BMJ Open Protocol for a large-scale prospective observational study with alogliptin in patients with type 2 diabetes: J-BRAND Registry

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ABSTRACT

Introduction: Dipeptidyl peptidase-4 (DPP-4) inhibitors including alogliptin are categorised as a newer class of oral hypoglycaemic, antidiabetic drugs to suppress the degradation of incretin hormones ((glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)) by DPP-4. We have scheduled a large-scale, multicentre, prospective, observational study (Japan-Based clinical ReseArch Network for Diabetes Registry: J-BRAND Registry) to construct an extensive database over a long-term clinical course in patients with type 2 diabetes receiving oral hypoglycaemic agents (OHAs) and to evaluate the safety and efficacy of alogliptin in Japanese population.

Methods and analysis: 20 000 patients with type 2 diabetes will be registered into two groups of 10 000 each: group A patients will be treated with alogliptin, while group B patients will be treated with non-DPP-4 inhibitor OHAs. Approximately 300 institutions nationwide will enrol and assign eligible patients equally to either group. Each patient’s data will be collected every 6 months for a 3-year period, during which time treatment with OHAs may be changed or discontinued, as per package insert for each OHA. Primary end points are safety variables to be compared between the two groups and their subgroups, with respect to hyperglycaemia, pancreatitis, skin disorders, infections and cancer. Secondary end points are efficacy variables including from-baseline changes of A1c, fasting glucose, fasting insulin and urinary albumin, which will be compared between groups/subgroups. New onset and progression of microangiopathy will also be evaluated against OHAs. Overall, the J-BRAND Registry will evaluate the safety and efficacy of antidiabetic OHA(s) including alogliptin, based on a large-scale database.

Ethics and dissemination: This study will be conducted with the highest respect for individual participants according to this protocol, the Declaration of Helsinki, the Ethical Guidelines for Clinical Research (Japan Ministry of Health, Labour and Welfare, 2008) and relevant laws/regulations. The present study will construct a valuable database of patients with type 2 diabetes treated with OHAs including alogliptin.

Trial registration number: UMIN000007976.

Strengths and limitations of this study

- This study will be conducted as a first non-randomised, observational study to establish a large-scale database with regard to the safety and efficacy profiles of a dipeptidyl peptidase-4 (DPP-4) inhibitor in comparison to non-DPP-4 inhibitor oral hypoglycaemic agents.
- The database is expected to promote appropriate use of DPP-4 inhibitors when used alone or in combination with other antidiabetic agents.
- It will need several years for the full construct of database.

INTRODUCTION

Type 2 diabetes mellitus is a metabolic disease in which patients experience chronic hyperglycaemia and is very often associated with various complications including macrovascular as well as microvascular diseases, such as cardiovascular disease, retinopathy, nephropathy and neuropathy. As of 2011, an estimated 366 million people have been affected with diabetes globally including Japan, where more than 24 million people have been diagnosed or are suspected to have diabetes1–5 and the prevalence is rapidly increasing worldwide.1–5

There have been different classes of agents developed for the treatment of type 2 diabetes including insulin and oral hypoglycaemic agents (OHAs).1,3–6 Among those, incretin-related drugs have been noted in recent years as a novel class of antidiabetic agents4–7 and are widely used in daily clinical practice, expanding the range of treatment options for patients with type 2 diabetes. Specifically, dipeptidyl peptidase-4 (DPP-4) inhibitors have attracted clinical attention because of the convenience of once-daily or twice-daily oral administration and the pancreatic β-cell protective effect,8 which conventional OHAs for
The objective of this prospective study is to construct a database regarding the long-term (3-year) clinical course in patients with type 2 diabetes who receive OHAs in daily clinical practice and to evaluate the safety and efficacy of alogliptin, a novel DPP-4 inhibitor.

**Primary end points**

The incidence, type and severity of adverse events will be compared between group A patients initiated with alogliptin treatment and group B patients initiated with OHA treatment other than DPP-4 inhibitors at the time of registration (between-group comparison) and among subgroups defined by baseline characteristics and by concomitant medication (between-subgroup comparison). All adverse events will be included in the safety evaluation, and major safety concerns will include hypoglycaemia, pancreatitis, skin disorders, infections and cancer.

