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Non-Interventional Study (NIS) Report

Study number: 1245-0194

Document number: <insert>

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance, Glyxambi, Synjardy, Bydureon, Victoza, Lyxumia, Trulicity, Ozempic, Rybelsus, Xultophy, Suliqua			
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Report date: 31May2023	Study number: 1245-0194	Version/Revision: 1.0	Version/Revision date: 31May2023
Title of study:	Cardiovascular outcomes, and mortality in Danish patients with type 2 diabetes who initiate empagliflozin versus Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA): A Danish nationwide comparative effectiveness study [EMPLACE™]		
Keywords:	Type 2 diabetes, Empagliflozin, Glucagon-Like Peptide-1 Receptor Agonists, effectiveness, health-care resource use		
Rationale and background:	Utilization of the glucose-lowering drugs Glucagon-Like Peptide 1 Receptor Agonists (GLP-1RA) and Sodium-glucose Cotransporter-2 Inhibitors (SGLT2i) has increased substantially in people with type 2 diabetes (T2D) worldwide. Trials have shown that the GLP-1RA liraglutide (Marso S, 2016) and the SGLT2i empagliflozin (Zinman B, 2015) caused (13% and 14%, respectively) reductions in major adverse cardiac events among T2D patients with high cardiovascular risk, with similar reductions in HbA1c of 0.4% and 0.3%. Little is known about how these therapies compare regarding clinical and health care resource use (HCRU) outcomes in routine clinical care. In Denmark, nationwide population-based databases holding individual-level patient data enable comparative effectiveness studies among non-selected patients with T2D.		
Research question and objectives:	The primary objective was to compare clinical outcomes (cardiovascular outcomes, and mortality) among empagliflozin initiators and GLP-1RA initiators in Denmark. Secondary objectives were inpatient hospital admission with a diagnosis of heart failure (HF) and/or initiation of community prescription drug therapy with loop diuretics; inpatient hospital admission with a diagnosis of HF and/or all-cause death;		

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		composite of all-cause hospitalization or death; all-cause hospitalization; all-cause death, and hospitalization for HF. Hospitalization was defined as any inpatient hospital admission at any Danish hospital, independent of admissions being through emergency room contact, by ambulance, self-referral, or via referral from General Practitioner (GP), outpatient clinic, or other health care provider. An amendment was also done to protocol at a later stage to compare healthcare resource utilization and costs among empagliflozin initiators and GLP-1RA initiators in Denmark. In general, there were 5 different analyses looked at regarding this study: 1. Clinical comparison of empagliflozin vs. liraglutide from 2014 to 2017 (interim analysis) 2. Clinical comparison of empagliflozin vs. liraglutide from 2015 to 2018 (interim analysis) 3. Healthcare resource utilization of empagliflozin vs. GLP-1 from 2015 to 2018 (interim analysis) 4. Clinical comparison of empagliflozin vs. GLP-1 from 2015 to 2020 was not completed due to differences in patient populations 5. Exploratory analysis of empagliflozin vs. liraglutide from 2015 to 2018 extended to 2020	
Study design:		Non-interventional cohort study using existing data. The study used a new user design and compared new users of empagliflozin with new users of GLP-1RA. The study protocol and analysis plan were registered on the European Network of Centres for Pharmacoepidemiology and	

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		Pharmacovigilance website (http://www.encepp.eu/encepp/viewResource.htm?id=37726 , first protocol registration June 4, 2019), and on clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT03993132 , first posted June 20, 2019).	
Setting:	The study population included all eligible adult patients (>18 years) with T2D initiating treatment with either empagliflozin or with GLP-1RA. The planned study period was 1 January 2015 to 31 December 2020.		
Subjects and study size, including dropouts:	To ensure that only patients with T2D and not any other type of diabetes were included in the study, all patients were required to meet all of the following criteria: • Having T2D before the index date • Have at least one new filled prescription for empagliflozin or any GLP-1RA during the study period • Having no filled prescription of any other SGLT2i or GLP-1RA during the preceding 12 months including index date Follow-up started the day after the index date, which was the date of the first prescription for empagliflozin or GLP-1RA including the index date. For the analysis of each outcome, follow-up time in each cohort in a given exposure category for each patient ended at whichever of the following dates occurred first: • The date of the composite outcome event; acute hospital admission with heart failure (or initiation of loop diuretics), stroke, myocardial infarction,		

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		unstable angina, or coronary revascularization, or all-cause acute hospital admission • The date of death • The date of study end • The emigration date out of Denmark This did not apply to the HCRU/Cost analysis. <i>Study size</i> During 2015-2020 study period we identified 28,928 new users of empagliflozin and 28,166 new users of GLP-1RA, when applying the mentioned in and exclusion criteria. For the exploratory analysis, 14,498 new users of empagliflozin and 12,705 new users of liraglutide were included in 2015-18 and followed them through 2020. For the HCRU/cost analysis, we included 13,249 new users of empagliflozin and 13,747 new users of GLP-1RAs, between Jan 1, 2015, and to Dec 31, 2018.	
Variables and data sources:		Data sources: Danish population-based linked registries: The Civil Registration System, The Danish National Patient Register, The National Database of Reimbursed Prescriptions, The LABKA Database. Exposure: Patients included on the index date of their first prescription for empagliflozin or GLP-1RA, respectively (either as monotherapy or fixed-dose combination with another drug), with or without treatment with other glucose-lowering drugs (GLD). We also excluded patients prescribed liraglutide with the brand-name Saxenda® (liraglutide 3.0 mg daily, approved as a treatment for obesity in 2015).	

