Statistical Analysis Plan for non-interventional studies based on existing data

BI Trial No.:	1245-0187
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
Investigational Product(s):	Jardiance® Synjardy® Trajenta® Jentadueto®
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	25MAY2021
Version:	Final 3.0
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2. LIST OF ABBREVIATIONS

Term	Definition / description
AMI	Acute Myocardial Infarction
CEE	Central Eastern Europe
CHF	Congestive Heart Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
CTP	Clinical Trial Protocol
CVD	Cardiovascular Disease
DPP4	Dipeptidyl-peptidase 4
DPP4 i	Dipeptidyl-peptidase 4 inhibitor
FAS	Full Analysis Set
GLP1	Glucagon-like peptide 1
GLP1 a	Glucagon-like peptide 1 agonist
HCP	Health Care Provider
IHD	Ischemic Heart Disease
Max	Maximum
Min	Minimum
PAD	Peripheral Arterial Disease
PPS	Prescribed Patient Set
PV	Protocol Violation
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard deviation
SGLT2i	Sodium Glucose Transporter 2 inhibitor
T2D	Type 2 Diabetes

3. INTRODUCTION

As per ICH E9[1], the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Observational plan, including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in Observational plan Section 9.7 “Data Analysis”. Therefore, TSAP readers may consult the Observational plan for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

SAS® Version 9.4 or higher will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Discontinuation rate, reason for discontinuation, duration of T2D therapy after one year (± 2 months) added as parameters collected on study index date 2

All adverse events and adverse drug reactions collected per study protocol will be included and summarized in the final study report.

5. OUTCOME(S)

5.1 PRIMARY OUTCOME(S)

The primary outcome of the presented study is to describe T2D patients' baseline characteristics when initiating either empagliflozin - or other SGLT2i, DPP4i or GLP-1 RA on top of current antidiabetic treatment by different HCP specialties in CEE countries.

5.2 SECONDARY OUTCOME(S)

- 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 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 GLP-1 RA, DPP4i and SGLT2i after a follow up of approximately one year from the initial time point (= index date 2)

6. GENERAL ANALYSIS DEFINITIONS

6.1 EXPOSURE(S)

Exposure to SGLT2i, DPP4i or GLP-1 RA is defined as having received a first prescription of the respective treatment of interest between September and December 2018.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Table 6.2: 1 defines the different categories of important protocol violations (PVs). The final column describes which PVs will be used to exclude subjects from the different patient analysis sets[2].

Table 6.2: 1 Important protocol violations

Category/ Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1.1	Inclusion criterion 2 (Female and male patients >=18 years of age)	Not met as specified in the protocol	PPS
	A1.2	Inclusion criterion 3 (Patients with T2D diagnosis)	Not met as specified in the protocol	PPS
	A1.3	Inclusion criterion 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))	Not met as specified in the protocol	PPS
	A1.4	Inclusion criterion 5 (Patients have been naïve to treatment with empagliflozin or other SGLT2i, DPP4i or GLP1a at study index date 1)	Not met as specified in the protocol	PPS
	A2.1	Exclusion criterion 1 (Patients age < 18 years)	Met as specified in the protocol	PPS
	A2.2	Exclusion criterion 2 (Patients with diagnosis of other types of diabetes than T2D)	Met as specified in the protocol	PPS
	A2.3	Exclusion criterion 3 (Patients who do not provide written consent to the terms of the study)	Met as specified in the protocol	PPS
B		**Exclusion criteria**		
	B1	Informed consent not available/not done (Inclusion criterion 1)	IC 01 not met as specified in the protocol or informed consent date	All

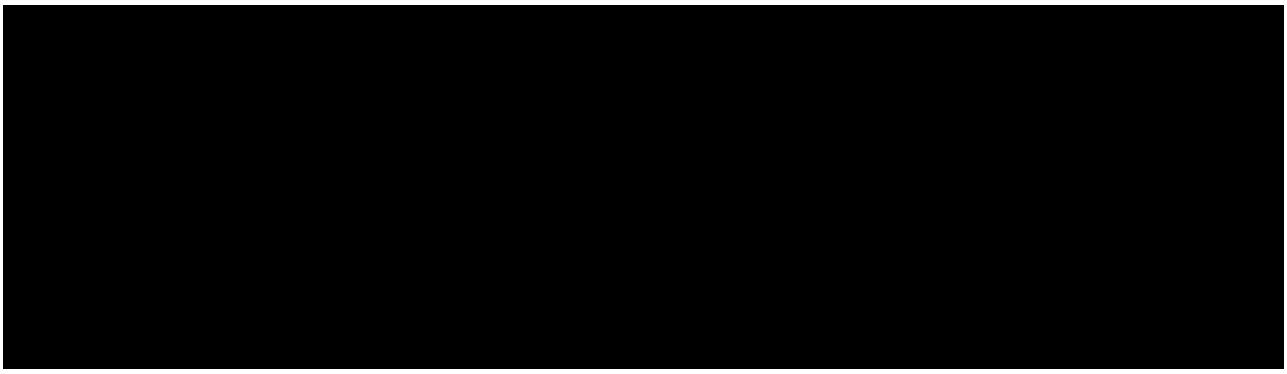
6.3 PATIENT SETS ANALYZED

Prescribed patient set (PPS): All patients fulfilling inclusion and exclusion criteria who have received a first prescription of a respective study medication.