**Secondary end points**

Efficacy variables will be compared according to patient grouping or subgrouping as above. The efficacy variables will include the changes from baseline values (at the time of registration) in the levels of A1c (glycated haemoglobin (HbA1c); National Glycohemoglobin Standardization Program (NGSP)), fasting blood glucose, fasting insulin and urinary albumin, as well as the effect of OHA(s) on the new onset of microangiopathy (diabetic retinopathy, diabetic nephropathy, diabetic neuropathy) and its progression.

**Other measurements**

Laboratory tests include serum lipids such as high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides. Standard 12-lead ECGs, weight and diastolic and systolic blood pressure in a sitting position will also be measured.

**Overall study design**

This is a large-scale, multicentre, prospective, observational study in which 20 000 patients with type 2 diabetes will be consecutively registered by a central registration procedure. An OHA should be newly started, added to previous treatment or switched from the previous OHA(s) in patients at the time of study registration. The type of a newly prescribed OHA will be designated hereinafter as ‘start’, ‘addition’ or ‘switch’. Patients will be treated in daily clinical practice and followed up for 3 years.

A total of 20 000 patients will be registered and divided into two groups (A and B) consisting of 10 000 each, according to the type of OHA that has been started, added on or switched at the time of registration (see figure 2). Group A will include 10 000 patients treated with alogliptin, while group B will include 10 000 patients not treated with any DPP-4 inhibitor but with other OHA(s). Each participating patient will choose either treatment group according to his or her free will. Approximately 300 medical institutions nationwide will participate in the present study, and each investigational site is expected to enrol eligible patients at a 1:1 ratio as assigned to groups A and B, respectively. See Statistical
and analytical plans for the rationale for planned sample size.

The study design is schematised in figure 1.

Each participant’s data will be registered every 6 months, totalling 7 times of data registration for a 3-year follow-up period (also see table 1). The 6-month interval of data registration appears reasonable to observe safety and efficacy parameters, e.g. plasma glucose control in participants who will be in daily clinical practice along with diet and exercise therapy after a change in pharmacotherapy (e.g. ‘start’, ‘addition’, ‘switch’ or dose increase or reduction) and to ease the burden on each participant.

Participant eligibility

Participant eligibility will be determined as summarised in box 1 (also see figure 2 for participant grouping).

Participation of a participant will be discontinued at the discretion of the principal investigator or subinvestigator if any of the following conditions occur: major protocol deviation, lost to follow-up, voluntary withdrawal, study termination, pregnancy or any other reason for which the investigator judges that discontinuation would be necessary.

Treatment

Treatment with an OHA will be provided in daily clinical practice and may be changed or discontinued within the 3-year observation period, as per the package insert for each OHA. Similarly, non-OHA antidiabetic therapies as well as treatment for concurrent medical conditions will be provided in daily clinical practice, as needed.

Study procedures

The principal investigator and subinvestigator will observe and assess each participant from the time of informed consent through the completion of observation according to the procedures depicted in table 1.

All examinations, observations and evaluations should be performed by the principal investigator (or subinvestigator) at the designated time points.

Figure 1  Schematic of study design (OHA, oral hypoglycaemic agent).

Figure 2  Schematic of participant grouping (DPP-4, dipeptidyl peptidase-4; OHA, oral hypoglycaemic agent).
Informed consent and participant registration

The principal investigator (or subinvestigator) will consecutively provide an explanation regarding the study to each eligible participant, using the informed consent document. Participants who give written consent will be registered in the electronic case report form in order, and then observations will be initiated. Participant registration will be closed at each investigational site at the time the target number of participants has been enrolled in alogliptin-treated group (group A) and DPP-4 inhibitor-untreated group (group B). The participant registration for the entire study will also be closed at the time the planned total number of participants for each group (10 000 participants) has been reached nationwide. The principal investigator will prepare a list of participant identification numbers and assign a study-specific, anonymised and uniquely given number to each participant at the time of informed consent to protect the participant’s private information. These unique numbers will be used and not changed throughout the study.

Data collection

Demographics, medical history and medication history

Demographic information to be obtained will include date of birth, gender, height, weight, waist circumference, blood pressure, and pulse. Medical history will include past medical history, current medical history, and medication history. Medications will be classified into concomitant medications and concomitant conditions. Safety end points will be collected throughout the study. Other concurrent conditions will be applied as per the inclusion/exclusion criteria. Clinical laboratory tests will be performed to assess the metabolic control and safety end points. Adverse events will be monitored throughout the study.

