Protocol for non-interventional studies based on existing data

<table>
<thead>
<tr>
<th>Document Number:</th>
<th>c12992044-01</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI Study Number:</td>
<td>1218.178</td>
</tr>
<tr>
<td>BI Investigational Product(s):</td>
<td>Trazenta (Linagliptin)</td>
</tr>
<tr>
<td>Title:</td>
<td>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)</td>
</tr>
<tr>
<td>Protocol version identifier:</td>
<td>Version 1</td>
</tr>
<tr>
<td>Date of last version of protocol:</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>PASS:</td>
<td>No</td>
</tr>
<tr>
<td>EU PAS register number:</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Active substance:</td>
<td>Linagliptin</td>
</tr>
<tr>
<td>Medicinal product:</td>
<td>Trazenta</td>
</tr>
<tr>
<td>Product reference:</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Procedure number:</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Joint PASS:</td>
<td>No</td>
</tr>
<tr>
<td>Research question and objectives:</td>
<td>To understand the prescription pattern in T2DM patients of each compound and each class for all OADs, available throughout study period.</td>
</tr>
<tr>
<td>Country(-ies) of study:</td>
<td>Japan</td>
</tr>
<tr>
<td>Author:</td>
<td>Nippon Boehringer Ingelheim Co., Ltd.</td>
</tr>
<tr>
<td>Marketing authorisation holder(s):</td>
<td>2-1-1, Osaki, Shinagawa-ku, Tokyo 141-6017, Japan</td>
</tr>
</tbody>
</table>
| **MAH contact person:** | Clinical Development and Medical Affairs  
Nippon Boehringer Ingelheim Co., Ltd.  
2-1-1, Osaki, Shinagawa-ku, Tokyo 141-6017, Japan |
|------------------------|--------------------------------------------------|
| **In case of PASS, add:**  
**<EU-QPPV:>>** | Not Applicable |
| **<Signature of EU-QPPV:>>** | Not Applicable |
| **Date:** | 09 February 2017 |
1. TABLE OF CONTENTS

TITLE PAGE ........................................................................................................... 1
1. TABLE OF CONTENTS ....................................................................................... 3
2. LIST OF ABBREVIATIONS ............................................................................... 5
3. RESPONSIBLE PARTIES .................................................................................. 6
4. ABSTRACT ........................................................................................................... 7
5. AMENDMENTS AND UPDATES ........................................................................ 13
6. MILESTONES .................................................................................................... 14
7. RATIONALE AND BACKGROUND .................................................................. 15
8. RESEARCH QUESTION AND OBJECTIVES ................................................... 17
9. RESEARCH METHODS ...................................................................................... 18
  9.1 STUDY DESIGN ............................................................................................. 18
  9.2 SETTING ........................................................................................................ 19
  9.3 VARIABLES .................................................................................................. 20
    9.3.1 Exposures ................................................................................................ 20
    9.3.2 Outcomes ................................................................................................ 21
      9.3.2.1 Primary outcomes ............................................................................. 21
      9.3.2.2 Secondary outcomes ........................................................................ 21
    9.3.3 Covariates ............................................................................................... 21
  9.4 DATA SOURCES ............................................................................................ 22
  9.5 STUDY SIZE .................................................................................................. 22
  9.6 DATA MANAGEMENT .................................................................................... 22
  9.7 DATA ANALYSIS .......................................................................................... 22
    9.7.1 Main analysis ........................................................................................... 22
    9.7.2 ................................................................................................................... 23
  9.8 QUALITY CONTROL ........................................................................................ 24
  9.9 LIMITATIONS OF THE RESEARCH METHODS .......................................... 24
  9.10 OTHER ASPECTS ........................................................................................ 24
  9.11 SUBJECTS .................................................................................................... 24
    9.11.1 Cases ..................................................................................................... 24
    9.11.2 Controls ................................................................................................ 24
  9.12 BIAS .............................................................................................................. 24
10. PROTECTION OF HUMAN SUBJECTS .............................................................. 26
11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

13. REFERENCES

13.1 PUBLISHED REFERENCES

13.2 UNPUBLISHED REFERENCES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ANNEX 3. ADDITIONAL INFORMATION
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
3. RESPONSIBLE PARTIES

- Medical Advisor

Department of Diabetes and Metabolic Diseases
Graduate School of Medicine
The University of Tokyo

Drug Development & Regulatory Science
Faculty of Pharmacy
Keio University

- Person responsible for trial (Alphabetic order in each affiliation)

Clinical Development and Medical Affairs
Nippon Boehringer Ingelheim Co., Ltd.
2-1-1, Osaki, Shinagawa-ku, Tokyo 141-6017, Japan

(Alliance partner)
Diabetes products, Medicine Development Unit Japan
Eli Lilly Japan K.K.
4-15-1, Akasaka, Minato-ku, Tokyo 107-0052, Japan

(Statistics/Data analysis)
Japan Healthcare Practice and Data Analytics
Milliman, Inc.
1-6-2, Kojimachi, Chiyoda-ku, Tokyo 102-0083, Japan
4. **ABSTRACT**

