STUDY REPORT SYNOPSIS

Observational, Retrospective, Multicenter Study to Evaluate Clinical Outcome Variables Change with Dapagliflozin Treatment Introduced in Patients with T2D Uncontrolled by the Current Therapy in Real Clinical Practice in Russia (GLORIA)

Milestones:

1. Development of the study design concept.
2. Drawing up of the final study protocol.
3. Study kick-off meeting.
4. Data collection period.
5. Statistical report development.
6. Drawing up of the final study report.

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:

Inhibition of sodium-glucose cotransporter-2 (SGLT2) is a novel pathway for the management of hyperglycemia regardless of insulin secretion or effect. The inhibitory action of the study group of drugs additionally leads to mild osmotic diuresis and enhances urinary excretion of glucose. It also leads to calorie loss, which decreases body weight.

Clinical studies showed that SGLT2 inhibitors improved glycemic control in patients with type 2 diabetes mellitus (T2DM) both when used as monotherapy and when combined with metformin, sulfonylureas (SU), insulin and thiazolidinedione.

In particular, an extensive phase 2b/3 clinical research program was conducted in various countries including Europe, the USA and Japan, to assess the efficacy and safety of dapagliflozin, SGLT2 inhibitor.

Although SGLT2 inhibitors have been increasingly used in Russia, there is still inadequate data on the experience with the novel pharmacotherapeutic group under examination, in real clinical practice. Therefore, a more comprehensive study is needed.

Dapagliflozin was authorized by the Ministry of Healthcare, Russia in November 2014 and has been prescribed to patients with T2DM since December 2014. Thus, by the time data collection for the study started, dapagliflozin had been used in Russia for at least 2 years.

About 3.9 million adults with T2DM were registered in Russia as of December 31, 2015 (its prevalence was 2689.7 cases per 100,000 people). Hence, at least 0.3% of them were assumed to receive dapagliflozin therapy.

This observational study was aimed at describing the efficacy of dapagliflozin in patients with T2DM in in real clinical practice in Russia, retrospectively.

Objectives:

Primary objective: Describe the changes in glycated hemoglobin (HbA1c) levels on follow-up as compared to the baseline.

Secondary objectives:

- Determine the percentage of patients with HbA1c lowered by 0.5% and more on follow-up as compared to the baseline.
- Determine the percentage of patients who reached target HbA1c levels (<7.0%) on follow-up as compared to the baseline.
- Describe the changes in fasting blood glucose levels on follow-up as compared to the baseline.
- Assess the changes in body weight on follow-up as compared to the baseline.
- Determine the percentage of patients with body weight decreased by at least 5% on follow-up as compared to the baseline.
- Determine the percentage of patients with HbA1c lowered by 0.5% and more and with body weight decreased by at least 5% on follow-up as compared to the baseline.
- Describe the changes in systolic and diastolic blood pressure (in mmHg) on follow-up as compared to the baseline.

Study design: Observational, retrospective, multicenter clinical study.

Data source: Paper medical records of patients with T2DM who started treatment with dapagliflozin after the previous failure/inefficacy of other treatment options (i.e. patients who had not reached target HbA1c levels). The records were analyzed by endocrinologists of 23 outpatient facilities in various cities of Russia. The data were recorded in electronic medical records (EMR).

Study population: 922 patients with T2DM uncontrolled by conventional therapy, who started receiving dapagliflozin as monotherapy, in combination with oral hypoglycemic agents (OHA) or as add-on to insulin, with available data on HbA1c obtained within 3 months prior to the first dapagliflozin dose.

Inclusion criteria:

- Patients with type 2 diabetes mellitus.
- Male or female aged between 18 and 65 (inclusively).
- Patients with type 2 diabetes mellitus who have been first prescribed with dapagliflozin since December 2014.

Exclusion criteria:

- Gestational diabetes.
- Type 1 diabetes mellitus.
- Contraindications to SGLT2 inhibitors (high individual sensitivity to SGLT2 inhibitors, type 1 diabetes mellitus, diabetic ketoacidosis, moderate to severe renal impairment (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^3), end-stage renal disease, lactose intolerance, glucose and galactose intolerance, pregnancy and breast-feeding, age below 18 years, intake of loop diuretics, volume depletion due to an acute condition, age 77 and older.
- Previous use of SGLT2 inhibitors.

Statistical methods:

Statistical programming language R version 3.4.3 was used for the statistical analysis.

The level of statistical significance was set at $p < 0.05$. Full analysis set (FAS) population was the main population for the statistical analysis.

Quantitative parameters were described using the number of observations (N), mean value (M), standard deviation (SD), 95% CI for the mean, median (Me), interquartile range (IQR), minimum (Min) and Maximum (Max) values. Qualitative parameters were described as an absolute number of observations, percentages and 95% CI.

