Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

Document Number:	c24436488-02
BI Study Number:	1245-0187
BI Investigational Product(s):	Jardiance® Synjardy® Trajenta® Jentadueto®
Title:	CORDIALLY® - CEE: Characteristics of patients with Type 2 Diabetes treated with modern antidiabetic drugs. A real-world data collection of patient baseline characteristics, treatment patterns and comorbidities in Central Eastern European (CEE) countries
Protocol version identifier:	2.0
Date of last version of protocol:	12 Dec 2018
PASS:	No
EU PAS register number:	EUPAS28505 Clinicaltrials.gov number: NCT03807440
Active substance:	empagliflozin (ATC: A10BK03) linagliptin (ATC: A10BH05)
Medicinal product:	Jardiance® 10mg empagliflozin oral tablet Jardiance® 25mg empagliflozin oral tablet Synjardy® 5 mg empagliflozin 850 mg metformin oral tablets Synjardy® 5 mg empagliflozin 1,000 mg metformin oral tablets Synjardy® 12.5 mg empagliflozin 850 mg metformin oral tablets Synjardy® 12.5 mg empagliflozin 1,000 mg metformin oral tablets Trajenta® 5mg linagliptin oral tablet Jentadueto® 2,5mg linagliptin / 850 mg metformin oral tablet Jentadueto® 2,5mg linagliptin / 1000 mg metformin oral tablet
Product reference:	Jardiance EMEA/H/C/2677 Synjardy EMEA/H/C/3770 Trajenta EMEA/H/C/707 Jentadueto EMEA/H/C/2279
Procedure number:	n.a.
Joint PASS:	No
Research question and objectives:	1. To describe and compare T2D patients baseline characteristics when initiating either empagliflozin- or other SGLT2i, DPP4i or GLP1a on top of current antidiabetic treatment by different HCP specialties in CEE countries 2. To describe the burden of comorbidities (prevalence of CVD, CKD) and CVD/CKD risk factors in this T2D patient population at index date 1 3. To describe and compare the actual treatment at study index date 1 in patients with and without established CVD Established CV disease defined as acute myocardial infarction (AMI), cardiology intervention, ischemic heart disease (IHD), congestive heart failure (CHF), peripheral arterial disease (PAD), or stroke.

	4. To describe the association of socioeconomic parameters with treatment decisions at index date 1 5. To assess the discontinuation rate, reasons for discontinuation and average duration of treatment for GLP1a, DPP4i and SGLT2i after a follow up of approximately one year from the initial time point (= index date 2)
Country(-ies) of study:	Bulgaria, Czech Republic, Hungary, Poland, Serbia, Slovenia, Russia
Author:	[redacted]
Marketing authorisation holder(s):	MAH: [redacted] This study is initiated, managed and sponsored by: [redacted]
In case of PASS, add: **<EU-QPPV:>**	n.a.
In case of PASS, add: <**Signature of EU-QPPV:>**	n.a.
Date:	11 May 2020

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
CEE	Central Eastern Europe
CKD	Chronic Kidney Disease
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CVD	Cardiovascular Disease
CVOT	Cardiovascular Outcomes Trial
eCRF	Electronic Case Report Form
DMP	Data Management Plan
DPP4	Dipeptidyl-peptidase 4
DPP4 i	Dipeptidyl-peptidase 4 inhibitor
EU	European Union
FDC	Fix Dose Combination
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GLP1	Glucagon-like peptide 1
GLP1 a	Glucagon-like peptide 1 agonist
GPP	Good Pharmacoepidemiology Practice
HCP	Health Care Provider
HDL	High Density Lipoprotein
IEC	Independent Ethics Committee
ISF	Investigator Site File
LDL	Low Density Lipoprotein
MedDRA	Medical Dictionary for Drug Regulatory Activities
mMRC	Modified Medical Research Council Scale
NIS	Non-Interventional Study
PGE	Physician's Global Evaluation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SGLT2i	Sodium Glucose Transporter 2 inhibitor
SmPC	Summary of Product Characteristics
T2D	Type 2 Diabetes
UACR	Urine Albumin Creatinin Ratio
WHO	World Health Organisation

3. RESPONSIBLE PARTIES

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Coordinating Investigator (CI) [redacted] associate [redacted] [redacted] ☎/🖷 [redacted] ☎ [redacted] ✉ [redacted]	[redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance® Synjardy® Trajenta® Jentadueto®			
Name of active ingredient: empagliflozin linagliptin			
Protocol date: 12 Dec 2018	**Study number:** 1245.187	**Version/Revision:** Version 2.0/ Revision 1.0	**Version/Revision date:** 11 May 2020

Title of study:	CORDIALLY® - CEE: Characteristics of patients with Type 2 Diabetes treated with modern antidiabetic drugs. A real-world data collection of patient baseline characteristics, treatment patterns and comorbidities in Central Eastern European (CEE) countries
Rationale and background:	Cardiovascular Disease (CVD) is the most common cause of mortality in T2D patients. Also, chronic kidney disease (CKD) is associated with increased all-cause mortality, which is substantially higher in patients with a diagnosis of diabetes. Registry outcomes imply that patient characteristics might differ between patients initiating empagliflozin or other glucose lowering drugs.
Research question and objectives:	The objective of CORDIALLY® - CEE is to get insights into T2D patient characteristics when initiating different types of T2D treatments, including associated comorbidities (CVD, CKD), concomitant medications and the association of socioeconomic factors with treatment decisions. 1. To describe and compare T2D patients' baseline characteristics when initiating either empagliflozin- or other SGLT2i, DPP4i or GLP1a by different HCP specialties in CEE countries 2. To describe the prevalence of comorbidities (prevalence of CVD, CKD) at index date 1 in this T2D patient population 3. To describe the actual treatment used at index date 1 in patients with and without established CVD. Established CV disease defined as acute myocardial infarction (AMI), cardiology intervention, ischemic heart disease (IHD), congestive heart failure (CHF), peripheral arterial disease (PAD), or stroke. 4. To describe the association of socioeconomic parameters with treatment decisions at index date 1 5. To assess the discontinuation rate, reasons for discontinuation and average duration of treatment for GLP1a, DPP4i and SGLT2i after a follow up of approximately one year from the initial time point (= index date 2)
Study design:	This is a non-interventional study using existing data including medical chart review.
Population:	Adult patients (18 years of age or older) with T2D diagnosis, naïve to treatment with empagliflozin or other SGLT2i, DPP4i or GLP1a at index date 1

