Boehringer Ingelheim

Non-intervention study Protocol

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Title:	Clinical characteristics, anti-hyperglycaemic treatment pattern and target attainment of type 2 diabetes mellitus patients in older population with or without albuminuria in China: A nationwide cross-sectional study
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Research question and objectives:	To investigate the level of glucose control, current anti-hyperglycaemic and the anti-hypertension/Lipid Lowering/anti-platelet treatment patterns, occurrence of the hypoglycaemia, and other potential factors associated with the level of glucose control in older population of T2DM in China
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Author:	

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2. LIST OF ABBREVIATIONS

ACR	Albumin-to-Creatinine Ratio
ADA	American Diabetes Association
AE	Adverse Event
ADR	Adverse Drug Reaction
ANOVA	Analysis of Variance
BMI	Body Mass Index
CA	Competent Authority
CDS	Chinese Diabetes Society
CKD	Chronic Kidney Disease
CKD-EPI	CKD Epidemiology Collaboration
CI	Confidence Interval
CRA	Clinical Research Associate
CRF	Case Report Form
DPP-4	Dipeptidyl Peptidase-4
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GLP-1	Glucagon Like Peptide-1
GPP	Good Pharmacoepidemiology Practices
HbA_{1c}	Glycated Haemoglobin A1c
HDL-C	High Density Lipoprotein Cholesterol
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
MAH	Marketing Authorisation Holder
OAD	Oral Antidiabetic Drug
PPG	Postprandial Plasma Glucose
LDL-C	Low Density Lipoprotein Cholesterol
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SEAP	Statistical and Epidemiological Analysis Plan
SCr	Serum Creatinine
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
TCM	Trial Clinical Monitor
TG	Triglyceride
UA	Uric Acid
UAE	Urinary Albumin Excretion

3. RESPONSIBLE PARTIES

BI Contact Person:

Trial Clinical Monitor

Address:

Contact details:

Principal Investigator:

Address:

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Not applicable			
Name of active ingredient: Not applicable			
Protocol date: 29 Sep 2016	**Study number:** 1218.174	**Version/Revision:** 2.0	**Version/Revision date:** 20 Dec 2016
Title of study:	Clinical characteristics, anti-hyperglycaemic treatment pattern and target attainment of type 2 diabetes mellitus patients in older population with or without albuminuria in China: A nationwide cross-sectional study		
Rationale and background:	China has the largest number of people with diabetes in the world, with the majority of the patient population over 60 years old and living in urban areas. However no data are available specifically on the clinical characteristics of the older population with type 2 diabetes mellitus (T2DM) in China		
Research question and objectives:	To investigate the level of glucose control, current anti-hyperglycaemic and the anti-hypertension/Lipid Lowering/anti-platelet treatment patterns, occurrence of the hypoglycaemia, and other potential factors associated with the level of glucose control in older population of T2DM in China		
Study design:	This is a multi-centre, cross-sectional, non-interventional study		
Population:	Outpatients with T2DM aged 60 years or older in China		
Variables:	**Primary outcome** • Proportion of patients attaining blood glucose control target defined as HbA_{1c}<7% **Secondary outcomes** • Renal function level of patients • Treatment regimens for T2DM that patient are currently taking • Proportion of macro-vascular and micro-vascular diabetic complications • Proportion of Hypoglycaemic occurrence • Proportion of Hypoglycaemia leading to therapy change • Proportion of Anti-hypertension therapy usage • Proportion of Lipid Lowering therapy usage • Proportion of Anti-Platelet therapy usage • Treatment adherence to Chinese T2DM guideline 2013		
Data sources:	Examination report, outpatient medical Chart or other original medical record		
Study size:	1500 patients		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Not applicable			
Name of active ingredient: Not applicable			
Protocol date: 29 Sep 2016	**Study number:** 1218.174	**Version/Revision:** 2.0	**Version/Revision date:** 20 Dec 2016
Data analysis:	Descriptive statistics will be used to summarize the data in the study. The proportion of patients attaining HbA_{1c} <7% will further be tabulated by subgroups of demographic and clinical characteristics. A logistic regression model will be conducted to identify associations between overall blood glucose control and demographic and clinical characteristics.		
Milestones:	Start of data collection: 28 Feb 2017 End of data collection: 04 Sep 2017 Final report of study results: 31 Dec 2017		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
<1>	29 Nov2016	Front Page	Research question and objectives: To investigate the level of glucose control, current anti-hyperglycaemic and the anti-hypertension/Lipid Lowering/anti-platelet treatment patterns, occurrence of the hypoglycaemia, and other potential factors associated with the level of glucose control in older population of T2DM in China.	According to the conclusion of the investigator meeting. The Secondary Objectives have been amended.
<2>	29 Nov2016	4	Research question and objectives: To investigate the level of glucose control, current anti-hyperglycaemic and the anti-hypertension/Lipid Lowering/anti-platelet treatment patterns, occurrence of the hypoglycaemia, and other potential factors associated with the level of glucose control in older population of T2DM in China.	According to the conclusion of the investigator meeting. The Secondary Objectives have been amended.
<3>	29Nov2016	4	add 6 secondary outcomes • Proportion of Hypoglycaemic occurrence • Proportion of Hypoglycaemia leading to therapy change. • Proportion of Anti-hypertension therapy. • Proportion of Lipid Lowering therapy. • Proportion of Anti-Platelet therapy. • Treatment adherence to Chinese T2DM guideline 2013.	The Secondary Objectives have been amended. Variable has been changed accordingly.

