Title: Title: Post Marketing Surveillance Protocol for Nesina® Tablet

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Statistical Analysis Plan

For the PMS Protocol No. Alogliptin-6001

Post Marketing Surveillance Protocol for Nesina® Tablet 「Single or Combination Use in Type 2 Diabetic Patients」

Sponsor	Takeda Pharmaceuticals Korea Co., Ltd.
Protocol Version/Date	Ver4.1/ 22MAY2019
CRF Version/Date	Ver3.0/ 18JUL2017
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Change Log

Version No.	Name	Date	Reason for Revision
V1.0	PPD	17DEC2014	NA
V2.0		26FEB2018	Protocol revision (Ver. 3.2), Including the AE analysis for long-term use subjects
V2.1		20NOV2018	Including the AE analysis by onset period
V2.2		12JUN2019	Including the 95% confidence interval for SOC and PT of AE analysis, Including table by each enrollment criterion of AE analysis Including the 95% confidence interval for effective of Effective analysis, Including the frequency and proportion for ineffective of Effective analysis

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Abbreviation

ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BS	Biostatistician
CRF	Case Report Form
DSM	Data management & Statistical Analysis Manager
PMS	Post Marketing Surveillance
PT	Preferred Term
PTM	PMS Team Manager
RAM	Regulatory Affairs Manager
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
WHOART	WHO Adverse Drug Reaction Terminology

1. Objective

This Statistical Analysis Plan is a guideline prepared so that the final results, conclusion and execution of PMS, as well as all important details on the presented analysis are evaluated in a reliable manner by minimizing the bias and maximizing the precision of Nesina Tab PMS (Protocol No. Alogliptin-6001, Version 3.2).

2. Purpose of PMS study

To examine the following conditions that may appear at single or combined administration of the study drug according to the Nesina Tab approved label.

(1) Serious Adverse Event(SAE)・Adverse Drug Reaction(SADR)

1) Causing death or life-threatening
2) Requiring hospitalization or extension of hospitalization
3) Causing continuous or significant disability or dysfunction
4) Causing congenital malformation or abnormality
5) Other medically significant event*

*This section included the [Takeda Medically Important Adverse Event List].

(2) Unexpected AE・ADR not reflected upon the Precautions

(3) ADRs already known

(4) Non-serious Adverse Drug Reaction

(5) Other safety・efficacy related information

3. PMS Design

3.1. Expected PMS period

1) Re-examination period: 31 May 2013 – 30 May 2019 (6 years)

2) Re-examination application period: 31 May 2019 – 30 Aug 2019

3.2. Subject

Patients will be enrolled by a continuous registration method. Patients who agree to participate in this study will sign the Informed Consent Form. Discontinuation of treatment will be determined by a patient's willingness to continue treatment and the investigator's discretion. The reason for discontinued treatment will be documented. Patients can also withdraw their consent to participate in this study.

3.3. Planned number of patients

In accordance with the guidelines provided by the MFDS(Ministry of Food and Drug Safety), at least 3,000 patients will be enrolled. The objective of the re-examination system in Korea is to reconfirm the clinical usefulness of the product through collecting, reviewing, identifying, and verifying the safety and efficacy information about the product in general practice for 3,000 patients during 6 years following Korean regulations.

4. In/Exclusion Criteria

4.1. Inclusion Criteria

The study should enroll adults aged 19 years or older who are diagnosed with T2DM(Type 2 Diabetes Mellitus) who correspond to one of the followings and are initiating treatment with Nesina Tab for the first time as an adjunct to diet and exercise to improve glycemic control;

1) Monotherapy Nesina
2) Combination therapy with the surveillance drug (Nesina) in case of inadequate glycemic control with metformin or sulfonylurea or thiazolidinedione single therapy
3) Combination therapy with the surveillance drug (Nesina) in case of inadequate glycemic control with thiazolidinedione and metformin combination therapy
4) Combination therapy with the surveillance drug (Nesina) in case of inadequate glycemic control with insulin(single therapy or combination with metformin) therapy
5) Combination therapy with metformin in patients who have no prior history of antidiabetic medication and may not achieve adequate glycemic control with monotherapy Nesina

4.2. Exclusion Criteria

(1) Patients treated with Nesina Tab outside of the locally approved label in Korea

(2) Patients with contraindication for the use of Nesina (as described in Korean produce label)

5. Statistical Analysis Population

The number of safety evaluation subjects and efficacy evaluation subjects will be presented as below;

5.1. Safety Set

The Safety Set (safety evaluation subjects) include patients who have been administered the study drug at least once and completed follow-up.

5.2. Efficacy Set

The Efficacy Set (efficacy evaluation subjects) include patients who completed study drug treatment for the period exceeding 13 weeks, and conducted efficacy evaluation according to the investigator's clinical judgment.

