STUDY REPORT SYNOPSIS

Retrospective study to describe characteristics of patients with type 2 diabetes mellitus who were initiating use or treatment with sodium-glucose co-transporter-2 inhibitors and other diabetes medications (other glucose lowering drugs) in 2015-17 based on National Russian Diabetes Registry data

Milestones:	December 2017	Development of Study Concept Sheet
	March 2018	Final Protocol
	Q2 2018	Internal scientific review of the protocol
	Q2 2018	Approval of the protocol
	Q2 2018	Data Collection
	Q3 2018	Data analysis
	Q3 2018	Publication
Phase of development:	Non-interventional study (NIS)	
Sponsor:	AstraZeneca	

This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Background/rationale: In December 2014 the first representative of the novel glucose-lowering drug class, SGLT-2 inhibitor dapagliflozin, was introduced on the Russian market. In September 2015, the EMPA-REG cardiovascular outcomes trial (CVOT) presented data on a reduction in CV events in patients exposed to empagliflozin, another SGLT-2 inhibitor, compared to placebo on top of standard of care. Since that time, the evidence of CV benefits of SGLT-2 inhibitors has been consistently increasing, including CVOT results for canagliflozin, several analyses with pooled data from shorter term trials and a plenty of real-world practice observations, including the largest CVD-REAL database study of a broad population of type 2 diabetes (T2DM) patients.

Objectives: The main aim of this study is to evaluate characteristics of T2DM patients who were initiated use of SGLT-2 inhibitors, compared with patients who started other glucose-lowering therapies, in Russia over time 2015-17, in the environment of emerging evidence of CV benefits of the novel drug class.

Study design: Cohort retrospective observational study

Data source: Russian National Diabetes Registry

Study population: New users of SGLT-2 inhibitors and other glucose lowering drugs (GLD) (total number of new users by year: 2015 n=536632, 2016 n=536534, 2017 n=322335). New users of SGLT-2 inhibitors by year were as follows: 2015 - 1420 (0.3% of all new users); 2016 – 9052 (1.7% of all new users), 2017 – 11959 (3.7% of all new users).

Inclusion criteria: 1) New user receiving or dispensed prescription of SGLT-2 inhibitor medication or other GLD treatments oral as well as injectable, including fixed-dose combination (FDC) products containing these medication groups; 2) T2DM diagnosis on or prior to the index year; 3) ≥ 18 years old at index year.

Exclusion criteria: 1) Patients with a T1DM diagnosis on or prior to index year and only insulin use in the year prior to index; 2) Patients with a gestational diabetes in the index year or 1 year prior to index.

Statistical methods: Patients' characteristics for each treatment group were summarized descriptively using means and proportions. Associations between SGLT-2 inhibitors initiation and baseline characteristics were evaluated crudely (univariate analysis) and with multivariate adjustment by odds ratios with 95% CI using logistic regression analysis

Results: A total of 1 395 501 T2DM patients who started use of antidiabetic treatment (new users) were identified over the course of three years according to the Russian National Diabetes Registry data (536 632 in 2015, 536534 in 2016, and 322335 in 2017). Number of study participants was

lower in 2017 as data collection cut-off date was October 2017. The total number of new SGLT-2 inhibitor users reached 22 431 over three years.

In line with the definition of the **primary objective,** it was identified that the proportion of patients who were initiated use of SGLT-2 inhibitors, in 2015, 2016, and 2017 was 0.3%, 1.7%, and 3.7% correspondingly. As the % of SGLT-2 users increased over time, the distribution of the total SGLT-2 new user population by year was skewed: 6.3% in 2015, 40.4% in 2016 and 53.3% in 2017, while for other GLD it was relatively uniformed: 39.0% in 2015, 38.4% in 2016 and 22.6% in 2017.