Table 1 Schedule of observations

<table>
<thead>
<tr>
<th>Study month (month)</th>
<th>Registration</th>
<th>Observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>−3</td>
<td>0</td>
<td>6 12 18 24 30 36</td>
</tr>
<tr>
<td>Visit number</td>
<td>−1</td>
<td>2 3 4 5 6 7 → −</td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Medical history/medication history (OHA)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vital signs (sitting blood pressure and pulse)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Safety end points</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Microangiopathy</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Macroangiopathy</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Other concurrent conditions</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Clinical laboratory tests †</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>HbA1c (NGSP)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fasting insulin †</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose †</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Casual blood glucose †</td>
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<td></td>
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<tr>
<td>Fasting and casual C peptide</td>
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</tr>
<tr>
<td>1,5-AG ‡</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Glycoalbumin ‡</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Amylase ‡</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chest X-ray ‡</td>
<td>X</td>
<td></td>
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<tr>
<td>12-lead ECG ‡</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

† Measurement should be performed in the fasting state (after at least 10 h of fasting), if possible.
‡ Optional test items.
AG, Anhydroglucitol; HbA1c, glycated haemoglobin; NGSP, National Glycohemoglobin Standardization Program; OHA, oral hypoglycaemic agent.
Box 1  Criteria for participant inclusion and exclusion

Inclusion criteria
1 Patients who have received a diagnosis of type 2 diabetes and are treated with at least one oral hypoglycaemic agent (OHA) as per the package insert for the OHA.
2 Patients who have started or added an OHA, or switched* from one OHA to another within the previous 3 months and meet one of the following criteria (see figure 2):
Group A: Participants treated with alogliptin at the time of registration (‘alogliptin-treated group’)
   I Start: Patients who were with no previous OHA treatment and have newly started alogliptin.
   II Addition: Patients who have added alogliptin to OHA(s) currently taken (excluding dipeptidyl peptidase-4 (DPP-4) inhibitors).
   III Switch: Patients who have switched a part or all of OHAs currently taken to alogliptin.
Group B: Participants not treated with any DPP-4 inhibitor at the time of registration (‘DPP-4 inhibitor-untreated group’)
   I Start: Patients who were with no previous OHA treatment and have newly started an OHA other than DPP-4 inhibitors.
   II Addition: Patients who have added another OHA, other than DPP-4 inhibitors, to OHA(s) currently taken (excluding DPP-4 inhibitors).
   III Switch: Patients who have switched a part or all of OHAs currently taken to another OHA, other than DPP-4 inhibitors, and are not treated with any DPP-4 inhibitor at the time of registration.

*This applies to active pharmaceutical ingredients only. A switch from one OHA (including combination drug products) to another of the same active pharmaceutical ingredient will not be included in the switch category.

Exclusion criteria
Any participant who meets any of the following criteria will not qualify for entry into the study:
1 Patients using parenteral hypoglycaemic agents (insulin and glucagon-like peptide-1 receptor agonists).
2 Patients with severe ketosis, diabetic coma or precoma, severe infection, or serious trauma and patients under perioperative management.
3 Pregnant or lactating women.
4 Patients judged by the principal investigator or subinvestigator to be ineligible for participation as study participants for any other reason.

smoking status, drinking habits, family history of cancer and diabetes in first-degree or second-degree relatives, and time of onset or diagnosis of type 2 diabetes.

Medical history will include the presence or absence of the following clinically significant symptoms or diseases that have disappeared or been resolved before the OHA start, addition or switch: severe ketosis (ketoacidosis), diabetic coma or precoma, severe infections, hypoglycaemia (excluding severe hypoglycaemia), severe hypoglycaemia (requiring assistance from others), pancreatitis, cancer (pancreatic cancer and other types), skin disorders, microangiopathy and other clinically significant symptoms or diseases judged by the principal investigator (or subinvestigator).

Ongoing conditions are considered concurrent medical conditions (see the later section of Concurrent medical conditions).

Medication history will include any OHAs stopped within 3 months before the defined OHA start, addition or switch (see figure 2).

