use MP of newer groups, which lack the mentioned side-effects. Among the oral antihyperglycemic medications DPP-4 inhibitors stand out as such, and they are used in the Russian practice as a part of type 2 DM treatment.

If a triple (non-insulin) treatment is needed for a type 2 DM patient, physicians often prescribe a combination of metformin, sulfonylurea derivative with addition of MP from another group, among which there is a SGLT2 inhibitor or a DPP-4 inhibitor.

Accordingly, basing on the current Russian practice of type 2 DM management and the actual data obtained during RCT, the following MP were used in this study:

1. canagliflozin (Invokana) 100 mg per day in combination with metformin (Glucophage) 2000 mg per day;
2. canagliflozin (Invokana) 300 mg per day in combination with metformin (Glucophage) 2000 mg per day;
3. sitagliptin (Januvia) 100 mg per day in combination with metformin (Glucophage) 2000 mg per day;
4. vildagliptin (Galvus) 100 mg per day in combination with metformin (Glucophage) 2000 mg per day;
5. glimepiride (Amaryl) 8 mg per day in combination with metformin (Glucophage) 2000 mg per day;
6. canagliflozin (Invokana) 300 mg per day in combination with metformin (Glucophage) 2000 mg per day and glimepiride (Amaryl) 4 mg per day;
7. sitagliptin (Januvia) 100 mg per day in combination with metformin (Glucophage) 2000 mg per day and glimepiride (Amaryl) 4 mg per day.

In the present study, the original medications were compared, as they were used in the RCT to evaluate the effectiveness.

Effectiveness analysis

During the literature search for the effectiveness analysis of the compared treatment regimens we chose a number of trials, which compared therapy with SGLT2 inhibitors, DPP-4 inhibitors and sulfonylurea derivatives in combination with metformin regarding their capacity of reducing HbA1c and sBP and the patient´s weight. The primary endpoint of all trials was the change in HbA1c level till the end of the trial. The secondary endpoints included changes in body weight, sBP, fasting blood glucose, glucose concentration before and after each meal and before bedtime, as well as the specific side-effects.

In the study held by F. J. Lavalle-González , A. Januszewicz, J. Davidson. et al., "Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial" (n=1 284, duration – 52 weeks) the authors investigated the efficacy and safety of adding canagliflozin 100 mg and 300 mg per day to metformin therapy for patients with unsufficient glycemic control of type 2 DM as compared with sitagliptin 100 mg per day. The patients to whom metformin was administered in doses over 1500 mg per day, were randomized into groups, which were treated with canagliflozin in doses of 100 mg and 300 mg per day, with sitagliptin in dose of 100 mg or with placebo (n = 368, 367, 366, 183, respectively) in addition to metformin therapy. The initial average HbA1c level was 8,0% in the placebo group and 7,9% in other groups. By the end of the trial the average HbA1c level was -0,73% for the canagliflozin 100 mg group and the sitagliptin, and -0,88% for the canagliflozin 300 mg group. Average sBP was -3,5; -4,7 and -0,7 mm Hg for canagliflozin 100 mg, 300 mg and sitagliptin, respectively. Average impact on the body weight was -3,3; -3,7 and -1,2 kg for canagliflozin 100 mg, 300 mg and sitagliptin, respectively [7].

In the study performed by Cefalu WT, Leiter LA, Yoon KH, et al., "Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial" (n=1 452, duration – 52 weeks) the authors investigated the efficacy and safety of adding canagliflozin to metformin therapy for patients with unsufficient glycemic control of type 2 DM as compared with the maximum permissible dose of glimepiride. The patients were randomized into groups treated with canagliflozin 100 or 300 mg per day or with glimepiride in the dose of 6 to 8 mg per day (depending on which dose is the maximum permissible in the country where the research center in situated) in proportion of 1:1:1 in addition to the metformin therapy in doses over 1500 mg per day. The average initial HbA1c level was 7,8% for all randomized groups. By the end of the trial the average change of the HbA1c level was -0,81%; -0,82% and -0,93% for glimepiride, canagliflozin 100 mg and canagliflozin 300 mg groups, respectively. Average sBP change was -3,3; -4,6 and 0,2 for canagliflozin 100 mg and 300 mg, and glimepiride, respectively. Average impact on the body weight was -3,7; -4 and 0,7 for canagliflozin 100 mg and 300 mg, and glimepiride, respectively [8].