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Name of finished medicinal product: Jardiance® Synjardy® Trajenta® Jentadueto®			
Name of active ingredient: empagliflozin linagliptin			
Protocol date: 12 Dec 2018	**Study number:** 1245.187	**Version/Revision:** Version 2.0/ Revision 1.0	**Version/Revision date:** 11 May 2020
Variables:	1. Patient demographics (age, gender, height, weight, BMI, ethnicity) 2. Time since diagnosis of Type 2 Diabetes 3. Clinical parameters relevant for T2D, CVD, CKD assessment such as HbA1c, blood pressure as valid on index date 1 4. Comorbidities like cardiovascular diseases and related risk factors such as smoking, overweight and Comorbidities like chronic kidney disease and related risk factors such as smoking, overweight at index date 1 5. T2D medication the treating HCP newly prescribes at study index date 1 6. Concomitant T2D medications at index date 1 7. Concomitant CVD and CKD medications at index date 1 8. Involvement of other HCPs in treatment decisions at study index date 1 and study index date 2 9. Relevant socioeconomic parameters such as employment status, family status, type of health insurance at index date 1 10. Stop date and reason of therapy discontinuation at index date 2 (approximately one year after index date 1)		
Data sources:	Existing patient data (Medical chart review) previously collected by Health care professionals during routine documentation in patients treated for T2D in an endocrinologist, diabetologist or cardiologist office-based setting (nonhospital).		
Study size:	Approximately 4000 patients from 7 countries (Bulgaria, Czech Republic, Hungary, Poland, Serbia, Slovenia, Russia)		

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Data analysis:	**Primary outcomes:** T2D patients' baseline characteristics when initiating either empagliflozin - or other SGLT2i, DPP4i or GLP1a on top of current antidiabetic treatment by different HCP specialties in CEE countries. **Secondary outcomes:** • Burden of comorbidities (prevalence of CVD, CKD and CVD/CKD risk factors) in this T2D patient population at index date 1 • Actual treatment used at index date 1 in patients with and without established CVD (defined as acute myocardial infarction (AMI), cardiology intervention, ischemic heart disease (IHD), congestive heart failure (CHF), peripheral arterial disease (PAD), or stroke) • Discontinuation rate of actual treatment at index date 2, reasons for discontinuation and average duration of treatment for GLP1a, DPP4i and SGLT2i • The association of socioeconomic parameters with treatment decisions at index date 1 All analyses will be descriptive. Baseline patient characteristics will be tabulated for different subgroups (i.e. according to medication (empagliflozin or other GLP1a or DPP4i or SGLT2i), country and physician speciality). Results will be presented as means, standard deviations, medians, minimum and maximum and interquartile range (IQR) for continuous variables and as counts and percentages for categorical variables. Subgroup analyses will be done using $\chi 2$-test or Fisher's exact test for categorical variables and Willcoxon-Mann-Whitney test for continuous variables. Details regarding the statistical analysis will be specified within the statistical analysis plan.		
Milestones:	Planned start of data collection: Q1 2019 Planned end of data collection: Q1 2021 Planned database clean (Hard lock): Q3 2021 Planned final Report: Q4 2021		

5. AMENDMENTS AND UPDATES

Protocol v2.0, Amendment 1, 06 May 2020			
Number	**Section of study protocol**	**Change**	**Reason**
1	Cover page, Abstract, Section 8.2	Inclusion of new objective	Therapy duration and reasons for therapy discontinuation should be addressed by recording of data at a 2nd index date. This requires collection of new variables
2	Abstract, Section 9.1, Section 9.3, Section 9.3.2, Section 9.7.1, Section 9.10.2.2.1	- Inclusion of new variables - Defining of new secondary outcomes - Specification of parameters and variables to be collected at index date 2	
3	Abstract, Section 6	Change of milestones	Time delay due to insertion of amendment 1
4	Section 8.1	Inclusion of rationale for new objective	To address rationale for new objectives
5	Section 9.1, Section 9.2.1, Section 9.3.1, 9.11.1, Section 9.12	Extension of index date 1 from 1 month to 4 months	Due to change of milestones, index date 1 for eligible patients is extended, too.
6	Section 9.9	Adapting to new objective	Adapting to new study design
7	Section 9.10.2	Adapting to new study design with 2 index dates	
8	Section 11	Completely revised according to usual BI wording	Because of possible reporting of adverse drug reactions as reason for treatment discontinuation this section is completely adapted.
	All Sections	Former ‘index date’ is changed to index date 1	Introduction of a 2nd index date requires to specify former index date.

6. MILESTONES

Milestone	Planned Date
Start of data collection	Q3 2019
End of data collection	Q1 2021
Final report of study results:	Q4 2021

7. RATIONALE AND BACKGROUND

Prevalence of diabetes is high with about 425 million of patients worldwide and it is expected that this number will increase to more than 630 million in 2040 (1). Diabetes related complications including micro- and macrovascular complications, which have huge impact on patients' quality of life, as well as healthcare budgets.
The most common cause of mortality in patients with type 2 diabetes (T2D) is cardiovascular disease (CVD), accounting for more than 50 % of deaths and causing an average reduction of life years in a 60 years old male of about 12 years when compared with the general population (1-4). T2D patients have a wide range of cardiovascular (CV) risk factors which not only increase CV mortality but also CV morbidity rates (5-13). Even if diabetes related CV complications have declined with improved standard of care, a substantial burden remains (14) and all-cause mortality is still high in this vulnerable population, significantly reducing life expectancy (3). Also, chronic kidney disease (CKD) is associated with increased all-cause mortality which is substantially higher in patients with a diabetes diagnosis. (15).