<4>	29Nov2016	4	**Milestones:** Start of data collection: 28 Feb 2017 End of data collection: 04 Sep 2017 Final report of study results: 31 Dec 2017	According the protocol amendment, the milestone has been changed.
<5>	29Nov2016	6	**Milestones:** Start of data collection: 28 Feb 2017 End of data collection: 04 Sep 2017 Final report of study results: 31 Dec 2017	According the protocol amendment, the milestone has been changed.
<6>	29Nov2016	8	The secondary objectives are: • to investigate the anti-hyperglycaemic treatment patterns of the study population. • to investigate occurrence of the hypoglycaemia and hypoglycaemia leading to therapy change. • to investigate the anti-hypertension/Lipid Lowering/anti-platelet treatment patterns of the study population. • to investigate the clinical characteristics of the study population. • to investigate clinical characteristics, anti-hyperglycaemic treatment pattern and blood glucose control in older T2DM patients with albuminuria. • to investigate treatment adherence to Chinese T2DM guideline 2013	According to the conclusion of the investigator meeting. The Secondary Objectives have been amended.
<7>	29Nov2016	9.2.1	***Figure 1 – Study Flow of the cross-sectional study:*** Blood test:$HbA_{1c,}$ FPG, LDL-C, HDL-C, TC, TG, Scr, UA; Urine test: Albuminuria, Urine WBC	As the Second Objectives have been changed, the visit schedules have been changed accordingly.

<8>	29Nov2016	9.2.1	Inclusion Criteria #2: Outpatient with confirmed T2DM (According to Definition and Diagnosis Diabetes Mellitus :World Health Organization 1999 [R04-1142])	The diagnosis criteria changed according to the decision of investigator meeting.
<9>	29Nov2016	9.2.2	**Amend following information under Collect the following information** ○ **Personal health history** ▪ Diabetes Mellitus history ▪ Chronic Kidney Disease history ▪ Anti-Hypertension therapy history ▪ Lipid Lowering therapy history ▪ Anti-Platelet therapy history ▪ hypoglycaemic history ○ **Family health history (e.g., diabetes, hypertension, and Chronic kidney diseases)** ○ **Laboratory tests** ▪ HbA_{1c} ▪ Albuminuria ▪ Urine WBC ▪ Fasting plasma glucose (FPG), (examined within one month prior to the visit) ▪ Serum creatinine (SCr), uric acid (UA), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), total cholesterol (TC) (If examined within three months prior to the visit，record the result; if examined without three months prior to visit, record the date of last examination and re-examine by investigator's judgment.)	As the Second Objectives have been changed, the visit schedules have been changed accordingly

