Protocol for non-interventional studies based on existing data

Document Number:	**<document number>**
BI Study Number:	1245-0198
BI Investigational Product(s):	NA
Title:	*Description of Treatment and Population Characteristics of Type 2 Diabetic Patients in Germany receiving Empagliflozin: A retrospective Real-World Evidence (RWE) study based on German registries DPV & DIVE*
Protocol version identifier:	*1.0*
Date of last version of protocol:	16 August 2019
PASS:	*No*
EU PAS register number:	NA
Active substance:	*Empagliflozin*
Medicinal product:	Jardiance®, Synjardy®
Product reference:	NA
Procedure number:	NA
Joint PASS:	–
Research question and objectives:	*Description of the real-life treatment of adult patients with type-2 diabetes mellitus (T2DM) receiving Empagliflozin, comparing the characteristics of patients starting Empagliflozin in three time intervals:* - *The first analysis will include the patients receiving Empagliflozin before the EMPA-REG-OUTCOME study was published (time until mid-Sept. 2015; "Cohort 1").* - *The second analysis will include patients receiving Empagliflozin starting from the EMPA-REG-OUTCOME study being published until CV Label Change (time from mid-Sept. 2015-mid-Jan. 2017; "Cohort 2").* - *The third analysis will include all patients receiving Empagliflozin starting from mid-Jan. 2017 until last available data cut ("Cohort 3").*
Country of study:	*Germany*

Author:		
Marketing authorisation holder(s):		
MAH contact person:		
In case of PASS, add: **<EU-QPPV:>**	NA	
In case of PASS, add: <**Signature of EU-QPPV:>**	NA	
Date:	*16 August 2019*	
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ACE-i	Angiotensin-converting enzyme inhibitor
AD	Anti-diabetic Drug
aDCSI	adapted Diabetes Complications Severity Index
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ARB	Angiotensin receptor blocker
ASA	Acetylsalicylic acid (Aspirin)
ASCVD	Atherosclerotic cardiovascular disease
ATC	Anatomical Therapeutic Chemical / Defined Daily Dose Classification
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.
BÄK	Bundesärztekammer
Ba-Wue.	Baden-Wuerttemberg
BB	Beta blocking agents
BI	Boehringer Ingelheim
CAD	Coronary artery disease
CCB	Calcium-channel blockers
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CRO	Clinical Research Organization
CSME	Clinically significant macular edema/degeneration
CV	Cardiovascular
CVD	Cardiovascular disease
DDD	Defined Daily Dose
DMP	Diseases Management Program
DPP4-i	Dipeptidylpeptidase IV inhibitors
DRG	Diagnosis Related Group
EBM	Einheitlicher Bewertungsmaßstab
EU-QPPV	European Union Qualified Person for Pharmacovigilance
FGS	Fachgruppenschlüssel
GPP	Good Pharmacoepidemiology practices
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
Hosp.	Hospitalization
IC	Informed Consent
ICD	International Statistical Classification of Diseases and Related Health Problems
ICH-GCP	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IHD	Ischemic heart disease
IPAM	Institut für Pharmakoökonomie und Arzneimittellogistik
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research

KBV	Kassenärztliche Bundesvereinigung
KM	Kaplan-Meier
LOCF	Last observation carried forward
MAH	Marketing authorization holder
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonists / Aldosterone antagonists
NIS	Non-interventional study
NOAC	New Oral Anticoagulant
NYHA	New York Heart Association
OAC	Oral anticoagulation
OPS	"Operationsschlüssel"
PAD	Peripheral artery disease
PAI	Platelet aggregation inhibitor
PASS	post-authorization safety study
PhRMA	Pharmaceutical Research and Manufacturers Association
PVD	Peripheral vascular disease
PY	Patient year
PZN	"Pharmazentralnummer"
RAAS-i	Renin-angiotensin-aldosterone system inibitor
SU	Sulfonylureas
T2DM	Type-2 Diabetes Mellitus
TIA	Transient ischemic attack
VKA	Vitamin K antagonist

3. RESPONSIBLE PARTIES

Function	*Name*	*Affiliation*
Scientific Lead DPV		
Scientific Lead DIVE		
Project Consultant		*Boehringer Ingelheim*
Project Manager		*Boehringer Ingelheim*
Medical Project Member		*Boehringer Ingelheim*