While Cardiovascular outcomes Trials (CVOT) on DPP4 inhibitors just confirmed cardiovascular safety but did not provide significant CV benefits over placebo when added to standard of care, data from recent CVOTs with SGLT2 inhibitors and GLP1receptor agonists provided significant cardiovascular benefits (19). Empagliflozin in the EMPA-REG OUTCOME trial and liraglutide in the LEADER trial resulted in lower risk for CV and all-cause mortality when compared with placebo added to standard of care in patients with T2D and established CV disease and/or CV risk factors (17, 18). The number of patients needed to treat to prevent one premature death was 98 patients for 3 years with liraglutide (18) and 39 patients treated for 3 years with empagliflozin (17). Empagliflozin also reduced the risk of hospitalization for heart failure by 35% and was associated with slower progression of kidney disease and renal event rates (17).

In international and numerous national guidelines for T2D treatment it is currently stated, that in patients with T2D and CVD, cardioprotective drug(s) should be included early in the treatment pattern (20). Also in the European Cardiology (ESC) guidelines it was stated that empagliflozin should be considered early in T2D patients in order to prevent or delay hospitalization for heart failure and prolong life (20, 21).

8. RESEARCH QUESTION AND OBJECTIVES

8.1 RATIONALE FOR PERFORMING THE STUDY

Cardiovascular disease (CVD) is the most common cause of mortality in patients with type 2 diabetes (T2D), accounting for more than 50 % of deaths and significantly reducing patients' life expectancy. (1-4). Recent Diabetes and Cardiology guidelines have pointed out that modern antidiabetic drugs like empagliflozin and liraglutide should be used early in the treatment of T2D patients to reduce major adverse CV events and CV mortality (20, 21, 22).

Recent data from Sweden demonstrate a prevalence of CVD in T2D patients as high as 34% (16), while comparable data from CEE countries which would allow raising the awareness on this health topic do not exist. An extrapolation from other European countries to this region, mainly dominated by low income countries with limited healthcare spending will not allow useful conclusions on drug utilization with innovative medications.

In spite of these clear treatment recommendations (20, 21, 22), a recently published US real world study points out that a significant number of patients who would have met the criteria for treatment with drugs like empagliflozin or liraglutide, are not treated according to eligibility criteria (25). The real world use of these drugs based on the Diabetes Collaborative Registry (DCR) was low and these drugs were used mainly in the low-risk diabetes population in which the benefit of CV risk reduction is less likely to happen or was not studied (25).

Knowing the characteristics of T2D patients initiating different treatment for their diabetes can lead to a better understanding for the prescription patterns with modern antidiabetic drugs.

Due to the fact that Diabetes registries or other valid sources, which would allow monitoring of the quality of care in terms of risk factors and the potential complications of diabetes are not available in Central Eastern Europe, there is also a lack of information on patient profiles, receiving prescriptions for modern antidiabetic medications like sodium glucose transporter 2 inhibitor (SGLT2i), dipeptidyl peptidase 4 inhibitor (DPP4i), glucagon like peptide 1 agonist (GLP1a).

Knowledge on patient characteristics when treated with these drugs, their comorbidities, drug utilization in different HCP specialty groups as well as socioeconomic factors which could limit the use of these modern T2D medications have also not yet been evaluated in CEE. In addition, to learn more about the application of these medications in the real-world settings, status of their use over time, especially reasons for treatment discontinuation (if applicable), are of interest.

To address these questions, medical charts of T2D patients from health care professionals (HCPs) of different specialties who can initiate innovative antidiabetic treatment in the office-based setting (Endocrinologist, Diabetologist, Cardiologist) will be collected.

8.2 STUDY OBJECTIVES

The objective of the study is

1. To describe and compare T2D patients' baseline characteristics when initiating either empagliflozin - or other SGLT2i, DPP4i or GLP1a on top of current antidiabetic treatment by different HCP specialties in CEE countries

2. To describe the prevalence of comorbidities (prevalence of CVD, CKD) in this T2D patient population at index date 1

3. To describe and compare the actual treatment uses at index date 1 in patients with and without established CVD

Established CV disease defined as acute myocardial infarction (AMI), cardiology intervention, ischemic heart disease (IHD), congestive heart failure (CHF), peripheral arterial disease (PAD), or stroke.

4. To describe the association of socioeconomic parameters with treatment decisions at index date 1

5. To assess the discontinuation rate, reasons for discontinuation and average duration of treatment for GLP1a, DPP4i and SGLT2i after a follow up of approximately one year from the initial timepoint (= index date 2)

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional study using existing data including medical chart review. The study will include all patients fulfilling the inclusion and not fulfilling the exclusion criteria in the period of 4 months (September – December 2018) (= index date 1).

Parameter	Assessed at study index date 1
Written Informed Consent*	X
Inclusion / Exclusion Criteria	X
Patient demographics (age, gender, height, weight, BMI, ethnicity)	X
Time since diagnosis of Type 2 Diabetes	X
Clinical parameters relevant for T2D, CVD, CKD assessment	X
Comorbidities like cardiovascular diseases and related risk factors	X
Comorbidities like chronic kidney disease and related risk factors	X
T2D medication the treating physician newly prescribes at study index date	X
Concomitant T2D medications at study index date	X
Concomitant CVD and CKD medications at index date	X
Other HCPs involved in treatment decisions at study index date	X
Relevant socioeconomic parameters	X