<10>	29Nov2016	9.3.2	***Add following secondary outcomes*** • Proportion of Hypoglycaemic occurrence • Proportion of Hypoglycaemia leading to therapy change. • Proportion of Anti-hypertension therapy. • Proportion of Lipid Lowering therapy. • Proportion of Anti-Platelet therapy. • Treatment adherence to Chinese T2DM guideline 2013	As the Second Objectives have been changed, some secondary outcomes have been added accordingly.
<11>	29Nov2016	9.3.3	PPG has been deleted.	As the Second Objectives have been changed, the visit schedules have been changed accordingly.
<12>	29Nov2016	9.7.1	The definition of FAS-Albuminuria has been updated, which takes urinary tract infection into account.	Based on investigators' consideration for determining micro-albuminuria diagnosis.
<13>	29Nov2016	9.7.3	The analyses for additional secondary endpoints have been added.	As the secondary endpoints have been updated, the corresponding analyses have been added.
<14>	29Nov2016	13	R04-1142 Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus. WHO/NCD/NCS/99.2. Geneva: World Health Organization, Department of Noncommunicable Disease Surveillance, , 1 - 59 (1999)	Diabetes diagnosis criteria Changed as the investigator meeting decision. So the reference document changed.

6. MILESTONES

Milestone	Planned Date
Start of data collection	28 Feb 2017
End of data collection	04 Sep 2017
Final report of study results:	31 Dec 2017

7. RATIONALE AND BACKGROUND

Type 2 diabetes mellitus (T2DM) is a progressive disease caused by insulin resistance and decreased pancreatic β-cell function. The management of diabetes is very important in preventing diabetes complications, as well as long-term health problems. Despite a wide range of available therapies, the epidemic continues. Worldwide, the International Diabetes Federation estimates the global prevalence of diabetes in the older population (60–79 years) to be 18.6%—more than 134.6 million people—accounting for over 35% of all cases of diabetes in adults [R14-1806]. In 2013, China reported the highest number of people with diabetes in the world at 113.9 million and a prevalence of 11.6%, with a majority of the diabetes population over the age of 60 years and living in urban areas [*R13-5351*]. The high prevalence of diabetes is a public health issue as it increases the risk of other age-related diseases [*R16-4557*].

Diabetes in older adults is multifaceted in aetiology, caused by a combination of genetic and environmental factors. The risk factors include family history, age, lifestyle, illnesses and medications, as well as age-related decline in body functions [*P16-10791*]. The clinical profile of older patients with T2DM and their response to glycaemic control regimens are often different from that in younger patients [*P13-17218*]. Older patients with T2DM are at greater risk of hypoglycaemia [*R16-4558*]and other complications such as stroke and diabetic nephropathy [*R16-4559*]. Albumin is an abundant serum protein, which is undetectable in urine under normal health conditions. Therefore, increased urinary albumin excretion is an early clinical manifestation of diabetic nephropathy. Albuminuria is also associated with cardiovascular disease in patients with or without diabetes. Moreover, (micro-) albuminuria is often present at diagnosis in patients with T2DM and may reflect both underlying cardiovascular disease and diabetic nephropathy. Albuminuria is hence an established biomarker that identifies patients with T2DM at increased risk for vascular complications. It is reported that 26.1% of T2DM patients in Shanghai have albuminuria [*R16-4560*]. Therefore, T2DM management in older patients should be driven by strategies for effective and safe treatment aiming to reduce risk of chronic vascular complications of T2DM, as well as for improving or maintaining functional status and quality of life. The high burden of T2DM treatment in older patients and the associated adverse outcomes result in high health-care costs to both public and private payers.

Due to the lack of a large-scale, nationwide and systematically conducted survey, there are very limited data available on the characteristics and treatment patterns of older patients with T2DM in China. Furthermore, no data are available from patients with both T2DM and albuminuria in China. This makes it difficult for clinicians to effectively make medical decisions for patients with a variety of risk factors and complications, for healthcare professionals to assess the unmet medical needs and for healthcare organizations to assess the quality of patient care.

This study will help to better understand the current anti-hyperglycaemic treatment patterns, level of glucose control and unmet medical needs in older population of T2DM patients with or without albuminuria in China. In addition, it may improve the public awareness on anti-hyperglycaemic treatment, and provide evidence and direction for improving clinical practice.

8. RESEARCH QUESTION AND OBJECTIVES

The present study is to be conducted in older (≥60 years old) outpatients with T2DM in hospitals of China.

The primary objective is:

- to assess the level of blood glucose, measured by the proportion of patients attaining the blood glucose control target defined as HbA_{1c}<7%.