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance®, Synjardy®			
Name of active ingredient: Empagliflozin			
Protocol date: 16 August 2019	**Study number:** 1245-0198	**Version/Revision:** 1.0	**Version/Revision date:**
Title of study:	*Description of Treatment and Population Characteristics of Type 2 Diabetic Patients in Germany receiving Empagliflozin: A retrospective Real-World Evidence (RWE) study based on German registries DPV & DIVE*		

Rationale and background:	In the following years, new data for empagliflozin in type 2 diabetes (T2D) from clinical studies and PMO data will be limited. To gain a comprehensive picture of a drug´s (long-term) effectiveness, the medical community, payers and health politicians demand real-world evidence (RWE). In general, collaboration with a registry allows a continuous scientific exchange (e.g. scientific discussions and publications). RWE is also part of the basis for generating payer partnerships, e.g. managed-care projects. Furthermore, the data can be used for value communication for payers and medical communities (e.g. via digital channels). In addition, AMNOG price negotiations could be supported by such data. Therefore, we plan to perform a retrospective, non-interventional study on the real-life treatment and treatment-associated outcomes of German T2D patients receiving Empagliflozin. We will set up this study based on data from the two largest German registries (Diabetes-Patienten-Verlaufs-dokumentation (DPV) & Diabetes Versorgungs-Evaluation (DIVE)) covering currently around 500,000 adult T2D patients in Germany. The number of SGLT2i patients in Germany is steadily increasing. In this study, only Empagliflozin patients will be analyzed. They will be divided in three consecutive cohorts to assess potential differences over time.
Research question and objectives:	Description of the real-life treatment of adult patients with T2DM receiving empagliflozin, comparing the characteristics of patients starting empagliflozin in three time intervals: - The first analysis will include the patients receiving Empagliflozin before the EMPA-REG-OUTCOME study was published (time until mid-Sept. 2015; “Cohort 1”). - The second analysis will include patients receiving Empagliflozin starting from the EMPA-REG-OUTCOME study being published until CV Label Change (time from mid-Sept. 2015-mid-Jan. 2017; “Cohort 2”). - The third analysis will include all patients receiving Empagliflozin starting from mid-Jan. 2017 until last available data cut (“Cohort 3").
Study design:	Retrospective non-interventional cross-sectional study using real-world data from German patient registries. Data will be provided by the largest German T2D patient registries DPV& DIVE covering more than 500,000 patients.
Population:	Inclusion criteria: • Adult patients with at least two outpatient T2DM diagnoses (ICD E11.-) in two different quarters and/or at least one inpatient T2DM diagnosis (ICD E11.-) – AND – • At least one prescription of an empagliflozin-containing antidiabetic drug: Jardiance® (Empagliflozin, ATC A10BK03, former

	A10BX12) or Synjardy® (Empagliflozin/Metformin, ATC A10BD20) Exclusion criteria • Any diagnosis of T1DM.

Variables:	For all three cohorts receiving empagliflozin, the baseline values of the following variables will be assessed:
	• Age (<65; 65 – <75; 75 – 80 , >80)
	• Gender
	• Weight [kg]
	• Height [cm]
	• HbA1c [% or mmol/ mol], FPG (available in subgroup only)
	• Previous occurrence of
	  o Typical CV comorbidities:
	  ▪ MI
	  ▪ Stroke
	  ▪ CAD
	  ▪ PAD
	  ▪ CHF (form (HFrEF/ HFpEF)
	  o Other typical diabetes complications
	  ▪ Neuropathy
	  ▪ Nephropathy / Renal function (eGFR, micro-/ macroalbuminuria)
	  ▪ Diabetic foot syndrome
	  ▪ Retinopathy (background and proliferative)
	• Antidiabetic and cardiovascular co-medication (lipid-lowering agents, RAAS blockers, other antihypertensives, beta blockers, diuretics, antiplatelets and anticoagulants)
	• Duration of diabetes (time since diagnosis)
	• Previous glucose-lowering treatment
	• Dosage of empagliflozin (10mg vs 25mg) (available in subgroup only)
	• Participation in Disease Management Programme (DMP) Type 2 Diabetes (from DPV registry)
	• Hospitalizations (from DPV registry)

Data sources:	Data will be provided by the largest German T2D patient registries DPV& DIVE covering more than 500,000 patients. The aim of the DPV initiative is to improve treatment outcomes in individuals with diabetes through standardized documentation and objective comparison of quality indicators as well as through multi-centre outcome research. Up to date, there are more than 400 centres participating in the initiative predominantly from Germany and from Austria. DIVE is a national initiative for quality management of diabetes care. The aim is to transfer the already existing initiatives and software systems which collect patient-related data to a national diabetes registry. The DIVE registry is one of the biggest, most updated diabetes registries in Germany and part of the current development of a national diabetes registry. It is part of the first and second registry conference held by German Federal Ministry of Health (BMG) and Robert-Koch Institute (RKI).

