Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

The synopsis is supplied for informational purposes only in the interests of scientific disclosure. It must not be used for any commercial purposes and must not be distributed, published, modified, reused, posted in any way, or used for any other purpose without the express written permission of Boehringer Ingelheim.

1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: empagliflozin (Jardiance®)			
Name of active ingredient: Empagliflozin			
Report date: 26 NOV 2018	**Study number:** 1245-0190	**Version/Revision:** 1.0	**Version/Revision date:** N/A
Title of study:	Prevalence of cardiovascular disease in Swedish patients with type 2 diabetes and in patients initiating on empagliflozin		
Keywords:	Type 2 Diabetes, empagliflozin, cardiovascular disease		
Rationale and background:	Patients with type 2 diabetes mellitus (T2DM) are at high risk for developing cardiovascular disease (CVD) complications. Registry data has showed considerable reductions in mortality and cardiovascular complications in patients with T2DM between 1998 and 2013. However, these risks still remain higher in patients with T2DM compared to the general population. Cardiovascular disease management is an essential part of diabetes treatment and should be considered in the process of treatment selection for patients with T2DM. The EMPA-REG OUTCOME study (ERO) demonstrated a reduction in cardiovascular death, hospitalization from heart failure and all-cause mortality with empagliflozin treatment on top of other glucose-, blood pressure, and blood lipid-lowering treatment, compared with placebo in patients with type 2 diabetes at high cardiovascular risk (in line with the EMPA-REG OUTCOME trial, defined as a history of either coronary heart disease, stroke, amputation, percutaneous coronary intervention, coronary artery bypass surgery, peripheral vascular disease, or carotid or femoral angioplasty). Empagliflozin treatment (ATC code A10BK03) also reduced the risk for new onset or worsening of nephropathy, progression to macroalbuminuria and doubling of serum creatinine accompanied by eGFR of $\leqslant$45 ml/min/1,73 m^2, and is also associated with some weight loss.		
Research question and objectives:	The overall aim of this study was to describe the prevalence of T2DM patients with established CVD according to ERO study definition in a Swedish population. The aim was also to describe the prevalence of established CVD according to ERO study definition in patients with T2DM who initiated treatment with empagliflozin. **The primary objectives of this study are:** • Prevalence of a history of cardiovascular disease (according to the EMPAREG outcome trial definition) among persons with T2DM who were alive on 31 December 2017		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: empagliflozin (Jardiance®)			
Name of active ingredient: Empagliflozin			
Report date: 26 NOV 2018	**Study number:** 1245-0190	**Version/Revision:** 1.0	**Version/Revision date:** N/A
	• Prevalence of a history of cardiovascular disease among persons with type 2 diabetes who started empagliflozin treatment between 1 January 2015 and 31 December 2017		
Study design:	Non-interventional, cross-sectional study based on existing data collected from the Swedish National Diabetes Register (NDR) as well as the Swedish Prescribed Drug Register and the Swedish National Patient Register (National Board of Health and Welfare)		
Setting:	Two populations were used to answer the questions in this study. For question 1, relating to the estimation of the prevalence of established CVD within patients with T2DM, the population consisted of all patients with T2DM who were alive on 2017-12-31 and with at least one registration in the NDR. For question 2, the description of patients with T2DM who initiated on Empagliflozin between 2015-01-01 to 2017-12-31, all patients with T2DM who initiated on Empagliflozin during this period and who had at least one registration in the NDR were included.		
Subjects and study size, including dropouts:	The study population for question 1 included a total of 460558 patients with T2DM and age ⩾18 years on 2017-12-31 and who had at least one registration in the NDR between 1996 - 2017. Out of these, 364 145 patients had at least one registration in the NDR up to 12 months before 2017-12-31. Out of these 460 558 patients, the number of patients with cardiovascular disease (CVD) was 130508 (28.3%), and the number of patients without CVD was 330050 (71.7%). Patients who started with empagliflozin from launch of product 2015-01-01 until 2017-12-31 and who are T2DM patients in NDR and age ⩾18 years were 16 985. Patients receiving empagliflozin with CVD were 1952 (11.5%), and without CVD were 15033 (88.5%).		
Variables and data sources:	**Primary variables:** • Established CVD • Initiation on Empagliflozin The study database was created using the unique personal identity number assigned to every Swedish resident as the identifier to cross-link a number of Swedish national health-care registers. The NDR works with systematic quality improvements in diabetes care since 1996, and provides information on risk factors and potential		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: empagliflozin (Jardiance®)			
Name of active ingredient: Empagliflozin			
Report date: 26 NOV 2018	**Study number:** 1245-0190	**Version/Revision:** 1.0	**Version/Revision date:** N/A
	complications of diabetes registered directly online to the NDR or reported continuously by physicians and nurses in hospitals and primary care clinics nationwide via electronic patient records. Each patient provides informed consent for inclusion in the register. The NDR is estimated to include 90% of all Swedish patients with T2DM aged ⩾18 years.		
Results:	All data was only analysed descriptively, and no testing of hypotheses was performed. No safety relevant data was collected in the study The study population for question 1 included a total of 460 558 patients with T2DM and age ⩾18 years on 2017-12-31 and who had at least one registration in the NDR between 1996 - 2017. Out of these, 364 145 patients had at least one registration in the NDR up to 12 months before 2017-12-31. Out of these 460 558 patients, the number of patients with cardiovascular disease (CVD) was 130508 (28.3%), and the number of patients without CVD was 330 050 (71.7%). Patients who started with empagliflozin from launch of product 2015-01-01 until 2017-12-31 and who are T2DM patients in NDR and age ⩾18 years were 16 985. Patients receiving empagliflozin with CVD were 1952 (11.5%), and without CVD were 15033 (88.5%).		