The secondary objectives are:

- to investigate the anti-hyperglycaemic treatment patterns of the study population.
- to investigate occurrence of the hypoglycaemia and hypoglycaemia leading to therapy change.
- to investigate the anti-hypertension/Lipid Lowering/anti-platelet treatment patterns of the study population.
- to investigate treatment adherence(follow up duration) to Chinese T2DM guideline 2013
- to investigate the clinical characteristics of the study population.
- to investigate clinical characteristics, anti-hyperglycaemic treatment pattern and blood glucose control in older T2DM patients with albuminuria.

9. RESEARCH METHODS

9.1 STUDY DESIGN

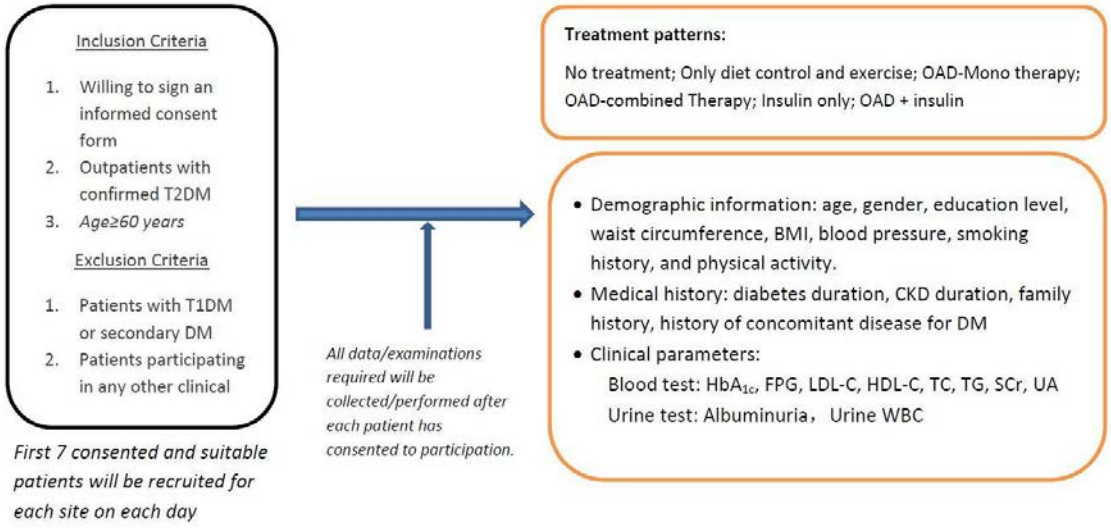
This is a multi-centre, cross-sectional, non-interventional study assessing blood glucose target attainment, anti-hyperglycaemic treatment pattern and the clinical characteristics in older outpatients with T2DM in hospitals of China. This study is designed to collect information of older T2DM patients in a real life setting. The primary outcome of this study is the proportion of patients attaining blood glucose control target defined as HbA_{1c}<7%. Demographic, clinical characteristics and treatment patterns of the study population will also be investigated. The primary method to be used is descriptive analysis.

9.2 SETTING

9.2.1 Study population

In this cross-sectional study, approximately 1500 patients will be recruited. Older outpatients with T2DM will be selected consecutively from departments of endocrinology in at least 30 hospitals of China.

Figure 1 – Study Flow of the cross-sectional study



Inclusion criteria

- Patient should fully know and understand the content of consent form, and the patient is willing and able to sign an informed consent form
- Outpatient with confirmed T2DM (According to Definition and Diagnosis Diabetes Mellitus :World Health Organization 1999[R04-1142])
- Age≥60 years

Exclusion criteria

- Patients with type 1 diabetes mellitus or secondary DM
- Patients who are participating in any other clinical study, including any questionnaire-based study, any interventional study (including diet/counselling

based intervention), or any clinical study in which any medications (including Chinese herbal medications) are administered

9.2.2 Visit schedule

Patients will be recruited into the study in the order of their clinical visits scheduled. First 7 consented and suitable patients will be recruited for each site on each day, or fewer if without enough patients. One study visit is planned for each patient. Clinical assessments will be performed as part of routine clinical practice. Some laboratory tests results prior to the study can be used as source data as specified below. All data required should be entered into the Electronic Data Capture (EDC) System only after each patient has consented to participation.