Physical examination procedures
A baseline physical examination will consist of the following body systems: eyes, ears, nose, throat, cardiovascular system, respiratory system, gastrointestinal system, dermatological system, extremities, musculoskeletal system, nervous system, lymph nodes, genitourinary system and others. All physical examinations performed after the OHA start, addition or switch should assess clinically significant changes from the baseline examination.

Major safety end points
The major safety end points are set in the J-BRAND Registry study as below, and the baseline physical examination will include an assessment of these end points.

▸ Hypoglycaemia (presence or absence; severity; symptomatic or asymptomatic; blood glucose level at onset);
▸ Pancreatitis (presence or absence; type i.e. acute, chronic—chronic or progressive stage—or other);
▸ Skin disorders (presence or absence; disease name);
▸ Infections (presence or absence; disease name);
▸ Cancer (presence or absence; pathogenesis i.e. primary, recurrent, metastatic or unknown; disease name).

Microangiopathy and other measurements
Microangiopathy will be assessed for new onset or progression of disease. A funduscopic method will be used for the diagnosis of diabetic retinopathy based on Davis classification as simple retinopathy or more advanced. The diagnosis of diabetic nephropathy will be made based on the classification proposed by Toronto Diabetic Neuropathy Expert Group as Probable DPN. Diabetic nephropathy will be made based on urinary albumin/creatinine ratio as 30 mg/g Cr or higher.

Height, waist circumference and weight will be measured in each participant. Body mass index (BMI) will be calculated using metric units with a formula: BMI=weight (kg)/height (m)². Vital sign measurements will include diastolic and systolic blood pressure (mm Hg) and pulse (bpm) in a sitting position after a rest of 5 min or longer.

Severe hypoglycaemia is defined as hypoglycaemia requiring assistance from others and will be separately collected.
Concomitant medications
Detailed information (drug name, duration and daily dose) will be obtained on all OHAs administered during the period from the OHA start, addition or switch to the completion of observation. Information on any medication other than OHAs will be similarly collected for drug name and duration of use.

Concurrent medical conditions
Concurrent medical conditions are ongoing conditions or diseases that are present at the OHA start, addition or switch. This will include clinically significant abnormalities observed in laboratory tests, ECG or physical examination, as judged by the principal investigator (or subinvestigator). An investigation will be performed for the presence or absence of (1) microangiopathy; (2) macroangiopathy (cerebral infarction, cerebral haemorrhage, myocardial infarction, angina pectoris and foot lesions such as arteriosclerosis obliterans of the lower extremities (Fontaine stages I–IV), foot deformity/callus formation, tinea pedis including tinea unguium, and other infections); and (3) the following conditions.

Other concurrent conditions:
- Lifestyle-related diseases (hypertension, dyslipidaemia and hyperuricaemia);
- Pulmonary disease (interstitial pneumonia);
- Hepatic diseases (fatty liver, alcoholic hepatitis, chronic hepatitis, viral hepatitis and cirrhosis);
- Pancreatic diseases (chronic pancreatitis and acute pancreatitis);
- Renal diseases (nephrotic syndrome, glomerulonephritis and chronic renal failure);
- Cardiac diseases (cardiac failure: New York Heart Association (NYHA) class II, III or IV);
- Allergic diseases (bronchial asthma, pollinosis, allergic rhinitis and allergic dermatitis);
- Autoimmune diseases (rheumatoid arthritis and other autoimmune diseases);
- Cancer (gastric cancer, lung cancer, colorectal cancer, pancreatic cancer, thyroid cancer and other cancers);
- Other symptoms or diseases deemed to be concurrent medical conditions based on the judgement of the principal investigator (or subinvestigator).