Due to the observational nature of the study (processing of registry data), **laboratory results** were not available for 100% of study participants, yet, availability of laboratory results was increasing over time (from average 30% of participants in 2015 to average 50% of participants in 2017). Hb1Ac, total cholesterol, LDL, HDL and creatinine values remained on the same level for three years, there was slight decrease in the baseline systolic and diastolic blood pressure over time (not exceeding, however, 2 mm Hg), and decrease in EGFR values (from 86.6 in 2015 to 76.9 in 2017).

Majority of **comorbities** had the same point prevalence for each year (changes were less than 1%), yet, there were several changes over time: point prevalence of hypertension increased by 1.5% by 2016 compared to 2015, then decreased by 1.8% by 2017 compared to 2016; point prevalence of heart failure doubled from 2015 to 2017 (from 0.6% to 1.2%); point prevalence of hyperlipidemia increased from 1.2% in 2015 to 4.1% in 2017; point prevalence of neuropathy decreased from 13.8% in 2015 to 12.1% in 2017; finally, point prevalence of retinopathy decreased from 8.9% in 2015 to 7.8% in 2017.

The most frequent concomitant medications were metformin, SU, and ACE inhibitors. The use of the following concomitant medications increased over time (from 2015 to 2017): lipid-lowering medications (by 2.5%), diuretics (by 1.7%), ACE (by 1.6%), beta blockers (by 1.6%), antiplatelets (by 1.5%), metformin (by 1.2%), ARB (by 1.1%), and DPP-4 (by 1%).

When comparing SGLT-2 with oGLD group, it was identified that new SGLT-2 users were significantly younger (OR=0.96, p<0.001), less likely to be female (OR=0.89, p<0.001), had longer duration of diabetes (OR=1.05, p<0.001), they also had higher height (OR=1.03, p<0.001), weight (OR=1.03, p<0.001) and BMI (OR=1.06, p<0.001). The following baseline laboratory parameters and vital signs were lower in SGLT-2 group: systolic and diastolic blood pressure (OR=0.99 for both parameters, (p<0.001)) and HDL (OR=0.78, (p<0.001)). The following baseline laboratory parameters were higher in SGLT-2 group: Hb1Ac (OR=1.16, (p<0.001)), total cholesterol (OR=1.04, (p<0.001)), LDL (OR=1.03, (p<0.001)). Creatinine was lower in SGLT-2 group, and this was statistically significant (p<0.001), yet, the OR per one point of creatinin change was too small to be detected using the predefined accurary of the

output, so, it is shown to be equal to 1.0. EGFR was similar in both groups (OR=1.00). Generally, baseline comorbidities in SGLT-2 group were similar compared to other GLD group, with the exclusion for stroke that was less frequent in other GLD group (OR=0.86, p<0.001). No difference was identified in the frequency of transitory ischemic attack between two groups. The most significant differences in terms of OR values were for hyperlipidemia (OR=4.38), neuropathy (2.31), and nephropathy (2.29). There were significant differences between the groups in all concomitant medication types (p<0.05) except for direct renin inhibitors (p=0.380).

Multivariate analysis provided more accurate data with regards to the association and was conducted on limited data (i.e. including only patients with available vital signs and laboratory data) and full data (i.e. 100% patients but including only comorbidities as risk factors).

Pooling all years together and performing multivariate analysis on limited data, it was identified that new users were less likely to be treated with SGLT-2 inhibitors if had anamnesis of stroke (OR=0.68) and heart failure (OR=0.71). Myocardial infarction was not significant, and all other parameters (HbA1c per unit increase, hypertension, neuropathy, nephropathy and retinopathy) increased the probability of being treated with SGLT-2 inhibitors. While hypertension increased the probability of being treated with SGLT-2 inhibitors, there was no apparent prognostic correlation between the increase of systolic or diastolic BP (per 10 unit increase) with a likelihood of being initiated with SGLT2 inhibitors. Pooling all years together and performing multivariate analysis on full data, we achieved results that were similar to the limited data analysis, with the exclusion of heart failure that was not significant for the full data analysis. Patients with stroke (OR=0.67) were less likely to be treated with SGLT-2 inhibitors, and patients with hypertension, neuropathy, nephropaty, and retinopathy were more likely to be treated with SGLT-2 inhibitors. Thus, assessing the pooled data over the three years studied, it can be concluded that SGLT-2 inhibitors were prescribed less frequently to patients with stroke and more frequently to patients with hypertension and all major complications of diabetes (neuropathy, nephropathy, and retinopathy).