During the study visit, the following procedures will be performed:

- Signature of informed consent and recording of the date informed consent was given
- Determination of eligibility by checking the inclusion/exclusion criteria
- Collect the following information
    - Demographic information
    - Personal health history
        - Diabetes Mellitus history
        - Chronic Kidney Disease history
        - Anti-Hypertension therapy history
        - Lipid Lowering therapy history
        - Anti-Platelet therapy history
        - hypoglycaemic history
    - Family health history (e.g., diabetes, hypertension, and Chronic kidney diseases)
    - Lifestyle
    - Physical examination
        - body weight
        - height
        - waist circumference
    - Vital sign
        - blood pressure
        - heart rate
    - Laboratory tests
        - HbA_{1c}
        - Albuminuria
        - Urine WBC
        - Fasting plasma glucose (FPG), (examined within one month prior to the visit)
        - Serum creatinine (SCr), uric acid (UA), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), total cholesterol (TC) (If examined within three months prior to the visit，record the result; if examined without three

months prior to visit, record the date of last examination and re-examine by investigator's judgment.)

All of the laboratory tests will be performed by local laboratory and will be required on the same day of visit. The laboratory tests performed prior to the visit which can be used as source data are specified above.

Albuminuria can be measured in a random spot urine sample, a 24-h urine sample, or a timed urine sample. The results of albuminuria measurement will be categorized as normal, micro- and macro-albuminuria based on the definition in Table_1.

Table 1 Definition of Albuminuria

Urinary albumin excretion	Random spot urine	24-h urine	timed urine
	ACR (mg/g)	24h UAE (mg/24h)	UAE (µg/min)
Normal	<30	<30	<20
Micro-albuminuria	30-300	30-300	20-200
Macro-albuminuria	>300	>300	>200

ACR: albumin-to-creatinine ratio; UAE: urinary albumin excretion

A log of all patients included in the study (i.e. having given informed consent) will be maintained in the Investigator Site File (ISF) at the investigational site.

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment 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.
3. Violation of Good Clinical Practice (GCP), the study protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study.

The investigator / the study site will be reimbursed for reasonable expenses incurred in case of study termination (except in case of the third reason).

9.3 VARIABLES

9.3.1 Primary outcome

The primary outcome is the proportion of patients attaining blood glucose control target defined as HbA_{1c}<7%, according to 2015 American Diabetes Association (ADA) [R16-1532] and 2013 Chinese Diabetes Society (CDS) guidelines.

9.3.2 Secondary outcomes

Secondary outcomes are:

- Renal function of patients

- Estimated glomerular filtration rate (eGFR) evaluated by CKD Epidemiology Collaboration (CKD-EPI) equation expressed as:
  $GFR = 141 \times min(SCr/\kappa,1)^{\alpha} \times max(SCr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018\ [if\ female] \times 1.159\ [if\ black]$
  If SCr is in mg/dL, κ = 0.7 if female, κ = 0.9 if male
  If SCr is in μmol/L, κ = 61.9 if female, κ = 79.6 if male
  α = -0.329 if female
  α = -0.411 if male
  min = the minimum of Scr/κ or 1
  max = the maximum of Scr/κ or 1
- Albuminuria categorized as micro-albuminuria and macro-albuminuria according to the definition in Table 1.

- Treatment regimens for T2DM that the patients are currently taking, categorized as follow: (GLP-1 has been regard as OAD even though it's an injection treatment)
  - No treatment
  - Only diet control and exercise
  - Oral antidiabetic drug (OAD)-Mono therapy
    - Biguanide
    - α-glucosidase inhibitor
    - Sulfonylureas
    - Thiazolidinediones
    - Meglitindes
    - Dipeptidyl peptidase-4 (DPP-4) inhibitors
    - Sodium-glucose co-transporter (SGLT-2) inhibitors
    - Glucagon like peptide-1 (GLP-1) analogue
  - OAD-Combined therapy
    - Dual
    - Triple
  - Insulin only
  - OAD + Insulin
- Proportion of macro-vascular and micro-vascular diabetic complications:
  - Cardiovascular disease (i.e., coronary artery disease)
  - Cerebrovascular disease (i.e., ischemic stroke)
  - Peripheral vascular disease (i.e., diabetic foot)
  - Kidney disease (i.e., diabetes nephropathy)
  - Retinopathy
  - Neuropathy
- Proportion of Hypoglycaemic occurrence
- Proportion of Hypoglycaemia leading to therapy change
- Proportion of Anti-hypertension therapy usage
- Proportion of Lipid Lowering therapy usage
- Proportion of Anti-Platelet therapy usage
- Treatment adherence to Chinese T2DM guideline 2013
  - 0-3 month
  - 3-6 month
  - 6-12 month
  - >12 month