5.3. Special Population Set

Elderly (65 years or older), pregnant women, patients with renal impairment, and patients with hepatic impairment shall be categorized into specific subjects, and once data of such subjects are collected, their safety and efficacy shall be analyzed additionally.

5.4. Long-term use Set

In this PMS, all patients taking the drug for more than 26 weeks (total administration period(days)* ≥ 26x7) shall be categorized into the Long-term use Set (long-term use subjects), and their safety and efficacy shall be analyzed. Among subjects of safety evaluation, at least 50% of long-term use subjects shall be secured.

While, short-term users are defined as the subjects who were administered the study drug for under 26 weeks (Administration end date - Administration start date +1<26x7).

*Total administration period (Days): Administration end date - Administration start date +1

5.5. Subjects Excluded from Safety Analysis

If patients excluded from safety analysis are collected, such as in off-label use cases, any AE occurring

during the PMS period shall be additionally checked or separately analyzed as the per needed.

6. Changes from the Protocol

There is no change in this SAP, compared to the corresponding protocol.

7. Handlings for Valuation Variables

7.1. Transformation for the laboratory test results

If results of the laboratory test contains inequality (e.g. >) or corresponding expressions, then the result values deleted the inequality would be used in the analysis.

Before	After
<2.0	2.0
Over 2.0	2.0

7.2. Handling for the "date" formatted variables

If the "date" formatted variables contain "UK (missing)", then it would be transformed as the followings;

Case	Imputation
If 'Day' variable is missing (YYYY-MM-*UK*)	The UK shall be replaced with '30' ('28' if it is February)
If 'Month' variable is missing (YYYY-*UK*-DD)	The UK shall be replaced with '12 (DEC)'
If both 'Day' and 'Month' variables are missing (YYYY-*UK*-*UK*)	The UK-UK shall be replaced with '12 (DEC)-30'
If 'Year' variable is missing	Entire date variable shall be considered as missing

7.3. Missing Imputation

In this PMS, all variables (except for the 'Date' variable) shall not be imputed. If there is a missing variable, it would be excluded in the corresponding analysis.

8. Definitions for Demographic information and Medical history variables

8.1. Demographic information

Gender, age* (year, and categorized), geriatric (<65 years old, and ≥65 years old), pregnancy status (yes, no, and not applicable), type of hospital visit (inpatient, inpatient↔outpatient, outpatient), height (cm), body weight (kg), drinking history (yes, no, and unknown), smoking history (never smoked before, current smoker, smoked in the past-but does not smoke not, and unknown).

*Age: Years of "Administration start date – Day of birth"
*Categorized Age: '≥19 years to ≤29 years/ ≥30 years to ≤39 years/ ≥40 years to ≤49 years/ ≥50 years to ≤59 years/ ≥60 years to ≤69 years/ ≥70 years to ≤79 years/and ≥80 years'

8.2. History of type 2 diabetes mellitus

8.2.1. Duration of type diabetes mellitus

Duration of type 2 diabetes mellitus* (continuous: year), categorized duration of type 2 diabetes mellitus (<1 year, ≥1 to <5 years, ≥5 to <10 years, and ≥10 years),

*Duration of type 2 diabetes mellitus = (Nesina Tab administration start date - Date of type 2 diabetes diagnosis + 1)/365.25

8.2.1. HbA1c and fasting blood glucose prior to treatment with the surveillance drug

Pre-treatment HbA1c (%) & fasting blood glucose (mg/dl), and categorized HbA1c (<7.00, ≥7.00 to <8.00, and ≥8.00) & categorized fasting blood glucose (<130.00, ≥130.00 to <200.00, and ≥200.00).

8.3. Concomitant disease

Existence of concomitant disease (yes or no), renal impairment (yes or no, and classification of severity (mild, moderate, and severe)), diabetic complications (yes or no, and classification: diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy), lifestyle related diseases (yes or no, and classification: hypertension, lipodystrophy, and hyperuricemia), liver diseases (yes or no, and classification: fatty liver, alcoholic hepatitis, chronic hepatitis, and liver cirrhosis), kidney diseases (yes or no, classification: nephrotic syndrome, glomerulonephritis, and chronic renal failure), gastro-intestinal diseases (yes or no, classification: pancreatic cancer, pancreatitis, and gallbladder disease), cardiac cerebrovascular (yes or no, classification: heart failure, myocardial infarction, angina pectoris, and cerebral infarction (including sequela of cerebral infarction)), allergic diseases (yes or no, classification: bronchial asthma, pollenosis, allergic rhinitis, and allergic dermatitis), malignant tumor (yes or no, classification: stomach cancer, lung cancer, and colorectal cancer), and others**(yes or no).