Full Analysis set (FAS): All patients from PPS with documentation at index date 2. Patients included before the protocol amendment need an additional signed informed consent at index date 2.

Table 6.3: 1 Patient sets analyzed

	Patient set	
Class of outcome	PPS	FAS
Primary and secondary outcomes at index date 1	X	
Secondary outcomes at index date 2		X



6.5 POOLING OF CENTRES

Not applicable

6.6 HANDLING OF MISSING DATA AND OUTLIERS

No missing data will be imputed. If patients have missing values for an outcome, those patients will be excluded for that outcome's analysis.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

At Index Date 1 the patients initially prescribed with T2D medication (empagliflozin or other SGLT2i, DPP4i or GLP-1 RA). At Index Date 2 (after 1 year (± 2 months) the discontinuation rate, reason for discontinuation and average duration of T2D treatment will be assessed.

7. 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 at index date 1 will be performed on the prescribed patient set and analyses at index date 2 will be performed on the full analysis 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 GLP-1 RA), 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. Presence of cardiovascular disease and related risk factors at index date 1
5. Presence of 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.

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.

To allow a country specific interpretation of the results, data from research question 1 to 5 will be evaluated in a descriptive manner for the total number of prescribed patients per country enrolled in the study.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. All baseline analyses will be done for the prescribed patient set.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. All analyses will be done for the prescribed patient set.

7.3 PRIMARY OUTCOME

For the primary outcome, the baseline characteristics will be analysed in a descriptive manner. Frequencies and 95% CI will be given when appropriate.

In addition the baseline characteristics will be compared by medication, physician speciality and country using χ^2-Test or Fisher's exact test, if χ^2-Test is not valid, for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables.

7.4 SECONDARY OUTCOME(S)

All analysis will be descriptive and will be performed on PPS.

The prevalence of CVD and CKD will be displayed in frequency tables as well as the reasons for treatment choice, concomitant T2D medication and concomitant CVD/CKD medication. Furthermore other physicians involved in the treatment decision as well as the decision to discontinue the treatment will be given.

The "10 year risk for fatal CVD" will be calculated by applying the 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 1.

Moreover, the discontinuation rate and the reason for discontinuation will be displayed in frequency tables.
To assess the duration of T2D therapy after one year (± 2 months) the time to discontinuation will be analysed by Kaplan-Meier estimates and subgroups will be compared using log-rank test.

For comparison of subgroups, χ^2-test or Fisher's exact test, if χ^2-test is not valid, will be used.
If the treatment decision depends on socioeconomic factors will be analysed using χ^2-test or Fisher's exact test.

[redacted]

7.6 EXTENT OF EXPOSURE

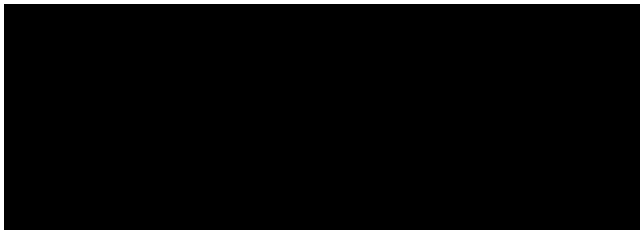
Not applicable.

7.7 SAFETY ANALYSIS

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-1 RA 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, all adverse events and adverse drug reactions collected per study protocol will be included and summarized in the final study report.

8. REFERENCES

1	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2	*001-MCS-50-413*: "Handling of Protocol Violations in Clinical Trials and Projects", current version; group: Study Conduct; IDEA for CON.
3	European Guidelines on CVD Prevention in Clinical Practice 2016 Eur J Prev Cardiol. 2016 Jul;23(11):NP1-NP96. doi: 10.1177/2047487316653709



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Draft v0.1	30-APR-2019	[redacted]	None	This is the first Draft-Version of TSAP without any modification
Draft v0.2	**24-JUN-2019**		Headline, 3, 5, 5.1, 5.2, 5.3, 6.1, 6.3, 6.4, 6.6, 7.7	Adjusted wording to be conform with NIS status of the study
Draft v0.3	24-JUL-2019		[redacted]6.3,[redacted]	Deleted obsolete information from 5.3 and 6.3 since these points were already part of primary and secondary outcomes. [redacted]
Final v1.0	**13-Sep-2019**		7.4, 8	Added reference for calculation of 10 year fatal CVD risk
Draft v.1.1	**10-Aug-2020**		4,5,6,7	Adjusted to protocol amendment
Draft v1.2	**23-OCT-2020**		Titlepage, 5.1, 5.2, 6.1, 6.3, 6.4, 7, 7.4, 7.7	Adjusted wording according to reviewer comments/adaptations
Draft v 1.3	**30-NOV-2020**		7.4	Changed analysis method for duration of treatment to Kaplan-Meier assesment of time to discontinuation.
Final 2.0	**10.DEC-2020**		Page 1	Adapted Version and date. Applied all changes to finalize document.
Final 3.0	**25.May-2021**		6.3	Added FAS definition