<table>
<thead>
<tr>
<th>Name of company:</th>
<th>Boehringer Ingelheim</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name of finished medicinal product:</strong></td>
<td>If applicable, list centrally-authorised medicinal product(s) subject to the study.</td>
</tr>
<tr>
<td>Name of active ingredient:</td>
<td>List pharmacotherapeutic group(s) {ACT codes} and active substance(s) subject to the study</td>
</tr>
<tr>
<td>Protocol date:</td>
<td>09 February 2017</td>
</tr>
<tr>
<td>Study number:</td>
<td>1218.178</td>
</tr>
<tr>
<td>Version/Revision:</td>
<td>1.0</td>
</tr>
<tr>
<td>Title of study:</td>
<td>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)</td>
</tr>
<tr>
<td>Rationale and background:</td>
<td>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 tenelaglitin are not required dose reduction. On the other hand, other five drugs are recommended dose...</td>
</tr>
<tr>
<td>Name of company:</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Name of finished medicinal product:</td>
<td>Trazenta</td>
</tr>
<tr>
<td>If applicable, list centrally-authorised medicinal product(s) subject to the study.</td>
<td></td>
</tr>
<tr>
<td>Name of active ingredient:</td>
<td>A10N,A10H,A10J,A10K,A10L,A10M</td>
</tr>
<tr>
<td>List pharmacotherapeutic group(s){ACT codes} and active substance(s) subject to the study</td>
<td></td>
</tr>
<tr>
<td>Protocol date:</td>
<td>09 February 2017</td>
</tr>
<tr>
<td>Study number:</td>
<td>1218.178</td>
</tr>
<tr>
<td>Version/Revision:</td>
<td>1.0</td>
</tr>
<tr>
<td>Version/Revision date:</td>
<td></td>
</tr>
</tbody>
</table>

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
### Protocol for non-interventional studies based on existing data

**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  

**Protocol date:**  
09 February 2017

**Study number:**  
1218.178

**Version/Revision:**  
1.0

**Version/Revision date:**

- 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
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.

Limitation: 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)
<table>
<thead>
<tr>
<th><strong>Name of company:</strong></th>
<th>Boehringer Ingelheim</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name of finished medicinal product:</strong></td>
<td>If applicable, list centrally-authorised medicinal product(s) subject to the study.</td>
</tr>
<tr>
<td></td>
<td>Trazenta</td>
</tr>
<tr>
<td><strong>Name of active ingredient:</strong></td>
<td>List pharmacotherapeutic group(s) {ACT codes} and active substance(s) subject to the study</td>
</tr>
<tr>
<td><strong>Protocol date:</strong></td>
<td>09 February 2017</td>
</tr>
<tr>
<td><strong>Study number:</strong></td>
<td>1218.178</td>
</tr>
<tr>
<td><strong>Version/Revision:</strong></td>
<td>1.0</td>
</tr>
</tbody>
</table>

- 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
<table>
<thead>
<tr>
<th>Name of company:</th>
<th>Boehringer Ingelheim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of finished medicinal product:</td>
<td>Trazenta</td>
</tr>
<tr>
<td>If applicable, list centrally-authorised medicinal product(s) subject to the study.</td>
<td></td>
</tr>
<tr>
<td>Name of active ingredient:</td>
<td>A10N,A10H,A10J,A10K,A10L,A10M</td>
</tr>
<tr>
<td>List pharmacotherapeutic group(s) {ACT codes} and active substance(s) subject to the study</td>
<td></td>
</tr>
<tr>
<td>Protocol date:</td>
<td>Study number:</td>
</tr>
<tr>
<td>09 February 2017</td>
<td>1218.178</td>
</tr>
<tr>
<td>Version/Revision:</td>
<td>Version/Revision date:</td>
</tr>
<tr>
<td>1.0</td>
<td>10th February 2017</td>
</tr>
<tr>
<td>Milestones:</td>
<td></td>
</tr>
<tr>
<td>Submission to IRB (Keio University)</td>
<td>10th February 2017</td>
</tr>
<tr>
<td>IRB (Keio University) meeting</td>
<td>17th February 2017</td>
</tr>
<tr>
<td>Registration to clinicaltrials.gov and ENCePP</td>
<td>28th February 2017</td>
</tr>
<tr>
<td>Start of data analysis</td>
<td>1st March 2017</td>
</tr>
<tr>
<td>Start of manuscript preparation</td>
<td>1st March 2017</td>
</tr>
<tr>
<td>End of data analysis</td>
<td>10th March 2017</td>
</tr>
<tr>
<td>Draft study report</td>
<td>31st March 2017</td>
</tr>
<tr>
<td>Final report of study results</td>
<td>20th April 2017</td>
</tr>
<tr>
<td>Submission of manuscript to Journal</td>
<td>26th June 2017</td>
</tr>
</tbody>
</table>
## 5. AMENDMENTS AND UPDATES