Study size:	There will be about 7,900 patients on Empagliflozin included in the analysis.
Data analysis:	Variables will be assessed in half-yearly periods after index date (date of first prescription of empagliflozin), for total study population and separated by study cohort. Anonymized data from the DIVE and the DPV registries will be combined; nonparametric descriptive analyses will be used. Group comparison will be based on Wilcoxon rank sum test (continuous variables) and X^2-test for binary/categorial values. Analysis will be implemented using SAS 9.4. Complete case analysis will be used. Analysis will be done by an experienced biostatistician with detailed knowledge of the DIVE and the DPV registries. A second independent programmer will check the generated SAS code for inconsistencies. The medical team (will evaluate the results from a clinical background to ensure plausibility. Quality assurance and control will be the responsibility of the medical team (
Milestones:	• Project kick-off: 09 November 2018 • Draft of study protocol: 5 July 2019 • Final study protocol & approval by: 31 August 2019 • Start of data access/data validation: 01 September 2019 • End of data analysis by: 31 October 2019 • Final report of study results by: 31 December 2019 • Finalization of publication draft by: 31 December 2019

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date

7. RATIONALE AND BACKGROUND

In the following years, new data for empagliflozin in type 2 diabetes (T2D) from clinical studies and PMO data will be limited. To gain a comprehensive picture of a drug´s (long-term) effectiveness, the medical community, payers and health politicians demand real-world evidence (RWE).

In general, collaboration with a registry allows a continuous scientific exchange (e.g. scientific discussions and publications). RWE is also part of the basis for generating payer partnerships, e.g. managed-care projects. Furthermore, the data can be used for value communication for payers and medical communities (e.g. via digital channels). In addition, AMNOG price negotiations could be supported by such data.

Therefore, we plan to perform a retrospective, non-interventional study on the real-life treatment and treatment-associated outcomes of German T2D patients receiving Empagliflozin. We will set up this study based on data from the two largest German registries (Diabetes-Patienten-Verlaufsdokumentation (DPV) & Diabetes Versorgungs-Evaluation (DIVE)) covering currently around 500,000 adult T2D patients in Germany. The number of SGLT2i patients in Germany is steadily increasing.

In this study, only Empagliflozin patients will be analyzed. They will be divided in three consecutive cohorts to assess potential differences over time.

8. RESEARCH QUESTION AND OBJECTIVES

Description of the real-life treatment of adult patients with T2DM receiving empagliflozin, comparing the characteristics of patients starting Empagliflozin in three time intervals:

- The first analysis will include the patients receiving Empagliflozin before the EMPA-REG-OUTCOME study was published (time until mid-Sept. 2015; “Cohort 1”).
- The second analysis will include patients receiving Empagliflozin starting from the EMPA-REG-OUTCOME study being published until CV Label Change (time from mid-Sept. 2015-mid-Jan. 2017; “Cohort 2”).
- The third analysis will include all patients receiving Empagliflozin starting from mid-Jan. 2017 (“Cohort 3") until last available data cut.

9. RESEARCH METHODS

9.1 STUDY DESIGN

Retrospective non-interventional cross-sectional study using real-world data from German patient registries. Data will be provided by the largest German T2D patient registries DPV& DIVE covering more than 500,000 patients. An anonymized dataset will be delivered by DIVE and DPV, respectively. The two datasets will then be combined.

9.2 SETTING AND INCLUSION/EXCLUSION CRITERIA

Description of the real-life treatment of adult patients with T2DM receiving empagliflozin, comparing the characteristics of patients starting empagliflozin in three time intervals:

- The first analysis will include the patients receiving Empagliflozin before the EMPA-REG-OUTCOME study was published (time until mid-Sept. 2015; “Cohort 1”).
- The second analysis will include patients receiving Empagliflozin starting from the EMPA-REG-OUTCOME study being published until CV Label Change (time from mid-Sept. 2015-mid-Jan. 2017; “Cohort 2”).
- The third analysis will include all patients receiving Empagliflozin starting from mid-Jan. 2017 until last available data cut (“Cohort 3").

