Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

Document Number:	c12992044-01
BI Study Number:	1218.178
BI Investigational Product(s):	Trazenta (Linagliptin)
Title:	Clinical characteristics and practice patterns of type 2 diabetes mellitus (T2DM) patients treated with oral antidiabetic drugs (OAD) in Japan: analysis of medical and health care database of the Medical Data Vision (MDV)
Protocol version identifier:	Version 1
Date of last version of protocol:	Not Applicable
PASS:	No
EU PAS register number:	Not Applicable
Active substance:	Linagliptin
Medicinal product:	Trazenta
Product reference:	Not applicable
Procedure number:	Not applicable
Joint PASS:	No
Research question and objectives:	To understand the prescription pattern in T2DM patients of each compound and each class for all OADs, available throughout study period.
Country(-ies) of study:	Japan
Author:	████████ ████████████████
Marketing authorisation holder(s):	*Nippon Boehringer Ingelheim Co,, Ltd.* 2-1-1, Osaki, Shinagawa-ku, Tokyo 141-6017, Japan

001-MCS-90-124_RD-01 (4.0)

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Date:	09 February 2017

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2.   LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Confidence Interval
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
IEC	Independent Ethics Committee
IRB	Institutional Review Board
i.v.	Intravenous
MedDRA	Medical Dictionary for Drug Regulatory Activities
OAD	Oral Antidiabetic Drugs
OPU	Operative Unit
p.o.	per os (oral)
q.d.	quaque die (once a day)
SAE	Serious Adverse Event
s.c.	Subcutaneous
T2DM	Type 2 Diabetes Mellitus
TCM	Trial Clinical Monitor
t.i.d.	ter in die (3 times a day)
TMM	Team Member Medicine

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3.   RESPONSIBLE PARTIES

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4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: If applicable, list centrally-authorised medicinal product(s) subject to the study.	Trazenta		
Name of active ingredient: List pharmacotherapeutic group(s){ACT codes} and active substance(s) subject to the study	A10N,A10H,A10J,A10K,A10L A10M		

Protocol date:	**Study number:**	**Version/Revision:**	**Version/Revision date:**
09 February 2017	1218.178	1.0	

Title of study:	Clinical characteristics and practice patterns of type 2 diabetes mellitus (T2DM) patients treated with oral antidiabetic drugs (OADs) in Japan: analysis of medical and health care database of the Medical Data Vision (MDV)
Rationale and background:	Renal impairment (RI) is a common complication in patients with type 2 diabetes. In Japanese patients with T2DM, about 40% of patients have microalbuminuria or macroalbuminuria, and other report shows that 55% of Japanese patients with T2DM suffer from mild to moderate renal dysfunction. Many of OADs are contraindicated in severe RI patients or should be carefully administered in patients with declined renal function. For biguanide, a risk of lactic acidosis increases in RI and biguanide is contraindicated in moderate or severe RI. SU and Glinides require caution of a risk of hypoglycemia including prolonged hypoglycemia in patients with RI. Pioglitazone is used with no contraindication in patients with RI in USA, meanwhile in Japan it is contraindicated in severe RI patients and it requires careful administration to mild to moderate RI patients. Alpha-glucosidase inhibitors (α-GIs) also require careful administration in RI patients although the levels of severity of RI with caution are different from each drug in some measure. The prescriptions of DPP-4 inhibitors are rapidly increasing in T2DM patients after its introduction to the Japanese clinical practice in 2009. The reason of this trend might result from well-balanced drug characteristics with its safety profile, especially low frequency of hypoglycaemia and its acceptable efficacy on blood glucose lowering. Therefore many of physicians consider DPP-4 inhibitor is widely chosen as a monotherapy and one of combination therapy. As for DPP-4 inhibitors administered on a daily basis, there are seven single ingredient drugs in this class and their dose-reduction manners are various in RI patients. Linagliptin and teneligliptin are not required dose reduction. On the other hand, other five drugs are recommended dose

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	reduction or careful administration as excretion might be delayed and blood levels also might rise in patients with RI due to the mechanism of renal excretion. Furthermore sitagliptin and alogliptin have four and three of drug formulations of different contained amount respectively in Japan. Japanese physicians are required proper use of complicated regimen in accordance with each patient's renal function. Thus, appropriate use of OADs including dose-reduction is important for patient's safety in T2DM patients with RI. However, there are insufficient data on dose adjustment in accordance with the prescription pattern and the risk of RI of OADs, in particular DPP-4 inhibitors, in clinical practice in Japan. Therefore, we will investigate OADs usage conditions in T2DM patients by using Medical Data Vision clinical database in clinical practice in Japan.