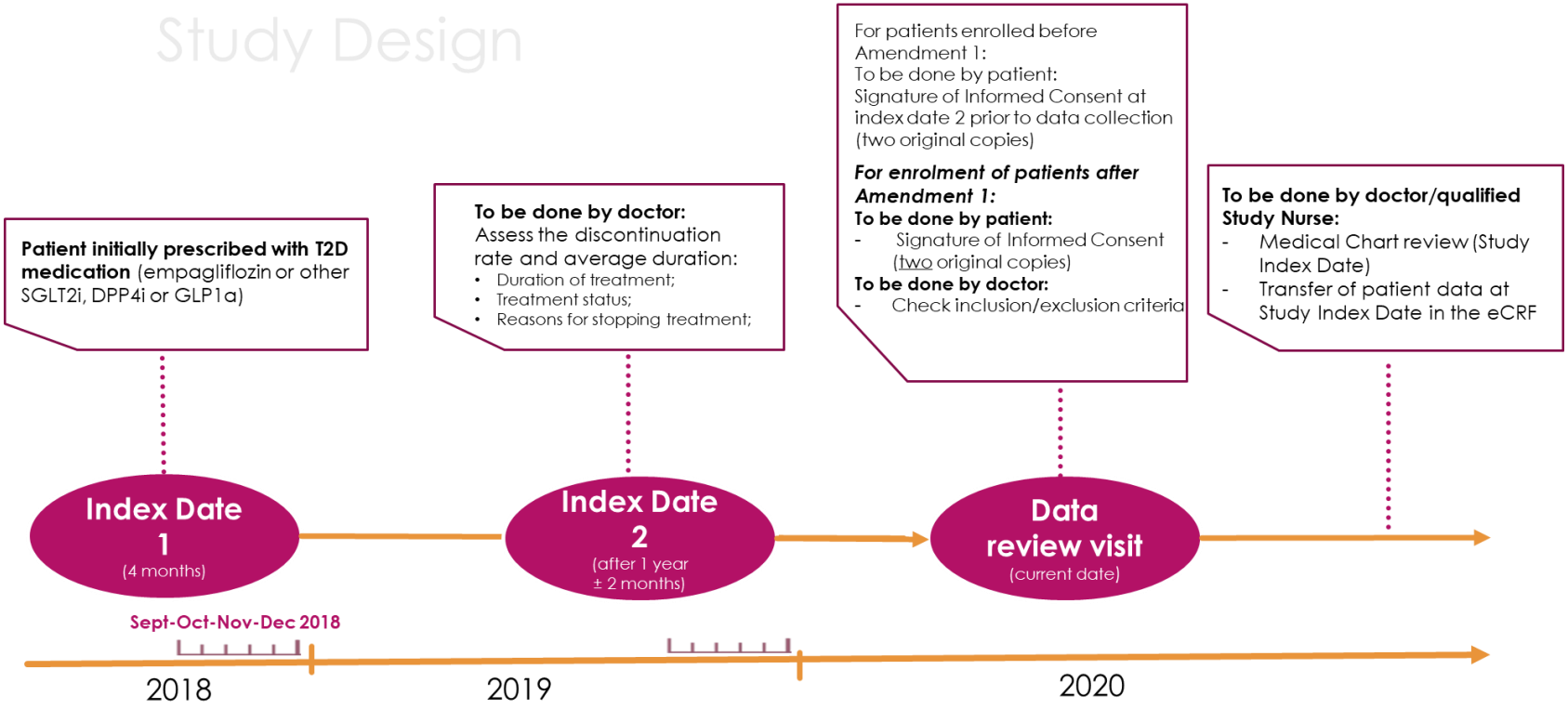
* Patients who were enrolled before amendment 1 and who have consented to data collection at index date 1 have to consent to data collection at index date 2 separately. Newly enrolled patients have to give their consent for data collection at index date 1 and 2 before data transfer into eCRF.

Approximately 1 year (± 2 months) after index date 1, parameters regarding status of newly initiated T2D treatment will be collected.

Parameter	Assessed at study index date 2
Continuation / Discontinuation of T2D therapy initiated at index date 1	X
In case of discontinuation: stop date	X
In case of discontinuation: reason for discontinuation	X
In case of discontinuation: other HCPs involved in treatment decision	X

An overview of study design is given in Figure 1.

Figure 1: Overview of study design



9.2 SETTING

Data collection from approximately 4000 patients from up to 8 countries is planned. Site selection will be performed to reflect routine T2D care in the participating countries in order to secure representativeness of the T2D population. The following countries will participate in this non-interventional study: Bulgaria, Czech Republic, Hungary, Poland, Russia, Serbia, Slovenia.
A log of all patients included into the study (i.e. having given informed consent) will be maintained in the Investigator Site File (ISF).

Boehringer Ingelheim reserves the right to discontinue the study or to remove a patient at a particular study site for the following reasons:
1. Failure to meet expected enrollment goals overall or at a particular study site.
2. Emergence of any efficacy/safety information that could significantly affect continuation of the study, or any other administrative reasons, i.e. lack of recruitment.
3. Violation of the protocol, the contract, or applicable laws and regulations for non-interventional studies, which could disturb the appropriate conduct of the NIS.

Site selection:

Office based HCP of different medical specialties (endocrinologist, diabetologist or cardiologist) will be requested in order to check for feasibility prior to site selection. Amongst other criteria, sites will be eligible if HCPs have access and can prescribe at least 2 of the T2D drug classes of interest (SGLT2i, DPP4i and/or GLP1a). Sites will also be asked for the number of expected patients meeting inclusion/exclusion criteria in a given time window (1 month September 2018) by means of being newly initiated with empagliflozin or other SGLT2i, DPP4i or GLP1a in September 2018. In case that more than a representative number of sites which will be assessed during the feasibility, are signaling their willingness to participate in the study, the sites will be randomly selected.
To get basic information into demographics for site distribution, data on physicians' age, gender, office postal code will be collected.