In the study held by Schernthaner G, Gross JL, Rosenstock J, Guarisco M. et. al., "Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial" (n=755) the authors investigated the efficacy and safety of adding canagliflozin as compared with sitagliptin, both in a triple combination with metformin and sulfonylurea derivatives in patients with insufficient glycemic control in type 2 DM. The patients were randomized into two groups treated with canagliflozin 300 mg per day or sitagliptin 100 mg per day in proportion 1:1 in addition to metformin therapy (2000 mg per day or 1500 mg, if tolerance is low) and sulfonylurea derivatives. The average initial HbA1c level was 8,1% for both groups. By the end of the study the average HbA1c level change was -1,03%, -0,66% for canagliflozin 300 mg group and sitagliptin group. Average sBP change was -5,1 and 0,9 for canagliflozin 300 mg and sitagliptin, respectively. Average impact on the body weight was -2,3 and 0,1 for canagliflozin 300 mg sitagliptin, respectively [9].

As in studies, in which canagliflozin 100 mg and 300 mg was compared to sitagliptin (study 1 [7]) and to sulfonylurea derivatives (study 2 [8]), there were no significant differences in the study design, the final efficacy data were obtained by indirect comparison. There were no statistically significant differences between the selected effectiveness criteria in studies 1 and 2, the average efficacy indexes for canagliflozin were calculated according to the formula:

$$Av.\ Eff. = Ef.1 \times W1 + Ef.2 \times W2,$$ where

Av.eff. is the efficacy index obtained by indirect comparison,

Ef1,2 – efficacy index (HbA1c, sBP, body weight) in the corresponding trial,

W1,2 – specific weight (%) of the group of patients respect to all patients in both trials, regarding which the indirect comparison was made.

Table 1 represents canagliflozin efficacy data obtained by consolidation of materials of study 1 and study 2.

In the same way, the indexes used in the effectiveness analysis of sitagliptin and glimepiride were changed by the same part, by which these

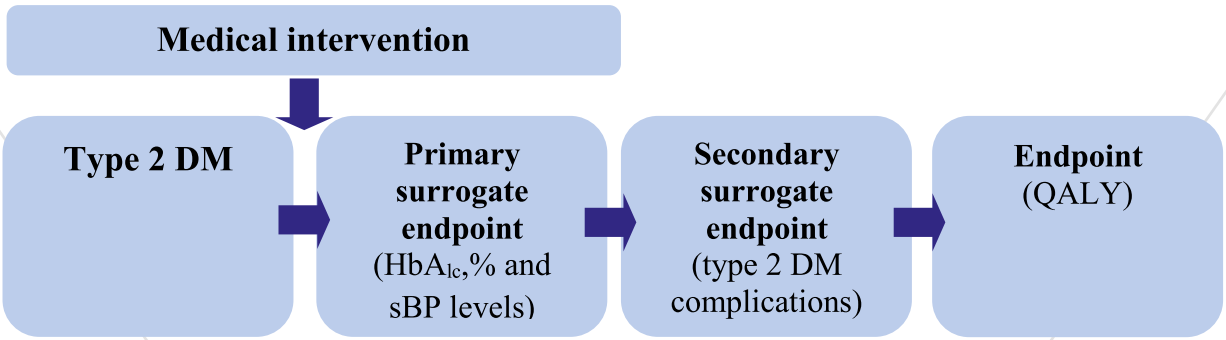

Figure 1. Correlation structure of the endpoints of the Markov model used in the cost-effectiveness analysis

Table 1. **Canagliflozin effectiveness analysis results**

MP	Number of patients, persons			Proportion of the total number of patients (weight)		Average change in HbA1c level, %			Average impact on body weight, kg			Average impact on sBP, mm Hg		
	Study 1	Study 2	Common in both studies	Number of patients in study 1	Number of patients in study 2	Study 1	Study 2	Average effect	Study 1	Study 2	Average effect	Study 1	Study 2	Average effect
Invokana, 100 mg	368	478	846	0,43	0,57	−0,73	−0,82	−0,78	−3,3	−3,7	−3,53	−3,5	−3,3	−3,39
Invokana, 300 mg	367	474	841	0,44	0,56	−0,88	−0,93	−0,91	−3,7	−4	−3,87	−4,7	−4,6	−4,64

indexes for canagliflozin, obtained by indirect comparison, differ from indexes for canagliflozin in study 1 and study 2, respectively.