Clinical laboratory tests
Laboratory tests will be performed according to the schedule shown in table 1. The ‘essential items’ and ‘optional items’ are defined for the tests as below (also see table 2) and samples should be collected in the fasting state (after at least 10 h of fasting), whenever possible. The investigator should collect at-registration (baseline) laboratory data as much as possible on ‘essential items’ and ‘optional items’, on a day within 6 months before registration (including the day of registration) and closest to the date of physical examination.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Essential items and optional items to be collected</th>
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<tbody>
<tr>
<td><strong>Haematology</strong></td>
<td><strong>Blood biochemistry</strong></td>
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<tr>
<td>Essential items</td>
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<tr>
<td>HbA1c</td>
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<tr>
<td>Fasting blood glucose*</td>
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<td>Fasting insulin*</td>
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<tr>
<td>Optional items†</td>
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<tr>
<td>Red blood cell count</td>
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<td>Haemoglobin</td>
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<td>Haematocrit</td>
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<td>Platelet count</td>
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<td>White cell count</td>
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<tr>
<td>Differential white blood cells (neutrophils, eosinophils, basophils, lymphocytes and monocytes)</td>
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<tr>
<td>Other</td>
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<td>Casual blood glucose</td>
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<td>1,5-AG</td>
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<td>Glycohaemoglobin</td>
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<td>Fasting C peptide concentration</td>
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<td>Casual serum C peptide concentration</td>
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<tr>
<td>Blood biochemistry items</td>
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<td>Serum creatinine</td>
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<td>Lipid profile (total cholesterol, HDL-C, LDL-C (calculated), fasting triglycerides)</td>
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<td>AST (GOT)</td>
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<td>ALT (GPT)</td>
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<td>Total protein</td>
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<td>Blood urea nitrogen</td>
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<td>Uric acid</td>
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<tr>
<td>Total bilirubin</td>
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<td>ALP</td>
<td></td>
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<tr>
<td>CK (CPK)</td>
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<td>LDH</td>
<td></td>
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<td>γ-GTP</td>
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<tr>
<td>Amylase</td>
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<td>Urinary albumin</td>
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<td>Protein (qualitative)</td>
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<td>Glucose (qualitative)</td>
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<td>Ketone bodies (qualitative)</td>
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<td>Occult blood (qualitative)</td>
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</table>

*These parameters must be measured at least once a year.
† ‘Optional items’ are the data to be collected if measured.
AG, anhydroglucitol; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein-cholesterol; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein-cholesterol; γ-GTP, γ-glutamyl transpeptidase.
Three different analysis sets are defined in this study. Full analysis set (FAS) is defined as a group of registered participants who have visited the investigational site at least once after the OHA start, addition or switch. Safety analysis set (SAS) is defined as a group of registered participants who will meet the eligibility criteria (based on the inclusion/exclusion criteria; see box 1) and who have visited the investigational site at least once after the OHA start, addition or switch. Efficacy analysis set (EAS) is defined as a group of registered participants who will meet the eligibility criteria and have visited the investigational site at least once after the registration.

For safety analyses, SAS will be the primary set while FAS will be the secondary. EAS will be used for efficacy analyses. As for new onset or progression of microangiopathy among the efficacy endpoints, however, analyses will be performed for the SAS population.

Hypoglycaemia, pancreatitis, skin disorders, infections and cancer will be of particular interest for the safety assessment. These outcomes will be analysed primarily by Kaplan-Meier method for estimation of cumulative incidence and by log-rank test for between-group comparison. If necessary, multivariate methods including Cox regression may be used to adjust the baseline differences.

Of efficacy outcomes, A1c, fasting blood glucose, fasting insulin and urinary albumin will be measured at each visit and the change from baseline (at registration) will be compared between groups by two-sided t test. Missing data will be imputed by last-observation-carried-forward method. If necessary, multivariate methods including analysis of covariance may be used for adjustment of baseline differences. The effect of OHA(s) on the new onset of microangiopathy and its progression will be assessed by Kaplan-Meier method and log-rank test, as performed in hypoglycaemia assessment.

**Rationale for planned sample size**

With respect to the sample size described above, approximately 9200 patients will be required to evaluate the safety of alogliptin as the primary end point, detecting at least one adverse event occurring with an incidence of less than 0.05% with a probability of at least 99%. The same sample size also needs to be set for the DPP-4 inhibitor-untreated group (group B) in order to compare the safety end point. Assuming that 5–7% of participants are excluded from analysis population, a total of 20 000 patients will be required.

Based on the experience in preapproval clinical studies of alogliptin, the incidence of hypoglycaemia is assumed to be 14 events/1000 patient-years in group A and 1.3 times higher in group B than in group A. Assuming that 10 000 participants in each group are followed up for 3 years, with a dropout rate of 20% per annum, the statistical power of log-rank test will be 93.7% at a two-sided significance level of 5%.