9.2.1 Inclusion criteria

Patients can be included if all of the following criteria are met:
1. Written informed consent prior to participation
2. Female and male patients age ≥ 18 years
3. Patients with T2D diagnosis
4. Patients who have been newly initiated (first ever use) with empagliflozin or other SGLT2i, DPP4i or GLP1a between September 2018 and December 2018 (study index date 1)
5. Patients have been naïve to treatment with empagliflozin or other SGLT2i, DPP4i or GLP1a at study index date 1

9.2.2 Exclusion criteria

1. Patients age < 18 years
2. Patients with diagnosis of other types of diabetes than T2D
3. Patients who do not provide written consent to the terms of the study

9.3 VARIABLES

The following parameters will be collected and assessed at study index date 1:

1. Patient demographics (age, gender, height, weight, BMI, ethnicity)
2. Time since diagnosis of Type 2 Diabetes
3. Clinical parameters relevant for T2D, CVD, CKD assessment (see below) as valid on study index date 1
4. Comorbidities like cardiovascular disease and related risk factors (see below) and Comorbidities like chronic kidney disease and related risk factors (see below) at study index date 1
5. T2D medication the treating physician newly prescribes at study index date 1
6. Concomitant T2D medications at study index date 1
7. Concomitant CVD and CKD medications at index date 1
8. Involvement of other HCPs in treatment decisions at study index date 1
9. Relevant socioeconomic parameters (see below) at index date 1

The following parameters will be collected and assessed at study index date 2 (= approximately one year ± 2 months after index date 1):

1. Status of T2D medication (continuation / discontinuation)
2. If discontinuation:
    a. stop date of initial(index date 1) T2D medication (if available)
    b. Reason for therapy discontinuation (see below)
    c. Involvement of other HCPs in decision for therapy discontinuation

9.3.1 Exposures

Exposure to each treatment of interest is defined as having received a first prescription of the treatment of interest between September and December 2018.

9.3.2 Outcomes

1. Patient demographics:
   - age
   - gender
   - height
   - weight
   - BMI
   - Ethnicity*

   *assessment of ethnicity (black or non-black) necessary for calculation of eGFR

2. Time since diagnosis of Type 2 Diabetes (years)

3. Clinical parameters relevant for T2D, CVD, CKD assessment (last available and date when it was collected) as valid on study index date 1
   - T2D
     - HbA1c (numeric value)
   - CVD
     - Blood pressure (numeric value for systolic and diastolic blood pressure)
     - LVEF (numeric value and info on whether an Echo was performed)
     - Blood lipids (numeric values for total cholesterol, LDL, HDL, and triglycerides)
   - CKD
     - Serum creatinine (numeric value)
     - eGFR (calculated for analysis according to the CKD-EPI formula considering serum creatinine level, gender, age, and ethnicity)
     - UACR (numeric value)

4. Prevalence of comorbidities and related risk factors for CVD, CKD at index date 1
   - Comorbidities
     - History of acute myocardial infarction (yes/no)
     - History of cardiology intervention (such as Percutaneous Coronary Intervention (PCI), Coronary Artery Bypass Grafting (CABG)) (yes/no)
     - Ischemic heart disease (defined as coronary artery disease, angina) (yes/no)
     - Heart failure (yes/no)
       - Confirmed by echocardiography (yes/no)
     - History of stroke (yes/no)

- Peripheral arterial disease (including limb angioplasty, stenting, bypass surgery, amputation, significant peripheral artery stenosis,) (yes/no)

- Risk factors
  - Being overweight (BMI ≥25 to <30) (yes/no) or obese (BMI ≥30) (yes/no) according to the WHO criteria (26)
  - Hypertension (defined as systolic blood pressure ≥140 mmHg and / or diastolic blood pressure ≥90 mmHg) (y/n)
  - 10-year Risk for fatal CVD according to the applying SCORE Risk Chart (European Society of Cardiology) taking into account patient´s age, gender, systolic blood pressure, smoking status, and total cholesterol value at index date.
  - Tobacco smoking (current smoker/ ex-smoker/ never smoker)
  - Being physically inactive (defined as less than 2.5 hours of moderate-intensity aerobic exercise or less than 75 minutes of vigorous aerobic exercise per week) (yes/no)
  - Having a family history of early heart disease (yes/no)
  - Having a family history of early kidney disease (yes/no)

5. T2D medication the treating physician newly prescribes at study index date 1 and reason for the choice

   - SGLT2i
     - canagliflozin
     - dapagliflozin
     - empagliflozin
     - ertugliflozin

   - DPP4i
     - alogliptin
     - linagliptin
     - sitagliptin
     - saxagliptin
     - vildagliptin

   - GLP1a
     - dulaglutide
     - exenatide
     - liraglutide
     - semaglutide
     - lixisenatide

   - Reasons for choosing the treatment rated as not relevant at all/ moderately relevant/ highly relevant
     - HbA1c lowering
     - Weight loss

  - Cardiovascular risk reduction
  - Favorable side effect profile
  - Simple dosing / administration
  - Guideline recommendation

6. Concomitant T2D medications (given as monotherapy or as fix combination with main T2D medication) at study index date 1
   - Metformin
   - Sulfonylurea
   - Acarbose
   - Pioglitazone
   - Insulin
   - others

7. Concomitant CVD and CKD medications at index date 1 (on class level only)
   - Antihypertensives ACEi or ARBs
   - Statins
   - Low dose aspirin
   - Beta blockers
   - Diuretics

8. Involvement of other HCPs in treatment decisions with regard to SGLT2i, DPP4i or GLP1a prescription at study index date 1 and with regard to discontinuation at index date 2 (yes/no; if yes, the medical specialty of the involved physician(s) should be specified)

9. Association of socioeconomic parameters with treatment decisions (such as employment status, family status, type of health insurance) at study index date 1

10. Status of T2D therapy approximately one year (± 2 months) after start
    - Stop date, if available
    - Reasons for discontinuation
      - Investigator's decision
      - Patient's request (difficulties in medication handling)
      - Patient's request (financial burden regarding co-payment)
      - Patient's request (other)
      - Lost to follow-up
      - Adverse event (in case of adverse reaction to empagliflozin or linagliptin or fatal adverse event, see Section 11)
      - Death
      - Unknown
      - Other

Primary outcomes

- T2D patients' baseline characteristics when initiating either empagliflozin - or other SGLT2i, DPP4i or GLP1a on top of current antidiabetic treatment by different HCP specialties in CEE countries.