<table>
<thead>
<tr>
<th>Number</th>
<th>Date</th>
<th>Section of study protocol</th>
<th>Amendment or update</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6. **MILESTONES**

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Planned Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submission to IRB (Keio University)</td>
<td>10&lt;sup&gt;th&lt;/sup&gt; February 2017</td>
</tr>
<tr>
<td>IRB (Keio University) meeting</td>
<td>17&lt;sup&gt;th&lt;/sup&gt; February 2017</td>
</tr>
<tr>
<td>Registration to clinicaltrials.gov and ENCePP</td>
<td>28&lt;sup&gt;th&lt;/sup&gt; February 2017</td>
</tr>
<tr>
<td>Start of data analysis</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; March 2017</td>
</tr>
<tr>
<td>Start of manuscript preparation</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; March 2017</td>
</tr>
<tr>
<td>End of data analysis</td>
<td>10&lt;sup&gt;th&lt;/sup&gt; March 2017</td>
</tr>
<tr>
<td>Draft study report</td>
<td>31&lt;sup&gt;st&lt;/sup&gt; March 2017</td>
</tr>
<tr>
<td>Final report of study results</td>
<td>20&lt;sup&gt;th&lt;/sup&gt; April 2017</td>
</tr>
<tr>
<td>Submission of manuscript to Journal</td>
<td>26&lt;sup&gt;th&lt;/sup&gt; June 2017</td>
</tr>
</tbody>
</table>
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.

**Comparison within class**

<table>
<thead>
<tr>
<th>Case</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sitagliptin†, Linagliptin†</td>
</tr>
<tr>
<td>2</td>
<td>Sitagliptin†</td>
</tr>
<tr>
<td>3</td>
<td>Sitagliptin†</td>
</tr>
<tr>
<td>4</td>
<td>Sitagliptin 25mg†</td>
</tr>
</tbody>
</table>

**Comparison between class**

<table>
<thead>
<tr>
<th>Case</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Sulfonylurea†, DPP-4 inhibitor†</td>
</tr>
<tr>
<td>6</td>
<td>Sulfonylurea†</td>
</tr>
<tr>
<td>7</td>
<td>Sulfonylurea†</td>
</tr>
<tr>
<td>8</td>
<td>Sulfonylurea†</td>
</tr>
</tbody>
</table>

†: drug prescription that is assigned as index date

* 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
  - Anaglaptin
  - Linagliptin
  - Saxagliptin
  - Sitagliptin
  - Teneligliptin
  - Vildaglaptin
- **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-Gl:**
  - 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.

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

*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>
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:
  - (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.
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


13.2 UNPUBLISHED REFERENCES

N/A
ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

<table>
<thead>
<tr>
<th>Number</th>
<th>Document Reference Number</th>
<th>Date</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

N/A
ANNEX 3. ADDITIONAL INFORMATION

1. Stage of renal function by eGFR

<table>
<thead>
<tr>
<th>Stage</th>
<th>eGFR (ml/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 Normal or high</td>
<td>≥90</td>
</tr>
<tr>
<td>G2 Normal or mildly decreased</td>
<td>60-89</td>
</tr>
<tr>
<td>G3a Mildly to moderately decreased</td>
<td>45-59</td>
</tr>
<tr>
<td>G3b Moderately to severely decreased</td>
<td>30-44</td>
</tr>
<tr>
<td>G4 Severely decreased</td>
<td>15-29</td>
</tr>
<tr>
<td>G5 ESKD</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

ESKD: End Stage Kidney Disease

2. Stage of renal function by serum creatinine value

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine (Cr) (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Male: 0.6 &lt; Cr ≤ 1.2</td>
</tr>
<tr>
<td></td>
<td>Female: 0.4 &lt; Cr ≤ 0.9</td>
</tr>
<tr>
<td>Mild</td>
<td>Male: 1.2 &lt; Cr ≤ 1.4</td>
</tr>
<tr>
<td></td>
<td>Female: 0.9 &lt; Cr ≤ 1.2</td>
</tr>
<tr>
<td>Moderate</td>
<td>Male: 1.4 &lt; Cr ≤ 2.4</td>
</tr>
<tr>
<td></td>
<td>Female: 1.2 &lt; Cr ≤ 2.0</td>
</tr>
<tr>
<td>Severe/ESKD</td>
<td>Male: Cr &gt; 2.4</td>
</tr>
<tr>
<td></td>
<td>Female: Cr &gt; 2.0</td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>Meaning of Signature</th>
<th>Signed by</th>
<th>Date Signed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval-Clinical Program</td>
<td></td>
<td>10 Feb 2017 01:46 CET</td>
</tr>
<tr>
<td>Approval-Medical</td>
<td></td>
<td>10 Feb 2017 03:37 CET</td>
</tr>
<tr>
<td>Approval Medical Affairs</td>
<td></td>
<td>10 Feb 2017 04:10 CET</td>
</tr>
</tbody>
</table>
(Continued) Signatures (obtained electronically)

<table>
<thead>
<tr>
<th>Meaning of Signature</th>
<th>Signed by</th>
<th>Date Signed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>