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.

3 Gender and age: men and women of at least 20 years of age at the time of informed consent.
4 Patients willing and able to provide written informed consent prior to participation in this study.

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[i]; 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 neuropathy will be made based on the classification proposed by Toronto Diabetic Neuropathy Expert Group as Probable DPN.[18] 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.

[i]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 2 Essential items and optional items to be collected

Haematology	Blood biochemistry	Urinalysis
Essential items		
HbA1c	Serum creatinine	Urinary albumin
Fasting blood glucose*	Lipid profile (total cholesterol, HDL-C, LDL-C (calculated), fasting triglycerides)	
Fasting insulin*	AST (GOT)	
	ALT (GPT)	
Optional items†		
Red blood cell count	Total protein	Protein (qualitative)
Haemoglobin	Blood urea nitrogen	Glucose (qualitative)
Haematocrit	Uric acid	Ketone bodies (qualitative)
Platelet count	Total bilirubin	Occult blood (qualitative)
White cell count	ALP	
Differential white blood cells (neutrophils, eosinophils, basophils, lymphocytes and monocytes)	CK (CPK)	
	LDH	
	γ-GTP	
	Amylase	
Other		
Casual blood glucose		
1,5–AG		
Glycoalbumin		
Fasting C peptide concentration		
Casual serum C peptide concentration		

*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.

after the OHA start, addition or switch. A1c (%) will be collected as NGSP conversion of a conventional HbA1c determination.

Chest X-ray

Chest radiography will be performed in daily clinical practice, as required. The principal investigator (or subinvestigator) or a radiologist at each investigational site will assess chest X-ray images based on the following categories: normal; abnormal but not clinically significant or abnormal and clinically significant.

Standard 12-lead ECG procedure

A standard 12-lead ECG will be recorded in daily clinical practice, as required. The principal investigator (or subinvestigator) or a specialist at each investigational site will interpret the ECG based on the following categories: normal; abnormal but not clinically significant; abnormal and clinically significant.

Adverse event collection periods

Adverse events will be collected during the three collection periods as follows:

- All adverse events occurring between the time of OHA start, addition or switch (Visit -1; see the visit number in table 1) and start of observation (Visit 1);
- All adverse events occurring between the start of observation (Visit 1) and the end of observation (Visit 7);
- Adverse events occurring after completion of observation and are judged to be related to OHA(s).

Any adverse event will be assessed with respect to its name, seriousness, severity, causality to OHA(s) used, date of onset, date of resolution, frequency, action taken with regard to OHAs and outcome.

Statistical and analytical plans

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 end points, 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*,[19] 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, anonymysed 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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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.

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