Secondary outcomes

- Burden of comorbidities (prevalence of CVD, CKD and CVD/CKD risk factors) in this T2D patient population at study index date 1
- Actual treatment use at study index date 1 in patients with and without established CVD (Established CV disease defined as acute myocardial infarction (AMI), cardiology intervention, ischemic heart disease (IHD), congestive heart failure (CHF), peripheral arterial disease (PAD), or stroke)
- To describe the association of socioeconomic parameters with treatment decisions at study index date 1
- To assess the discontinuation rate, reasons for discontinuation and average duration of treatment for GLP1a, DPP4i and SGLT2i after a follow up of approximately one year from the initial time point (= index date 2)

[redacted]

9.3.3 Covariates

Not applicable

9.4 DATA SOURCES

Data will be collected retrospectively from existing patient data (Medical chart review) previously documented by Health care professionals during routine practice in patients treated for T2D in an endocrinologist, diabetologist or cardiologist office-based setting (nonhospital). Medical records of patients meeting inclusion/exclusion criteria and having provided written informed consent will be used to collect all study data. The delegated site personnel of the participating sites will enter the relevant parameters into the electronic Case Report Forms (eCRF) in a timely manner. This method has been chosen as method of data collection as systematic diabetes registries do not exist in CEE countries.

Patients who are potentially eligible for study participation will be contacted by the delegated site personnel by phone or by sending a letter, inviting the patient to the next routine visit. In addition, patients will be informed about the study project and his/her potential eligibility for participating into the study.

9.5 STUDY SIZE

No formal sample size calculation is provided for this study. This NIS has been designed to describe, in a real-world setting, usage patterns and outcomes associated with empagliflozin or other SGLT2i or DPP4i or GLP1a in the clinical routine practice. The sample size of approximately 4000 patients is driven by the need to enroll an adequate number of patients to address the mentioned objectives, also across various subgroups, such as physician or country specific analyses. It is aspired to document at least 500 patients in the GLP1a and at least 1000 patients each in the SGLT2i and DPP4i subgroups. However, no formal limitations will be applied for recruitment of patients to subgroups with regard to medication of interest.

9.6 DATA MANAGEMENT

A data validation plan (DVP) and a data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection via the electronic Case Report Forms (eCRFs). The eCRF will include programmable edits to obtain immediate feedback if data are missing (also negative answers, unknown), out of range, illogical or potentially erroneous. These rules may encompass simple checks such as range validation or presence/absence of data. Concurrent manual data review including query processes may be performed as defined in the data management plan (DMP). This involves ad hoc queries within the eCRF which will be followed up for resolution. The database will be hosted in a physically and logically secure computer system maintained in accordance with a written security policy. The system will meet the standards of the International Committee on Harmonization guideline E6R1 regarding electronic study data handling. Data confidentiality will be strictly maintained.

9.7 DATA ANALYSIS

Details will be described in the statistical epidemiological analysis plan (SEAP)

9.7.1 Planned analyses

All patients who have received a first prescription of respective study medication will be included in the analysis; this is the prescribed patient set. All analyses will be performed on the prescribed patient set. If patients have missing values for an outcome, those patients will be excluded for that outcome's analysis.

The assessment will be carried out using SAS® software. The statistical characteristics presented in the end-of-text tables will be N / mean / SD / min / median / max for continuous variables. Tabulations of relative and absolute frequencies will be presented for categorical variables. Incidence rates and 95% CI will be given when appropriate. Subgroup analyses e.g. according to medication (i.e. empagliflozin or SGTL2i or DPP4i or GLP1a), country and physician specialty are planned, as well as per history of CV disease. Descriptive analyses will be supplemented using $\chi 2$-test or Fisher's exact test for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables. The analyses are purely explorative, hence no correction for multiple testing is needed.

The analyses will relate to the following data as recorded in the eCRF:

1. Patient demographics (age, gender, height, weight, BMI, ethnicity)
2. Time since diagnosis of Type 2 Diabetes
3. Clinical parameters relevant for T2D, CVD, CKD assessment as valid on index date 1
4. Comorbidities like cardiovascular disease and related risk factors at index date 1
5. Comorbidities like chronic kidney disease and related risk factors at index date 1
6. T2D medication the treating physician newly prescribes at study index date 1
7. Reason(s) for treatment decision at index date 1
8. Concomitant T2D medications at study index date 1
9. Concomitant CVD and CKD medications at index date 1
10. Other HCPs involved in treatment decisions at study index date 1 and at index date 2
11. Relevant socioeconomic parameters
12. Discontinuation rate, reason for discontinuation, duration of T2D therapy after one year (± 2 months)

All adverse events and adverse drug reactions collected per study protocol will be included and summarized in the final study report. Refer to the corresponding Section 11.

Main analysis

For the main analysis data from research question 1 to 5 will be evaluated in a descriptive manner for the total number of prescribed patients enrolled in the study.

[redacted]

9.7.2 Handling of missing data

By using a simple and non-complex eCRF in which the amount of data to be assessed is limited, the amount of missing data is expected to be low. Every effort will be made to collect complete data by using validation checks within the eCRF and possibly involving manual query processes (see Section 9.8). Please refer to the analysis plan for details.

9.8 QUALITY CONTROL

The study sites will be trained on the study procedures and on handling of the eCRF before documentation of the first patient at the respective study site.
To ensure data quality, automatic data checks upon data entry (eChecks) will be programmed within the eCRF. Therefore, plausible ranges of values for numeric data entries as well as logical data entries and listings will be provided for the respective entry field. Based on this, checks on completeness and plausibility will be performed upon data entry in the eCRF.
Validity of data entry thus is ensured by integrated validation checks performed by the system, indicating missing or implausible entries to the document list or investigator. All corrections will be visible from the systems audit trail. Data management activities by means of manual query processes might be implemented as defined in the DMP to increase data integrity.
No regular source data verification is planned in this study. However, in case of decreasing data quality (i.e. of missing data, data discrepancies, protocol violations, etc.) a for-cause audit or risk-based monitoring visit will be performed.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The intention of this NIS is to analyze existing data of T2D patients when initiating on different types of T2D drugs, their comorbidities, their co-medications and socioeconomic factors with possible influence on treatment decisions and treatment duration.
A NIS is the most suitable instrument for obtaining information about the use of medicines in everyday clinical practice.
A possible limitation of the retrospective study design of this NIS is that the time windows of 4 months (index date 1) and of 12 (± 2) months (index date 2) will give limited information in the population at a specific point in time. Medication availability might differ between countries due to different reasons (commercial availability, reimbursement status) which will be collected in research question 4 for further data interpretation.