The processing results of primary endpoints of the effectiveness analysis are set forth in table 2.

Evaluation of the impact of changed HbA1c and sBP on type 2 DM complications frequency

In order to evaluate the impact of the primary efficacy endpoints (HbA1c and sBP) on forecasting type 2 DM complications, we used the data set forth in the UKPDS (The United Kingdom Prospective Diabetes Study) [10, 13, 14].

The study "UKPDS 35" 4 585 patients were observed, on average, during ten years, when the authors were evaluating the reduction of risks associated with 1%-reduction of HbA1c level taking into account possible confounding factors, which were in effect as type 2 DM was diagnosed. The final supervision endpoints were the following: death caused by DM or otherwise, acute myocardial infarction, cerebral hemorrhage, amputation and microvascular complications (mainly retonipathy, neuropathy and renopathy), as well as cardiac failure and cataract [13].

In a similar way, in the study "Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study" (n=4 801, average supervision duration – 8,4 года) the authors evaluated the reduction of risks associated with sBP reduction by 10 mm Hg in patients with type 2 DM. Final endpoints were similar to those used in the UKPDS 35 [10].

The results of UKPDS 35 and UKPDS 36, as well as the average death rate with the initial patients'characteristics similar to the ones observed during the studies described in the effectiveness analysis, are set forth in table 3.

Table 2. **Results of the analysis of primary efficacy endpoints**

MP	Average impact on HbA1c, %	Average impact on body weight, kg	Average impact on sBP, mm Hg	Source
Invokana, 100 mg	−0,78	−3,53	−3,39	[7,8]*
Invokana, 300 mg	−0,91	−3,87	−4,64	[7,8]*
Januvia, 100 mg	−0,77	−1,27	−0,68	[7]*
Galvus, 100 mg	−0,77	−1,27	−0,68	[7]**
Amaryl, 8 mg	−0,78	0,67	0,20	[8]*
Invokana, 300 mg + Amaryl, 4 mg	−1,03	−2,3	−5,1	[9]
Januvia, 100 mg+ Amaryl, 4 mg	−0,66	0,1	0,9	[9]

* - indirect comparison data,
** - assumption regarding equal efficacy of Sitagliptin (Januvia) and Vildagliptin (Galvus).

Table 3. **Frequency of type 2 DM complications**

	UKPDS 35	*UKPDS 36*	*UKPDS 35*
Event	**Risk reduction with HbA1c 1%-decrease**	**Risk reduction with sBP decrease by 10 mm Hg**	**Events per 1000 person-years***
Death caused by DM	21%	17%	23,5
Death caused by another factors	14%	12%	8,3
Cerebral hemorrhage	12%	19%	7,4
Acute myocardial infarction	14%	20%	30
Cardiac failure	16%	12%	4,4
Amputation	43%	16%	4
Microvascular complications	37%	13%	22,8
Cataract	19%	0%	6,9

*- with average HbA1c level of 8,0% and average age of 54, average observation period of 10 years.

In addition to the data obtained during the UKPDS, the present study includes data regarding the reduction of frequency of ischemic heart disease (IHD) and angina pectoris, when HbA1c is reduced by 1%, obtained during the study held by Khaw KT et al. (n=10232; 2,4% c DM), which are 23% and 14%, respectively [15]. From the meta-analysis made by Law MR et al., we took the IHD and angina pectoris risk reduction index calculated for the sBP reduced by 10 mm Hg, which were 22% and 12%, respectively [16]. We decided to assume that the average incidence of IHD and angina pectoris with the average HbA1c level of 8,0% and average age of 54 years is equal to 30 events per 1000 person-years (similar to cardiac failure incidence).

QALY index

In order to calculate the aggregate QALY index for the whole modelling period, we used the utility indicator for each condition, in which the patient remains during certain periods. The existence of different utility indicators is subject to the patient's DM complications and body weight changes [20].

The initial QALY for type 2 DM patients, who didn't have any major microvascular or macrovascular complications before being included into the study, was considered to be 0,82, according to "Using the EQ-5D index score as a predictor of outcomes in patients with type 2 diabetes" (n=738) [17]. The QALY reduction in the year of event was made by set values, if certain complications occurred. Most complications were characterized by losses in QALY every year after the complication had occurred (table 4). In case of death QALY was reduced to zero from the year of complication up to the end of the modelling period. Body weight reduction meant an increase of QALY in the year of event.