In addition, for the analysis of detailed concomitant disease, all concomitant disease shall be coed as SOC (System Organ Class) and PT (Preferred Term) or IT(Included Term) using WHO-ART (World Health Organization Adverse Reaction Terminology dictionary, the latest version), and total concomitant diseases, "renal impairment", "liver diseases" and "others" diseases shall be analyzed additionally by the SOC and PT or IT.

* If a concomitant disease is reported as "others" in CRF because it has no detailed classification, then this disease shall be re-classified as "yes" of the corresponding disease, not "yes" of "others".

In other words, a certain concomitant disease (included in the "Liver disease", however not be affiliated with "Fatty liver", "Alcoholic hepatitis", "Chronic hepatitis", and "Liver cirrhosis") shall be analyzed as a case of "Liver disease", although it is reported as "others" disease in CRF.

8.4. History of previous use of GLP-1 Agonist or DPP-4 Inhibitor

Using history of GLP-1 Agonist or DPP-4 Inhibitor (yes or no).

8.5. Status of surveillance drug use

Administered dose (6.25mg/ 12.5mg/ 25mg), total administration period (week), categorized total administration period* ($\leq$13 weeks, >13 weeks to <26 weeks, and $\geq$26 weeks), and status of long term user (yes or no)**.

*Total administration period (week) = Total administration period (Days) / 7

**Long term user: The patients taking the drug for more than 26 weeks ($\geq$26 weeks or $\geq$26x7 days)

8.6. Compliance status

Medication compliance with the surveillance drug (status of treatment compliance; Taking properly a directed, Taking mostly as directed, Not taking properly as directed, and Little taking as directed), and status of compliance with diet and exercise therapy (Conducting properly as directed, Conducting mostly as directed, Not conducting properly as directed, Little conducting as directed, and Not conducting or compliance status unknown). Compliance status values shall be selected at 13 weeks and 26 weeks at the administration period, respectively.

8.7. Past/Concomitant medications

Status of past/concomitant medications (yes or no), and the details of past/concomitant medications. All past/concomitant medications shall be coded as Level 1 and Level 5 of the WHO ATC Classification (the latest version), the details of past/concomitant medications shall be analyzed using the WHO ATC Classification.

8.8. Abnormal change in Laboratory data

Status of abnormal change, and relationship with Adverse Event (AE) in laboratory data (yes or no, both). The corresponding laboratory test levels pre or post treatment.

8.9. Status of completion and discontinuation

Status of completion and discontinuation (yes or no), and classification of discontinuation (Patient withdraws his/her consent, Lost to follow-up, Adverse Event, Insufficient efficacy, and Others).

9. Definitions for Safety Analysis

In Safety analyses, all AEs will be categorized into SOC (System Organ Class) and PT (Preferred Term) or IT(Included Term) of WHO ART (the latest version).

9.1. Adverse Events

Number of subjects, number of events, and incidence proportion (=the number of subjects with AE (or ADR, SAE, and etc.), during the whole study period/ total number of subjects included in Safety Set) shall be calculated by the following AE classifications.

(1) Adverse Event (AE): Adverse Event (AE) means any and all undesirable or unintended signs (including abnormal clinical laboratory values), symptoms, or diseases that are incurred when the drug is administered, and is not related to causal relationship with the drug.

(2) Adverse Drug Reaction (ADR): Adverse Drug Reaction (ADR) means a harmful and unintended reaction resulting from usual administration and use of the drug, whose causal relationship with the drug cannot be excluded, and if causal relationship with the drug is unknown among AEs reported spontaneously, it is regarded as ADR. Therefore, it shall be classified as ADR if the causality with study drug (see 9.2. (3) Classification by causal relationship to the surveillance drug) is [Certain], [Probably], [Possible], [Unclassified] and [Unassessible], but not [Unlikely].

(3) Serious Adverse Event (SAE) / Serious Adverse Drug Reaction (SADR): AEs or ADRs refers to any of the following conditions;

1)	Causing death or life-threatening
2)	Requiring hospitalization or extension of hospitalization
3)	Causing continuous or significant disability or dysfunction

4)	Causing congenital malformation or abnormality
5)	Other medically significant event

(4) Serious Adverse Drug Reaction (SADR): ADRs belonging to SAE.

(5) Unexpected AE: Unexpected AE means an AE with difference in the nature or severity, specificity, or the outcome, compared to the product licensure/notification of the drug.

(6) Unexpected ADR: ADRs belonging to Unexpected AE.

