Clinical Study Report Synopsis

Study code	D1690R00008
ClinicalTrials.gov Identifier:	NCT02695173
Date	09 November 2020

Comparison of the Risk of Severe Complications of Urinary Tract Infections Between Patients With Type 2 Diabetes Exposed to Dapafliglozin and Those Exposed to Other Antidiabetic Treatments

POST-AUTHORISATION SAFETY STUDY INFORMATION

Title	Post-authorisation Observational Study: Comparison of the Risk of Severe Complications of Urinary Tract Infection Between Patients With Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatments
Version identifier of the final study report	Version 1.0
Date of last version of study report	09 November 2020
European Union Post-Authorisation Studies Register number	ENCEPP/SDPP/12113
Active substance	A10BX09 (dapagliflozin) A10BD15 (metformin and dapagliflozin) A10BD21 (saxagliptin and dapagliflozin)
Medicinal product	Dapagliflozin (Edistride, Forxiga [EU]; Farxiga [US]) Dapagliflozin + metformin (Ebymect, Xigduo) Dapagliflozin + saxagliptin (Qtern)
Product reference	Forxiga: EU/1/12/795/001-010 Edistride: EU/1/15/1052/001-010 Xigduo: EU/1/13/900/001-012 Ebymect: EU/1/15/1051/001-012 Qtern: EU/1/16/1108/001-004
Procedure number	Forxiga: EMEA/H/C/002322 Edistride: EMEA/H/C/004161 Xigduo: EMEA/H/C/002672 Ebymect: EMEA/H/C/004162 Qtern: EMEA/H/C/004057
Marketing authorisation holder(s)	AstraZeneca AB

Is this a joint post-authorisation safety study (PASS)?	No
Research question and objectives	This study was a multinational cohort study to estimate the risk of severe complications of urinary tract infection in patients with type 2 diabetes mellitus (T2DM) who are new users of dapagliflozin compared with those who are new users of antidiabetic drugs (ADs) other than sodium-glucose cotransporter 2 (SGLT2) inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy. The main study objective was to compare, by insulin use at the date of the index episode, the sex-specific incidence of hospitalisation or emergency department visit for severe complications of urinary tract infection, among patients with T2DM who are new users of dapagliflozin with those who are new users of ADs other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.
Country/countries of study	United Kingdom (UK) United States of America (US)
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ABSTRACT

Title: Post-authorisation Observational Study: Comparison of the Risk of Severe Complications of Urinary Tract Infection Between Patients With Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatments

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Date: 09 November 2020

Keywords: Diabetes mellitus type 2, dapagliflozin, severe complications of urinary tract infection

Rationale and background: Post-authorisation safety study (PASS) evaluating risk of severe complications of urinary tract infection in real-world use of dapagliflozin.

Research question and objectives: The primary objective was to compare, by insulin use at the date of the index episode, the sex-specific incidence of "hospitalisation or emergency department visit for severe complications of urinary tract infection" ("UTI") among patients with type 2 diabetes mellitus (T2DM) who were new users of dapagliflozin compared with that of patients with T2DM who were new users of antidiabetic drugs (ADs) other than sodium-glucose cotransporter 2 (SGLT2) inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy. Additional analyses were also conducted on the overall exposure cohorts without stratification by insulin use at the date of the index episode.

Secondary objectives were to (1) compare baseline characteristics of both exposure groups; (2) compare the sex-specific incidence of hospitalisation or emergency department visit for pyelonephritis or outpatient diagnosis of pyelonephritis among the exposure groups; and (3) examine potential risk factors for UTI if an increased risk was found with dapagliflozin new use compared with new use of other ADs.

Study design: Non-interventional cohort study using data from three longitudinal, population-based data sources. Separate cohorts were created for males and females, and all analyses were conducted separately in each cohort because of the known higher risk of urinary tract infection in women than in men. The study cohorts were defined by new use of an eligible study medication (ie, new use of dapagliflozin or comparator AD). The date of prescription or dispensing of this medication was considered the date of the index episode if all study eligibility criteria were met. The unit of analysis was the index episode. A single patient could have multiple index episodes if a different comparator AD had been initiated on a different date, the eligibility criteria were met at the time of the new index episode, and the episodes did not overlap. Comparator AD index episodes were randomly matched—by calendar year of the index episode, age, sex, and geographic region—to each dapagliflozin index episode in the following ratios of comparator

AD to dapagliflozin: up to 6 to 1 in the Clinical Practice Research Datalink (CPRD) and up to 15 to 1 in the HealthCore Integrated Research Database (HIRD®) and Medicare.

Propensity score trimming and stratification were used to adjust for multiple possible confounding variables. Descriptive analyses for the primary outcome, UTI, were conducted before and after propensity score trimming on the overall sample (with insulin use groups combined) and were stratified by concomitant insulin use at the date of the index episode. Incidence and comparative analyses were conducted on the sample after propensity score trimming.