Research question and objectives:	Research question:
	
	    To understand the prescription pattern in T2DM patients of each compound and each class for all OADs, available throughout study period.
	
	Study objectives:
	
	  1. To analyze the demographic and clinical characteristics of T2DM patients who have been treated with OADs
	
	  █ ██
	      ████████████████████████
	
	  █ ██
	      ███████████████████

Study design:	Descriptive cohort study
Population:	Medical Data Vision (MDV) clinical database is used. Inclusion criteria: · Patients with T2DM

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	· Patients must have their first prescription for any study drugs between 01/01/2014 and 30/09/2016. The index date will be set as the first prescription of each drug during the study period. · Patients must have at least 6 month enrolment verified by the presence of any record except for the study drug prescriptions within the database (look back period) prior to the index date for each drug. Exclusion criteria: · Patients who were under 40 y.o. at the time of diagnosis of diabetes. · Patients with record of type 1 diabetes mellitus. · Patients who prescribed the study drugs during 6 month prior to index date for each drug. · Patients whose mean visit interval are more than 92 days
Variables:	Number of patients, age at index date, sex, prior and concomitant use of glucose-lowering medications and insulin, comorbidities, serum creatinine. eGFR will be calculated using serum creatinine, age, and sex.
Data sources:	Medical Data Vision (MDV) clinical database. The database is health insurance claim database. As of end of July 2015, facilities: 200, patients: 10.95 million, which is covering approximately 12% of acute hospitals in Japan. Lab results are also available but number of hospitals providing with lab test results are limited. Study period is from 01/01/2014 to 30/09/2016 in MDV database at the time of study protocol approval. The MDV database is broadly representative of the Japanese population with similar distribution comparing with Japanese population; therefore we believe our study sample will provide reasonable description of the characteristics of patients treated with diagnosis of type 2 diabetes mellitus in the general Japanese population. There is research experience using the data, 19 publications, 5 conference presentations (as of August 2015).
Study size:	All available data from 01/01/2014 to 30/09/2016 will be included to ensure the maximum number of patient. All patients with a prescription of OADs and DPP-4 inhibitors from

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Protocol date: 09 February 2017	**Study number:** 1218.178	**Version/Revision:** 1.0	**Version/Revision date:**

	01/01/2014 to 31/08/2015 and a diagnosis of T2DM is estimated that approximately 9,890 and 7,579 patients respectively have been prescribed a study drug in the MDV database to be included in the study. The power calculation has not been conducted as there will not be any hypothesis testing in the analysis. Data of MDV is from all DPC hospitals. Data is collected directly from hospitals, so it holds every data of all insurances. Limitaion: Number of hospitals providing with lab test results are limited.

Data analysis:	• For the 1st objective, descriptive statistics of each compound and each class of OAD will be presented for the baseline demographic and clinical characteristics:
	 • Number of patients
	 • Age (mean ± SE, mean ± SD)
	 • Concomitant medications (drug prescribed at index day) :
	    • Use of biguanide (Yes/No)
	    • Use of sulfonylurea (Yes/No)
	    • Use of thiazolidinediones (Yes/No)
	    • Use of glinide (Yes/No)
	    • Use of α-GI (Yes/No)
	    • Use of GLP-1RA (Yes/No)
	    • Use of SGLT2 inhibitors (Yes/No)
	    • Use of insulin (Yes/No)
	 • Premedications (drug prescribed before index day):
	    • Use of biguanide (Yes/No)
	    • Use of sulfonylurea (Yes/No)
	    • Use of thiazolidinediones (Yes/No)
	    • Use of glinide (Yes/No)
	    • Use of α-GI (Yes/No)
	    • Use of GLP-1RA (Yes/No)
	    • Use of SGLT2 inhibitors (Yes/No)