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Outcomes: The primary outcome in our study was a composite of hospitalization due to stroke, myocardial infarction, unstable angina, coronary revascularization, hospitalized heart failure (HHF), or all-cause death (expanded major adverse cardiac events (MACE)). Secondary outcomes were inpatient hospital admission with a diagnosis of heart failure (HF) and/or initiation of community prescription drug therapy with loop diuretics; inpatient hospital admission with a diagnosis of HF and/or all-cause death; composite of all-cause hospitalization or death; all-cause hospitalization; all-cause death, and hospitalization for HF. Hospitalization was defined as any inpatient hospital admission at any Danish hospital, independent of admissions being through emergency room contact, by ambulance, self-referral, or via referral from General Practitioner (GP), outpatient clinic, or other health care provider. In further analyses, we examined total health care resource use associated with empagliflozin or GLP-1RA, including total inpatient days, length-of-stay of patients with admissions, total hospital specialist outpatient clinic services provided, total cost of hospital care, total general practitioner services provided in primary care and their costs, total drug prescription use and pharmacy costs, and total medical costs. Confounders: Age, gender, year of inclusion, diabetes duration, number of diabetes drugs used, metformin use, insulin use, diagnoses of retinopathy, neuropathy, or nephropathy, estimated glomerular filtration rate (eGFR), history of ischemic heart disease, cerebrovascular disease, peripheral vascular disease, heart failure (further divided by duration and primary/secondary diagnosis), medical obesity, chronic obstructive pulmonary disease, cancer, use of angiotensin converting-enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs), other antihypertensives, statins, antiplatelet drugs, social and frailty markers,			

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		marital status, prescriptions for mental disorders, alcoholism, and number of prior hospital admission days.	
Results:		The first interim analysis (Thomsen R K. J., Cardiovascular events, acute hospitalisations and mortality in patients with type 2 diabetes who initiate empagliflozin vs. liraglutide: a comparative effectiveness study, 2019) compared empagliflozin vs. liraglutide in a timeframe of 2014 to 2017. The first interim analysis, included 8,296 patients with a first-time prescription for empagliflozin and 11,855 patients with a first-time prescription for liraglutide during 2014-2017, During mean follow-up of 1.5 years (30,455 person-years in total), the crude incidence rate of expanded MACE per 1,000 pyrs was 34.9 (n=284) among empagliflozin and 32.4 (n=723) among liraglutide initiators, and rate of HF hospitalization or all-cause death was 22.8 (n=187) for empagliflozin and 22.6 (n=512) for liraglutide. After IPTW, time-to-event analysis showed an aHR for expanded MACE of 0.97 (95% CI: 0.86-1.09) and an aHR for HF hospitalization or all-cause death of 0.87 (95% CI 0.67-1.12) associated with empagliflozin vs liraglutide. The aHR for all-cause acute hospitalization or death was 0.88 (95% CI: 0.79-0.98). The second interim analysis (Thomsen R K. J., Cardiovascular Events, Acute Hospitalizations, and Mortality in Patients with type 2 diabetes mellitus who initiate empagliflozin versus liraglutide: a comparative effectiveness study, 2021) was completed comparing empagliflozin vs. liraglutide from 2015 to 2018. The second interim analysis included 14,498 new users of empagliflozin and 12,706 new users of liraglutide, between 2015 to 2018. During mean follow-up of 1.1 years in OT and 1.5 years in ITT analyses, empagliflozin versus liraglutide was associated with	

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		a similar rate of expanded major adverse cardiac events (OT aHR, 1.02; 95% CI, 0.91-1.14; ITT aHR, 1.06; 95% CI, 0.96-1.17), and HHF or all-cause death (OT aHR, 0.97; 95% CI, 0.85-1.11; ITT aHR, 1.02; 95% CI, 0.91-1.14); and a decreased rate of a first incident HHF or loop-diuretic initiation (OT aHR, 0.80; 95% CI, 0.68-0.94; ITT aHR, 0.87; 95% CI, 0.76-1.00), and of all-cause hospitalization or death (OT aHR, 0.93; 95% CI, 0.89-0.98; ITT aHR, 0.93; 95% CI, 0.90-0.97). In conclusion, empagliflozin and liraglutide initiators had comparable rates of expanded major adverse cardiac events, and HHF or all-cause death, whereas empagliflozin initiators had a lower rate of a first HHF or loop-diuretic initiation. The third interim analysis (Thomsen R C. L., 2022) was completed to assess the total average healthcare costs per patient after drug initiation with empagliflozin versus GLP-1RAs in Denmark. We included 13,249 new users of empagliflozin and 13,747 new users of GLP-1RAs, between Jan 1, 2015, and to Dec 31, 2018. Healthcare costs in the year prior to drug initiation were also well-balanced. Mean follow-up on-treatment after initiation was 11.3 months (SD 9.8 months) in empagliflozin vs 12.3 (SD 10.9) months in GLP-1 RA initiators, with a total of 12,657 years of drug exposure with empagliflozin and 13,554 years with GLP-1RAs. Average costs per patient per year were very similar in empagliflozin and GLP-1 RA initiators regarding inpatient hospitalizations (13,565 DKK versus 13,275 DKK), hospital outpatient clinic visits (12,007 DKK versus 12,152 DKK), emergency room visits (370 DKK versus 399 DKK), and primary care services (4,108 DKK versus 4,302 DKK). Total costs of any prescription drugs were lower in empagliflozin initiators (8,946 DKK versus 14,029 DKK). Total healthcare costs on-treatment were lower in	