9.2. Classification of AEs by detailed items

(1) Classification by onset period

AEs shall be classified by five onset periods:

(Onset period: AE onset date - Nesina Tab administration start date +1; unit: day)

1) Nesina Tab administration start date ~ 91 days (13 weeks)

2) 92 days ~ 182 days (26 weeks)

3) 183 days ~ 273 days (39 weeks)

4) 274 days ~ 364 days (52 weeks)

5) Over 365 days (>52 weeks)

(2) Classification by enrollment criterion

AEs shall be classified by five enrollment criterion:

1) Monotherapy Nesina

2) Combination therapy with the surveillance drug (Nesina) in case of inadequate glycemic control with metformin or sulfonylurea or thiazolidinedione single therapy

3) Combination therapy with the surveillance drug (Nesina) in case of inadequate glycemic control with thiazolidinedione and metformin combination therapy

4) Combination therapy with the surveillance drug (Nesina) in case of inadequate glycemic control with insulin(single therapy or combination with metformin) therapy

5) Combination therapy with metformin in patients who have no prior history of antidiabetic medication and may not achieve adequate glycemic control with monotherapy Nesina

In this analysis, date data including "UK" shall not be input. If it is uncertain* to identify the "UK" data belongs to any of the five onset periods, the data will be excluded from the analysis*.

*Certain/Uncertain

Certain: If both the longest and shortest onset period that can be assumed are in one certain period.
Uncertain: Not certain case.

(Example)
Case1) Administration start date: 2015-05-UK & AE onset date: 2015-06-UK -> Period 1) (13 weeks)
∵ Longest period: 2015-05-01 ~ 2015-06-30 (61 days) < 91 days
& shortest period: 2015-05-31~2015-06-01 (2 days) < 91 days
Case2) Administration start date: 2015-05-UK & AE onset date: 2015-08-UK -> Exclude
∵ Longest period: 2015-05-01 ~ 2015-08-31 (123 days) > 91 days, <182 days
& shortest period: 2015-05-31~2015-08-01 (63 days) < 91 days

Number of subjects, number of events, and incidence proportion* (=the number of subjects with AE within each administration period/ total number of subjects within each administration period) of each period-specific AE shall be calculated.

*Incidence proportion of each period-specific AE (e.g. Period 1) Administration start date ~ 91 days)
Incidence proportion (%) in period 1) = Number of subjects with AE occurrence within Period 1) / Total number of subjects with Nesina tab administration within Period 1).

Further, all the onset period-specific AEs will be categorized into SOC (System Organ Class) and PT (Preferred Term) or IT(Included Term) of WHO ART (the latest version). And, the same analysis shall be performed for ADR, UAE, and UADR.

(2) Classification by severity
AEs shall be analyzed by severity as 'mild/ moderate/ severe'.

Number of events, and incidence proportion of events (=the corresponding number of events during the whole study period / total number of events during the whole study period) shall be calculated.

(3) Classification by outcome
AEs shall be classified by outcome as 'recovered/ recovering/ not recovered/ recovered with sequelae/ unknown/ and fatal'.

Number of events, and incidence proportion of events (=the corresponding number of events during the whole study period / total number of events during the whole study period) shall be calculated.

(4) Classification by causal relationship to the surveillance drug

AEs shall be classified by causal relationship to the surveillance drug as 'certain/ probable or likely/ possible/ unlikely/ conditional or unclassified/ and non-assessable or unclassifiable'.

Number of events, and incidence proportion of events (=the corresponding number of events during the whole study period / total number of events during the whole study period) shall be calculated.

(5) Classification by causal relationship except the surveillance drug

AEs shall be classified by causal relationship except the surveillance drug as 'concomitant medication/ complication/ other/ not related/ and unknown'.

Number of events, and incidence proportion of events (=the corresponding number of events during the whole study period / total number of events during the whole study period) shall be calculated

(6) Classification by action taken to the surveillance drug due to AE

AEs shall be classified by action taken to the surveillance drug due to AE as 'stopped administration/ decreased dosage/ increased dosage/ maintained dosage/ unknown/ and not applicable'.

Number of events, and incidence proportion of events (=the corresponding number of events during the whole study period / total number of events during the whole study period) shall be calculated.

(7) Classification by treatment of adverse events

AEs shall be classified by treatment of AEs as 'no treatment/ non-medication therapy/ and other medication treatment'.

Number of events, and incidence proportion of events (=the corresponding number of events during the whole study period / total number of events during the whole study period) shall be calculated.

10. Definitions for Efficacy Analysis

10.1. Overall improvement

For efficacy assessment, the overall improvement shall be evaluated by referring to the pre- and post-treatment HbA1c or fasting blood glucose levels of subjects. The overall improvement will be classified as followings:

Overall improvement	Reference
Improved	Signs and symptoms are significantly improved.
Unchanged	Improvement in signs and symptoms is not significant or there is no change in signs and symptoms.
Worsened	Signs and symptoms are worsened.
Assessment impossible	Assessment is impossible because the surveillance drug was discontinued before 13 weeks*.