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Protocol date:	Study number:	Version/Revision:	Version/Revision date:
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- Use of insulin (Yes/No)
- Comorbidities:
  - Hypertension: Percentage of patients with a diagnosis of hypertension
  - Ischemic heart disease (IHD): Percentage of patients with a diagnosis of IHD
  - Myocardial Infarction (MI): Percentage of patients with a diagnosis of MI
  - Heart Failure (HF): Percentage of patients with a diagnosis of HF
  - Stroke: Percentage of patients with a diagnosis of stroke
  - Renal impairment: Percentage of patients with a diagnosis of renal impairment
  - Amputation: Percentage of patients with a diagnosis of amputation

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Milestones:	Submission to IRB (Keio University)	10th February 2017
	IRB (Keio University) meeting	17th February 2017
	Registration to clinicaltrials.gov and ENCePP	28th February 2017
	Start of data analysis	1st March 2017
	Start of manuscript preparation	1st March 2017
	End of data analysis	10th March 2017
	Draft study report	31st March 2017
	Final report of study results	20th April 2017
	Submission of manuscript to Journal	26th June 2017

5.   AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
	None			

6.   MILESTONES

Milestone	Planned Date
Submission to IRB (Keio University)	10th February 2017
IRB (Keio University) meeting	17th February 2017
Registration to clinicaltrials.gov and ENCePP	28th February 2017
Start of data analysis	1st March 2017
Start of manuscript preparation	1st March 2017
End of data analysis	10th March 2017
Draft study report	31st March 2017
Final report of study results	20th April 2017
Submission of manuscript to Journal	26th June 2017

7. RATIONALE AND BACKGROUND

Renal impairment (RI) is a common complication in patients with T2DM. In Japanese patients with T2DM, about 40% of patients have microalbuminuria or macroalbuminuria [1], and other report shows that 55% of Japanese patients with T2DM suffer from mild to moderate renal dysfunction [2].

Many of OADs are contraindicated in severe RI patients or should be carefully administered in patients with declined renal function. For biguanide, a risk of lactic acidosis increases in RI and biguanide is contraindicated in moderate or severe RI. Pioglitazone is used with no contraindication in patients with RI in USA, meanwhile in Japan it is contraindicated in severe RI patients and it requires careful administration to mild to moderate RI patients. Glinides and α-GIs also require careful administration in RI patients although the levels of severity of RI with caution are different from each drug in some measure.

The prescriptions of DPP-4 inhibitors are rapidly increasing in T2DM patients after its introduction to the Japanese clinical practice [3]. The reason of this trend might result from well-balanced drug characteristics with its safety profile, especially low frequency of hypoglycaemia and its acceptable efficacy on blood glucose lowering. Therefore many of physicians consider DPP-4 inhibitor is widely chosen as a monotherapy and one of combination therapy.

As for DPP-4 inhibitors administered on a daily basis, there are seven single ingredient drugs in this class and their dose-reduction manners are various in RI patients. Linagliptin and teneligliptin are not required dose reduction. On the other hand, other five drugs are recommended dose reduction or careful administration. Furthermore sitagliptin and alogliptin have four and three of drug formulations of different contained amount respectively in Japan. Japanese physicians are required proper use of complicated regimen in accordance with each patient's renal function.

Currently, there is no publication of actual situation on the prescription patterns of OADs and dose-reduction especially in DPP-4 inhibitors and other OADs needed to dose-reduction. However from viewpoint of appropriate use, relevant dose-reduction can contribute patients benefit. This study aims to assess the actual condition of dose selection of OADs among RI patients in Japan by using MDV database.

MDV provides commercial claims database for inpatient and outpatient consisting medical records from more than 12.94 million patients from 230 large acute care DPC hospitals as of Feb 2016. According to the data released by the company in Sept 2016 [1], in one year period between July 2015 and June 2016, cumulative number of patients in the claims database was 7,546,862 patients. 82% of patients (6,152,732) were associated with outpatient claims only, while 15% of patients (1,131,869) had claims from both in and out-patient care. Only 3% of patients (262,261) had exclusively in-patient claims. Laboratory data is available for approximately 10% of patients contained in the database. The DPC is a case-mix system, similar to Medicare in the US. It comprises of 18 Major Diagnosis Categories, 520 diagnostic groups and 2,658 case-mix groups. In the DPC algorithm, the diagnosis, procedure and comorbidities/complications are the 3 key variables for classification. The diagnosis and comorbidities/complications are coded using the ICD10 scheme, while the procedures are coded using the Japanese Procedure Codes. Not only administrative claims data but also

detailed patient data are collected for all the inpatients discharged from the participating hospitals.

