

Statistical and Epidemiological Analysis Plan

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1. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
ADR	Adverse Drug Reaction
ANOVA	Analysis of Variance
BMI	Body Mass Index
CRF	Case report form
CKD	Chronic Kidney Disease
DBLM	Database lock meeting
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
HbA1c	Glycated Haemoglobin A1c
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
NSP	Non-interventional Study Protocol
PT	Preferred term
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
RPM	Report planning meeting
SD	Standard deviation
SEAP	Statistical and Epidemiological Analysis Plan
SOC	System organ class
T2DM	Type 2 Diabetes Mellitus

2. INTRODUCTION

As per International Conference on Harmonisation (ICH) guideline E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Statistical and Epidemiological Analysis Plan (SEAP) assumes familiarity with the Non-interventional Study Protocol (NSP). In particular, the SEAP is based on the planned analysis specification as written in NSP Section 9 “Research Methods”. Therefore, SEAP readers may consult the NSP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size.

3. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Three additional further outcomes (Hyperuricemia, Hypercholesteremia and Hypertriglyceridemia) are identified from the lab test results, and collected on eCRF, due to the consideration that missing values of lab tests results are inevitable and those diagnosis/diseases are more interested outcomes. In the analyses, they will be considered as part of medical history.

The analysis population Full Analysis Set (FAS), which includes all patients with an HbA1c measurement, is modified to: Full Analysis Set – Eligible (FAS – E), which includes all eligible patients regarding to inclusion and exclusion criteria with an HbA1c measurement.

Two additional sets, FAS – E with Hypoglycaemia and FAS – E with Hypoglycaemia leading to therapy change, are created for the analysis of treatment pattern.

5. OUTCOMES

5.1 MAIN OUTCOMES

The primary outcome is the proportion of patients attaining blood glucose control target of HbA1c<7%.

NSP 9.3.2 defines the following parameters as 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

5.3 OTHER VARIABLES

All adverse drug reactions (ADRs) (serious and non-serious) and all AEs with fatal outcome (death) for any BI drug approved for the indication of T2DM must be collected by the investigator from signing the informed consent onwards until the end of the study.

6. GENERAL ANALYSIS DEFINITIONS

6.1 EXPOSURE

Not applicable.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Not applicable.

6.3 PATIENT SETS ANALYSED

- Full Analysis Set – Eligible (FAS – E):
The FAS – E includes all eligible patients regarding to inclusion and exclusion criteria with an HbA1c measurement.
- FAS – Albuminuria:
The FAS – Albuminuria dataset is a subset of patients of FAS – E, which includes T2DM patients with albuminuria (micro-albuminuria without urinary tract infection based on urine WBC result and macro-albuminuria).
- FAS – E with Hypoglycaemia:
The FAS – E with Hypoglycaemia dataset is a subset of patients of FAS – E, which includes T2DM patients with Hypoglycaemia as medical history.
- FAS – E with Hypoglycaemia leading to therapy change:
The FAS – E with Hypoglycaemia leading to therapy change dataset is a subset of patients of FAS – E, which includes T2DM patients with Hypoglycaemia leading to therapy change as medical history.

6.5 HANDLING OF MISSING DATA AND OUTLIERS

If patients have missing values for an outcome, those patients will be excluded for that outcome's analysis. No imputation approach will be applied. Any removal from the analysis will be documented.

6.6 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Not applicable.

7. PLANNED ANALYSIS

The following standard descriptive statistical parameters will be displayed in summary tables of all continuous variables:

N	number of non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Median	median
Max	maximum

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all subjects in the respective subject set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

For logistic regression model, adjusted odds ratio with 95% confidence interval, and p-value will be provided for the factors involved.

All data processing, summarization and analyses will be performed using Version 9.2 (or later) of the SAS statistical software package (Windows OS).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Summary statistics will be provided for the following demographics and baseline characteristics: Age, Age category, Gender, Education level, Smoking history, Physical activity, Body height, Body weight, BMI, Waist circumference, Heart rate, Systolic blood pressure, Diastolic blood pressure, Medical history, Treatment adherence to Chinese T2DM guideline 2013, Family history, Follow-up duration and Albuminuria. Descriptive statistics will be presented for continuous variables. Frequency and proportion will be used to summarize categorical variables. These will be based on both FAS – E and FAS – Albuminuria.

By-subject listings will be produced accordingly.

7.2 CONCOMITANT DISEASES AND MEDICATION

The treatment pattern for T2DM will be summarized descriptively with frequency and proportion on FAS – E, FAS – E with Hypoglycaemia, FAS – E with Hypoglycaemia leading to therapy change, and FAS – Albuminuria.

The proportion of using anti-hypertension therapy, lipid-lowering therapy, and antiplatelet therapy will be calculated respectively. The concomitant medications will be coded according to the most recent version of the World Health Organization – Drug Dictionary

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Enhanced/Herbal Dictionary (WHO DDE/HD), and summarized by ATC level 4 and preferred term.

The proportion of each macro-vascular and micro-vascular diabetic complication will be summarized respectively.

By-subject listings will be produced accordingly.

7.3 METHODS ADDRESSING BIAS

Not applicable.

7.4 METHODS ADDRESSING CONFOUNDING / EFFECT MEASURE MODIFICATION

Identified confounders will be included in the logistic regression model to adjust the main outcome result. However unidentified confounders cannot be controlled for using statistical analyses.

7.6 MAIN ANALYSES

The blood glucose control proportion (HbA1c<7%) will be tabulated on FAS – E.

The analyses for parameters below will be performed on both FAS – E and FAS – Albuminuria:

- Renal function variables (eGFR, albuminuria, and CKD staging) will be summarized
- The proportion of the occurrence of hypoglycaemia and the proportion of hypoglycaemia leading to therapy change will be summarized descriptively.

7.8 EXPOSURE TIME

Not applicable.

7.9 SAFETY ANALYSIS

7.9.1 Adverse events

AEs will be summarized on both FAS – E and FAS – Albuminuria.

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

An overall summary of adverse events will be presented.

Adverse events will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). The frequency of subjects with adverse events will be summarized by treatment, system organ class and preferred term. The system organ classes will be sorted in alphabet order, preferred terms will be sorted by frequency (within system organ class).

7.9.2 Laboratory data

Refer to section 7.7 of this document.

7.9.3 Vital signs

Refer to section 7.1 of this document.

7.9.4 ECG

Not applicable.

7.9.5 Others

The subject disposition summaries will be provided. The number of enrolled subjects and of entered subjects will be included. The completion status of data collection and the reason for discontinuation will be summarized.

By-subject listing will be provided.

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8. REFERENCES

- 1 *001-MCS-50-413_RD-01*: "Protocol Violation Handling Definitions", current version, IDEA for CON.

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10. HISTORY TABLE

Version No.	Date (dd Mmm yyyy)	Author	Sections changed	Brief description of change
1.0	09Feb2018		NA	Final version before database lock.