As an example we will set forth QALY calculation for a patient who suffered a cerebral hemorrhage during the second year of treatment, taking into account the time horizon of ten years. During the first year of treatment QALY was 0,82. During the second year, due to the cerebral hemorrhage suffered by the patient, QALY reduced by 0,164 and turned out to be 0,656. Each of the modelled years, due to the cerebral hemorrhage, which occurred during the second year, meant the loss of 0,04 of the initial level, which was 0,78 QALY. Thus, within ten years the patient's quality of life was 0,82+0,656+0,78 *8 = 7,716 QALY.

Cost analysis

Cost analysis for the disease consists of the estimate of type 2 therapy direct costs for each of the compared treatment regimens (cost of the treatment with the compared medicines and metformin, as well as the cost of medical procedures according to the standards of medical assistance to type 2 DM patients) and indirect costs (costs associated with type 2 DM complications).

The information we use regarding the dosage was taken from the studies, on which the effectiveness analysis is based. Treatment regimens referred to in the studies also comply with the Standards of primary medical care in type 2 diabetes (outpatients) of January, 18th 2013 and the directions for use of the drugs used [24]. The cost of the drugs was estimated according to the registered manufacturer's maximum sale price of the vital and essential drugs or, if the drug was not included in the vital and essential drugs list, it was estimated basing on the tender prices set forth in http://zakupki.gov.ru for the fourth quarter of 2014. The information referred to the cost estimate of treatment with the drugs included into the compared treatment regimens, are set forth in table 5.

Medical assistance costs were taken from the Health Insurance Fund tariffs (by 2014) [11]. The estimated treatment costs of DM-associated complications is based on the Russian data (Dedov I.I., 2010 г.) with inflation in the fourth quarter of 2014 (table 6) [12].

Table 4. Value of utility in the model

Condition	**Impact on QALY (utility reduction)**
Cerebral hemorrhage	-0,164[a]
Cerebral hemorrhage (subsequent years)	-0,04[b]
Acute myocardial infarction	-0,055[a]
Acute myocardial infarction (subsequent years)	-0,012[c]
Angina pectoris	-0,041[b]
Angina pectoris (subsequent years)	-0,024[b]
Cardiac failure	-0,108[a]
Cardiac failure (subsequent years)	-0,018[c]
IHD	-0,09[a]
Amputation	-0,28[a]
Microvascular complications	-0,0252[d]
Cataract	-0,017[b]
Blindness (one eye)	-0,074[a]
Body weight increases by 1 kg	-0,001762115[e]

a- According to the study "Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62)" [18];
b- According to the pharmacoeconomic study "Cost-effectiveness of insulin analogues for diabetes mellitus" [19];
c- From "Methods for the economic evaluation of health care programs" [21];
d- We use an aggregate utility reduction index applied to renal insufficiency (-0,0263) from "A model to estimate the lifetime health outcomes of patients with type 2 diabetes: UKPDS Outcomes Model (UKPDS 68)" and neuropathy (-0,024) from the pharmacoeconomic study "Cost-effectiveness of insulin analogues for diabetes mellitus" [22];
e- We use the utility value based on the data obtained from the clinical guidelines NICE regarding obesity for a man with the BMI of 28-35 [23].

Table 5. **Estimated average cost of treatment with the drugs included into the compared treatment regimens**

Drug, daily dose	Treatment cost per day, rub.	Annual treatment costs (drugs expenses), rub.
Invokana, 100 mg	72,70	26 535,14
Invokana, 300 mg	122,98	44 886,73
Januvia, 100 mg	65,10	23 761,76
Galvus, 100 mg	43,62	15 922,60
Amaryl, 8 mg	65,67	23 968,33
Glucophage, 2000 mg	18,15	6 625,35

Cost-effectiveness analysis

At the final cost estimate stage we calculated the aggregate type 2 DM management within time horizon of 20 years. Direct costs comprise expenses for treatment with the comparator drugs and metformin / metformin + glimepiride, as well as the expenses for medical assistance according to the Standard of medical care in type 2 diabetes issued by the Ministry of Healthcare of the Russian Federation. Indirect costs comprise the expenses on type 2 DM treatment.