Inclusion criteria:

- At least two outpatient T2DM diagnoses (ICD E11.-) in two different quarters and/or at least one inpatient T2DM diagnosis (ICD E11.-)
- At least one prescription of an empagliflozin-containing antidiabetic drug: Jardiance® (Empagliflozin, ATC A10BK03, former A10BX12) or Synjardy® (Empagliflozin/ Metformin, ATC A10BD20)

Exclusion criteria

- Any diagnosis of T1DM

9.3 VARIABLES

9.3.1 Outcomes

For all three cohorts receiving empagliflozin, the following variables will be assessed:

9.3.1.1 Primary outcomes

- Previous occurrence (percentages) of
  - Typical CV comorbidities:
    - MI
    - Stroke
    - CAD
    - PAD
    - CHF (form (HFrEF/ HFpEF)

  - Other typical diabetes complications:
    - Neuropathy
    - Nephropathy / Renal function (eGFR, micro-/ macroalbuminuria)
    - Diabetic foot syndrome
    - Retinopathy (background and proliferative)
- Antidiabetic and cardiovascular co-medication (lipid-lowering agents, RAAS blockers, other antihypertensives, beta blockers, diuretics, antiplatelets and anticoagulants)

9.3.1.2 Secondary outcomes

- Age (<65; 65 – <75; 75 – 80 , >80)
- Gender
- Weight [kg]
- Height [cm]
- HbA1c [% or mmol/ mol], FPG (available in subgroup only)
- Duration of diabetes (time since diagnosis)
- Previous glucose-lowering treatment
- Dosage of empagliflozin (10mg vs 25mg) (available in subgroup only)
- Participation in Disease Management Programme (DMP) Type 2 Diabetes (from DPV registry)
- Hospitalizations (from DPV registry)

9.4 DATA SOURCES

Data will be provided by the largest German T2D patient registries DPV& DIVE covering more than 500,000 patients.

The aim of the DPV initiative is to improve treatment outcomes in individuals with diabetes through standardized documentation and objective comparison of quality indicators as well as through multi-centre outcome research. Up to date, there are more than 400 centres participating in the initiative predominantly from Germany and from Austria.

DIVE is a national initiative for quality management of diabetes care. The aim is to transfer the already existing initiatives and software systems which collect patient-related data to a national diabetes registry. The DIVE registry is one of the biggest, most updated diabetes registries in Germany and part of the current development of a national diabetes registry. It is part of the first and second registry conference held by German Federal Ministry of Health (BMG) and Robert-Koch Institute (RKI).

9.5 STUDY SIZE

There will be about 7,900 patients on Empagliflozin included in the analysis.

9.6 DATA MAIN MANAGEMENT

The medical team (
will be responsible for data management, including quality checking of the data. It is pointed out that no individual patient data will be used in this study and that data will only be presented in aggregated form.

9.7 DATA ANALYSIS

9.7.1 Main analysis

Variables will be assessed in half-yearly periods after index date (date of first prescription of empagliflozin), for total study population and separated by study cohort.

Anonymized data from the DIVE and the DPV registries will be combined; nonparametric descriptive analyses will be used. Group comparison will be based on Wilcoxon rank sum test (continuous variables) and X^2-test for binary/categorial values. Analysis will be implemented using SAS 9.4. Complete case analysis will be used.

Analysis will be done by an experienced biostatistician with detailed knowledge of the DIVE and the DPV registries. A second independent programmer will check the generated SAS code for inconsistencies. The medical team (
will evaluate the results from a clinical background to ensure plausibility.

Quality assurance and control will be the responsibility of the medical team (

9.7.2 Missing data

In general, imputation of missing data will not be applied. In addition to that, no “Last observation carried forward” (LOCF) approach will be applied.

Implausible values will be set to missing values, as no correcting of values is possible due to the nature of the dataset. The defined lower and upper bounds for an acceptable range of continuous study variables are listed in Table 1; note that these ranges are defined with regards to obvious documentation mistakes.

Table 1: Lower and upper bounds for continuous study variables

Variable	Unit	Acceptable range
Age	Years	40 to 110
Prescriptions of CV or AD drugs per patient year	Number	1 to 300

In case of missing data for specific variables, reporting category “not reported/not available” will be used.

9.8 QUALITY CONTROL

Analysis will be done by an experienced biostatistician with detailed knowledge of the DIVE and the DPV registries. A second independent programmer will check the generated SAS code for inconsistencies. The medical team (will evaluate the results from a clinical background to ensure plausibility/validity.