9.3.4 Safety events

All adverse drug reactions (ADRs) (serious and non-serious) and all AEs with fatal outcome (death) must be collected by the investigator from signing the informed consent onwards until the end of the study.

9.4 DATA SOURCES

Data will be newly collected from the patient by the investigator and recorded as source data at the site, i.e. the physician's records, and entered in the eCRF by the investigator or site staff.

9.5 STUDY SIZE

According to a recent study, the proportion of patients with diabetes in China who achieved a target blood glucose level of HbA_{1c} <7% was 39.8% in patients aged 60-69 years old and 38.9% in patients aged 70 years old or above [1]. It is assumed that the proportion of patients

attaining the target blood glucose level in the present study will be 39%. To ensure the accuracy of the estimate for proportion of patients with HbA_{1c} <7%, the length of a two-sided 95% confidence interval (CI) should not extend beyond 5%. A sample size of 1463 patients is required to achieve the expected accuracy. Assuming HbA_{1c} measurements are available for 97.5% of the enrolled patients, a total of 1500 patients will be recruited.

9.6 DATA MANAGEMENT

All data generated by the site personnel will be captured electronically at each study centre using eCRFs. Data from external sources (such as laboratory data) will be imported into the database.

In order to maintain source documentation of the outpatient record, Investigators will have complete access to the data for their patients, thus facilitating quality improvement initiatives and single-centre research. Each investigator will be required to first report all patient data on the outpatient medical chart or other acceptable original medical record.
Local Clinical Research Associate (CRA) will conduct routine on-site monitoring of the original data quality and review the study material and data.

Data queries generated from the database will be created on an ongoing basis; queries will be based on the data management system logic deck and database validation for adequacy and consistency.

9.7 DATA ANALYSIS

All the following analyses are exploratory in nature and the p-values provided by these analyses will only be nominal. Missing data will not be imputed. Details of all analyses will be provided in the statistical and epidemiological analysis plan (SEAP).

9.7.1 Analysis population

The statistical analysis will be based on the following populations.

Full Analysis Set (FAS)
The FAS includes all patients with an HbA_{1c} measurement.

FAS – Albuminuria
The FAS – Albuminuria dataset is a subset of patients of FAS, which includes T2DM patients with albuminuria (micro-albuminuria without urinary tract infection based on urine WBC result and macro- albuminuria).

9.7.2 Primary analyses

The proportion of patients attaining blood glucose control target of HbA_{1c}<7% will be summarized descriptively on FAS.

Detailed information about variable categorization will be specified in SEAP.

9.7.3 Secondary analyses

The analyses for following secondary outcomes will be performed on both FAS and FAS - Albuminuria as below:

- For renal function variables, eGFR and albuminuria, descriptive statistics will be calculated

- The treatment pattern for T2DM will be summarized descriptively with frequency and proportion,
- The proportion of the occurrence of hypoglycaemia and the proportion of hypoglycaemia leading to therapy change will be summarized descriptively.

Then for the other secondary outcomes, the analyses will only be performed on FAS:

- The proportion of each macro vascular and micro-vascular diabetic complications will be calculated.
- The proportion of using anti-hypertension therapy, lipid –lowering therapy, and anti-platelet therapy will be calculated respectively.
- The treatment adherence will be summarized using the proportion of each follow-up duration category.

9.8 QUALITY CONTROL

Once the eCRF clinical data have been submitted to the central server at the independent data centre, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate staff at the study site will answer queries sent to the investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

All the laboratory tests will be conducted in the qualified local clinical laboratory.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Some limitations are unavoidable given the design of this cross-sectional study; however, this study will generate substantial new knowledge that applies to the real-world clinical setting.

Secondly, due to cross-sectional nature of our study, there may be potential reverse causation bias. Therefore the data need to be interpreted with cautions.