8.   RESEARCH QUESTION AND OBJECTIVES

Research question:

   To understand the prescription pattern in T2DM patients of each compound and each class for all OADs, available throughout study period i.e. DPP-4 inhibitors, sulfonylureas, biguanides, thiazolidinediones, α-GIs, glinides.

Study objectives:

   1. To analyze the demographic and clinical characteristics of T2DM patients who have been treated with OADs
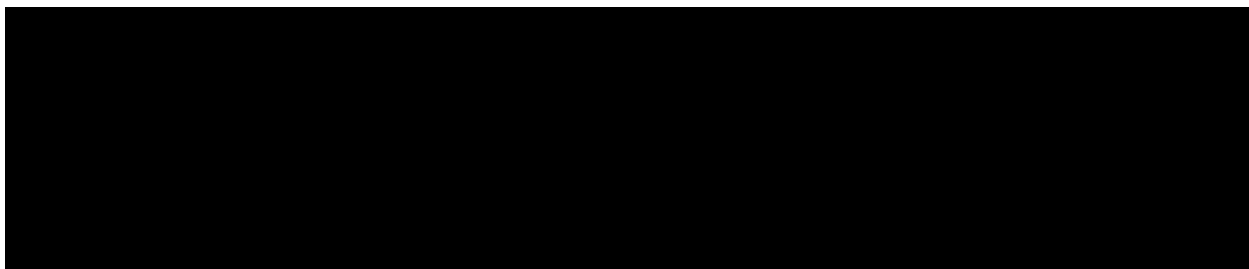
9.   RESEARCH METHODS

9.1   STUDY DESIGN

Study design:
*   Descriptive cohort study

Comparison group
*   OAD group, DPP-4 inhibitors group, SU group, BG group, TZD group, α-GI group, and Glinide group.

Strength of the study design
*   Up-to-date information can be obtained and nationwide actual treatment status can be illustrated with using large-scale real-world database.

Analysis
*   First analysis: type and dosage of drug prescribed for T2DM patients.
*   ███
    ███████████████████████████████
*   Main measures: number of patients, baseline characteristics at index month (age, sex), prior and concomitant use of glucose-lowering medications and insulin (type, dose), comorbidities (types and their percentages of patients), stage of RI defined by eGFR or serum creatinine value, glucose-lowering medications and their dosages (based on daily dose) for patients with RI, ██
*   ██
    ██████████████████████████████████

Potential limitation
*   The data held in MDV database is collected from DPC hospitals, not GP data. However they are including outpatient data because many of Japanese patients prefer to visit a hospital even though chronic disease.
*   The rate of laboratory test data held in MDV database is limited. About 350,000 patients out of 2,600,000 patients (13.5%, April 2008 ~ April 2016) have laboratory data.
*   The MDV database does not hold the time diagnosis of T2DM if it is out of study period. Therefore the onset date of diabetes or the first record of T2DM cannot obtain for all patients.
*   The information on medication is based on prescribed record, not include adherence result. It means that exact dosage may not reveal actual dispensed prescription and dosage perfectly.
*   Laboratory test date is not exactly matched with the index day of the first prescription of OAD. The sample size will have some impacts (reduction) to assure simultaneous timing of data. The latest lab result 30 days before the index date will be considered the status at the time of prescription
*   All information of each patient is from consent given DPC hospitals. If patients have visits to other medical institutions, these data are not included in the MDV data.

- MDV database is composed of data from patients who hospitalized in DPC hospital so that more severe patient will be included in the database.

9.2   SETTING

Medical Data Vision (MDV) clinical database is used.

Inclusion criteria
- Patients with T2DM (ICD code: E11 or E14).
- Patients must have their first prescription (defined as index date*) for any study drugs between 01/01/2014 and 30/09/2016.
- Patients must have at least 6 months enrolment verified by the presence of any record except for the study drug prescriptions within the database (look back period) prior to the index date for each drug.