Study design and study conduct will be in line with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices such as Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines, Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines and similar rules.

9.9 LIMITATIONS OF THE RESEARCH METHODS

DPV & DIVE data are observational data; treatment, especially the use of Empagliflozin, is not randomized to the patients. This has to be kept in mind for the interpretation of the results. Also, a systematic difference (bias) between patients documented in the registry versus patients treated at facilities not participating in either of the registries cannot be entirely excluded.

9.10 SUBJECTS

All patients with T2DM from the DPV & DIVE registries receiving Empagliflozin will be included. The patients will be divided in three cohorts based on the time point of Empagliflozin treatment start to better identify the differences between these cohorts.

9.11 BIAS

DPV & DIVE data are observational data; treatment, especially the use of Empagliflozin, is not randomized to the patients. This has to be kept in mind for the interpretation of the results. Also, a systematic difference (bias) between patients documented in the registry versus patients treated at facilities not participating in either of the registries cannot be entirely excluded.

10. PROTECTION OF HUMAN SUBJECTS

In this study, only anonymized data will be analyzed.

10.1 PRINCIPLES OF GOOD RESEARCH PRACTICE

The guidelines of Good Clinical Practice developed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-GCP guidelines) will be followed whenever applicable.

10.2 PATIENT INFORMATION AND CONSENT

No informed consent is needed due to the exclusive use of anonymized data.

10.3 INDEPENDENT ETHICS COMMITTEE (IEC)

Not applicable for this analysis. However, the registries have been approved by the respective local ethics commission (for DIVE and for DPV).

10.4 CONFIDENTIALITY

BI as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in anonymized form only. The entire documentation made available to BI does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons.

Study findings stored on a computer will be stored in accordance with local data protection laws.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable based on secondary use of data without any potential that any employee of BI or agent working on behalf of BI will access individually identifiable patient data.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study shall be published.

Current guidelines and recommendation on good publication practice will be followed (e.g. GPP2 Guidelines [1], STROBE [2]).

REFERENCES

1. Graf C, Battisti WP, Bridges D, Bruce-Winkler V, Conaty JM, Ellison JM, Field EA, Gurr JA, Marx M-E, Patel M, Sanes-Miller C, Yarker YE: Research Methods & Reporting. Good publication practice for communicating company sponsored medical research: the GPP2 guidelines. BMJ (Clinical research ed.) 2009;339:b4330.
2. Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ (Clinical research ed.) 2007;335:806–808

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Documents listed in Annex 1 can be maintained separately from the study protocol. They should be clearly identifiable and provided on request. Write "None" if there is no document or list documents in a table as indicated below.

None.

ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) 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, 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). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Description of Treatment and Population Characteristics of Type 2 Diabetic Patients in Germany receiving Empagliflozin: A retrospective Real-World Evidence (RWE) study based on German registries DPV & DIVE

Study reference number: 1245-0198

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
1.1.3 Study progress report(s)	☐	☒	☐	–
1.1.4 Interim progress 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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	–
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	7

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, new or alternative 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. incidence rate, absolute risk)	☒	☐	☐	9.7

[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 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7
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)	☐	☐	☒	(11)

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.4
4.2 Is the planned study population defined in terms of:				9.2
4.2.1 Study time period?	☒	☐	☐	9.2
4.2.2 Age and sex?	☒	☐	☐	9.2
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☒	☐	☐	9.2
4.2.5 Duration of follow-up?	☒	☐	☐	9.2
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

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 categorizing 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 classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	–
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	–

Comments:

As this is a cross-sectional study, there will be no follow-up period and thus no exposure measurement. A patient will be included after the first available record of drug use.

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
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	9.8
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HrQoL, QALYs, DALYS, health care services utilization, burden of disease, disease management)	☐	☐	☒	9.3

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	–
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☐	☒	
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect 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:				
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?	☐	☐	☒	
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? (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)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	–

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.3 Are stratified analyses included?	☒	☐	☐	9.7.1
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.8
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2
10.6 Is sample size and/or statistical power estimated?	☐	☐	☒	

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?	☒	☐	☐	9.8

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?	☒	☐	☐	9.11
12.1.2 Information bias?	☒	☐	☐	9.9
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, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	–
13.3 Have data protection requirements been described?	☒	☐	☐	10

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?	☐	☐	☒	–

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: _____

Date: 8/12/2020

Signature: _____