Results of limited analysis (with vital signs and laboratory parameters) show that associations with vital signs, myocardial infarction, heart failure, and retinopathy were not significant, yet, increase of HbA1c by one unit (OR=1.16), presence of hypertension (OR=1.75), neuropathy (OR=1.41) and nephropathy (OR=1.54) increased the chances of prescription of SGLT-2 inhibitors, while stroke (OR=0.25) descreased these changes. Full data analysis for 2015 showed that myocardial infarction, heart failure, nephropathy and retinopathy were insignificant; hypertension (OR=1.26) and neuropathy (OR=1.23) increased the chances of SGLT-2 inhibitior prescription, and stroke (OR=0.52) descreased these chances.

Limited data analysis for year 2016 showed that patients were less likely to be prescribed with SGLT-2 inhibitors if they had higher systolic blood pressure (OR=0.93 per 10 unit increase), stroke (OR=0.68) and heart failure (OR=0.62), and were more likely to be prescribed with

SGLT-2 inhibitors if they had higher HbA1c (OR=1.15 per unit increase), hypertension (OR=1.37), neuropathy (OR=2.14), nephropathy (OR=1.20) and retinopathy (OR=1.14). Myocardial infarction was insignificant factor in multivariate analysis. Full data analysis for year 2016 showed that myocardial infarction, hypertension, heart failure and retinopathy were insignificant factors in multivariate analysis; neuropathy and nephropathy increased the changes of initiation of SGLT-2 inhibitors, and stroke decreased the changes of initiation of SGLT-2 inhibitors.

Limited data analysis for year 2017 showed that diastolic blood pressure increment by 10 mm Hg and myocardial infarction were not significant; patients with higher systolic blood (OR=0.90 per 10 units increase), stroke (OR=0.68) and high failure (OR=0.68) were less likely to be prescribed with SGLT-2 inhibitors while patients with higher HbA1c (OR=1.16 per unit increase), hypertension (OR=1.49), neuropathy (OR=2.15), nephopathy (OR=1.52) and retinopathy (OR=1.16) were more likely to be prescribed with SGLT-2 inhibitors.

Full data multivariate analysis for year 2017 showed that myocardial infarction was not significant; stroke (OR=0.66) and heart failure (OR=0.66) descreased the chances for the initiation of SGLT-2 inhibitors, while hypertension (OR=1.29), neuropathy (OR=2.14), nephropathy (OR=1.50) and retinopathy (OR=1.11) increased these chances.

Conclusion: This analysis showed that the number and proportion of new SGLT-2 inhibitor users substantially increased over time (0.3% in 2015, 1.7% in 2016, and 3.7% in 2017) that indicates on broader acceptance of this group of antidiabetic medication in Russia. Patients, to whom SGLT-2 inhibitors were initiated, were younger, less likely to be female, and more likely to be obese compared to the new users of other GLDs.

Concomitant acarbose and meglitinides were less frequent in SGLT-2 inhibitor group, and GLP1, insulin and DPP-4 were more frequent in SGLT-2 group, and this was consistent for both single concomitant medications and their combinations.

Based on the pooled analysis of comorbidities and on analysis by year, stroke was consistently the factor that decreased the probability of SGLT-2 inhibitor initiation, heart failure also decreased this probability in 2017. SGLT-2 were also more likely to be prescribed in subjects with hypertension and diabetic microvascular complications (neuropathy, nephropathy, retinopathy) based on 2016 and 2017 data (as 2015 data were not reliable due to low number of subjects in the analysis).