On the basis of a report by Garg et al., the incidence of acute pancreatitis is assumed to be 5 events/1000 patient-years in group B and 1.5 times higher in group A than in group B. The statistical power of log-rank test under the same conditions as above will be 91.9% at a significance level of 5%.

Based on the presented rationale, the planned sample size (10 000 participants per group; 20 000 in total) will have a sufficient statistical power to meet the objective of this study.

**Biological sample use, retention and destruction**

The principal investigator should establish a management system required to protect the participants’ personal information and comply with the investigational site’s rules regarding sample collection, retention and destruction.

**ETHICS AND DISSEMINATION**

This study will be conducted with the highest respect for individual participants according to the protocol, the Declaration of Helsinki, the Ethical Guidelines for Clinical
Research (Japan Ministry of Health, Labour and Welfare, 2008 Revision), and relevant laws and regulations.

Each study participant will be protected against invasion of privacy. The source data of a participant will be linked throughout the study to the study database or relating documentation(s) via a study-specific, anonymised and uniquely given number. As permitted by all applicable laws and regulations, limited participant attributes such as gender and date of birth may be used to verify the participant and accuracy of the participant’s unique number.

**DISCUSSION AND DISSEMINATION**

Based on a search for English language clinical trials previously published, a review article was recently published in which the tolerability of DPP-4 inhibitors was supported on the basis of 5 drugs within this class.\(^9\) However, in order to provide more comprehensive information with respect to efficacy, safety and tolerability of this class of medications, a contributing database construction needs to be established. The J-BRAND Registry will thus help promote the appropriate use of DPP-4 inhibitors such as alogliptin through long-term (3-year) follow-ups in 10 000 DPP-4 inhibitor (alogliptin)-receiving patients with type 2 diabetes and another 10 000 patients receiving non-DPP-4 inhibitor OHA(s).

The findings of this study will be presented at relevant conferences and published in peer-reviewed journals.

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**Acknowledgements** At each study site and committee, the investigator is responsible for patient recruitment and performance of all study-related procedures including analysis of the study data, independent of Takeda Pharmaceutical Company Limited.

**Contributors** NI led the committee to elaborate the study design and study protocol. He was responsible for journal selection and preparation of this article as the principal author. He incorporated coauthors’ comments collectively in the article for finalisation. KU, YT and HW elaborated the study design and study protocol and reviewed this article. JN, YY, IS and RN reviewed this article. TY prepared the statistical analysis plan (SAP) for this study. He reviewed this article. TK leads and controls the whole study’s activities. He reviewed this article. All authors and coauthors finally approved the manuscript presently submitted.