Then, basing on the data obtained by expenses and effectiveness analysis, we performed the cost-effectiveness analysis.

Cost-effectiveness analysis was calculated using the formula:

CER = Cost/QALY, where
CER – cost-effectiveness ratio,
Cost – total expenditure for the compared treatment regimen, rub.,
QALY – quality-adjusted life year.

The results of cost-effectiveness analysis are set forth in table 7. The results of modelling of complications incidence in each of the compared treatment regimens, are set forth in table 8.

Table 6. **Costs associated with DM complications**

Health condition / adverse event	Expenses, rub.	
	During the first year	Next year
Cerebral hemorrhage	307 446	23 532
Acute myocardial infarction	417 027	259 575
Blindness	48 404	-
Angina pectoris	260 552	259 575
Cardiac failure	27 946	27 840
Amputation	450 996	-
Cataract	27 000	-
Other microvascular complications (neuropathy, renal insufficiency)	522 789	522 789

Table 7. **Results of the cost-effectiveness analysis, rub. Time horizon is 20 years, discount rate is 3%, number of patients - 1**

Treatment regimen + metformin	Invokana, 100 mg	Invokana, 300 mg	Januvia, 100 mg	Galvus, 100 mg	Amaryl, 8 mg	Invokana, 300 mg + Amaryl, 4 mg	Januvia, 100 mg + Amaryl, 4 mg
Total direct costs, rub.	1 215 177	1 420 940	1 184 082	1 096 187	1 186 398	1 689 679	1 452 821
Total indirect costs, rub.	1 911 653	1 831 020	1 992 080	1 992 080	2 011 874	1 774 719	2 074 648
Aggregate expenses, rub.	3 126 831	3 251 960	3 176 162	3 088 267	3 198 272	3 464 398	3 527 469
QALY	5,91237	6,11781	5,67146	5,67146	5,58509	6,22605	5,44138
CER	528 862,24	531 556,29	560 025,28	544 527,58	572 644,62	556 435,59	648 267,70

Table 8. **Results of modelling of complications incidence in each of the compared treatment regimens in 1000 patients within 20 years**

Complication denomination	Complication incidence in treatment						
	Invokana, 100 mg	Invokana, 300 mg	Januvia, 100 mg	Galvus, 100 mg	Amaryl, 8 mg	Invokana, 300 mg + Amaryl, 4 mg	Januvia, 100 mg + Amaryl, 4 mg
Cerebral hemorrhage	125	119	132	132	135	115	139
Acute myocardial infarction	510	490	531	531	536	477	551
Blindness	152	138	161	161	163	126	175
Angina pectoris	510	490	531	531	536	477	551
IHD	448	413	485	485	495	391	521
Cardiac failure	73	70	76	76	77	68	80
Amputation	49	43	53	53	53	38	58
Microvascular complications	304	275	323	323	325	252	350
Cataract	118	114	118	118	118	111	121
Death caused by diabetes	366	343	389	389	395	328	412
Death due to another cause	141	136	147	147	148	132	152

Budget impact analysis

Budget impact analysis helps to make a financial evaluation of the effectiveness of a new medical technology being implemented, which is of great importance for taking decisions in healthcare [27]. This analysis supposes a comparative and competitive approach: the result of the budget impact analysis is the difference between the aggregate economic effects of the studies medical technologies.

The result of the budget impact analysis was calculated according to the formula:

BIA = S(1) - S(2), where

BIA – the result of budget impact analysis in monetary terms (budget economy or additional costs),

S(1), S(2) – expenditures for medicines.

In order to make a clear representation of the results, we calculated the economic impact produced within 20 years as a result of switching of 100 patients from the treatment regimens listed in table 9 to similar ones, which include Invokana instead of the comparator. We evaluated only the economic part, which included the expenditures for MP, medical assistance according to the Standard of medical care in type 2 diabetes of the Ministry of Healthcare of the Russian Federation, as well as costs of type 2 DM complications.

Total expenditure for the treatment of 100 patients with type 2 DM during 20 years was 324 754 250 rub. with current percentage ratio of iDPP-4 and sulfonylurea derivatives; and 322 373 565 rub. with the planned proportion including canagliflozin. Budget saving of 2 380 685 rub. was reached mainly by reducing the incidence of type 2 DM complications, which, in the longer term, were the most expensive cost item in the treatment.