Exclusion criteria
- Patients who were under 40 y.o. at the time of diagnosis of diabetes.
- Patients with record of type 1 diabetes mellitus (ICD code: E10).
- Patients who prescribed the study drugs during 6 month prior to index date for each drug.
- Patients whose mean visit interval are more than 92 days

*Index date is defined as follows:
- In case of comparing drugs within class, index date is defined as the date of first prescription for any study drugs as general name. Change of dosage is not counted as the index.
- In case of comparing drugs between class, index date is defined as the date of first prescription for study drug of class. Change of dosage is not counted as the index.
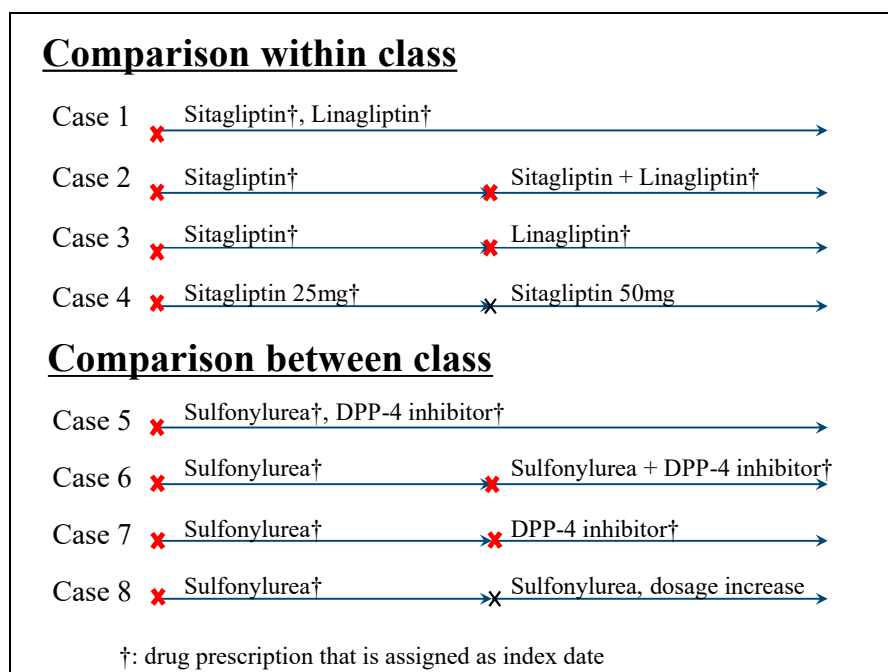
* The hospitalization period is not included in the mean visit interval.

Figure 1   Definition of Index data(date of first prescription for any study drugs)

9.3   VARIABLES

Number of patients, age at index date, sex, prior and concomitant use of glucose-lowering medications and insulin, comorbidities and serum creatinine.
Potential confounding for the type and dosage (based on daily dose)of medications and their

██

age, sex, comorbidities, serum creatinine.

9.3.1   Exposures

Prescriptions for an OAD issued between 01/01/2014 and 30/09/2016 described below:
- DPP-4 inhibitors therapies:
  - Alogliptin
  - Alogliptin/Pioglitazone single-pill combination
  - Anagliptin
  - Linagliptin
  - Saxagliptin
  - Sitagliptin
  - Teneligliptin
  - Vildagliptin
- Sulfonylurea therapies:
  - Acetohexamide
  - Glyclopyramide
  - Glibenclamide
  - Chlorpropamide
  - Tolbutamide Tablets
  - Tolbutamide Powders
  - Gliclazide
  - Glimepiride
  - Glimepiride Orally-disintegrating tablet
- Biguanide therapies:
  - Buformine
  - Metformin
- Thiazolidinedione therapies:
  - Pioglitazone
  - Pioglitazone Orally-disintegrating tablet
  - Glimepiride/Pioglitazone single-pill combination OD
  - Metformin/Pioglitazone single-pill combination OD
- α-GI:
  - Acarbose
  - Acarbose Orally-disintegrating tablet
  - Voglibose
  - Voglibose Orally-disintegrating tablet
  - Miglitol
  - Miglitol Orally-disintegrating tablet
- Glinide therapies:
  - Nateglinide

- Mitiglinide
- Repaglinide
- Mitiglinide/Voglibose single-pill combination

* Combined in general name if the drug has been sold in several brand name.