Since it was a retrospective, observational study, there was no formal statistical hypothesis to be tested. The primary endpoint was analyzed using the Wilcoxon test and expressed as the median difference between baseline HbA1c levels and follow-up HbA1c levels and as two-sided non-parametric 95% CI for the median.

The analysis of primary endpoint and secondary endpoints was stratified for the duration of dapagliflozin use (less than 24 weeks vs more than 24 weeks) and therapeutic regimen (monotherapy, combined with OHA, combined with insulin, combined with insulin and OHA). Among patients receiving dapagliflozin combined with OHA, it was additionally stratified for the total number of OHA used (one OHA, two OHAs), and for those receiving one OHA combined

with dapagliflozin — also for OHA classes (biguanides, sulfonylureas, DPP IV inhibitors, fixed combination of metformin/DPP IV inhibitors, fixed combination of metformin/sulfonylureas).

Mann-Whitney test was used to compare the levels of primary variable and secondary variables between two subpopulations, Kruskal-Wallis test was used for three or more subpopulations. If a statistically significant difference was found between three or more subpopulations, post-hoc comparison of subpopulation pairs was additionally done using Nemenyi test with Holm procedure for multiple comparisons.

Wilcoxon test was used to assess changes in the levels of secondary quantitative variables (follow-up vs baseline) in subpopulations, χ^2 test was used for qualitative variables. If a statistically significant difference was found between subpopulations for qualitative variables, post-hoc comparison of subpopulation pairs was additionally done using χ^2 test with Holm procedure for multiple comparisons.

Two-tailed z-test with Holm procedure for multiple comparisons was used to compare the number (percentage) of patients with different levels of qualitative variables within subpopulations.

Medical history including documented allergic reactions, traumas and surgeries, concomitant diseases and AEs were termed according to MedDRA (Medical Dictionary for Regulatory Activities) version 21.1 with SOC (system organ class) and Preferred Term mentioned.

Previously and concomitantly used drugs were codified according to the Anatomical Therapeutic Chemical Classification System (ATC) with 4th and 5th level ATC codes mentioned.

Race was not considered a possible predictor of reaching target HbA1c level in 6±3 months of dapagliflozin therapy, since all the patients were white.

The number of completed cases used for model development and Akaike information criterion value were added to the logistic regression model parameters. Sensitivity analysis as a part of logistic regression model testing was done after missing values were replaced by modes for qualitative parameters or by mean values for quantitative parameters.

Results
Summary of efficacy:

Dapagliflozin therapy demonstrated efficacy in the primary endpoint and in part of the secondary endpoints in patients with T2DM uncontrolled by the current therapy in real clinical practice in Russia. The use of dapagliflozin showed statistically significant decrease in HbA1c levels in FAS patients followed up (in 6±3 months of the therapy). The median parameter reduced from 7.9% to 7.1%; the median difference between baseline HbA1c level and follow-up HbA1c level was 0.90% (95% CI: 0.85%–0.95%), $p < 0.001$.

Assessment of HbA1c changes considering stratification of subjects into subpopulations different in the duration of dapagliflozin therapy (less than 24 weeks vs 24 weeks or more) showed that dapagliflozin induced statistically significant decrease in median HbA1c in both subgroups (from 8.2% to 7.1% in patients receiving dapagliflozin for less than 24 weeks and from 7.9% to 7.1% in patients receiving dapagliflozin for 24 weeks or more).

Moreover, statistically significant positive changes in HbA1c levels were demonstrated in the subpopulations formed on the basis of therapeutic regimen (dapagliflozin monotherapy, dapagliflozin combined with one or more OHA, dapagliflozin combined with insulin and dapagliflozin combined with OHA and insulin), on the basis of the total number of OHAs used and on the basis of individual classes of OHA combined with dapagliflozin (biguanides, sulfonylureas, metformin/DPP IV inhibitors, metformin/sulfonylureas) at various timepoints (at baseline and in 6±3 months of follow-up).

Assessment of the number (percentage) of patients with HbA1c lowered by 0.5% or more showed that by the time of follow-up, target values of the parameter were reached by 89.3% of patients (95% CI: 87.1%-91.2%). Moreover, statistically significant positive changes in the number of patients with HbA1c lowered by 0.5% or more were demonstrated both in patients receiving dapagliflozin for less than 24 weeks and in patients receiving dapagliflozin for 24 weeks or more.

Similar results were obtained in the analysis of the number of patients with HbA1c lowered by 0.5% or more from the baseline and with HbA1c lowered by less than 0.5% from the baseline levels, within subpopulations different in therapeutic regimen, total number of OHAs used and OHA classes. The percentage of patients with HbA1c lowered by 0.5% or more on follow-up as compared to the baseline was higher in all the above subpopulations (at least 87.26% in a certain subpopulation).