In order to evaluate the impact of the indefinite variables on the reliability of the modelling results, we performed the sensitivity analysis. We made a univariate sensitivity analysis, which is normally performed, if there is no need to perform a more detailed analysis or if it is impossible to be made (for example, due to many variables) within the framework of the study scope [26]. The variables defining the cost of the comparator drugs had the highest degree of uncertainty in this model. As used in the sensitivity analysis, they were changing by 1% up to the point, in which the impact of such changes on the study results became significant (for example, budget savings were replaced by additional expenses). The univariate sensitivity analysis demonstrated that the results of the cost-effectiveness analysis are resistant to canagliflozin price fluctuations over 10%, which means that the modelling results are highly reliable.

Conclusions

Effectiveness analysis showed that treatment with canagliflozin at a dose of 300 mg per day in combination with metformin is associated with a better glycemic control and sBP values. HbA1c level reduced at canagliflozin therapy, and the reduction value was 0,14 and 0,15% higher than the one associated with iDPP-4 and glimepiride therapy, respectively. The sBP level reduction was 3,96 and 4,84 mm Hg higher if compared with the mentioned drugs.

The performed modelling demostrated to which extent these indexes reduce type 2 DM complications incidence. Thus, within 20-year period the use of canagliflozin, as against a iDPP-4 medicine and glimepiride, helps to reduce the number of deaths caused by diabetes by 46 and 51 events, the number of acute myocardial infarction by 40 and 46 events, the number of cerebral hemorrhages by 14 and 16 events by every 1000 patients, respectively.

The best possible indirect HbA1c and sBP control along with the best body weight contol are reflected as the integral effectiveness index QALY. This value for Invokana at a dose of 300 mg per day was 6,1178, when Invokana was combined with metformin, and 6,2261, when Invokana was combined with metformin and glimepiride. These values were the highest among all the compared treatment regimens with a 20-year time horizon and at a discount rate of 3%.

The cost analysis demonstrated that the lowest direct expenses correspond to vildagliptin, due to its low price and better glycemic control, when compared to sulfonylurea derivatives. At that, the lowest indirect expenses (associated with type 2 DM complications) correspond to the use of Invokana at a dose of 300 mg per day, due to the best level of incidence reduction, as the complications are, over the longer term, the most cost-intensive issue.

According to the cost-effectiveness analysis, the lowest CER level among the combinations of the comparator drugs with metformin is associated with the use of Invokana at a dose of 100 mg per day (528 862 rub.). When it comes to treatment regimens, which include Invokana 300 mg per day, Januvia, Galvus and Amaryl, CER values were 531 556 rub., 560 025 rub., 544 528 rub. and 572 645 rub., respectively.

From the point of view of pharmacoeconomics, it seems viable to use a triple combination, which includes Invokana, glimepiride and metformin. The CER in this case is 556 436 rub., while the use of the same combination with Januvia was characterized by CER value of 648 268 rub.

In conclusion, we believe that the use of canagliflozin (Invokana) in combinations with metformin or with metformin and glimepiride helps to improve the quality of life in patients with type 2 DM, because of a better glycemic control, sBP management and body weight reduction, when compared with iDPP-4 drugs and sulfonylurea derivatives in similar combinations. Thus, the use of Invokana reduces the expenses incurred by the healthcare system, which is also the result of decreased type 2 DM complication incidence and, consequently, the expenses associated with such complications.

Table 9. **The budget impact of the analyzed treatment options for type 2 DM according to the forecast change in the percentage of their application. Time horizon is 20 years, discount rate is 3%, number of patients - 1**

Treatment regimen*	Part of patients treated during the current year, %	Part of patients treated during the planned years, %	Aggregate expenses for treatment during the current year, rub.	Aggregate expenses for treatment during the planned years, rub.
Invokana, 100 mg	0	65	0	203 244 015
Invokana, 300 mg	0	10	0	32 519 600
Januvia, 100 mg	25	0	79 404 050	0
Glavus, 100 mg	25	0	77 206 675	0
Amaryl, 8 mg	25	0	79 956 800	0
Invokana, 300 mg + Amaryl, 4 mg	0	25	0	86 609 950
Januvia, 100 mg + Amaryl, 4 mg	25	0	88 186 725	0
Total	100	100	324 754 250	322 373 565

*All compared treatment regimens include metformin in a dose of 2000 mg.

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