9.3.2   Outcomes

9.3.2.1   Primary outcomes

Outcome name: demographic and clinical characteristics of patients who had a prescription of OADs.
Time frame: on the index month
Safety issue: N/A

9.3.2.2   Secondary outcomes

Outcome name: drug and dosage (based on daily dose) they are prescribed as there are different cut-offs for renal functions.
Time frame: on the index month
Safety issue: N/A

9.3.3   Covariates

Age at index date
Sex
Prior and concomitant use of glucose-lowering medications and insulin (type, dose): drug name was defined by ATC code and drug name.
Comorbidities (types and their percentages of patients): defined by ICD-10 code
Stage of RI: defined by eGFR or serum creatinine value (See Annex 3).
eGFR is calculated using serum creatinine, age, and sex as follows (formula for Japanese):
The latest serum creatinine value within 6 months from index date will be used.
  *where Cr is serum creatinine (mg/dL), age is the age at index date.

- eGFR formula[*]:
  $$\text{eGFR (mL/min/1.73m}^2) = 194 \times \text{Cr}^{-1.094} \times \text{age (year)}^{-0.287} \ (\times 0.739 \text{ if female})$$

  [*]The formula recommended by the Japanese Society of Nephrology in clinical practice in Japan is the above formula calculated from three data of serum creatinine, age and sex.

<References>

・(Japanese) Evidence-based Clinical Practice Guideline for CKD 2013 (the Japanese Society of Nephrology)
　　URL (accessed on 1st Feb, 2017):
　　http://www.jsn.or.jp/guideline/pdf/CKD_evidence2013/all.pdf
- (English) Japanese Society of Nephrology. Clin Exp Nephrol 2014;18: 346.

9.4　　　DATA SOURCES

Medical Data Vision (MDV) clinical database. The database is health insurance claim database. As of end of July 2015, facilities: 200, patients: 10.95 million, which is covering approximately 12% of acute hospitals in Japan. Lab results are also available but number of hospitals providing with lab test results are limited.
Study period is from 01/01/2014 to 30/09/2016 in MDV database at the time of study protocol approval.
The MDV database is broadly representative of the Japanese population with similar distribution comparing with Japanese population; therefore we believe our study sample will provide reasonable description of the characteristics of patients treated with diagnosis of type 2 diabetes mellitus in the general Japanese population. There is research experience using the data, 19 publications, 5 conference presentations (as of August 2015).

9.5　　　STUDY SIZE

All available data from 01/01/2014 to 30/09/2016 will be included to ensure the maximum number of patient.
All patients with a prescription of OADs and DPP-4 inhibitors from 01/01/2014 to 31/08/2015 and a diagnosis of T2DM is estimated that approximately 9,890 and 7,579 patients respectively have been prescribed a study drug in the MDV database to be included in the study.
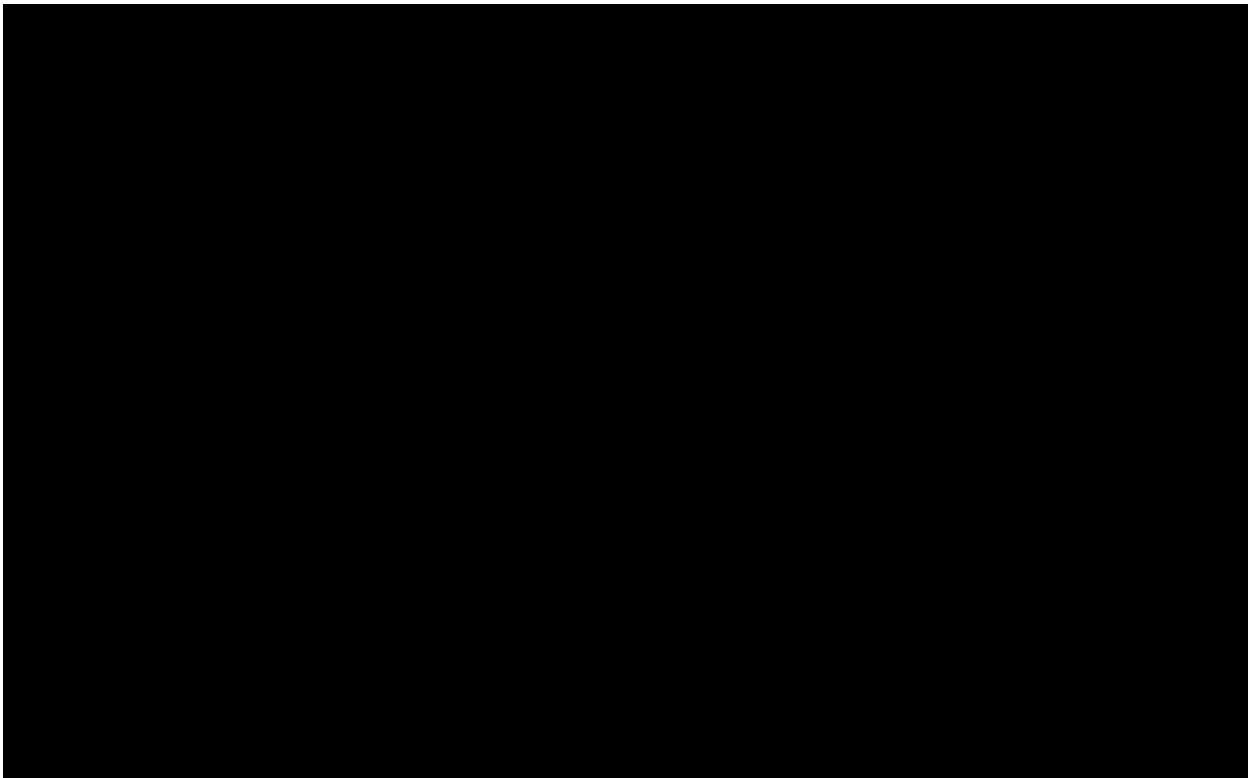
9.6　　　DATA MANAGEMENT