The target HbA1c level (<7.0%) was reached in 40.1% of FAS subjects by the end of follow-up. The comparison of patients receiving dapagliflozin for 24 weeks or more to the baseline showed significant differences between the number of patients who reached target HbA1c (<7.0%) and the number of patients who did not: 61% (95% CI: 57.3%–64.6%) of the subjects receiving dapagliflozin for 24 weeks or more failed to reach the target HbA1c level.

Comparison of the number of patients who reached the target HbA1c value on follow-up as compared to the baseline, to the number of patients who failed to reach the target HbA1c value in all subpopulations based on the therapeutic regimen, revealed a significant decrease in the parameter. In the subpopulation receiving dapagliflozin as monotherapy, the percentage of patients who reached the target HbA1c value (<7.0%) was significantly higher than the percentage of those who did not. The number of patients who failed to reach the target HbA1c value (<7.0%) was significantly higher within other subpopulations based on the therapeutic regimen.

The percentage of patients who reached the target HbA1c level in the subpopulation on dapagliflozin monotherapy was found to be significantly higher than that of patients receiving dapagliflozin combined with OHA, or dapagliflozin combined with insulin, or dapagliflozin combined with OHA and insulin.

Positive changes were also recorded for the fasting blood levels of glucose: there was a significant decrease in the median parameter from 8.6 mmol/L (interquartile range: 7.61–10.6 mmol/L) at baseline to 6.73 mmol/L (interquartile range: 5.9–7.9 mmol/L) on follow-up, which was 22.01% (interquartile range: 10.7%–31.09%). Assessment of the changes in this parameter in the subpopulations based on the duration of the therapy (less than 24 weeks vs 24 weeks or more) also revealed significant reduction in the fasting blood level of glucose in both populations: the median

difference was 2.34 mmol/L (95% CI: 1.90–2.85 mmol/L) in the patients receiving dapagliflozin for less than 24 weeks and 1.88 mmol/L (95% CI: 1.75–2.00 mmol/L) in the patients receiving dapagliflozin for 24 weeks or more.

All the subpopulations based on the therapeutic regimen showed positive changes in the parameter. The patients receiving dapagliflozin combined with OHA and insulin showed higher fasting blood levels of glucose at both timepoints than other subpopulations analyzed here (dapagliflozin monotherapy and dapagliflozin combined with OHA and insulin, dapagliflozin combined with OHA and dapagliflozin combined with OHA and insulin). Significant reduction in fasting blood levels of glucose on follow-up as compared to the baseline was found in all the subpopulations based on the total number of OHAs used and on individual classes of OHA.

The body weight of patients in the FAS population decreased by 2.41% from the baseline ($p<0.001$) during the study. Statistically significant positive changes were also shown when comparing patients' body weight between subpopulations different in the duration of dapagliflozin therapy, in subpopulations based on therapeutic regimen, in subpopulations based on the total number of OHAs used and on individual classes of OHA (significant reduction in subjects' body weight was recorded in all of them). Statistically significant difference in the follow-up body weight was revealed between the dapagliflozin monotherapy subpopulation and the dapagliflozin combined with OHA and insulin subpopulation: patients receiving dapagliflozin alone had significantly lower body weight on follow-up than those receiving dapagliflozin in combination with OHA and insulin.

The percentage of patients with the body weight decreased by at least 5% was 18.4% of the study population (95% CI: 15.8%-21.3%). The analysis of this efficacy parameter showed that the percentage of patients with the body weight decreased by less than 5% was significantly higher than that of patients with the body weight decreased by at least 5%, within all the subpopulations examined (based on the duration of dapagliflozin therapy, based on the therapeutic regimen, based on the total number of OHAs used, based on the individual classes of OHA, except for the patients receiving the fixed combination of metformin/DPP IV inhibitors). At the same time, there were no significant differences between the subpopulations.

The number of patients with HbA1c lowered by 0.5% and more and with body weight decreased by at least 5% on follow-up as compared to the baseline, was assessed as a separate secondary efficacy endpoint. Calculations showed that the percentage of patients with the above endpoints reached simultaneously was 17.2% of FAS population (95% CI: 14.7%-20.1%).

The percentage of patients with HbA1c lowered by 0.5% or more and with body weight decreased by at least 5% by the control timepoint as compared to the baseline, was significantly lower than the percentage of patients who failed to reach those values, in all the subpopulations based on the therapeutic regimen (dapagliflozin monotherapy, dapagliflozin combined with one or several OHAs, dapagliflozin combined with insulin and dapagliflozin combined with OHA and insulin). There were no statistically significant differences in the above efficacy parameter between subpopulations based on the therapeutic regimen.

Similar results were obtained when subpopulations based on the total number of OHAs used and those based on individual classes of OHA were compared in that parameter: the number of patients

who failed to simultaneously achieve HbA1c reduction by 0.5% or more and body weight loss by at least 5% during follow-up was significantly higher. There were no statistically significant differences between subpopulations.