* Total administration period (days) < 13x7 (days)

And, the overall improvement shall be re-classified as "Effective (Improved)" and "Ineffective" (Unchanged and Worsened).

10.2. HbA1c and fasting blood glucose levels

HbA1c (%) and fasting blood glucose (mg/dl) levels will be measured at Baseline, 13 weeks of observation period (±2weeks), and 26 weeks of observation period (±2weeks). And changes from Baseline to each time points (13 & 26 weeks) will be included in the analyses. In addition, proportions of subjects with HbA1C < 7.00% at each time points (Baseline, 13, and 26 weeks) shall be calculated.

Cases that exceed the measurement window (for 13 weeks: measurement at <11 or >15 weeks, for 26 weeks: measurement at <24 or >28 weeks) will be excluded from the HbA1c, and fasting blood glucose analyses.

However, as an additional analysis, HbA1c (%) and fasting blood glucose (mg/dl) levels shall be analyzed with subjects exceed the measurement window (>15 weeks to <24 weeks, and >28 weeks, respectively).

10.3. Effective/Ineffective

Effective/Ineffective shall be re-classified according to the followings: 'Effective' for 'improved' as overall improvement, and 'Ineffective' for 'unchanged' or 'worsened' as overall improvement.

11. Statistical Analysis

All statistical analyses described in this SAP are based on the Protocol Alogliptin-6001 (version 3.1).

11.1. General principles

If there is not special comments, the statistical analysis of the clinical study are conform to the following principles.

(1) Statistical considerations

1) If the target variable is a continuous, then the number of subjects, mean, standard deviation, median, min, max values are provided. And if the target variable is a categorical, frequency and ratio are provided. 2) The Exact method is used to estimate 95% confidence interval of a proportion. 3) For categorical analysis, Fisher's exact test shall be applied in priority. 4) In order to test the difference between two specific time points within a group, paired t-test or Wilcoxon signed rank test shall be used, following the results from the test for normality assumption. 5) All statistical tests is based on the 'two sides' test with alpha=0.05, without any specific comments.

(2) Other consideration

1) The descriptive statistics (mean, standard deviation, median, minimum, maximum, percentage, etc.) are rounded to the second decimal place. 2) The p-value is rounded to the fourth decimal place.

11.2. Analyses for demographic information and medical history variables

The analyses for demographic information and medical history variables will be analyzed using the **Safety Set**. In addition, the analysis for demographic information also will be conducted using the **Subjects Excluded from Safety Analysis**.

(1) Demographic information

The frequency and percentage are presented for gender, categorized age, geriatric, pregnancy status, type of hospital visit, drinking history, and smoking history.

The number of subjects, mean, standard deviation, median, minimum, and maximum values are presented for age (continuous; year), height, and body weight.

(2) History of type 2 diabetes mellitus

The frequency and percentage are presented for categorized duration of type 2 diabetes mellitus, categorized HbA1c, and categorized fasting blood glucose.

The number of subjects, mean, standard deviation, median, minimum, and maximum values are presented for duration of type 2 diabetes mellitus (continuous; year), pre-treatment HbA1c, and pre-treatment fasting blood glucose.

(3) Concomitant disease

1) Existence of concomitant disease

The frequency and percentage are presented for existence (Yes or No) of concomitant disease, renal impairment, diabetic complications, lifestyle related diseases, liver diseases, kidney diseases, gastro-intestinal diseases, cardiac cerebrovascular, allergic diseases, malignant tumor, and others.

2) Classification of disease

The frequency and percentage of classified (e.g. severity, or specific disease) renal impairment, diabetic complications, lifestyle related diseases, liver diseases, kidney diseases, gastro-intestinal diseases, cardiac cerebrovascular, allergic diseases, and malignant tumor are presented.

3) Detailed disease

The number of subjects, frequency, number of incidence are presented for detailed total concomitant diseases, detailed renal impairment, detailed liver disease, and detailed other diseases coded as SOC (System Organ Class) and PT (Preferred Term) or IT(Included Term) using WHO ART.

(4) History of previous used of GLP-1 Agonist or DPP-4 Inhibitor

The frequency and percentage are presented for using history (Yes or No) of GLP-1 Agonist or DPP-4 Inhibitor.

(5) Status of surveillance drug use

The frequency and percentage are presented for administered dose, categorized total administration period, and status of long-term user.

The number of subjects, mean, standard deviation, median, minimum, and maximum values are presented for total administration period (continuous; week).

(6) Compliance status

The frequency and percentage are presented for medication compliance with the surveillance drug (status of treatment compliance), and status of compliance with diet and exercise therapy at 13 weeks and 26 weeks at the administration period, respectively.