Data were provided as electrical data formatted csv by Medical Data Vision Co., Ltd.
SAS and Microsoft Excel were used for statistics.

9.7　　　DATA ANALYSIS

9.7.1　　　Main analysis

- For the primary objective, descriptive statistics of patients prescribed each compound and each class of OAD at least once will be presented for the baseline demographic and clinical characteristics:
  - Number of patients (n, % of total patients)
  - Age (mean ± SE, mean ± SD)
  - Sex
  - Concomitant medications (drug prescribed at index day) :
    - Use of biguanide (Yes/No)
    - Use of sulfonylurea (Yes/No)
    - Use of thiazolidinediones (Yes/No)

- Use of glinide (Yes/No)
- Use of α-GI (Yes/No)
- Use of GLP-1RA (Yes/No)
- Use of SGLT2 inhibitors (Yes/No)
- Use of insulin (Yes/No)
- Premedications (drug prescribed before index day):
  - Use of biguanide (Yes/No)
  - Use of sulfonylurea (Yes/No)
  - Use of thiazolidinediones (Yes/No)
  - Use of glinide (Yes/No)
  - Use of α-GI (Yes/No)
  - Use of GLP-1RA (Yes/No)
  - Use of SGLT2 inhibitors (Yes/No)
  - Use of insulin (Yes/No)
- Comorbidities:
  - Hypertension: Percentage of patients with a diagnosis of hypertension
  - Ischemic heart disease (IHD): Percentage of patients with a diagnosis of IHD
  - Myocardial Infarction (MI): Percentage of patients with a diagnosis of MI
  - Heart Failure (HF): Percentage of patients with a diagnosis of HF
  - Stroke: Percentage of patients with a diagnosis of stroke
  - Renal impairment: Percentage of patients with a diagnosis of renal impairment
  - Amputation: Percentage of patients with a diagnosis of amputation

9.8   QUALITY CONTROL

Milliman, Inc. will conduct a quality check as below:
Calculation check: both of program codes for calculation and the data codes used the calculation will be checked by different person from that who calculated.
Pre-release peer review: comprehensive check on methodology, calculation process, and consistency of results will be performed by qualified peer-reviewer.
Post-release peer review: comprehensive check on the project will be conducted by qualified peer-reviewer belonging to another office.

9.9   LIMITATIONS OF THE RESEARCH METHODS

- The data held in MDV database is collected from DPC hospitals, not GP data. However they are including outpatient data because many of Japanese patients prefer to visit a hospital even though chronic disease.
- The rate of laboratory test data held in MDV database is limited. About 350,000 patients out of 2,600,000 patients (13.5%, April 2008 ~ April 2016) have laboratory data.
- The MDV database does not hold the time diagnosis of T2DM if it is out of study period. Therefore the onset date of diabetes or the first record of T2DM cannot obtain for all patients.
- The information on medication is based on prescribed record, not include adherence result. It means that exact dosage may not reveal actual dispensed prescription and dosage perfectly.
- Laboratory test date is not exactly matched with the index day of the first prescription of OAD. The sample size will have some impacts (reduction) to assure simultaneous timing of data. The latest lab result 30 days before the index date will be considered the status at the time of prescription
- All information of each patient is from consent given DPC hospitals. If patients have visits to other medical institutions, these data are not included in the MDV data.
- MDV database is composed of data from patients who hospitalized in DPC hospital so that more severe patient will be included in the database.