The study also demonstrated significant changes in the reduction of blood pressure (both SBP and DBP): the median difference between baseline and follow-up SBP was 6.50 mmHg (95% CI: 5.50–7.50 mmHg), the median difference for DBP was 4.50 mmHg (95% CI: 3.50–5.00 mmHg).

Comparison of baseline and follow-up SBP and DBP within subpopulations based on the duration of dapagliflozin therapy showed that the studied parameters got significantly decreased in both subpopulations.

Significant decrease in SBP was reported in patients of all the subpopulations based on the therapeutic regimen. Statistically significant changes in DBP were revealed only for the subpopulation of patients receiving dapagliflozin as monotherapy and dapagliflozin combined with one or more OHAs.

The study data showed that patients of both subpopulations based on the total number of OHAs used, achieved statistically significant reduction in SBP and DBP by the final follow-up timepoint. The median SBP difference was 7.00 mmHg (95% CI: 5.50–8.00 mmHg) for the subpopulation with one OHA, and 5.00 mmHg (95% CI: 2.50–7.50 mmHg) for that with two OHAs. The median DBP differences in the same subpopulations were 5.00 mmHg (95% CI: 4.00–6.00 mmHg) and 4.00 mmHg (95% CI: 1.50–5.50 mmHg).

Statistically significant reduction in SBP (efficacy parameter) was found in all subgroups in the subpopulations based on individual classes of OHA, except in patients receiving the fixed combination of metformin/DPP IV inhibitors. Significant reduction in DBP was revealed in the same subpopulations only in the subgroups of patients receiving biguanides and sulfonylureas.

Patients receiving biguanides were found to have significantly lower baseline SBP at both timepoints than patients receiving sulfonylureas and patients receiving the fixed combination of metformin/sulfonylureas. Patients receiving biguanides also had significantly lower follow-up SBP than patients receiving the fixed combination of metformin/sulfonylureas.

Patients of the subpopulations based on individual classes of OHA showed no statistically significant differences in DBP levels.

To assess the relationship between reaching target HbA1c levels and patients' profile, logistic regression models were developed in compliance with the study protocol. The statistical analysis revealed 11 predictors of reaching target HbA1c levels: microvascular events in T2DM, macrovascular events in T2DM, baseline HbA1c levels, baseline glucose levels, baseline SBP, early discontinuation of dapagliflozin during treatment, dapagliflozin use as monotherapy, dapagliflozin use in combination with OHA, dapagliflozin use in combination with OHA and insulin, biguanides as OHA combined with dapagliflozin and fixed combination of metformin/SUs as OHA combined with dapagliflozin. Thus, it was demonstrated that the probability of reaching the target HbA1c level could be predicted from all those parameters.

Among the available models, the one with baseline HbA1c levels as a predictor has the highest predictive capability. It is also the best model in terms of information theory.

Among the predictors inversely related to the outcome, baseline HbA1c levels and the use of dapagliflozin combined with OHA and insulin influence the probability of an outcome the most.

Among the predictors directly related to the outcome, the use of dapagliflozin as monotherapy influences the probability of an outcome the most.

Summary of safety:

Since the study was non-interventional and secondary sources of data were used, no active collection of safety data was carried out.

There were 355 cases of adverse events reported during the study.

Nervous and cardiovascular system and eye disorders were the most common adverse events, according to the study data. The majority of AEs reported were of vascular nature (in particular microvascular events in T2DM).

There were 64 cases of serious adverse events (SAE), including 21 cases of severe SAEs, reported during the study. Nervous system and vascular disorders were the most common SAEs. SAE analysis showed that cases with "requires hospitalization or prolongation of existing hospitalization" record as a seriousness criterion were highly prevalent (48 SAEs).

Only 6.8% of total AEs were reported as related to dapagliflozin. They occurred in 21 patients (2.3% of FAS population patients).

The majority of AE reported (incl. SAE) was typical of T2DM course (micro- and macrovascular events, clinical symptoms). Contraindications to SGLT2 inhibitors were revealed in 1.2% of patients during the study.

Conclusions:

The study demonstrated the efficacy of dapagliflozin being examined in patients with type 2 diabetes mellitus. Dapagliflozin-containing therapeutic regimens significantly decrease HbA1c, lower fasting blood levels of glucose, positively influence patient's body weight and blood pressure. Moreover, the majority of patients with T2DM reach the target HbA1c level of <7.0%, which is a criterion of controlled diabetes mellitus. All the above parameters were directly relevant to the improvement of clinical laboratory findings of the examined patients with T2DM, which indicated the study drug was therapeutically effective.

Considering the small number of adverse events related to the study drug during the study, dapagliflozin use can be regarded as safe.

Publications: Not applicable