(7) Past/concomitant medications

The frequency and percentage are presented for status (Yes or No) of past/concomitant medications.

The number of subjects, frequency, number of incidence are presented for past/concomitant medication in detail coded by WHO ATC (Level1/Level5).

(8) Abnormal change in laboratory data

The subject list including subject ID, test dates (pre and post treatments, both), test values (pre and post treatments, both), relation to AE occurrence (Yes or No), and comments' of PI, shall be presented.

(9) Status of completion and discontinuation

The frequency and percentage are presented for status (Yes or No) of completion and discontinuation, and classified reasons of discontinuation.

11.3. Analyses for safety evaluation

All analyses for safety evaluation shall be conducted with **Safety Set**.

Additionally, the analysis for adverse event, the analysis for classification AEs, and the covariate analysis also will be conducted with **the Special Population Set** (included in **Safety Set**), **Long-term use Set** (included in **Safety Set**).

The analysis for adverse event will be also conducted with **Subjects Excluded from Safety Analysis.**

11.3.1. Analysis for adverse event

Present the number of subjects with AE, incidence proportion, 95% confidence interval of incidence proportion, number of incidence cases and number of Subjects, proportion of Subjects (the corresponding number of subjects / total number of subjects) for AE, ADR, SAE, SADR, Unexpected AE, and Unexpected ADR, respectively.

Also, present the number of subjects with AE, incidence proportion, 95% confidence interval of incidence proportion and number of incidence cases by SOC and PT or IT of AE, ADR, SAE, SADR, Unexpected AE, and Unexpected ADR terms, respectively.

In addition, present the subject list of SAE including subject No., gender, age, adverse event term (PT), date of onset, date of resolution (or date of death), severity, outcome, causal relationship to the surveillance drug, action taken for the surveillance drug, and listedness in label.

And also present the subject list of UAE including subject No., adverse event term (PT), date of onset, date of resolution (or date of death), seriousness, severity, outcome, causal relationship to the surveillance drug, and action taken for the surveillance drug.

11.3.2. Analysis for classification of AEs

(1) AE by onset period

Present the number of subjects with AE, incidence proportion, 95% confidence interval of incidence proportion, number of incidence cases and number of Subjects, proportion of Subjects (the corresponding number of subjects / total number of subjects) for AE, ADR, Unexpected AE, and Unexpected ADR for each specific onset period, respectively.

Also, present the number of subjects with AE, incidence proportion, 95% confidence interval of incidence proportion and number of incidence cases by SOC and PT or IT of AE, ADR, Unexpected AE, and Unexpected ADR terms for each onset specific period, respectively.

(2) AE by each enrollment criterion

Present the number of subjects with AE, incidence proportion, 95% confidence interval of incidence proportion, number of incidence cases and number of Subjects, proportion of Subjects (the corresponding number of subjects / total number of subjects) for AE, ADR, Unexpected AE, and Unexpected ADR by each specific enrollment criterion, respectively.

Also, present the number of subjects with AE, incidence proportion, 95% confidence interval of incidence proportion and number of incidence cases by SOC and PT or IT of AE, ADR, Unexpected AE, and Unexpected ADR terms by each specific enrollment criterion, respectively.

(3) Other AE classification

Present the number of incidence cases, and incidence proportion for classification by severity, outcome, causal relationship to the surveillance drug, causal relationship except the surveillance drug, action taken to the surveillance drug due to AE, and treatment of adverse events.

11.3.3. Covariate analysis for safety evaluation

(1) The number of subjects with AE, incidence proportion (=the corresponding number of subjects with AE/ total number of subjects), 95% confidence interval of incidence proportion, number of incidence cases and number of Subjects, proportion of Subjects (the corresponding number of subjects / total number of subjects) will be presented by each demographic information (gender, categorized age, type of hospital visit, categorized height (divided into median value), categorized body weight (divided into median), drinking history, and smoking history, respectively).

Group difference of the AE between each the demographic information will be tested using chi-square test or Fisher's exact test.

(2) The number of subjects with AE, incidence proportion (=the corresponding number of subjects with AE/ total number of subjects), 95% confidence interval of incidence proportion, number of incidence cases and

number of Subjects, proportion of Subjects (the corresponding number of subjects / total number of subjects) will be presented by the history of type 2 diabetes mellitus (duration of type 2 diabetes mellitus, categorized HbA1c prior to treatment, and categorized fasting blood glucose prior to treatment, respectively).

-Group difference of the AE between each history of type 2 diabetes mellitus will be tested using chi-square test or Fisher's exact test.