9.10   OTHER ASPECTS

9.11   SUBJECTS

9.11.1   Cases

Not Applicable

9.11.2   Controls

Not Applicable

9.12   BIAS

- All information of each patient is from consent given DPC hospitals. If patients have visits to other medical institutions, these data are not included in the MDV data.

- MDV database is composed of data from patients who hospitalized in DPC hospital so that more severe patient will be included in the database.

10.   PROTECTION OF HUMAN SUBJECTS

As this is a study based on databases using anonymous and personally unidentifiable data; therefore protection of human subjects is not applicable for this study.

Ethical considerations:
·   Ethical guidelines to be followed
    ➢ This study is to be carried out according to "Ethical Guidelines for Medical and Health Research Involving Human Subjects" (April 1, 2015).
        URL:
        •   (Japanese) http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000069410.pdf
        •   (Provisional Translation, as of March 2015) http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf

·   Protection of personal information and consent
    ➢ This survey is a study using existing record/information. These materials to be used are anonymized with permission of secondary use from the providing medical institution. Therefore, in accordance with "Ethical Guidelines for Medical and Health Research Involving Human Subjects" (April 1, 2015), consent from patients to be investigated subject is not required.

We will apply the study for Institutional Review Board in Keio University. We will start the analysis after the IRB approval.

11.   MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The outcomes of the study are the baseline characteristics (pre-treatment) and medication prescriptions. We will not be looking at outcomes during the treatment period; therefore safety reporting is not applicable for this study.

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12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be written as a conference abstract as well as a manuscript to be submitted to a peer-reviewed journal.
Target of journal submission: End of June 2017.

13.   REFERENCES

13.1   PUBLISHED REFERENCES

[1] Yokoyama H, et al; Diabetes Care. 2007; 30: 989-992.
[2] Kanatsuka A, et al; J. Japan Diab. Soc. 2012; 55: 671-680.
[3] Kohro T, et al; Int Heart J. 2013; 54(2): 93-97.

13.2   UNPUBLISHED REFERENCES

N/A

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
None			

ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

N/A

ANNEX 3. ADDITIONAL INFORMATION

1. Stage of renal function by eGFR

		eGFR (ml/min/1.73m^2)
G1	Normal or high	≥90
G2	Normal or mildly decreased	60-89
G3a	Mildly to moderately decreased	45-59
G3b	Moderately to severely decreased	30-44
G4	Severely decreased	15-29
G5	ESKD	<15

ESKD: End Stage Kidney Disease

2. Stage of renal function by serum creatinine value

	Serum Creatinine (Cr) (mg/dL)
Normal	Male：$0.6 < Cr \leq 1.2$ Female：$0.4 < Cr \leq 0.9$
Mild	Male：$1.2 < Cr \leq 1.4$ Femal：$0.9 < Cr \leq 1.2$
Moderate	Male：$1.4 < Cr \leq 2.4$ Female：$1.2 < Cr \leq 2.0$
Severe/ ESKD	Male：$Cr > 2.4$ Female：$Cr > 2.0$

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APPROVAL / SIGNATURE PAGE

Document Number: c12992044   **Technical Version Number:1.0**

Document Name: nis_protocol_based_on_existing data_1218_0178

Title: Clinical characteristics and practice patterns of Type 2 Diabetes Mellitus (T2D) patients treated with oral antidiabetic drugs (OAD) in Japan: analysis of medical and health care database of the Medical Data Vision (MDV)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Program ▮▮▮▮	▮▮▮▮▮▮▮▮	10 Feb 2017 01:46 CET
Approval-Medical ▮▮▮▮	▮▮▮▮▮▮▮	10 Feb 2017 03:37 CET
Approval ▮▮▮ Medical Affairs	▮▮▮▮▮▮▮▮	10 Feb 2017 04:10 CET

(Continued) Signatures (obtained electronically)

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