**Funding** The J-BRAND Registry is funded by a research grant from Takeda Pharmaceutical Company, Limited.

**Competing interests** NI is on the Advisory Board of Takeda, Mitsubishi Tanabe, Nippon Boehringer Ingelheim and Sanofi. He has received honoraria for lectures from MSD, Sanofi, Novartis, Eli Lilly, Kyowa Hakko Kirin, Nippon Boehringer Ingelheim and Mitsubishi Tanabe, and has clinical commissions from MSD, Eli Lilly and Mitsubishi Tanabe. He has research grants supported by MSD. Nippon Boehringer Ingelheim, Sanofi, Daiichi-Sankyo, Takeda, Mitsubishi Tanabe, Novartis, Kyowa Hakko Kirin and AstraZeneca. KU has received honoraria for lectures from Nippon Boehringer Ingelheim, Eli Lilly, MSD, Novartis and Takeda. He has research grants supported by Astellas, Daiichi-Sankyo, MSD, Novartis, Sanofi and Takeda. YT has received honoraria for lectures from MSD, Ono, Sanofi, Dainippon Sumitomo, Takeda, Mitsubishi Tanabe, Nippon Boehringer Ingelheim, Novartis and Novo Nordisk. He has research grants supported by Astellas, MSD, Kyowa Hakko Kirin, Sanofi, Dainippon Sumitomo, Daiichi-Sankyo, Takeda, Nippon Boehringer Ingelheim and Novartis. HW has received honoraria for lectures from Nippon Boehringer Ingelheim, Sanofi, Ono, Novo Nordisk, Novartis, Eli Lilly, Sanwa Kagaku Kenkyusho, Daiichi-Sankyo, Takeda, MSD, Dainippon Sumitomo and Kowa. He has research grants supported by Nippon Boehringer Ingelheim, Pfizer, Mochida, Sanofi, Novo Nordisk, Novartis, Sanwa Kagaku Kenkyusho, Tenumo, Eli Lilly, Mitsubishi Tanabe, Daiichi-Sankyo, Takeda, MSD, Shinonogi, Dainippon Sumitomo, Kissei and AstraZeneca. JN has received honoraria for lectures from MSD, Ono, Pfizer, Novo Nordisk, Eli Lilly, Novartis, Sanofi, MSD and Takeda. He has research grants supported by Ono, Mitsubishi Tanabe, JT, Sanofi, MSD and Takeda. YY is on the Advisory Board of Ono and Novo Nordisk. He has received honoraria for lectures from Takeda, Sanofi and Mitsubishi Tanabe. He has research grants supported by Nippon Boehringer Ingelheim and Novartis, and has clinical commissions from Takeda, Eli Lilly and Novartis. He has research grants supported by MSD, Kissei, Kyowa Hakko Kirin, Sanofi, Daiichi-Sankyo, Takeda, Mitsubishi Tanabe, Teijin, Nippon Boehringer Ingelheim, Novartis, Novo Nordisk, Pfizer and Mochida. RN has research grants supported by Astellas, Nippon Boehringer Ingelheim, Novartis, Takeda and Japan Diabetes Foundation. TY has received honoraria for lectures from AstraZeneca, MSD, Kyowa Hakko Kirin, Kowa, Shinonogi, Daiichi-Sankyo, Dainippon Sumitomo, Takeda, Novartis and Pfizer, and has clinical commissions from AstraZeneca, MSD, Shinonogi and Takeda. He has research grants supported by AstraZeneca, MSD, Kowa, Daiichi-Sankyo, Dainippon Sumitomo, Takeda, Mitsubishi Tanabe and Pfizer. TK is on the Advisory Board of Takeda, Chugai, Sanofi, Mitsubishi Tanabe and AstraZeneca. He has research grants supported by MSD, Ono, Novartis, Takeda, Novo Nordisk A/S, Dainippon Sumitomo, Sanofi and Novo Nordisk Pharma A/S. He is also on the Speakers’ Bureau of Takeda, MSD, Sanofi, Eli Lilly, Novartis, Astellas and Dainippon Sumitomo.

**Ethics approval** Ethics approval was provided by the Institutional Review Board of a clinical study Trazenta Randomized study for USing insulin patient of Type 2 Diabetes (TRUST 2 Study) under an agreement with Japan Society for Patient Reported Outcome. He has received honoraria for lectures from Astellas, MSD, Ono, Kowa, Takeda, Mitsubishi Tanabe, Nippon Boehringer Ingelheim and Novartis, and has clinical commissions from Takeda, Eli Lilly and Novartis. He has research grants supported by MSD, Kissei, Kyowa Hakko Kirin, Sanofi, Daiichi-Sankyo, Takeda, Mitsubishi Tanabe, Teijin, Nippon Boehringer Ingelheim, Novartis, Novo Nordisk, Pfizer and Mochida. RN has research grants supported by Astellas, Nippon Boehringer Ingelheim, Novartis, Takeda and Japan Diabetes Foundation. TY has received honoraria for lectures from AstraZeneca, MSD, Kyowa Hakko Kirin, Kowa, Shinonogi, Daiichi-Sankyo, Dainippon Sumitomo, Takeda, Novartis and Pfizer, and has clinical commissions from AstraZeneca, MSD, Shinonogi and Takeda. He has research grants supported by AstraZeneca, MSD, Kowa, Daiichi-Sankyo, Dainippon Sumitomo, Takeda, Mitsubishi Tanabe and Pfizer. TK is on the Advisory Board of Takeda, Chugai, Sanofi, Mitsubishi Tanabe and AstraZeneca. He has research grants supported by MSD, Ono, Novartis, Takeda, Novo Nordisk A/S, Dainippon Sumitomo, Sanofi and Novo Nordisk Pharma A/S. He is also on the Speakers’ Bureau of Takeda, MSD, Sanofi, Eli Lilly, Novartis, Astellas and Dainippon Sumitomo.

**Provenance and peer review** Not commissioned; externally reviewed.

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BMJ Open 2014 4:
doi: 10.1136/bmjopen-2013-004760

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