Among patients initiating empagliflozin during 2015-2017, the percentage of patients with CVD was lower (11.5%) as compared to the population of all patients with T2DM on 2017-12-31 (28.3%). It was seen that patients who were initiating with empagliflozin were younger than the overall population of patients with T2DM (54.5 (± 10.4) vs. 68.4 (± 12.3) years). Despite the difference in age, the duration of diabetes was slightly longer in the patients initiating on empagliflozin.

In the overall population of patients with T2DM, 57.13% of patients were male, 42.87% female. In this overall population, of the patients with CVD 64.41% were males, 35.59% were females; of the patients without CVD, 54.25% were males, 45.75% were females.

In the population of patients with T2DM initiating with empagliflozin, 65.09% of patients were male, 34.91% female. In this population, of the patients with CVD 75.36% were males, 24.64% were females; of the patients without CVD, 63.76% were males, 36.24% were females.

Out of the baseline characteristics it was observed that there were also more males (65.09% vs 57.13%) in the patients initiating with empagliflozin and both HbA1c and BMI are higher. Lipid lowering treatment and anti-hypertensives were used by more patients in the patients initiating on empagliflozin as compared to the overall T2DM population (76.43% vs. 62.83% and 82.18% vs. 79.58%, respectively). In addition, more patients among those initiating with empagliflozin were previously treated with tablets (100% vs. 70.92%) and insulins (42.33% vs. 28.51%) as compared to the overall T2DM population in the NDR at 2017-12-31.

There were higher proportions of males in the groups who were identified as having CVD, both in the overall T2DM population and in patients with T2DM initiating with empagliflozin. Patients who have CVD were also older on the average and higher proportions were previously treated with anti-hypertensives, lipid lowering drugs and insulins.

	Overall T2DM population		Patients with T2DM initiating empagliflozin	
	Without CVD (n=330050)	With CVD (n=130508)	Without CVD (n=15033)	With CVD (n=1952)
Gender, male Count (%)	54.25	64.41	63.76	75.36
Age, years Mean (SD)	66.2 (± 12.6)	73.7 (± 9.9)	54.1 (± 10.5)	57.4 (± 9.5)
Lipid lowering treatment Count (%)	55.84	80.50	74.04	94.83
Diabetes treatment,	24.92	37.58	40.57	55.89

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: empagliflozin (Jardiance®)			
Name of active ingredient: Empagliflozin			
Report date: 26 NOV 2018	**Study number:** 1245-0190	**Version/Revision:** 1.0	**Version/Revision date:** N/A

insulin-A10A Count (%)				
Anti hypertensive treatment Count (%)	73.89	93.96	80.07	98.46

Discussion:	A total of 460 558 patients with T2DM patients who were alive on 2017-12-31 and with at least one registration in the NDR were identified. Patients identified with established cardiovascular disease were 130508 (28,3%), and without cardiovascular disease were 330050 (71,7%). A total of 16985 patients who started with empagliflozin (11,5 %) were identified through SPDR and were also registered as having T2DM in NDR, of which 1952 patients (11,5%) had CVD. The prevalence of T2DM patients with established CVD according to EMPA-REG OUTCOME trial study definition was 28.3%. Corresponding percentage in the patients who initiated on empagliflozin during 2015-2017 was 11.5%.
Marketing Authorisation Holder(s):	Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein Germany
Names and affiliations of principal investigators:	[redacted] Sweden