(3) The number of subjects with AE, incidence proportion (=the corresponding number of subjects with AE/ total number of subjects), 95% confidence interval of incidence proportion, number of incidence cases and number of Subjects, proportion of Subjects (the corresponding number of subjects / total number of subjects) will be presented by the status of concomitant diseases (Yes or No).

Group difference of the AE between each status of concomitant diseases will be tested using chi-square test or Fisher's exact test.

(4) The number of subjects with AE, incidence proportion (=the corresponding number of subjects with AE/ total number of subjects), 95% confidence interval of incidence proportion, number of incidence cases and number of Subjects, proportion of Subjects (the corresponding number of subjects / total number of subjects) will be presented by the history of previous use of GLP-1 Agonist or DPP-4 Inhibitor.

Group difference of the AE between each history of previous use of GLP-1 Agonist or DPP-4 Inhibitor will be tested using chi-square test or Fisher's exact test.

(5) The number of subjects with AE, incidence proportion (=the corresponding number of subjects with AE/ total number of subjects), 95% confidence interval of incidence proportion, number of incidence cases and number of Subjects, proportion of Subjects (the corresponding number of subjects / total number of subjects) will be presented by the status of surveillance drug use (administered dose, categorized total administration period*, respectively).

*Excluded in the analysis using **Long-term use Set** (included in **Safety Set**)

Group difference of the AE between each status of surveillance drug use will be tested using chi-square test or Fisher's exact test.

(6) The number of subjects with AE, incidence proportion (=the corresponding number of subjects with AE/ total number of subjects), 95% confidence interval of incidence proportion, number of incidence cases and

number of Subjects, proportion of Subjects (the corresponding number of subjects / total number of subjects) will be presented by the compliance status (medication compliance with the surveillance drug, and compliance with diet and exercise therapy, respectively).

Group difference of the AE between each compliance status will be tested using chi-square test or Fisher's exact test.

(7) The number of subjects with AE, incidence proportion (=the corresponding number of subjects with AE/ total number of subjects), 95% confidence interval of incidence proportion, number of incidence cases and number of Subjects, proportion of Subjects (the corresponding number of subjects / total number of subjects) will be presented by the status of past/concomitant medication (Yes or No).

Group difference of the AE between each status of past/concomitant medication will be tested using chi-square test or Fisher's exact test.

(8) The number of subjects with AE, incidence proportion (=the corresponding number of subjects with AE/ total number of subjects), 95% confidence interval of incidence proportion, number of incidence cases and number of Subjects, proportion of Subjects (the corresponding number of subjects / total number of subjects) will be presented by each **Special Population Set** (elderly, pregnant women, patients with renal impairment, and patients with hepatic impairment) included in **Safety Set**.

Group difference of the AE between each **Special Population Set** will be tested using chi-square test or Fisher's exact test.

(9) The number of subjects with AE, incidence proportion (=the corresponding number of subjects with AE/ total number of subjects), 95% confidence interval of incidence proportion, number of incidence cases and number of Subjects, proportion of Subjects (the corresponding number of subjects / total number of subjects) will be presented by each **Special Population Set** (elderly, pregnant women, patients with renal impairment, and patients with hepatic impairment) for **Subject Excluded from Safety Analysis**.

Group difference of the AE between each **Special Population Set** will be tested using chi-square test or Fisher's exact test.

(10) Multiple logistic regression will be conducted with significant factors (P-value<0.05) of AE incidence. Corresponding conditional (adjusted) P-value, Odds ratio, and 95% confidence interval of odds ratio will be reported by factors. If there is no significant factor, Logistic regression will not be applied.

11.4. Analyses for efficacy evaluation

All analyses for efficacy evaluation shall be conducted with **Efficacy Set**.

Additionally, all efficacy analyses also will be conducted with **Long-term use Set** (included in **Efficacy Set**).

And also efficacy analyses for HbA1c and fasting blood glucose levels also will be performed using both **Efficacy Set**, and **Long-term use Set** (included in **Efficacy Set**), however the subjects that exceed the measurement window will be excluded in the analyses.

11.4.1. Overall efficacy assessment

The frequency and percentage are presented for overall improvement, effectiveness (effective/ Ineffective) and number of subjects. In addition, 95% confidence interval of Effective proportion is presented for effectiveness.

11.4.2. HbA1c and fasting blood glucose

The number of subjects, mean, standard deviation, median, minimum, and maximum values are presented for HbA1c and fasting blood glucose values at each time point (Baseline, 13 weeks, and 26 weeks), changes in HbA1c and fasting blood glucose values (from Baseline) at each time point (13 weeks-Baseline, and 26 weeks-Baseline, each), respectively. The significance of the changes from Baseline shall be tested with Paired t-test or Wilcoxon signed rank test.