A further limitation of the study is that albuminuria is estimated based on a single measurement. Hence, no data on the reproducibility of the urinary albumin excretion measurements will be available. Moreover, the data regarding HbA_{1c} will have to be interpreted with caution as blood measurement are not performed at central laboratory.

9.10 OTHER ASPECTS

9.10.1 Study compliance, data protection and study result

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP and relevant Boehringer Ingelheim Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation 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 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of China. 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 authorised monitors (Local Clinical Monitor /CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

9.10.3 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by IRBs/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.

9.10.4 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via remote data capture.

9.10.4.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents include laboratory test report outpatient medical chart, e-outpatient medical chart and other original medical record. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For eCRFs, all data must be derived from source documents.

9.10.4.2 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, IRB / 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 (e.g. Food and Drug Administration [FDA]). The 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 9.10.4.1.

9.10.4.3 Statement of confidentiality

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. 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 IRB / IEC and the regulatory authorities.

10. PROTECTION OF HUMAN SUBJECTS

The procedures set out in this study protocol are designed to ensure that the sponsor and investigator abide by the principles of the International Society for Good Pharmacoepidemiology Practices (GPP) guidelines [*R09-0182*]. The study also will be carried out in keeping with local legal requirements.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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 AE can therefore be any unfavourable 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 reaction
An adverse reaction 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 AE is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event (SAE) 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 judgment 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 jeopardise 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 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 REACTION AND FATAL ADVERSE EVENT REPORTING

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

Collection of AEs
The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorisation. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the (e)CRF from signing the informed consent onwards until the end of the study for any BI drug approved for the indication of T2DM

- all ADRs (serious and non-serious),
- all AEs with fatal outcome (death).

All ADRs, including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

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 study. Once a subject has been enrolled into the study, after having taken any BI drug approved for the indication of T2DM, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

Expedited Reporting of AEs and Drug Exposure during Pregnancy (DEDP)

The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study:

Type of Report	Timeline
All **Serious ADRs (SADRs)** associated with the any BI drug approved for the indication of T2DM	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to any BI drug approved for the indication of T2DM	immediately within 24 hours

All **non-serious ADRs** associated with the any BI drug approved for the indication of T2DM	7 calendar days
All **pregnancy monitoring** forms concerning DEDP to any BI drug approved for the indication T2DM	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate (e)CRF pages and the NIS AE form.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than the BI drug approved for the indication of T2DM according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the marketing authorisation holder (MAH) according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

By signing the study protocol, the investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the investigator's name, address, qualifications and extent of involvement.
An investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the sponsor in advance.

The results obtained within the study are the exclusive property of the sponsor. After validation, the results will be shared with the investigators of the study. The sponsor recognizes the ethical obligation to disseminate findings of potential scientific or public health importance (e.g., results pertaining to the safety of a marketed medication). Study results will be included in abstracts sent to scientific congresses and articles sent to scientific reviews. Specific plans for disseminating and communicating the study results will be produced when the results are available.

Results of this non-interventional study will be disclosed on encepp.eu and clinicaltrials.gov and a study specific publication plan will be developed to describe planned publications.

13. REFERENCES

13.1 PUBLISHED REFERENCES

R14-1806 International Diabetes Federation. IDF Diabetes Atlas. 6th ed. Brussels, Belgium: International Diabetes Federation; 2013.

R13-5351 Xu Y, Wang LM, He J, Bi YF, Li M, Wang TG, et al. Prevalence and control of diabetes in Chinese adults JAMA. 2013; 310: 948-959

R16-4557 Ji LN, Lu JM, Guo XH, Yang WY, Weng JP, Jia WP, et al. Glycemic control among patients in China with type 2 diabetes mellitus receiving oral drugs or injectables. BMC Public Health. 2013; 13: 602

P16-10791 Dardano A, Penno G, Del Prato S, Miccoli R. Optimal therapy of type 2 diabetes: a controversial challenge. Aging (Albany NY). 2014; 6: 187-206.