9.10 OTHER ASPECTS

9.10.1 Informed Consent, Data Protection, Study Records

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, and as close as possible to the standards of the International Conference of Harmonisation (ICH) Tripartite Guideline for Good Clinical Practice (GCP), Guidelines for Good Epidemiological Practice (GEP) [R10-4560], Good Pharmacoepidemiology Practice (GPP) [R09-0182] and relevant BI Standard Operating Procedures (SOPs).

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

9.10.2 Study Approval, Patient Information, and Informed Consent

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Independent Ethics Committee (IEC) and competent authority (CA), if needed according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Patients potentially eligible for study participation will be contacted by the delegated site personnel by phone or by sending a letter, reminding the patient of the next routine visit. In addition, patients will be informed about the study project and his/her potential eligibility for participating in the study.

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative). Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorized monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IEC members, and by inspectors from regulatory authorities.

After having provided written informed consent, the patients will be registered within the study's EDC system to document all relevant variables.

Patients already registered before protocol amendment 1 will have to consent to additional data collection at index date 2.

9.10.2.1 Data Quality Assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

9.10.2.2 Records

All of the clinical data and site/investigator characteristics will be captured via a web-based Electronic Data Capturing system. The delegated site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained.

Patients must not be identified on the eCRF by name. Appropriately coded identification (i.e. Patient numbers) must be used.

9.10.2.2.1 Source documents

The relevant study data will be derived from the patient´s medical record, which is maintained either paper-based or electronically depending on the routine at the respective study site. Data relevant for this study will be reviewed and entered into the study´s eCRF by delegated site staff. Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents.

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected.

For the eCRF, the following data must be derived from source documents:

1. Patient demographics (age, gender, height, weight, BMI, ethnicity)
2. Time since diagnosis of Type 2 Diabetes
3. Clinical parameters relevant for T2D, CVD, CKD assessment as valid on index date 1
4. Comorbidities like cardiovascular disease and related risk factors at index date 1
5. Comorbidities like chronic kidney disease and related risk factors at index date 1
6. T2D medication the treating physician newly prescribes at study index date 1
7. Reason(s) for treatment decision at index date 1
8. Concomitant T2D medications at study index date 1
9. Concomitant CVD and CKD medications at index date 1
10. Other HCPs involved in treatment decisions at study index date 1 and at index date 2
11. Relevant socioeconomic parameters
12. Status of T2D treatment (stop date and reason for discontinuation, if available) at index date 2

9.10.2.2.2 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities. The Clinical Research Associate (CRA) / on site monitor and auditor may review all eCRFs and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.

9.10.2.3 Statement of Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Patient confidentiality will be ensured by using patient identification code numbers.

Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IEC and the regulatory authorities, i.e. the competent authority (CA).

9.10.2.4 Completion of Study

The EC/competent authority in each participating EU member state needs to be notified about the end of the study (last patient out) or early termination of the study.

9.10.2.5 Protocol Violations

There are no protocol waivers. All protocol violations must be reported to the sponsor immediately.

9.11 SUBJECTS

9.11.1 Cases

The study will include all patients fulfilling inclusion/exclusion criteria and receiving a first filled prescription for medication of interest in the period of 4 months (September – December 2018)

Inclusion criteria

Written informed consent prior to participation
Female and male patients age ≥ 18 years
Patients with T2D diagnosis
Patients who have been newly initiated with empagliflozin or other SGLT2i, DPP4i or GLP1a between September 2018 and December 2018 (study index date 1)
Patients have been naïve to treatment with empagliflozin or other SGLT2i, DPP4i or GLP1a at study index date 1

Exclusion criteria

Patients age < 18 years
Patients with diagnosis of other types of diabetes than T2D
Patients who do not provide written consent to the terms of the study

9.11.2 Controls

Not applicable

9.12 BIAS

Selection bias could occur at the site level and the patient level.

To minimize the site level selection bias, sites will be eligible if HCPs initiate second line medications in their T2D patients. In addition to that, the number of proposed sites will be 150% of sites to be finally included which will allow random selection of site.

In order to limit the variability of outcomes, sites will be eligible if they have access and can prescribe at least 2 of the T2D drug classes of interest (SGLT2i, DPP4i, GLP1a) for the targeted T2D.

To minimize selection bias at the patient level, physicians are requested to include all patients meeting inclusion and exclusion criteria in the study period of 4 months (September – December 2018) into the study. However, there may be a bias regarding patient groups at index date 1 and 2, since not all patients who have consented to documentation at index date 1 may or can give their consent (e.g. due to death or loss to follow-up) to further documentation at index date 2.

Information bias will be minimized by the use of standard eCRF and physicians' training on the study protocol and handling of the eCRF.

10. PROTECTION OF HUMAN SUBJECTS

Please refer to Section 9.10.1

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS & ADVERSE DRUG REACTIONS

Screening for potential treatment naïve study subjects occurs outside of the study. Therefore, patients included into the study will have no previous exposure to any BI product for the disease in scope of the study (DM type 2) or any other SGLT-2i, DPP4-i or GLP-1a prior to index date. No prospective data collection will occur as part of the study after having received prescription at index date 1.
However, due to the possibility that adverse drug reactions are reported as reason for T2D treatment discontinuation at index date 2, definitions and reporting are stated below.

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse drug reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other

situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.
Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)

The term Adverse Event of Special Interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.
Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**
- A **plausible time to onset of the event** relative to the time of drug exposure
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).

- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event

The intensity of the AE should be judged based on the following:
Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate: Enough discomfort to cause interference with usual activity
Severe: Incapacitating or causing inability to work or to perform usual activities

Pregnancy:

In rare cases, pregnancy might occur in a NIS. Once a patient has been enrolled in the study and has taken study medication, the investigator must report any drug exposure during pregnancy in a study participant within 7 days after becoming aware by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form (Part B).

The following must be reported to the Sponsor on the NIS AE Form and/or Pregnancy Monitoring Form for Studies in case such AE/drug exposure during pregnancy information is identified in the course of the review of the individual records:

All serious ADRs associated with Jardiance®, Synjardy®, Trajenta®, Jentadueto®	immediately within 24 hours after becoming aware
All AEs with fatal outcome in patients exposed to Jardiance®, Synjardy®, Trajenta®, Jentadueto®	immediately within 24 hours after becoming aware
All non-serious ADRs associated with Jardiance® Synjardy® Trajenta® Jentadueto®	7 calendar days after becoming aware
Drug exposure during pregnancy	7 calendar days after becoming aware

The same timelines apply if follow-up information becomes available for the respective events.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the Marketing Authorization Holder according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results of this non-interventional study will be disclosed on encepp.eu and clinicaltrials.gov. A study specific publication plan will be developed.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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2. **R12-1453** Morrish et al Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. Diabetologia (2001) 44 supplement 2: 24-21.

3. **R18-3104** Emerging Risk Factors Collaboration, Di Angelantonio E, Kaptoge S, et al. Association of cardiometabolic multimorbidity with mortality. *JAMA*. 2015; 314(1):52–60.

4. **R18-3103** Heart UK -Risk factors for CVD: https://heartuk.org.uk/files/uploads/documents/huk_fs_mfsI_riskfactorsforchd_v2.pdf _(accessed February 5, 2018)

5. **R15-5186** Nwanari C et al., Mortality in type 2 diabetes mellitus: magnitude of the evidence from a systematic review and meta-analysis. British Journal of Diabetes&Vascular Disease 2013;13

6. **R18-3102** Svensson MK et al Albuminuria and renal function as predictors of cardiovascular events and mortality in a general population of patients with type 2 diabetes: A nationwide observational study from the Swedish National diabetes register. Diab Vasc Dis Res 2013;10;520-9.

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9. **R11-5199** Seshasai SRK et al. Diabetes mellitus, fasting glucose and risk of cause-specific death, NEJM 2011;364:829-41.

10. **R04-4255** Lewington S et al. Age specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002, 1903-13.

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13. **R13-0026** Balkau B et al., International Day for the evaluation of Abdominal Obesity (IDEA) a Study of Waist Circumference, Cardiovascular Disease and Diabetes Mellitus in 168000 Primary Care Patients in 63 Countries. Circulation 2007, 116;1942-51.

14. **R14-3924** Gregg et al. Changes in diabetes-related complications in the United States 990-2010, N Engl J Med 2014;370: 1514–1523.

15. **R18-3100** Tonelli M et al., Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. The Lancet, 2012; 380, 807.

16. **R18-2261** Norhammar et al. Incidence, prevalence and mortality of type 2 diabetes requiring glucose-lowering treatment, and associated risks of cardiovascular complications: a nationwide study in Sweden, 2006–2013. Diabetologia (2016) 59:1692–1701

17. **P15-09840** Zinman B et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28. doi: 10.1056/NEJMoa1504720. Epub 2015 Sep 17.

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19. **P17-13883** Cefalu W et al., Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a Diabetes Care Editors Expert Forum. Diabetes Care 2018: 41:14-31

20. **R18-1776** ADA guidelines: Standards of Medical Care in Diabetes 2018, Diabetes Care 2018;41(Suppl. 1):S1–S2

21. **P16-06194** Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Societyof Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts), developed with the specialcontribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European Heart Journal, Advance Access published May 23, 2016, doi: 10.1093/eurheartj/ehw106; 2016.

22. **P16-05920** Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC), developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal, Advance Access published May 20, 2016, doi: 10.1093/eurheartj/ehw128; 2016.

23. **R10-4560** Good Epidemiological Practice (GEP). IEA Guidelines for Proper Conduct of Epidemiological Reseach (2007).

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26. **R05-0351**World Health Organization, Obesity: preventing and managing the global epidemic. Report of WHO consultation. World Health Organ Rep Ser 894, 1-253 (2000)

13.2 UNPUBLISHED REFERENCES

n.a.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	eCRF formfakes	21 November 2018	cordially_formfakes_2018-11-21.pdf

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The *European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)*(website.encepp.eu) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the *ENCePP Guide on Methodological Standards in Pharmacoepidemiology* (website.encepp.eu/standards_and_guidances/index.html), which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the *Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies.*
(website.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133174.pdf). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
CORDIALLY® - CEE: Characteristics of patients with Type 2 Diabetes patients treated with modern antidiabetic drugs.
A real-world data collection of patient baseline characteristics, treatment patterns and comorbidities in Central Eastern European (CEE) countries

EU PAS Register® number: EUPAS28505
Study reference number (if applicable): 1245-0187

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8.1
2.1.2 The objective(s) of the study?	☒	☐	☐	8.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.11, 9.7.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2, 9.2.1, 9.2.2, 9.11
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1
4.2.2 Age and sex	☒	☐	☐	9.2.1
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	9.2.1
4.2.5 Duration of follow-up	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Data of patients who are newly initiated with SGLT2i, DPP4i, or GLP1a for Type 2 Diabetes between September 2018 and December 2018 are retrospectively collected. Since this study doesn't address safety outcomes, exposure is only collected

qualitatively by means of being newly prescribed with the medication of interest at index date 1 (September 2018 – December 2018).

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2, 9.7.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

To question 6.3: The study outcomes will be analyzed in a purely descriptive manner, no sensitivity analyses will be performed.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.12
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.12
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.12

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	
9.1.3 Covariates and other characteristics?	☒	☐	☐	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

To question 9.2.2, no safety outcomes will be analyzed as research question. Adverse events reported in this study are solely listed in the CSR, no analysis will be made in this regard.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.1
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	
10.4 Are stratified analyses included?	☒	☐	☐	9.7.1
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.1
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.12
12.1.2 Information bias?	☒	☐	☐	9.12
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.2

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9.10.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted]

Date: dd/Month/year

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

none