The frequency and percentage are presented for the subjects with HbA1c <7.00% by each time point (Baseline, 13 weeks, and 26 weeks).

HbA1c and fasting blood glucose analyses will be performed using both **Efficacy Set**, and **Long-term use Set** (included in **Efficacy Set**), however the subjects that exceed the measurement window will be excluded in the main analyses.

Instead, as an additional analysis, the number of subjects, mean, standard deviation, median, minimum, and maximum HbA1c and fasting blood glucose values of the subjects exceed the measurement window will be presented by each time point (>15 weeks & <24 weeks, and >28 weeks, respectively).

11.4.3. Covariate analysis for efficacy evaluation

In the factor analyses for efficacy evaluation, the Effective proportion (= Number of Effective (=Improved)/ Total number of **Efficacy set**) shall be used to find the corresponding factors.

(1) The frequency and percentage(effective/ Ineffective, number of subjects) and 95% confidence interval of

Effective proportion will be presented by each demographic characteristic (gender, categorized age, type of hospital visit, categorized height (divided into median value), categorized body weight (divided into median), drinking history, and smoking history, respectively).

Group difference of the effectiveness between each the demographic information will be tested using chi-square test or Fisher's exact test.

(2) The frequency and percentage(effective/ Ineffective, number of subjects) and 95% confidence interval of Effective proportion will be presented by the history of type 2 diabetes mellitus (duration of type 2 diabetes mellitus, categorized HbA1c prior to treatment, and categorized fasting blood glucose prior to treatment, respectively).

Group difference of the effectiveness between each history of type 2 diabetes mellitus will be tested using chi-square test or Fisher's exact test.

(3) The frequency and percentage(effective/ Ineffective, number of subjects) and 95% confidence interval of Effective proportion will be presented by the status of concomitant diseases (Yes or No).

Group difference of the effectiveness between each status of concomitant diseases will be tested using chi-square test or Fisher's exact test.

(4) The frequency and percentage(effective/ Ineffective, number of subjects) and 95% confidence interval of Effective proportion will be presented by the history of previous use of GLP-1 Agonist or DPP-4 Inhibitor.

Group difference of the effectiveness between each history of previous use of GLP-1 Agonist or DPP-4 Inhibitor will be tested using chi-square test or Fisher's exact test.

(5) The frequency and percentage(effective/ Ineffective, number of subjects) and 95% confidence interval of Effective proportion will be presented by the status of surveillance drug use (administered dose, categorized total administration period*, respectively).

*Excluded in the analysis using **Long-term use Set** (included in **Efficacy Set**)

Group difference of the effectiveness between each status of surveillance drug use will be tested using chi-square test or Fisher's exact test.

(6) The frequency and percentage(effective/ Ineffective, number of subjects) and 95% confidence interval of

Effective proportion will be presented by the compliance status (medication compliance with the surveillance drug, and compliance with diet and exercise therapy, respectively).

Group difference of the effectiveness between each compliance status will be tested using chi-square test or Fisher's exact test.

(7) The frequency and percentage(effective/ Ineffective, number of subjects) and 95% confidence interval of Effective proportion will be presented by the status of past/concomitant medication (Yes or No).

Group difference of the effectiveness between each status of past/concomitant medication will be tested using chi-square test or Fisher's exact test.

(8) The frequency and percentage(effective/ Ineffective, number of subjects) and 95% confidence interval of Effective proportion will be presented by each **Special Population Set** (elderly, pregnant women, patients with renal impairment, and patients with hepatic impairment) included in **Efficacy Set**.

Group difference of the effectiveness between each **Special Population Set** will be tested using chi-square test or Fisher's exact test.

(9) Multiple logistic regression will be conducted with significant factors (P-value<0.05) of effectiveness. Corresponding conditional (adjusted) P-value, Odds ratio, and 95% confidence interval of odds ratio will be reported by factors. If there is no significant factor, Logistic regression will not be applied.

12. Programming

CCI

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[redacted]

13. Interim Analysis

Interim analysis will not be conducted in this PMS study.

14. Others

(1) The tables contained WHO ATC information should be sorted by the number of subject (n). If the number of subjects is same, then sort by the number of cases. If the number of subject and number of case are same, then sort by an alphabet order.

(2) If the AE or effective assessment cases are less than 5, the corresponding covariate analysis shall not be conducted, because it does not enough to have statistical representativeness.

(3) If multi-collinearity problem will be arouse in multiple logistic regression (for both safety and efficacy evaluations) by non-identifiable or high-correlated variables (e.g. renal impairment and hepatic impairment), multiple logistic regression should be applied independently by each the corresponding variable. And following annotation should be described in the results.

15. References

(1) ICH Efficacy Guideline, Statistical principles for clinical trials (E9), 1998