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empagliflozin initiators at 38,995 DKK per person-year than in GLP-1RA initiators at 44,157 DKK per person-year, respectively. In feasibility analyses, we explored drug utilization patterns for the study drugs in 2019-2020 as compared to our interim analyses 2015-2018, to assess any major changes in use of drug types and user characteristics, and thus the feasibility of extending our previous interim results for 2015-2018 with 2019-2020 data. We observed dramatic shifts in the use of the GLP-1RA comparator drug class, with liraglutide being replaced by semaglutide during 2019-2020, i.e., almost exclusively (>90%) liraglutide initiators in 2015-18, versus almost exclusively semaglutide initiators (>80%) during 2019-20. At the same time, monotherapy initiators of GLP-1RA increased from 14% in 2018 to 41% in 2020, suggesting increased use of first-line therapy. There was a simultaneous shift in patient characteristics for GLP-1RA users indicating a shift in indication towards weight-loss therapy in many patients, as the prevalence of CVD in liraglutide initiators decreased and proportions of middle-aged obese females increased simultaneously. Many individuals switched from liraglutide to semaglutide in 2019-2020. At the same time, empagliflozin initiator characteristics shifted towards increasing rates of heart failure and kidney diseases (lower eGFR) and decreasing rates of obesity, suggesting marked changes in patient profile in empagliflozin initiators in recent years as well. Thus, from a rather comparable use as 2nd to 3rd line glucose-lowering therapy in similar patients in 2015-2018, drug comparability between empagliflozin and GLP1RA-appeared to be very limited in 2019-2020 due to rapidly changing patient characteristics, different medical indications, and line of therapy.			

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		For these reasons we deemed that these limitations would severely hamper a meaningful update of the interim analyses including new users in 2019-2020 as well as the planned comparison vs. GLP1RA as a drug class. Instead, we did an exploratory analysis and compared empagliflozin vs. liraglutide with an extended follow-up period until 2020. We included 14,498 new users of empagliflozin and 12,705 new users of liraglutide in 2015-18 and followed them through 2020. Cohorts were well-balanced at baseline (median age 61 years, 59% men, diabetes duration 6.6 years, 30% with pre-existing cardiovascular disease). During mean follow-up of 1.3 years in OT and 3.1 years in ITT analyses, empagliflozin vs. liraglutide was associated with a similar rate of expanded MACE (OT aHR 1.01 [95% CI 0.91-1.11]; ITT aHR 1.07 [95% CI 1.01-1.13]), and HHF or all-cause death (OT 0.95 [0.84-1.08]; ITT 1.03 [0.96-1.11]); and with a decreased rate of a first incident HHF or loop-diuretic initiation (OT 0.71 [0.61-0.83]; ITT 0.83 [0.76-0.91]), and of all-cause hospitalization (OT 0.92 [0.88-0.96]; ITT 0.93 [0.91-0.96]). These data including longer follow-up of the initial cohorts confirms the previous published findings that empagliflozin and liraglutide initiators had similar rates of expanded MACE, and HHF or all-cause death, while empagliflozin initiators had lower rate of a first HHF or loop-diuretic initiation, or all-cause hospitalization, compared with liraglutide initiators.	
Discussion:		In conclusion, the EMPLACE Danish results (Thomsen R K. J., 2019) (Thomsen R K. J., 2021), both interim analyses from 2014 to 2017 and 2015-2018 as well as the exploratory analysis confirm that empagliflozin and liraglutide initiators in routine clinical care have comparable rates of expanded MACE, all-cause hospitalization, and all-cause death. Rates of	

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		first HF hospitalization or loop diuretic initiation among HF-naïve individuals are lower in empagliflozin initiators compared to liraglutide. The cost analysis based on the EMPLACE study (Thomsen R C. L., 2022) found that total healthcare costs on-treatment were lower in empagliflozin initiators at 38,995 DKK per person-year than in GLP-1RA initiators at 44,157 DKK per person-year, respectively mainly driven by the cost of the medication. .	
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Names and affiliations of principal investigators:	[REDACTED] [REDACTED] [REDACTED] Denmark		