Crude and propensity score–adjusted incidence rates of UTI were calculated separately for dapagliflozin-exposed and comparator AD–exposed person-time for each insulin use group and for the overall sample not stratified by insulin use, separately for males and females. Incidence rate ratios (IRRs) compared the incidence of UTI in dapagliflozin index episodes with that of comparator AD index episodes. Adjusted IRRs were calculated using Mantel-Haenszel methods from propensity score–stratified IRRs for each insulin use group and for the overall sample. Similar analyses were conducted for the secondary outcome, pyelonephritis, using the propensity score–trimmed samples for the UTI outcome.

Due to very small numbers for the analyses stratified by insulin use at the index episode, particularly in the insulin use group in all data sources, and a lack of meaningful results in the stratified analyses, the text of this report focuses on the analyses performed overall without stratification by insulin use at the index episode.

Setting: The study used data from CPRD in the United Kingdom and the HIRD and Medicare in the United States of America. The study period began the day after regulatory approval of dapagliflozin in each country and ended at the last date of observation available at the time of data extraction in each data source.

Subjects and study size, including dropouts: After applying exclusion criteria, after matching and before propensity score trimming, the number of dapagliflozin index episodes in each data source in the overall cohort (with both insulin use groups combined) was as follows for females: CPRD, 5,508; the HIRD, 10,544; and Medicare, 12,561; and for males: CPRD, 7,610; the HIRD, 13,091; and Medicare, 12,783. After propensity score trimming, the number of dapagliflozin index episodes in each data source in the overall cohort was as follows for females: CPRD, 4,764; the HIRD, 9,413; and Medicare, 10,653; and for males: CPRD, 6,411; HIRD, 11,550; and Medicare, 10,744. For females, the number of person-years of dapagliflozin and comparator AD exposure, respectively, during the study period in the propensity score–trimmed cohorts was 5,361 and 14,424 in CPRD, 5,918 and 55,063 in the HIRD, and 5,986 and 91,689 in Medicare. For males, the number of person-years of dapagliflozin and comparator AD exposure, respectively, during the study period in the propensity score–trimmed cohorts was 7,926 and 21,490 in CPRD, 8,091 and 71,400 in the HIRD, and 6,577 and 101,498 in Medicare.

Variables and data sources: The occurrences of the primary outcome, UTI, and the secondary outcome, pyelonephritis, were identified with electronic algorithms. Validation of provisional cases of UTI identified by the electronic algorithms was performed in the three data sources.

The primary exposure was newly initiated dapagliflozin. Comparator AD exposure was defined as new initiation of an eligible AD, which did not include SGLT2 inhibitors or monotherapy with insulin, metformin, or sulfonylurea.

Potential confounding variables assessed at baseline were medical conditions related to diabetes severity, other medical comorbidities, selected medications, lifestyle factors as available in each data source, and health care resource utilisation.

Results: Before propensity score trimming, there were some relevant differences in baseline characteristics at the index episode when comparing patients presenting with episodes of dapagliflozin to patients presenting with episodes of comparator AD. The following differences were observed in the female and male cohorts in all data sources: patients on dapagliflozin had greater use of concomitant insulin; greater use of previous AD classes; fewer emergency department visits or hospitalisations; higher HbA1c (glycated haemoglobin) levels or higher number of HbA1c tests; and in CPRD, more frequent obesity and longer time since diagnosis of T2DM. After propensity score trimming and stratification, good balance was observed between exposure groups in the overall sample and in the two insulin use groups for most covariates for all data sources, as indicated by absolute standardised difference values less than 0.20.

For females, after propensity score trimming, the mean age (years) at baseline was as follows: CPRD—57, dapagliflozin; 58, comparator AD; the HIRD—52 in both index exposure groups; and Medicare—72 in both index exposure groups. The percentage of index episodes with concomitant insulin was as follows: CPRD—11.2%, dapagliflozin; 6.0%, comparator AD; the HIRD—14.4%, dapagliflozin; 12.1%, comparator AD; and Medicare—17.8%, dapagliflozin; 15.3%, comparator AD. The prevalence of "kidney diseases, all types, acute and chronic" at baseline was as follows: CPRD—8.5%, dapagliflozin; 12.1%, comparator AD; the HIRD—4.4%, dapagliflozin; 5.0%, comparator AD; and Medicare—17.4%, dapagliflozin; 20.9%, comparator AD. The prevalence of "urinary tract infections (chronic or recurring)" at baseline was as follows: CPRD—4.6%, dapagliflozin; 4.7%, comparator AD; the HIRD—11.2%, dapagliflozin; 11.6%, comparator AD; and Medicare—25.4%, dapagliflozin; 25.7%, comparator AD.

For males, after propensity score trimming, the mean age (years) at baseline was as follows: CPRD—58, dapagliflozin 59, comparator AD; the HIRD—52 in both index exposure groups; and Medicare—71 in both index exposure groups. The percentage of index episodes with concomitant insulin was as follows: CPRD—10.7%, dapagliflozin; 5.5%, comparator AD; the HIRD—13.8%, dapagliflozin; 11.5%, comparator AD; and Medicare—16.7%, dapagliflozin; 14.2%, comparator AD. The prevalence of "kidney diseases, all types, acute and chronic" at

baseline was as follows: CPRD—6.8%, dapagliflozin; 8.5%, comparator AD; the HIRD—5.0%, dapagliflozin; 6.0%, comparator AD; and Medicare—19.5%, dapagliflozin; 22.9%, comparator AD. The prevalence of "urinary tract infections (chronic or recurring)" at baseline was as follows: CPRD—1.3%, dapagliflozin; 1.4%, comparator AD; the HIRD—2.6%, dapagliflozin; 2.7%, comparator AD; and Medicare—10.1%, dapagliflozin; 9.8%, comparator AD.

The estimated positive predictive value of the electronic algorithm to identify cases of UTI was 48.3% (95% confidence interval [CI], 29.4%-67.5%) in CPRD, 73.2% (95% CI, 64.4%-82.0%) in the HIRD, and 80.0% (95% CI, 71.1%-87.2%) in Medicare.

For females, the overall adjusted incidence rate of UTI per 1,000 person-years, not stratified by insulin use at the index episode, for dapagliflozin and comparator AD index episodes, respectively, was 1.31 (95% CI, 0.52-2.69) and 1.88 (95% CI, 0.82-3.37) in CPRD, 5.41 (95% CI, 3.70-7.63) and 7.11 (95% CI, 6.39-7.88) in the HIRD, and 6.52 (95% CI, 4.63-8.91) and 8.70 (95% CI, 8.01-9.42) in Medicare. The overall adjusted IRR estimates were 0.91 (95% CI, 0.41-2.02) in CPRD, 0.76 (95% CI, 0.53-1.09) in the HIRD, and 0.74 (95% CI, 0.54-1.03) in Medicare. The overall pooled estimate across all three data sources for the adjusted IRR of UTI was 0.76 (95% CI, 0.60-0.96).

For males, the overall adjusted incidence rate of UTI per 1,000 person-years, not stratified by insulin use at the index episode, for dapagliflozin and comparator AD index episodes, respectively, was 0.63 (95% CI, 0.20-1.47) and 1.04 (95% CI, 0.44-1.88) in CPRD, 1.85 (95% CI, 1.04-3.06) and 2.93 (95% CI, 2.52-3.39) in the HIRD, and 4.41 (95% CI, 2.95-6.33) and 5.4646 (95% CI, 4.92-6.04) in Medicare. The overall adjusted IRR estimates were 0.73 (95% CI, 0.28-1.90) in CPRD, 0.62 (95% CI, 0.37-1.06) in the HIRD, and 0.82 (95% CI, 0.57-1.19) in Medicare. The overall pooled estimate across all three data sources for the adjusted IRR of UTI was 0.74 (95% CI, 0.56-1.00).

For pyelonephritis, the secondary outcome, the overall adjusted IRR estimates for females were 1.06, (95% CI, 0.47-2.41) in CPRD, 0.66 (95% CI, 0.42-1.04) in the HIRD, and 0.70 (95% CI, 0.51-0.96) in Medicare. The overall adjusted IRR estimates for males were 2.03 (95% CI, 0.57-7.17) in CPRD, 0.64 (95% CI, 0.32-1.28) in the HIRD, and 0.70 (95% CI, 0.45-1.08) in Medicare.

Discussion: For both females and males, the results of this final analysis did not find an increased risk of severe complications of urinary tract infection associated with dapagliflozin exposure compared with exposure to other ADs in the overall sample not stratified by insulin use at the index episode. All adjusted IRR estimates in the overall sample were below the null value but were imprecise due to the small number of observed outcome events in all data sources despite the large number of person-years of exposure in the cohorts. Pooled adjusted IRR estimates across data sources were more precise and were below the null value and of similar magnitude in the female and male cohorts. The observed results were generally robust to various

sensitivity analyses, and it is unlikely that an independent unmeasured confounder would cause enough bias to mask a true harmful association of dapagliflozin with severe complications of urinary tract infection. For the secondary outcome of pyelonephritis, all adjusted IRR estimates in the overall female sample were below the null, but imprecise. In the male sample, all adjusted IRR estimates of pyelonephritis were imprecise; the CPRD estimate was above the null and the estimates in the other two data sources were below the null.

Marketing Authorization Holder(s): AstraZeneca AB

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