P13-17218 Kountz D. The dipeptidyl peptidase (DPP)-4 inhibitors for type 2 diabetes mellitus in challenging patient groups. Adv Ther. 2013; 30: 1067-1085

R16-4558 Bramlage P, Gitt AK, Binz C, Krekler M, Deeg E, Tschope D. Oral antidiabetic treatment in type-2 diabetes in the elderly: balancing the need for glucose control and the risk of hypoglycemia. Cardiovasc Diabetol. 2012; 11: 122

R16-4559 Huang H, Li H, Zheng FP, Lu WN, Dong XH, Ruan y. Clinical features and risk factors of renal damage in elderly and non-elderly patients with type 2 diabetes mellitus. Zhonghua Yi Xue Za Zhi. 2010; 90:967-971

R16-4560 Lu B, Song XY, Dong XH, Yang YH, Zhang ZY, Wen J, etc. High prevalence of chronic kidney disease in population-based patients diagnosed with type 2 diabetes in downtown Shanghai. J Diabetes Complications. 2008; 22: 96-103

R16-1532 Standards of medical care in diabetes--2015: summary of revisions. Diabetes Care. 2015;38 Suppl:S4.

R04-1142 Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus. WHO/NCD/NCS/99.2. Geneva: WorldHealth Organization, Department of Noncommunicable Disease Surveillance, , 1 - 59 (1999)

R09-0182 International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf. 2008; 17: 200-208.

13.2 UNPUBLISHED REFERENCES

None

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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:
Clinical characteristics, anti-hyperglycaemic treatment pattern and target attainment of type 2 diabetes mellitus patients in older population with or without albuminuria in China: A nationwide cross-sectional study

Study reference number:
1218.174

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]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	4

[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.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
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.	☒	☐	☐	

Comments:

Total recruitment period is 7 months, no progress report was set in this NIS. And this study is conducted in China Mainland only, not in Europe.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
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)	☒	☐	☐	8,9.2.1
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

This is a cross-sectional non-interventional study based on newly collected data. All the analyses will be descriptive, and no hypothesis testing was set.

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)	☒	☐	☐	7
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)	☒	☐	☐	7

[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
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?	☒	☐	☐	9.2.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	
4.2.2 Age and sex?	☒	☐	☐	9.2.1
4.2.3 Country of origin?	☒	☐	☐	
4.2.4 Disease/indication?	☒	☐	☐	
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 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:

This is a cross-sectional non-interventional study based on newly collected data. All the analyses will be descriptive. We will not study the effects of drug exposure.

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)	☒	☐	☐	9.3
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

This Non-interventional study is a New Data Collection study of the T2DM of Old patient. There is not any Health Technology Assessment collected and the study outcomes are not relevant for Health Technology Assessment.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7
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)	☒	☐	☐	9.2.2
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.2.2
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

This is a cross-sectional non-interventional study based on newly collected data. All the analyses will be descriptive. Therefore, there will not be confounding by indication in the study. All the data will be newly collected so we are not planning to validate the study covariates.

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:

This is a cross-sectional non-interventional study based on newly collected data. All the analyses will be descriptive. Therefore, we will not examine effect modifiers.

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:

This is a non-interventional study based on newly collected data. We will not use existing data sources.

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
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

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)	☒	☐	☐	9.8
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:

This study is non-interventional study for real word data. The study result will reflect the real world situation, so no independent review for study result was conducted.

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?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	
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)	☒	☐	☐	9.9

Comments:

This Non-interventional Study is a cross-section and descriptive analysis study.

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	9.10
13.3 Have data protection requirements been described?	☒	☐	☐	9.10

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?	☒	☐	☐	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?	☐	☒	☐	

Comments:

There will be an independent publication plan.

Name of the main author of the protocol: _____

Date: dd/Month/year 10 May 2016

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

None

APPROVAL / SIGNATURE PAGE

Document Number: c14196017 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-2.0

Title: Clinical characteristics, anti-hyperglycaemic treatment pattern and target attainment of type 2 diabetes mellitus patients in older population with or without albuminuria in China: A nationwide cross-sectional study

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Trial Clinical Monitor		21 Dec 2016 03:46 CET
Approval-Biostatistics		21 Dec 2016 09:05 CET
Approval-Team Member Medical Affairs		22 Dec 2016 12:20 CET
Approval-Pharmacovigilance		31 Dec 2016 12:41 CET
Approval-Therapeutic Area		05 Jan 2017 03:51 CET
Approval-Medical		05 Jan 2017 03:59 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed