Title: Specified Drug-Use Survey of INISYNC Combination Tablets "Survey on long-term use in type 2 diabetes mellitus patients with renal or hepatic impairment or advanced age"

NCT Number: NCT03555565

Protocol Approve Date: 01-JUN-2019

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

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- Patient identifiers within the text, tables, or figures or in by-patient data listings.
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If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

Note; This document was translated into English as the language on original version was Japanese.

Protocol for Specified Drug-Use Survey of INISYNC Combination Tablets "Survey on long-term use in type 2 diabetes mellitus patients with renal or hepatic impairment or advanced age"

Survey Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol Number	**Alogliptin-Met-5003**
Version Number	**Version 5**
Date of Preparation	**June 1, 2019**

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1.0 Background

Drugs to treat type 2 diabetes mellitus are likely used over a long time in the routine clinical setting. Inisync Combination Tablets (hereinafter referred to as "this drug") contain two active ingredients: alogliptin benzoate (brand name, Nesina Tablets) and metformin hydrochloride. Long-term combination use of these drugs in the routine clinical setting was previously investigated in a specified drug-use survey. However, clinical trial data were limited on the safety and efficacy of this drug in patients with renal impairment, patients with hepatic impairment and elderly patients, and therefore data in these patient populations are designated as part of "important missing information" in the risk management plan for this drug. Thus, with a focus particularly on these patient populations, the present specified drug-use survey (hereinafter referred to as "this survey") has been planned to investigate the long-term safety and efficacy of this drug used in the routine clinical setting in type 2 diabetes mellitus patients with renal or hepatic impairment or advanced age.

This survey will be conducted in compliance with the Ministerial Ordinance on Good Post-Marketing Study Practice (GPSP) and relevant regulatory requirements.

2.0 Objectives

This survey aims to evaluate the long-term safety and efficacy of this drug in type 2 diabetes mellitus patients with renal impairment (mild), hepatic impairment (mild or moderate), or advanced age (≥65 years) in the routine clinical setting. In addition, this survey will enroll as many as possible patients who were switched from alogliptin 25 mg and metformin hydrochloride 500 mg (ie, 250 mg twice daily) in combination as a prior medication, to examine the relationship between the efficacy and improvement in medication adherence by the switching to this combination product in those who were taking alogliptin benzoate and metformin hydrochloride in combination.

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

600 subjects (including 300 subjects with hepatic impairment)

3.2 Rationale

Among the important identified risks and important potential risks of this drug, the following were reported in the alogliptin + metformin QD group (alogliptin 25 mg plus metformin hydrochloride 500 mg once daily) of Study SYR-322-MET/CCT-001: infection-related adverse events (26.3%, 40/152 subjects), gastrointestinal symptom-related adverse events (9.9%, 15/152 subjects), lactic acidosis-related adverse events (1.3%, 2/152 subjects), and hepatic function disorder-related adverse events (0.7%, 1/152 subjects). Based on these data, the incidence in this survey can be assumed to be ≥0.7% for such events among the important identified risks and important potential risks of this drug.

Assuming a Poisson distribution for the number of such events occurring in this survey, and with a sample size of 300 each for patients with renal impairment, patients with hepatic impairment, and elderly patients, adverse events occurring with an incidence of ≥0.7% in one of the patient subpopulations can be detected in at least one patient with a probability of ≥87%. Thus, with this sample size, the events reported in Study SYR-322-MET/CCT-001 and designated as important identified risks and important potential risks of this drug would be evaluable to a reasonable extent. For events occurring with a lower incidence, overall safety assessment will be performed based on information not only from this survey but also from other sources including spontaneous reports and literature in particular.

From the viewpoint of patient accrual, patients with hepatic impairment will be the most difficult subpopulation to be accrued in this survey, based on the accrual rates in a previously conducted specified drug-use survey of Nesina Tablets in type 2 diabetes mellitus patients with concomitant use of a biguanide, which also enrolled patients with renal impairment, patients with hepatic impairment, and elderly patients. Thus, in order to ensure that patients with hepatic impairment in particular are adequately enrolled in this survey, the accrual target is set to "300 patients with hepatic impairment". When this target is reached, in light of the extent of overlapping of the subpopulations in the above-mentioned Nesina Tablets specified drug-use survey, approximately 300 patients with renal impairment and approximately 300 elderly patients would have been accrued.

Also, with a total sample size of ≥600 in this survey, improvement in patient convenience by switching to this combination product from alogliptin benzoate and metformin hydrochloride in combination would be evaluable to a reasonable extent.

4.0 Target Patient Population

This survey will be conducted in patients with type 2 diabetes mellitus for whom combination therapy with alogliptin benzoate and metformin hydrochloride is appropriate in the opinion of a physician, and who fulfill the following inclusion criteria and who do not meet the following exclusion criteria. The PRECAUTIONS section of the package insert for this drug should also be referenced.

4.1 Inclusion Criteria

Subjects should meet one or more of the following:

(1) Have renal impairment (mild)
(2) Have hepatic impairment (mild or moderate)
(3) Elderly (aged ≥65 years)

4.2 Exclusion Criteria

Subjects who meet the following criterion will be excluded:

Patients with any contraindication for this drug

5.0 Dosage and Administration

The usual adult dosage of this drug is 1 tablet (ie, 25 mg of alogliptin and 500 mg of metformin hydrochloride) once daily orally immediately before a meal or after a meal. The package insert for this drug should be referenced.

6.0 Planned Number of Survey Sites by Specialty Department

Approximately 120 sites, including department of internal medicine

7.0 Methods

7.1 Duration of Observation

12 months

7.2 Data Collection Method

Data will be collected using a web-based electronic data capture system (CCI [redacted]).

7.3 Patient Enrollment Method

Patients will be enrolled using a centralized registration method via CCI [redacted].

7.4 Case Report Form (Electronic) Completion and Electronic Signature

The survey physician or designee* will enter data on patient background, treatment details, etc. into CCI [redacted] promptly after the end of observation at 12 months of treatment with this drug, and the survey physician will enter an electronic signature. If administration of this drug could not be confirmed, the fact of this should be entered (no other data are required).

For patients who discontinued treatment with this drug for certain reasons during the course of the observation period, the survey physician or designee will enter data on patient background, treatment details, etc. into CCI [redacted] promptly after the end of required observations, and the survey physician will enter an electronic signature. However, for patients who discontinued treatment with this drug because of onset of an adverse event, even after the discontinuation of this drug the survey physician will continue observation as far as possible up to resolution or improvement of the adverse event. The survey physician or designee will then enter the observation result into CCI [redacted], and the survey physician will enter an electronic signature.

*: The survey physician's designee must be a person who belongs to the medical institution (this includes a dispatched CRC or any other person with a signed consignment contract with the medical institution). Before the survey physician's designee can perform data

entry to CCI, the principal survey physician (ie, a person designated under contract at each survey site [medical institution or department] who is responsible for the conduct of the survey at the survey site) will prepare a written record (any format) of the designation and the date of designation and, after signing (or affixing name with seal), submit it to the person in charge of Takeda Pharmaceutical Company Limited (hereinafter referred to as "Takeda personnel").

8.0 Planned Survey Period

Survey period: February 2017 to October 31, 2019

Patient enrollment period: February 2017 to October 31, 2018 Note)

Note) Even if this drug is prescribed by October 31, 2018, no patient enrollment (via CCI) will be acceptable on or after November 1, 2018.

If the total number of patients enrolled in this survey reached the planned sample size before October 31, 2018, patient enrolment will be closed before the end of the patient enrollment period. If the patient enrollment period is shortened, the survey period will also be changed according to the shortened enrollment period.

9.0 Informed Consent

Prior to enrollment of a patient in this survey, the survey physician will obtain written or verbal consent of the patient or the patient's legally acceptable representative. Patients who provided consent will be assigned the subject identification numbers.

10.0 Survey Variables

The survey physician or designee will enter data on the following variables into CCI. The survey schedule is shown in Appendix 1.

10.1 Patient Enrollment

1) Survey variables

Date of prescription of this drug, subject identification number, patient initials, sex, age, assessment against the inclusion criteria (ie, the patient has renal impairment*1 [mild], hepatic impairment*2 [mild or moderate], or advanced age [≥65 years]), assessment against the exclusion criteria (ie, the patient does not have any contraindication for this drug), status of medication for type 2 diabetes mellitus immediately before use of this drug

As a guide to severity assessment of renal impairment and hepatic impairment, the following tables should be referenced.

*1: Severity classification of renal impairment

Severity of renal impairment	eGFR (mL/min/1.73m^2)	Serum creatinine (mg/dL) *	Creatinine clearance (Ccr, mL/min)
Mild	≥60 to <90	Male: >0.90 to ≤1.4 Female: >0.77 to ≤1.2	≥50 to ≤80
Moderate	≥30 to <60	Male: >1.4 to ≤2.4 Female: >1.2 to ≤2.0	≥30 to <50
Severe or end-stage renal disease	<30	Male: >2.4 Female: >2.0	<30

For end-stage renal disease, time of the measurement relative to a hemodialysis session is disregarded.

*: Estimated values corresponding to the Ccr (for persons who are aged 60 years and weigh 65 kg)
Adapted from the "Precautions related to Dosage and Administration" section of Nesina Tablets package insert (see Cockcroft DW, et al. Nephron 1976; 16: 31-41)

*2: Severity classification of hepatic impairment

Severity of hepatic impairment	Mild	Moderate	Severe
Total bilirubin (mg/dL)	≥1.6 to <3.0	≥3.0 to <10	≥10
AST or ALT (U/L)	≥50 to <100	≥100 to <500	≥500
ALP	≥1.25 × ULN to <2.5 × ULN	≥2.5 × ULN to <5 × ULN	≥5 × ULN
Gamma-GTP	≥1.5 × ULN	-	-
LDH	≥1.5 × ULN	-	-
Manifestations	-	Jaundice, hepatomegaly, pain in the right hypochondrium, hepatic steatosis	Bleeding tendency, disturbed consciousness and other signs of hepatic failure (fulminant hepatitis), liver cirrhosis, liver tumor, persistent jaundice over ≥6 months

ULN: Upper limit of normal of the study site

Adapted from Criteria for Seriousness/Severity Grading of Adverse Drug Reactions (Notification No. 80 of the Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated June 29, 1992)

2) Time of data collection

At enrollment of the patient

10.2 Patient Background

1) Survey variables

Time of the diagnosis of type 2 diabetes mellitus, inpatient/outpatient category, hypersensitive diathesis (presence or absence, and details), concurrent diseases (presence or absence, and details), medical history (presence or absence, and details), height, history of smoking, history of alcohol consumption, status of occupation (presence or absence), status

of treatment compliance with alogliptin benzoate and metformin hydrochloride within 3 months before the start of treatment with this drug*[3]

*3: Assessed using a scale from 0% to 100% in increments of 5%.

2) Time of data collection

At initiation of treatment with this drug

10.3 Treatment Details

1) Survey variables

Detailed use of this drug (therapy start date, therapy end date, and reason for discontinuation [if applicable]), detailed use of concomitant drugs*[4] (for the treatment of diabetes mellitus) (presence or absence, if present, name of the drug, daily dose, and therapy dates), detailed use of concomitant drugs (for other conditions than diabetes mellitus) (presence or absence, if present, name of the drug, reason for use)

*4: Including antidiabetic medication discontinued within 3 months before use of this drug (Also, alogliptin benzoate and metformin hydrochloride used before this drug will be investigated.)

2) Time of data collection

From initiation of treatment with this drug until 12 months later (or discontinuation of treatment)

10.4 Treatment Compliance Status for this Drug, and Daily Dosing Frequency and Number of Tablets for Concomitant Drugs

1) Survey variables

The status of treatment compliance with this drug will be assessed using a scale from 0% to 100% in increments of 5%.

Also regarding concomitant drugs (for the treatment of diabetes mellitus or other conditions), the maximum number of doses administered per day and the maximum number of tablets administered per day will be investigated at each time of data collection.

2) Time of data collection

At initiation of treatment with this drug (except treatment compliance status for this drug), and 1, 3, 6, 9, and 12 months later (or discontinuation of treatment)

10.5 Items of Tests and Observations

Data from tests and observations in the routine clinical setting, if performed at the respective time of data collection, will be entered.

10.5.1 Vital Signs

1) Items of tests and observations

Pulse rate, blood pressure (systolic /diastolic), body weight

2) Time of data collection

At initiation of treatment with this drug, and 1, 3, 6, 9, and 12 months later (or discontinuation of treatment), if performed

10.5.2 Laboratory Tests

1) Test variables

HbA1c, fasting blood glucose, fasting insulin, fasting glucagon, fasting triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, serum creatinine, BUN, urinary albumin (urine albumin/creatinine ratio), AST, ALT, gamma-GTP, ALP, LDH, total bilirubin, amylase, lipase, lactic acid

2) Time of data collection

At initiation of treatment with this drug, and 1, 3, 6, 9, and 12 months later (or discontinuation of treatment), if performed

10.5.3 Electrocardiogram

1) Test variable

Electrocardiogram (assessment)

2) Time of data collection

At initiation of treatment with this drug and 12 months later (or discontinuation of treatment), if performed

10.5.4 Waist Circumference and Testing Related to Coronary Arteries and Arteriosclerosis

1) Test variables

Waist circumference*5, testing related to coronary arteries and arteriosclerosis*6 (eg, pulse wave velocity , blood pressure pulse wave test, cervical artery ultrasound, intravascular ultrasound)

*5: Measured at the patient's umbilicus level in a standing position at gentle exhalation. However, in patients with marked fat accumulation with downward deviation of the umbilicus, the waist circumference will be measured at the level of the midpoint between the lowest rib and the anterior superior iliac spine.

*6: Any testing method is allowed, but in principle the same method should be used throughout the individual time points of evaluation. The testing may be omitted if no testing device is available.

2) Time of data collection

At initiation of treatment with this drug and 12 months later (or discontinuation of treatment), if performed

10.5.5 Other Items of Observation

1) Observation item(s)

Presence or absence of pregnancy during the observation (only in women)

2) Time of data collection

From initiation of treatment with this drug until 12 months later (or discontinuation of treatment)

10.6 Adverse Events

1) Survey variables

Presence or absence of adverse events (see Table 1), adverse event term, date of onset, seriousness and reason for the assessment as serious (see Table 2), reason for discontinuation of this drug, outcome assessment date, outcome, causal relationship to this drug*[7] (see Table 3)

If the event outcome is "Not resolved" or "Unknown", and if the causal relationship is "Unassessable", the event should be followed as far as possible.

If onset of any of the following is reported as an adverse event, detailed information should be collected as needed: lactic acidosis, hypoglycemia, acute pancreatitis, hepatic function disorder or jaundice, severe skin disorder such as oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme, rhabdomyolysis, intestinal obstruction, interstitial pneumonia, angioedema, gastrointestinal symptom, infection, malignant tumor, pemphigoid, cardiovascular event (eg, symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death).

*7: If the causal relationship to this drug is "Not related", the basis for the assessment should be collected. If the causal relationship to this drug is "Unassessable", the reason should be collected.

Note) Special guidance about reporting of adverse events:

Abnormal worsening of the target disease, eg, outside the predictable range of the natural course of the disease, is regarded as an adverse event.

2) Time of data collection

From initiation of treatment with this drug until 12 months later (or discontinuation of treatment)

Table 1 Definition of an Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Table 2 Criteria for Serious Adverse Events

An adverse event is assessed as "serious" if it results in any of the following outcomes:

1. results in death (Death),
2. is life-threatening (Life-threatening),
3. requires hospitalization or prolongation of existing hospitalization (Hospitalization/Prolongation of hospitalization),
4. results in persistent or significant disability/incapacity (Disability),
5. leads to a congenital anomaly or birth defect (Congenital anomaly), or
6. is any other important medical event that does not 1 to 5 above.

Note: Also, any reported adverse events consistent with the "Takeda Medically Significant AE List" (Appendix 2) will be handled as serious adverse events by Takeda Pharmaceutical Company Limited.

Table 3 Assessment of the Causal Relationship Between an Adverse Event and this Drug

Causality classification	Definition
Related	An adverse event that follows a temporal sequence from administration of this drug (including the course after withdrawal of the drug), or for which there is at least reasonable possibility of involvement of this drug and its causal role cannot be ruled out, although factors other than the drug, such as the primary disease, concurrent diseases, concomitant drugs or concurrent treatments, may also be responsible.
Not related	An adverse event that does not follow a temporal sequence from administration of this drug or that can be explained reasonably by other factors, such as the primary disease, concurrent diseases, concomitant drugs or concurrent treatments.
Unassessable	The causality cannot be assessed because of insufficiency of required information, such as temporal sequence of the event onset relative to administration of this drug (including the course after withdrawal of the drug), primary disease, concurrent diseases, concomitant drugs, and concurrent treatments.

11.0 Analytical Items and Methods

11.1 Disposition of Patients

Number of patients enrolled in the survey, number of patients with collected case report forms, numbers of patients evaluated for the safety and efficacy, number of patients excluded from analyses and reasons for exclusion, etc. will be summarized.

11.2 Patient Background

Patient background data such as sex, age, duration of type 2 diabetes mellitus, and concurrent diseases will be summarized.

11.3 Treatment Details

Detailed use of this drug and concomitant drugs will be summarized.

11.4 Treatment Compliance Status, and Daily Dosing Frequency and Number of Tablets for Concomitant Drugs

Treatment compliance status will be summarized for alogliptin benzoate and metformin hydrochloride within 3 months before use of this drug, and also for this drug at each time of data collection. Also regarding concomitant drugs (for the treatment of diabetes mellitus and other conditions), the maximum number of doses administered per day and the maximum number of tablets administered per day will be summarized.

11.5 Safety Data

The following data will be summarized using the safety analysis set. Adverse events will be coded using the MedDRA/J, and summarized by Preferred Term (PT) and System Organ Class (SOC).

11.5.1 Adverse Event Profile

Adverse events occurring during the observation period will be summarized using frequency distribution by event type, time to onset, seriousness, causal relationship to this drug, etc.

11.5.2 Factors Likely Affecting the Safety

Adverse drug reactions occurring during the observation period will be summarized using frequency distribution, with stratification of patients according to background factors (eg, sex, age, presence or absence of renal impairment, presence or absence of hepatic impairment) and treatment details (eg, detailed use of this drug).

11.6 Efficacy data

The following data will be summarized using the efficacy analysis set.

11.6.1 HbA1c over time

The HbA1c level and change (value at the respective time after initiation of treatment minus baseline value) at each time point of evaluation will be summarized.

11.6.2 Fasting blood glucose over time

The fasting blood glucose level and change (value at the respective time after initiation of treatment minus baseline value) at each time point of evaluation will be summarized.

11.6.3 Fasting insulin over time

The fasting insulin level and change (value at the respective time after initiation of

treatment minus baseline value) at each time point of evaluation will be summarized.

11.6.4 Factors likely affecting the efficacy

A subgroup analysis will be performed on change in HbA1c etc., with stratification of patients according to background factors (eg, sex, age, presence or absence of renal impairment, presence or absence of hepatic impairment, baseline HbA1c level) and treatment details (eg, detailed use of this drug). In addition, among the patients with no change in the dose of alogliptin benzoate and metformin hydrochloride between before and after the switching to this drug, and no change in the dose of any antidiabetic medication during the treatment with this drug, the treatment compliance status between before and after the use of this drug and change in HbA1c will be summarized, and the relationship between medication adherence and change in HbA1c will be analyzed. In this analysis, in order to minimize influence of other factors than reductions in the number of tablets per day and the number of doses per day by switching to this drug among factors likely contributing to medication adherence, subgroup analyses according to such other factors etc. will be used to characterize the relationship between medication adherence and change in HbA1c as far as possible.

11.6.5 Factors Likely Affecting Medication Adherence

Regarding change in the medication adherence, in order to minimize influence of other factors than reductions in the number of tablets administered per day and the number of doses per day by switching to this drug among factors likely contributing to medication adherence, subgroup analyses according to such other factors etc. will be used to characterize the influence of this drug on the medication adherence.

11.7 Special Patient Populations

For each of the subpopulations of patients with renal impairment, patients with hepatic impairment, and elderly patients in this survey, a similar analysis to Sections 10.1 to 10.8.3 will be performed.

12.0 Survey Informed Consent Form and Patient Consent

The survey informed consent form contains the description as to how the patients' personal information and medical information are used in this survey. The informed consent form also describes the survey overview, the freedom of patients to withdraw from the survey at any time without providing a reason without any disadvantages in treatment.

The survey physician will provide a potential survey subject (or legally acceptable representative) with explanation about this survey as provided in the informed consent form, and obtain verbal or written consent of the patient (or legally acceptable representative) to participate in this survey. For written consent, the patient (or legally

acceptable representative) will sign and date the informed consent form, and the survey physician will retain the original of the signed informed consent form. For verbal consent, the survey physician will document the verbal consent.

13.0 Registration of Survey Information

Before initiation of this survey, information on this survey will be registered with the following website.

- Japan Pharmaceutical Information Center (JAPIC) Clinical Trials Information

14.0 Administrative Structure

See Attachment.

15.0 Trustees

See Attachment.

16.0 Other Necessary Items

16.1 Amendments to the Protocol

During the survey period, monitoring will be performed regarding the progress of the survey, occurrence of adverse drug reactions unexpected from the PRECAUTIONS and serious adverse drug reactions, any increase in the incidence of particular adverse drug reactions, validity of the survey variables, etc., and the protocol will be reviewed and amended as necessary. If any partial change to the DOSAGE AND ADMINISTRATION, INDICATIONS, etc. is approved during the survey period, whether or not the protocol should be amended will be examined, and the protocol will be amended as necessary.

16.2 Actions to be Taken in Response to Detection of any Issues or Concerns

Whenever an issue is found regarding the safety or efficacy, the data will be investigated in detail, and necessary actions will be determined.

Appendix 1 Observation Schedule

Survey variables \ Time of data collection		Observation period							
		Enrollment	Start of treatment	1 month	3 months	6 months	9 months	12 months	Discontinuation of treatment
Scheduled day in the survey		-	0	30	90	180	270	360	-
Allowable window (day) (earliest to latest)		-	−30 to 0	1 to 60	61 to 136	137 to 226	227 to 316	317 to 456	-
Informed consent		○							
Patient enrollment	Date of prescription of this drug	○							
	Subject Identification Number	○							
	Patient Initials	○							
	Sex	○							
	Age	○							
	Inclusion/exclusion criteria	○							
	Usage of alogliptin benzoate and metformin hydrochloride immediately before use of this drug	○							
Patient background	Time of the diagnosis of type 2 diabetes mellitus		○						
	Inpatient/outpatient category		○						
	Hypersensitive diathesis		○						
	Concurrent diseases		○						
	Medical history		○						
	Height		○						
	History of smoking		○						
	History of alcohol consumption		○						
	Status of occupation		○						
	Status of treatment compliance with alogliptin benzoate and metformin hydrochloride within 3 months before the start of treatment with this drug		○						
Treatment details etc.	Detailed use of this drug		←	○	→				○
	Detailed use of concomitant drugs (for diabetes mellitus and other conditions)		←	○	→				○
	Treatment compliance status for this drug			○	○	○	○	○	○
	Concomitant drugs: number of doses per day and number of tablets per day		○	○	○	○	○	○	○
Assessments	Pulse rate, blood pressure, body weight		○	○	○	○	○	○	○
	Laboratory tests • HbA1c • Fasting blood glucose • Fasting insulin • Fasting glucagon • Fasting triglyceride • Total cholesterol • HDL cholesterol • LDL cholesterol • Serum creatinine • BUN • Urinary albumin • AST • ALT • Gamma-GTP • ALP • LDH • Total bilirubin • Amylase • Lipase • Lactic acid		○	○	○	○	○	○	○
	Electrocardiogram		○					○	○
	Waist circumference		○					○	○
	Tests related to coronary arteries and arteriosclerosis		○					○	○
	Any pregnancy (women only)		←		→	○	←	→	○
	Adverse events monitoring		←		→	○	←	→	○

○: Performed (Data from tests and observations in the routine clinical setting will be recorded if they were performed within the respective allowable time periods. Data from tests and observations at discontinuation of treatment will be entered within the allowable time period.)

← ○ → Performed throughout the period

Appendix 2 Takeda Medically Significant AE List

General
Malignancy
Endotoxic shock
Sepsis
Transmission of an infectious agent by a medicinal product

Blood and lymphatic System
Bone marrow failure
Disseminated Intravascular Coagulation
Haemolytic anaemia
Thrombotic Thrombocytopenic Purpura

Cardiovascular System
Cardiac arrest
Cardiac failure
Cardiomyopathy acute
Malignant hypertension
Myocardial infarction
Ventricular arrhythmias

Endocrine System
Adrenal crisis

Gastrointestinal System
Acute pancreatitis
GI haemorrhage
GI perforation
GI obstruction
Necrotising colitis
Peritonitis

Hepatobiliary System
Acute hepatic failure
Fulminant hepatitis

Urinary System
Acute renal failure

Immune system
Anaphylaxis
Progressive multifocal leukoencephalopathy (PML)
Transplant rejection

Musculoskeletal System
Rhabdomyolysis

Nervous System
Cerebrovascular accident
Coma
Convulsive seizures
Hyperthermia malignant
Macular oedema
Meningoencephalitis
Neuroleptic malignant syndrome
Suicidal behaviour

Reproductive System
Abortion
Uterine perforation

Respiratory System
Acute respiratory failure
Pulmonary hypertension
Pulmonary thromboembolism

Skin and subcutaneous tissue
Toxic epidermal necrolysis
Stevens-Johnson syndrome

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Survey Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol Number	**Alogliptin-Met-5003**
Version Number	**Version 4**
Date of Preparation	**November 27, 2017**

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3.2 Rationale

Among the important identified risks and important potential risks of this drug, the following were reported in the alogliptin + metformin QD group (alogliptin 25 mg plus metformin hydrochloride 500 mg once daily) of Study SYR-322-MET/CCT-001: infection-related adverse events (26.3%, 40/152 subjects), gastrointestinal symptom-related adverse events (9.9%, 15/152 subjects), lactic acidosis-related adverse events (1.3%, 2/152 subjects), and hepatic function disorder-related adverse events (0.7%, 1/152 subjects). Based on these data, the incidence in this survey can be assumed to be ≥0.7% for such events among the important identified risks and important potential risks of this drug.

Assuming a Poisson distribution for the number of such events occurring in this survey, and with a sample size of 300 each for patients with renal impairment, patients with hepatic impairment, and elderly patients, adverse events occurring with an incidence of ≥0.7% in one of the patient subpopulations can be detected in at least one patient with a probability of ≥87%. Thus, with this sample size, the events reported in Study SYR-322-MET/CCT-001 and designated as important identified risks and important potential risks of this drug would be evaluable to a reasonable extent. For events occurring with a lower incidence, overall safety assessment will be performed based on information not only from this survey but also from other sources including spontaneous reports and literature in particular.

From the viewpoint of patient accrual, patients with hepatic impairment will be the most difficult subpopulation to be accrued in this survey, based on the accrual rates in a previously conducted specified drug-use survey of Nesina Tablets in type 2 diabetes mellitus patients with concomitant use of a biguanide, which also enrolled patients with renal impairment, patients with hepatic impairment, and elderly patients. Thus, in order to ensure that patients with hepatic impairment in particular are adequately enrolled in this survey, the accrual target is set to "300 patients with hepatic impairment". When this target is reached, in light of the extent of overlapping of the subpopulations in the above-mentioned Nesina Tablets specified drug-use survey, approximately 300 patients with renal impairment and approximately 300 elderly patients would have been accrued.

Also, with a total sample size of ≥600 in this survey, improvement in patient convenience by switching to this combination product from alogliptin benzoate and metformin hydrochloride in combination would be evaluable to a reasonable extent.

4.0 Target Patient Population

This survey will be conducted in patients with type 2 diabetes mellitus for whom combination therapy with alogliptin benzoate and metformin hydrochloride is appropriate in the opinion of a physician, and who fulfill the following inclusion criteria and who do not meet the following exclusion criteria. The PRECAUTIONS section of the package insert for this drug should also be referenced.

4.1 Inclusion Criteria

Subjects should meet one or more of the following:

(1) Have renal impairment (mild)
(2) Have hepatic impairment (mild or moderate)
(3) Elderly (aged ≥65 years)

4.2 Exclusion Criteria

Subjects who meet the following criterion will be excluded:

Patients with any contraindication for this drug

5.0 Dosage and Administration

The usual adult dosage of this drug is 1 tablet (ie, 25 mg of alogliptin and 500 mg of metformin hydrochloride) once daily orally immediately before a meal or after a meal. The package insert for this drug should be referenced.

6.0 Planned Number of Survey Sites by Specialty Department

Approximately 120 sites, including department of internal medicine

7.0 Methods

7.1 Duration of Observation

12 months

7.2 Data Collection Method

Data will be collected using a web-based electronic data capture system ([CCI]).

7.3 Patient Enrollment Method

Patients will be enrolled using a centralized registration method via [CCI]

7.4 Case Report Form (Electronic) Completion and Electronic Signature

The survey physician or designee* will enter data on patient background, treatment details, etc. into [CCI] promptly after the end of observation at 12 months of treatment with this drug, and the survey physician will enter an electronic signature. If administration of this drug could not be confirmed, the fact of this should be entered (no other data are required).

For patients who discontinued treatment with this drug for certain reasons during the course of the observation period, the survey physician or designee will enter data on patient background, treatment details, etc. into [CCI] promptly after the end of required observations, and the survey physician will enter an electronic signature. However, for patients who discontinued treatment with this drug because of onset of an adverse event, even after the discontinuation of this drug the survey physician will continue observation as far as possible up to resolution or improvement of the adverse event. The survey physician or designee will then enter the observation result into [CCI], and the survey physician will enter an electronic signature.

*: The survey physician's designee must be a person who belongs to the medical institution (this includes a dispatched CRC or any other person with a signed consignment contract with the medical institution). Before the survey physician's designee can perform data

entry to [redacted], the principal survey physician (ie, a person designated under contract at each survey site [medical institution or department] who is responsible for the conduct of the survey at the survey site) will prepare a written record (any format) of the designation and the date of designation and, after signing (or affixing name with seal), submit it to the person in charge of Takeda Pharmaceutical Company Limited (hereinafter referred to as "Takeda personnel").

8.0 Planned Survey Period

Survey period: February 2017 to October 31, 2019

Patient enrollment period: February 2017 to October 31, 2018 Note)

Note) Even if this drug is prescribed by October 31, 2018, no patient enrollment (via [redacted]) will be acceptable on or after November 1, 2018.

If the total number of patients enrolled in this survey reached the planned sample size before October 31, 2018, patient enrolment will be closed before the end of the patient enrollment period. If the patient enrollment period is shortened, the survey period will also be changed according to the shortened enrollment period.

9.0 Informed Consent

Prior to enrollment of a patient in this survey, the survey physician will obtain written or verbal consent of the patient or the patient's legally acceptable representative. Patients who provided consent will be assigned the subject identification numbers.

10.0 Survey Variables

The survey physician or designee will enter data on the following variables into [redacted]. The survey schedule is shown in Appendix 1.

10.1 Patient Enrollment

1) Survey variables

Date of prescription of this drug, subject identification number, patient initials, sex, age, assessment against the inclusion criteria (ie, the patient has renal impairment*1 [mild], hepatic impairment*2 [mild or moderate], or advanced age [≥65 years]), assessment against the exclusion criteria (ie, the patient does not have any contraindication for this drug), status of medication for type 2 diabetes mellitus immediately before use of this drug

As a guide to severity assessment of renal impairment and hepatic impairment, the following tables should be referenced.

*1: Severity classification of renal impairment

Severity of renal impairment	eGFR (mL/min/1.73m^2)	Serum creatinine (mg/dL) *	Creatinine clearance (Ccr, mL/min)
Mild	≥60 to <90	Male: >0.90 to ≤1.4 Female: >0.77 to ≤1.2	≥50 to ≤80
Moderate	≥30 to <60	Male: >1.4 to ≤2.4 Female: >1.2 to ≤2.0	≥30 to <50
Severe or end-stage renal disease	<30	Male: >2.4 Female: >2.0	<30

For end-stage renal disease, time of the measurement relative to a hemodialysis session is disregarded.

*: Estimated values corresponding to the Ccr (for persons who are aged 60 years and weigh 65 kg)
Adapted from the "Precautions related to Dosage and Administration" section of Nesina Tablets package insert (see Cockcroft DW, et al. Nephron 1976; 16: 31-41)

*2: Severity classification of hepatic impairment

Severity of hepatic impairment	Mild	Moderate	Severe
Total bilirubin (mg/dL)	≥1.6 to <3.0	≥3.0 to <10	≥10
AST or ALT (U/L)	≥50 to <100	≥100 to <500	≥500
ALP	≥1.25 × ULN to <2.5 × ULN	≥2.5 × ULN to <5 × ULN	≥5 × ULN
Gamma-GTP	≥1.5 × ULN	-	-
LDH	≥1.5 × ULN	-	-
Manifestations	-	Jaundice, hepatomegaly, pain in the right hypochondrium, hepatic steatosis	Bleeding tendency, disturbed consciousness and other signs of hepatic failure (fulminant hepatitis), liver cirrhosis, liver tumor, persistent jaundice over ≥6 months

ULN: Upper limit of normal of the study site

Adapted from Criteria for Seriousness/Severity Grading of Adverse Drug Reactions (Notification No. 80 of the Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated June 29, 1992)

2) Time of data collection

At enrollment of the patient

10.2 Patient Background

1) Survey variables

Time of the diagnosis of type 2 diabetes mellitus, inpatient/outpatient category, hypersensitive diathesis (presence or absence, and details), concurrent diseases (presence or absence, and details), medical history (presence or absence, and details), height, history of smoking, history of alcohol consumption, status of occupation (presence or absence), status

of treatment compliance with alogliptin benzoate and metformin hydrochloride within 3 months before the start of treatment with this drug*[3]

*3: Assessed using a scale from 0% to 100% in increments of 5%.

2) Time of data collection

At initiation of treatment with this drug

10.3 Treatment Details

1) Survey variables

Detailed use of this drug (therapy start date, therapy end date, and reason for discontinuation [if applicable]), detailed use of concomitant drugs*[4] (for the treatment of diabetes mellitus) (presence or absence, if present, name of the drug, daily dose, and therapy dates), detailed use of concomitant drugs (for other conditions than diabetes mellitus) (presence or absence, if present, name of the drug, reason for use)

*4: Including antidiabetic medication discontinued within 3 months before use of this drug (Also, alogliptin benzoate and metformin hydrochloride used before this drug will be investigated.)

2) Time of data collection

From initiation of treatment with this drug until 12 months later (or discontinuation of treatment)

10.4 Treatment Compliance Status for this Drug, and Daily Dosing Frequency and Number of Tablets for Concomitant Drugs

1) Survey variables

The status of treatment compliance with this drug will be assessed using a scale from 0% to 100% in increments of 5%.

Also regarding concomitant drugs (for the treatment of diabetes mellitus or other conditions), the maximum number of doses administered per day and the maximum number of tablets administered per day will be investigated at each time of data collection.

2) Time of data collection

At initiation of treatment with this drug (except treatment compliance status for this drug), and 1, 3, 6, 9, and 12 months later (or discontinuation of treatment)

10.5 Items of Tests and Observations

Data from tests and observations in the routine clinical setting, if performed at the respective time of data collection, will be entered.

10.5.1 Vital Signs

1) Items of tests and observations

Pulse rate, blood pressure (systolic /diastolic), body weight

2) Time of data collection

At initiation of treatment with this drug, and 1, 3, 6, 9, and 12 months later (or discontinuation of treatment), if performed

10.5.2 Laboratory Tests

1) Test variables

HbA1c, fasting blood glucose, fasting insulin, fasting glucagon, fasting triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, serum creatinine, BUN, urinary albumin (urine albumin/creatinine ratio), AST, ALT, gamma-GTP, ALP, LDH, total bilirubin, amylase, lipase, lactic acid

2) Time of data collection

At initiation of treatment with this drug, and 1, 3, 6, 9, and 12 months later (or discontinuation of treatment), if performed

10.5.3 Electrocardiogram

1) Test variable

Electrocardiogram (assessment)

2) Time of data collection

At initiation of treatment with this drug and 12 months later (or discontinuation of treatment), if performed

10.5.4 Waist Circumference and Testing Related to Coronary Arteries and Arteriosclerosis

1) Test variables

Waist circumference*5, testing related to coronary arteries and arteriosclerosis*6 (eg, pulse wave velocity , blood pressure pulse wave test, cervical artery ultrasound, intravascular ultrasound)

*5: Measured at the patient's umbilicus level in a standing position at gentle exhalation. However, in patients with marked fat accumulation with downward deviation of the umbilicus, the waist circumference will be measured at the level of the midpoint between the lowest rib and the anterior superior iliac spine.

*6: Any testing method is allowed, but in principle the same method should be used throughout the individual time points of evaluation. The testing may be omitted if no testing device is available.

2) Time of data collection

At initiation of treatment with this drug and 12 months later (or discontinuation of treatment), if performed

10.5.5 Other Items of Observation

1) Observation item(s)

Presence or absence of pregnancy during the observation (only in women)

2) Time of data collection

From initiation of treatment with this drug until 12 months later (or discontinuation of treatment)

10.6 Adverse Events

1) Survey variables

Presence or absence of adverse events (see Table 1), adverse event term, date of onset, seriousness and reason for the assessment as serious (see Table 2), reason for discontinuation of this drug, outcome assessment date, outcome, causal relationship to this drug*[7] (see Table 3)

If the event outcome is "Not resolved" or "Unknown", and if the causal relationship is "Unassessable", the event should be followed as far as possible.

If onset of any of the following is reported as an adverse event, detailed information should be collected as needed: lactic acidosis, hypoglycemia, acute pancreatitis, hepatic function disorder or jaundice, severe skin disorder such as oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme, rhabdomyolysis, intestinal obstruction, interstitial pneumonia, angioedema, gastrointestinal symptom, infection, malignant tumor, pemphigoid, cardiovascular event (eg, symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death).

*7: If the causal relationship to this drug is "Not related", the basis for the assessment should be collected. If the causal relationship to this drug is "Unassessable", the reason should be collected.

Note) Special guidance about reporting of adverse events:

Abnormal worsening of the target disease, eg, outside the predictable range of the natural course of the disease, is regarded as an adverse event.

2) Time of data collection

From initiation of treatment with this drug until 12 months later (or discontinuation of treatment)

Table 1 Definition of an Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Table 2 Criteria for Serious Adverse Events

An adverse event is assessed as "serious" if it results in any of the following outcomes:

1. results in death (Death),
2. is life-threatening (Life-threatening),
3. requires hospitalization or prolongation of existing hospitalization (Hospitalization/Prolongation of hospitalization),
4. results in persistent or significant disability/incapacity (Disability),
5. leads to a congenital anomaly or birth defect (Congenital anomaly), or
6. is any other important medical event that does not 1 to 5 above.

Note: Also, any reported adverse events consistent with the "Takeda Medically Significant AE List" (Appendix 2) will be handled as serious adverse events by Takeda Pharmaceutical Company Limited.

Table 3 Assessment of the Causal Relationship Between an Adverse Event and this Drug

Causality classification	Definition
Related	An adverse event that follows a temporal sequence from administration of this drug (including the course after withdrawal of the drug), or for which there is at least reasonable possibility of involvement of this drug and its causal role cannot be ruled out, although factors other than the drug, such as the primary disease, concurrent diseases, concomitant drugs or concurrent treatments, may also be responsible.
Not related	An adverse event that does not follow a temporal sequence from administration of this drug or that can be explained reasonably by other factors, such as the primary disease, concurrent diseases, concomitant drugs or concurrent treatments.
Unassessable	The causality cannot be assessed because of insufficiency of required information, such as temporal sequence of the event onset relative to administration of this drug (including the course after withdrawal of the drug), primary disease, concurrent diseases, concomitant drugs, and concurrent treatments.

11.0 Analytical Items and Methods

11.1 Disposition of Patients

Number of patients enrolled in the survey, number of patients with collected case report forms, numbers of patients evaluated for the safety and efficacy, number of patients excluded from analyses and reasons for exclusion, etc. will be summarized.

11.2 Patient Background

Patient background data such as sex, age, duration of type 2 diabetes mellitus, and concurrent diseases will be summarized.

11.3 Treatment Details

Detailed use of this drug and concomitant drugs will be summarized.

11.4 Treatment Compliance Status, and Daily Dosing Frequency and Number of Tablets for Concomitant Drugs

Treatment compliance status will be summarized for alogliptin benzoate and metformin hydrochloride within 3 months before use of this drug, and also for this drug at each time of data collection. Also regarding concomitant drugs (for the treatment of diabetes mellitus and other conditions), the maximum number of doses administered per day and the maximum number of tablets administered per day will be summarized.

11.5 Safety Data

The following data will be summarized using the safety analysis set. Adverse events will be coded using the MedDRA/J, and summarized by Preferred Term (PT) and System Organ Class (SOC).

11.5.1 Adverse Event Profile

Adverse events occurring during the observation period will be summarized using frequency distribution by event type, time to onset, seriousness, causal relationship to this drug, etc.

11.5.2 Factors Likely Affecting the Safety

Adverse drug reactions occurring during the observation period will be summarized using frequency distribution, with stratification of patients according to background factors (eg, sex, age, presence or absence of renal impairment, presence or absence of hepatic impairment) and treatment details (eg, detailed use of this drug).

11.6 Efficacy data

The following data will be summarized using the efficacy analysis set.

11.6.1 HbA1c over time

The HbA1c level and change (value at the respective time after initiation of treatment minus baseline value) at each time point of evaluation will be summarized.

11.6.2 Fasting blood glucose over time

The fasting blood glucose level and change (value at the respective time after initiation of treatment minus baseline value) at each time point of evaluation will be summarized.

11.6.3 Fasting insulin over time

The fasting insulin level and change (value at the respective time after initiation of

treatment minus baseline value) at each time point of evaluation will be summarized.

11.6.4 Factors likely affecting the efficacy

A subgroup analysis will be performed on change in HbA1c etc., with stratification of patients according to background factors (eg, sex, age, presence or absence of renal impairment, presence or absence of hepatic impairment, baseline HbA1c level) and treatment details (eg, detailed use of this drug). In addition, among the patients with no change in the dose of alogliptin benzoate and metformin hydrochloride between before and after the switching to this drug, and no change in the dose of any antidiabetic medication during the treatment with this drug, the treatment compliance status between before and after the use of this drug and change in HbA1c will be summarized, and the relationship between medication adherence and change in HbA1c will be analyzed. In this analysis, in order to minimize influence of other factors than reductions in the number of tablets per day and the number of doses per day by switching to this drug among factors likely contributing to medication adherence, subgroup analyses according to such other factors etc. will be used to characterize the relationship between medication adherence and change in HbA1c as far as possible.

11.6.5 Factors Likely Affecting Medication Adherence

Regarding change in the medication adherence, in order to minimize influence of other factors than reductions in the number of tablets administered per day and the number of doses per day by switching to this drug among factors likely contributing to medication adherence, subgroup analyses according to such other factors etc. will be used to characterize the influence of this drug on the medication adherence.

11.7 Special Patient Populations

For each of the subpopulations of patients with renal impairment, patients with hepatic impairment, and elderly patients in this survey, a similar analysis to Sections 10.1 to 10.8.3 will be performed.

12.0 Survey Informed Consent Form and Patient Consent

The survey informed consent form contains the description as to how the patients' personal information and medical information are used in this survey. The informed consent form also describes the survey overview, the freedom of patients to withdraw from the survey at any time without providing a reason without any disadvantages in treatment.

The survey physician will provide a potential survey subject (or legally acceptable representative) with explanation about this survey as provided in the informed consent form, and obtain verbal or written consent of the patient (or legally acceptable representative) to participate in this survey. For written consent, the patient (or legally

acceptable representative) will sign and date the informed consent form, and the survey physician will retain the original of the signed informed consent form. For verbal consent, the survey physician will document the verbal consent.

13.0 Registration of Survey Information

Before initiation of this survey, information on this survey will be registered with the following website.

- Japan Pharmaceutical Information Center (JAPIC) Clinical Trials Information

14.0 Administrative Structure

See Attachment.

15.0 Trustees

See Attachment.

16.0 Other Necessary Items

16.1 Amendments to the Protocol

During the survey period, monitoring will be performed regarding the progress of the survey, occurrence of adverse drug reactions unexpected from the PRECAUTIONS and serious adverse drug reactions, any increase in the incidence of particular adverse drug reactions, validity of the survey variables, etc., and the protocol will be reviewed and amended as necessary. If any partial change to the DOSAGE AND ADMINISTRATION, INDICATIONS, etc. is approved during the survey period, whether or not the protocol should be amended will be examined, and the protocol will be amended as necessary.

16.2 Actions to be Taken in Response to Detection of any Issues or Concerns

Whenever an issue is found regarding the safety or efficacy, the data will be investigated in detail, and necessary actions will be determined.

Appendix 1 Observation Schedule

Survey variables \ Time of data collection		Observation period							
		Enrollment	Start of treatment	1 month	3 months	6 months	9 months	12 months	Discontinuation of treatment
Scheduled day in the survey		-	0	30	90	180	270	360	-
Allowable window (day) (earliest to latest)		-	−30 to 0	1 to 60	61 to 136	137 to 226	227 to 316	317 to 456	-
Informed consent		○							
Patient enrollment	Date of prescription of this drug	○							
	Subject Identification Number	○							
	Patient Initials	○							
	Sex	○							
	Age	○							
	Inclusion/exclusion criteria	○							
	Usage of alogliptin benzoate and metformin hydrochloride immediately before use of this drug	○							
Patient background	Time of the diagnosis of type 2 diabetes mellitus		○						
	Inpatient/outpatient category		○						
	Hypersensitive diathesis		○						
	Concurrent diseases		○						
	Medical history		○						
	Height		○						
	History of smoking		○						
	History of alcohol consumption		○						
	Status of occupation		○						
	Status of treatment compliance with alogliptin benzoate and metformin hydrochloride within 3 months before the start of treatment with this drug		○						
Treatment details etc.	Detailed use of this drug		←	○	→				○
	Detailed use of concomitant drugs (for diabetes mellitus and other conditions)		←	○	→				○
	Treatment compliance status for this drug			○	○	○	○	○	○
	Concomitant drugs: number of doses per day and number of tablets per day		○	○	○	○	○	○	○
Assessments	Pulse rate, blood pressure, body weight		○	○	○	○	○	○	○
	Laboratory tests • HbA1c • Fasting blood glucose • Fasting insulin • Fasting glucagon • Fasting triglyceride • Total cholesterol • HDL cholesterol • LDL cholesterol • Serum creatinine • BUN • Urinary albumin • AST • ALT • Gamma-GTP • ALP • LDH • Total bilirubin • Amylase • Lipase • Lactic acid		○	○	○	○	○	○	○
	Electrocardiogram		○					○	○
	Waist circumference		○					○	○
	Tests related to coronary arteries and arteriosclerosis		○					○	○
	Any pregnancy (women only)		←		→	○	←	→	○
	Adverse events monitoring		←		→	○	←	→	○

○: Performed (Data from tests and observations in the routine clinical setting will be recorded if they were performed within the respective allowable time periods. Data from tests and observations at discontinuation of treatment will be entered within the allowable time period.)

← ○ → Performed throughout the period

Appendix 2 Takeda Medically Significant AE List

General
Malignancy
Endotoxic shock
Sepsis
Transmission of an infectious agent by a medicinal product

Blood and lymphatic System
Bone marrow failure
Disseminated Intravascular Coagulation
Haemolytic anaemia
Thrombotic Thrombocytopenic Purpura

Cardiovascular System
Cardiac arrest
Cardiac failure
Cardiomyopathy acute
Malignant hypertension
Myocardial infarction
Ventricular arrhythmias

Endocrine System
Adrenal crisis

Gastrointestinal System
Acute pancreatitis
GI haemorrhage
GI perforation
GI obstruction
Necrotising colitis
Peritonitis

Hepatobiliary System
Acute hepatic failure
Fulminant hepatitis

Urinary System
Acute renal failure

Immune system
Anaphylaxis
Progressive multifocal leukoencephalopathy (PML)
Transplant rejection

Musculoskeletal System
Rhabdomyolysis

Nervous System
Cerebrovascular accident
Coma
Convulsive seizures
Hyperthermia malignant
Macular oedema
Meningoencephalitis
Neuroleptic malignant syndrome
Suicidal behaviour

Reproductive System
Abortion
Uterine perforation

Respiratory System
Acute respiratory failure
Pulmonary hypertension
Pulmonary thromboembolism

Skin and subcutaneous tissue
Toxic epidermal necrolysis
Stevens-Johnson syndrome

Protocol for Specified Drug-Use Survey of INISYNC Combination Tablets "Survey on long-term use in type 2 diabetes mellitus patients with renal or hepatic impairment or advanced age"

Survey Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol Number	**Alogliptin-Met-5003**
Version Number	**Version 3**
Date of Preparation	**January 12, 2017**

Table of Contents

1.0 Background

Drugs to treat type 2 diabetes mellitus are likely used over a long time in the routine clinical setting. Inisync Combination Tablets (hereinafter referred to as "this drug") contain two active ingredients: alogliptin benzoate (brand name, Nesina Tablets) and metformin hydrochloride. Long-term combination use of these drugs in the routine clinical setting was previously investigated in a specified drug-use survey. However, clinical trial data were limited on the safety and efficacy of this drug in patients with renal impairment, patients with hepatic impairment and elderly patients, and therefore data in these patient populations are designated as part of "important missing information" in the risk management plan for this drug. Thus, with a focus particularly on these patient populations, the present specified drug-use survey (hereinafter referred to as "this survey") has been planned to investigate the long-term safety and efficacy of this drug used in the routine clinical setting in type 2 diabetes mellitus patients with renal or hepatic impairment or advanced age.

This survey will be conducted in compliance with the Ministerial Ordinance on Good Post-Marketing Study Practice (GPSP) and relevant regulatory requirements.

2.0 Objectives

This survey aims to evaluate the long-term safety and efficacy of this drug in type 2 diabetes mellitus patients with renal impairment (mild), hepatic impairment (mild or moderate), or advanced age (≥65 years) in the routine clinical setting. In addition, this survey will enroll as many as possible patients who were switched from alogliptin 25 mg and metformin hydrochloride 500 mg (ie, 250 mg twice daily) in combination as a prior medication, to examine the relationship between the efficacy and improvement in medication adherence by the switching to this combination product in those who were taking alogliptin benzoate and metformin hydrochloride in combination.

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

600 subjects (including 300 subjects with hepatic impairment)

3.2 Rationale

Among the important identified risks and important potential risks of this drug, the following were reported in the alogliptin + metformin QD group (alogliptin 25 mg plus metformin hydrochloride 500 mg once daily) of Study SYR-322-MET/CCT-001: infection-related adverse events (26.3%, 40/152 subjects), gastrointestinal symptom-related adverse events (9.9%, 15/152 subjects), lactic acidosis-related adverse events (1.3%, 2/152 subjects), and hepatic function disorder-related adverse events (0.7%, 1/152 subjects). Based on these data, the incidence in this survey can be assumed to be ≥0.7% for such events among the important identified risks and important potential risks of this drug.

Assuming a Poisson distribution for the number of such events occurring in this survey, and with a sample size of 300 each for patients with renal impairment, patients with hepatic impairment, and elderly patients, adverse events occurring with an incidence of ≥0.7% in one of the patient subpopulations can be detected in at least one patient with a probability of ≥87%. Thus, with this sample size, the events reported in Study SYR-322-MET/CCT-001 and designated as important identified risks and important potential risks of this drug would be evaluable to a reasonable extent. For events occurring with a lower incidence, overall safety assessment will be performed based on information not only from this survey but also from other sources including spontaneous reports and literature in particular.

From the viewpoint of patient accrual, patients with hepatic impairment will be the most difficult subpopulation to be accrued in this survey, based on the accrual rates in a previously conducted specified drug-use survey of Nesina Tablets in type 2 diabetes mellitus patients with concomitant use of a biguanide, which also enrolled patients with renal impairment, patients with hepatic impairment, and elderly patients. Thus, in order to ensure that patients with hepatic impairment in particular are adequately enrolled in this survey, the accrual target is set to "300 patients with hepatic impairment". When this target is reached, in light of the extent of overlapping of the subpopulations in the above-mentioned Nesina Tablets specified drug-use survey, approximately 300 patients with renal impairment and approximately 300 elderly patients would have been accrued.

Also, with a total sample size of ≥600 in this survey, improvement in patient convenience by switching to this combination product from alogliptin benzoate and metformin hydrochloride in combination would be evaluable to a reasonable extent.

4.0 Target Patient Population

This survey will be conducted in patients with type 2 diabetes mellitus for whom combination therapy with alogliptin benzoate and metformin hydrochloride is appropriate in the opinion of a physician, and who fulfill the following inclusion criteria and who do not meet the following exclusion criteria. The PRECAUTIONS section of the package insert for this drug should also be referenced.

4.1 Inclusion Criteria

Subjects should meet one or more of the following:

(1) Have renal impairment (mild)
(2) Have hepatic impairment (mild or moderate)
(3) Elderly (aged ≥65 years)

4.2 Exclusion Criteria

Subjects who meet the following criterion will be excluded:

Patients with any contraindication for this drug

5.0 Dosage and Administration

The usual adult dosage of this drug is 1 tablet (ie, 25 mg of alogliptin and 500 mg of metformin hydrochloride) once daily orally immediately before a meal or after a meal. The package insert for this drug should be referenced.

6.0 Planned Number of Survey Sites by Specialty Department

Approximately 120 sites, including department of internal medicine

7.0 Methods

7.1 Duration of Observation

12 months

7.2 Data Collection Method

Data will be collected using a web-based electronic data capture system ([CCI]).

7.3 Patient Enrollment Method

Patients will be enrolled using a centralized registration method via [CCI].

7.4 Case Report Form (Electronic) Completion and Electronic Signature

The survey physician or designee* will enter data on patient background, treatment details, etc. into [CCI] promptly after the end of observation at 12 months of treatment with this drug, and the survey physician will enter an electronic signature. If administration of this drug could not be confirmed, the fact of this should be entered (no other data are required).

For patients who discontinued treatment with this drug for certain reasons during the course of the observation period, the survey physician or designee will enter data on patient background, treatment details, etc. into [CCI] promptly after the end of required observations, and the survey physician will enter an electronic signature. However, for patients who discontinued treatment with this drug because of onset of an adverse event, even after the discontinuation of this drug the survey physician will continue observation as far as possible up to resolution or improvement of the adverse event. The survey physician or designee will then enter the observation result into [CCI], and the survey physician will enter an electronic signature.

*: The survey physician's designee must be a person who belongs to the medical institution (this includes a dispatched CRC or any other person with a signed consignment contract with the medical institution). Before the survey physician's designee can perform data

entry to CCI, the principal survey physician (ie, a person designated under contract at each survey site [medical institution or department] who is responsible for the conduct of the survey at the survey site) will prepare a written record (any format) of the designation and the date of designation and, after signing (or affixing name with seal), submit it to the person in charge of Takeda Pharmaceutical Company Limited (hereinafter referred to as "Takeda personnel").

8.0 Planned Survey Period

Survey period: February 2017 to June 30, 2019

Patient enrollment period: February 2017 to June 30, 2018 Note)

Note) Even if this drug is prescribed by June 30, 2018, no patient enrollment (via CCI) will be acceptable on or after July 1, 2018.

If the total number of patients enrolled in this survey reached the planned sample size before June 30, 2018, patient enrolment will be closed before the end of the patient enrollment period. If the patient enrollment period is shortened, the survey period will also be changed according to the shortened enrollment period.

9.0 Informed Consent

Prior to enrollment of a patient in this survey, the survey physician will obtain written or verbal consent of the patient or the patient's legally acceptable representative. Patients who provided consent will be assigned the subject identification numbers.

10.0 Survey Variables

The survey physician or designee will enter data on the following variables into CCI. The survey schedule is shown in Appendix 1.

10.1 Patient Enrollment

1) Survey variables

Date of prescription of this drug, subject identification number, patient initials, sex, age, assessment against the inclusion criteria (ie, the patient has renal impairment*1 [mild], hepatic impairment*2 [mild or moderate], or advanced age [≥65 years]), assessment against the exclusion criteria (ie, the patient does not have any contraindication for this drug), status of medication for type 2 diabetes mellitus immediately before use of this drug

As a guide to severity assessment of renal impairment and hepatic impairment, the following tables should be referenced.

*1: Severity classification of renal impairment

Severity of renal impairment	eGFR (mL/min/1.73m^2)	Serum creatinine (mg/dL) *	Creatinine clearance (Ccr, mL/min)
Mild	≥60 to <90	Male: >0.90 to ≤1.4 Female: >0.77 to ≤1.2	≥50 to ≤80
Moderate	≥30 to <60	Male: >1.4 to ≤2.4 Female: >1.2 to ≤2.0	≥30 to <50
Severe or end-stage renal disease	<30	Male: >2.4 Female: >2.0	<30

For end-stage renal disease, time of the measurement relative to a hemodialysis session is disregarded.

*: Estimated values corresponding to the Ccr (for persons who are aged 60 years and weigh 65 kg)
Adapted from the "Precautions related to Dosage and Administration" section of Nesina Tablets package insert (see Cockcroft DW, et al. Nephron 1976; 16: 31-41)

*2: Severity classification of hepatic impairment

Severity of hepatic impairment	Mild	Moderate	Severe
Total bilirubin (mg/dL)	≥1.6 to <3.0	≥3.0 to <10	≥10
AST or ALT (U/L)	≥50 to <100	≥100 to <500	≥500
ALP	≥1.25 × ULN to <2.5 × ULN	≥2.5 × ULN to <5 × ULN	≥5 × ULN
Gamma-GTP	≥1.5 × ULN	-	-
LDH	≥1.5 × ULN	-	-
Manifestations	-	Jaundice, hepatomegaly, pain in the right hypochondrium, hepatic steatosis	Bleeding tendency, disturbed consciousness and other signs of hepatic failure (fulminant hepatitis), liver cirrhosis, liver tumor, persistent jaundice over ≥6 months

ULN: Upper limit of normal of the study site

Adapted from Criteria for Seriousness/Severity Grading of Adverse Drug Reactions (Notification No. 80 of the Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated June 29, 1992)

2) Time of data collection

At enrollment of the patient

10.2 Patient Background

1) Survey variables

Time of the diagnosis of type 2 diabetes mellitus, inpatient/outpatient category, hypersensitive diathesis (presence or absence, and details), concurrent diseases (presence or absence, and details), medical history (presence or absence, and details), height, history of smoking, history of alcohol consumption, status of occupation (presence or absence), status

of treatment compliance with alogliptin benzoate and metformin hydrochloride within 3 months before the start of treatment with this drug*[3]

*3: Assessed using a scale from 0% to 100% in increments of 5%.

2) Time of data collection

At initiation of treatment with this drug

10.3 Treatment Details

1) Survey variables

Detailed use of this drug (therapy start date, therapy end date, and reason for discontinuation [if applicable]), detailed use of concomitant drugs*[4] (for the treatment of diabetes mellitus) (presence or absence, if present, name of the drug, daily dose, and therapy dates), detailed use of concomitant drugs (for other conditions than diabetes mellitus) (presence or absence, if present, name of the drug, reason for use)

*4: Including antidiabetic medication discontinued within 3 months before use of this drug (Also, alogliptin benzoate and metformin hydrochloride used before this drug will be investigated.)

2) Time of data collection

From initiation of treatment with this drug until 12 months later (or discontinuation of treatment)

10.4 Treatment Compliance Status for this Drug, and Daily Dosing Frequency and Number of Tablets for Concomitant Drugs

1) Survey variables

The status of treatment compliance with this drug will be assessed using a scale from 0% to 100% in increments of 5%.

Also regarding concomitant drugs (for the treatment of diabetes mellitus or other conditions), the maximum number of doses administered per day and the maximum number of tablets administered per day will be investigated at each time of data collection.

2) Time of data collection

At initiation of treatment with this drug (except treatment compliance status for this drug), and 1, 3, 6, 9, and 12 months later (or discontinuation of treatment)

10.5 Items of Tests and Observations

Data from tests and observations in the routine clinical setting, if performed at the respective time of data collection, will be entered.

10.5.1 Vital Signs

1) Items of tests and observations

Pulse rate, blood pressure (systolic /diastolic), body weight

2) Time of data collection

At initiation of treatment with this drug, and 1, 3, 6, 9, and 12 months later (or discontinuation of treatment), if performed

10.5.2 Laboratory Tests

1) Test variables

HbA1c, fasting blood glucose, fasting insulin, fasting glucagon, fasting triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, serum creatinine, BUN, urinary albumin (urine albumin/creatinine ratio), AST, ALT, gamma-GTP, ALP, LDH, total bilirubin, amylase, lipase, lactic acid

2) Time of data collection

At initiation of treatment with this drug, and 1, 3, 6, 9, and 12 months later (or discontinuation of treatment), if performed

10.5.3 Electrocardiogram

1) Test variable

Electrocardiogram (assessment)

2) Time of data collection

At initiation of treatment with this drug and 12 months later (or discontinuation of treatment), if performed

10.5.4 Waist Circumference and Testing Related to Coronary Arteries and Arteriosclerosis

1) Test variables

Waist circumference*5, testing related to coronary arteries and arteriosclerosis*6 (eg, pulse wave velocity , blood pressure pulse wave test, cervical artery ultrasound, intravascular ultrasound)

*5: Measured at the patient's umbilicus level in a standing position at gentle exhalation. However, in patients with marked fat accumulation with downward deviation of the umbilicus, the waist circumference will be measured at the level of the midpoint between the lowest rib and the anterior superior iliac spine.

*6: Any testing method is allowed, but in principle the same method should be used throughout the individual time points of evaluation. The testing may be omitted if no testing device is available.

2) Time of data collection

At initiation of treatment with this drug and 12 months later (or discontinuation of treatment), if performed

10.5.5 Other Items of Observation

1) Observation item(s)

Presence or absence of pregnancy during the observation (only in women)

2) Time of data collection

From initiation of treatment with this drug until 12 months later (or discontinuation of treatment)

10.6 Adverse Events

1) Survey variables

Presence or absence of adverse events (see Table 1), adverse event term, date of onset, seriousness and reason for the assessment as serious (see Table 2), reason for discontinuation of this drug, outcome assessment date, outcome, causal relationship to this drug*[7] (see Table 3)

If the event outcome is "Not resolved" or "Unknown", and if the causal relationship is "Unassessable", the event should be followed as far as possible.

If onset of any of the following is reported as an adverse event, detailed information should be collected as needed: lactic acidosis, hypoglycemia, acute pancreatitis, hepatic function disorder or jaundice, severe skin disorder such as oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme, rhabdomyolysis, intestinal obstruction, interstitial pneumonia, angioedema, gastrointestinal symptom, infection, malignant tumor, pemphigoid, cardiovascular event (eg, symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death).

*7: If the causal relationship to this drug is "Not related", the basis for the assessment should be collected. If the causal relationship to this drug is "Unassessable", the reason should be collected.

Note) Special guidance about reporting of adverse events:

Abnormal worsening of the target disease, eg, outside the predictable range of the natural course of the disease, is regarded as an adverse event.

2) Time of data collection

From initiation of treatment with this drug until 12 months later (or discontinuation of treatment)

Table 1 Definition of an Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Table 2 Criteria for Serious Adverse Events

An adverse event is assessed as "serious" if it results in any of the following outcomes:

1. results in death (Death),
2. is life-threatening (Life-threatening),
3. requires hospitalization or prolongation of existing hospitalization (Hospitalization/Prolongation of hospitalization),
4. results in persistent or significant disability/incapacity (Disability),
5. leads to a congenital anomaly or birth defect (Congenital anomaly), or
6. is any other important medical event that does not 1 to 5 above.

Note: Also, any reported adverse events consistent with the "Takeda Medically Significant AE List" (Appendix 2) will be handled as serious adverse events by Takeda Pharmaceutical Company Limited.

Table 3 Assessment of the Causal Relationship Between an Adverse Event and this Drug

Causality classification	Definition
Related	An adverse event that follows a temporal sequence from administration of this drug (including the course after withdrawal of the drug), or for which there is at least reasonable possibility of involvement of this drug and its causal role cannot be ruled out, although factors other than the drug, such as the primary disease, concurrent diseases, concomitant drugs or concurrent treatments, may also be responsible.
Not related	An adverse event that does not follow a temporal sequence from administration of this drug or that can be explained reasonably by other factors, such as the primary disease, concurrent diseases, concomitant drugs or concurrent treatments.
Unassessable	The causality cannot be assessed because of insufficiency of required information, such as temporal sequence of the event onset relative to administration of this drug (including the course after withdrawal of the drug), primary disease, concurrent diseases, concomitant drugs, and concurrent treatments.

11.0 Analytical Items and Methods

11.1 Disposition of Patients

Number of patients enrolled in the survey, number of patients with collected case report forms, numbers of patients evaluated for the safety and efficacy, number of patients excluded from analyses and reasons for exclusion, etc. will be summarized.

11.2 Patient Background

Patient background data such as sex, age, duration of type 2 diabetes mellitus, and concurrent diseases will be summarized.

11.3 Treatment Details

Detailed use of this drug and concomitant drugs will be summarized.

11.4 Treatment Compliance Status, and Daily Dosing Frequency and Number of Tablets for Concomitant Drugs

Treatment compliance status will be summarized for alogliptin benzoate and metformin hydrochloride within 3 months before use of this drug, and also for this drug at each time of data collection. Also regarding concomitant drugs (for the treatment of diabetes mellitus and other conditions), the maximum number of doses administered per day and the maximum number of tablets administered per day will be summarized.

11.5 Safety Data

The following data will be summarized using the safety analysis set. Adverse events will be coded using the MedDRA/J, and summarized by Preferred Term (PT) and System Organ Class (SOC).

11.5.1 Adverse Event Profile

Adverse events occurring during the observation period will be summarized using frequency distribution by event type, time to onset, seriousness, causal relationship to this drug, etc.

11.5.2 Factors Likely Affecting the Safety

Adverse drug reactions occurring during the observation period will be summarized using frequency distribution, with stratification of patients according to background factors (eg, sex, age, presence or absence of renal impairment, presence or absence of hepatic impairment) and treatment details (eg, detailed use of this drug).

11.6 Efficacy data

The following data will be summarized using the efficacy analysis set.

11.6.1 HbA1c over time

The HbA1c level and change (value at the respective time after initiation of treatment minus baseline value) at each time point of evaluation will be summarized.

11.6.2 Fasting blood glucose over time

The fasting blood glucose level and change (value at the respective time after initiation of treatment minus baseline value) at each time point of evaluation will be summarized.

11.6.3 Fasting insulin over time

The fasting insulin level and change (value at the respective time after initiation of

treatment minus baseline value) at each time point of evaluation will be summarized.

11.6.4 Factors likely affecting the efficacy

A subgroup analysis will be performed on change in HbA1c etc., with stratification of patients according to background factors (eg, sex, age, presence or absence of renal impairment, presence or absence of hepatic impairment, baseline HbA1c level) and treatment details (eg, detailed use of this drug). In addition, among the patients with no change in the dose of alogliptin benzoate and metformin hydrochloride between before and after the switching to this drug, and no change in the dose of any antidiabetic medication during the treatment with this drug, the treatment compliance status between before and after the use of this drug and change in HbA1c will be summarized, and the relationship between medication adherence and change in HbA1c will be analyzed. In this analysis, in order to minimize influence of other factors than reductions in the number of tablets per day and the number of doses per day by switching to this drug among factors likely contributing to medication adherence, subgroup analyses according to such other factors etc. will be used to characterize the relationship between medication adherence and change in HbA1c as far as possible.

11.6.5 Factors Likely Affecting Medication Adherence

Regarding change in the medication adherence, in order to minimize influence of other factors than reductions in the number of tablets administered per day and the number of doses per day by switching to this drug among factors likely contributing to medication adherence, subgroup analyses according to such other factors etc. will be used to characterize the influence of this drug on the medication adherence.

11.7 Special Patient Populations

For each of the subpopulations of patients with renal impairment, patients with hepatic impairment, and elderly patients in this survey, a similar analysis to Sections 10.1 to 10.8.3 will be performed.

12.0 Survey Informed Consent Form and Patient Consent

The survey informed consent form contains the description as to how the patients' personal information and medical information are used in this survey. The informed consent form also describes the survey overview, the freedom of patients to withdraw from the survey at any time without providing a reason without any disadvantages in treatment.

The survey physician will provide a potential survey subject (or legally acceptable representative) with explanation about this survey as provided in the informed consent form, and obtain verbal or written consent of the patient (or legally acceptable representative) to participate in this survey. For written consent, the patient (or legally

acceptable representative) will sign and date the informed consent form, and the survey physician will retain the original of the signed informed consent form. For verbal consent, the survey physician will document the verbal consent.

13.0 Registration of Survey Information

Before initiation of this survey, information on this survey will be registered with the following website.

- Japan Pharmaceutical Information Center (JAPIC) Clinical Trials Information

14.0 Administrative Structure

See Attachment.

15.0 Trustees

See Attachment.

16.0 Other Necessary Items

16.1 Amendments to the Protocol

During the survey period, monitoring will be performed regarding the progress of the survey, occurrence of adverse drug reactions unexpected from the PRECAUTIONS and serious adverse drug reactions, any increase in the incidence of particular adverse drug reactions, validity of the survey variables, etc., and the protocol will be reviewed and amended as necessary. If any partial change to the DOSAGE AND ADMINISTRATION, INDICATIONS, etc. is approved during the survey period, whether or not the protocol should be amended will be examined, and the protocol will be amended as necessary.

16.2 Actions to be Taken in Response to Detection of any Issues or Concerns

Whenever an issue is found regarding the safety or efficacy, the data will be investigated in detail, and necessary actions will be determined.

Appendix 1 Observation Schedule

Survey variables \ Time of data collection		Observation period							
		Enrollment	Start of treatment	1 month	3 months	6 months	9 months	12 months	Discontinuation of treatment
Scheduled day in the survey		-	0	30	90	180	270	360	-
Allowable window (day) (earliest to latest)		-	−30 to 0	1 to 60	61 to 136	137 to 226	227 to 316	317 to 456	-
Informed consent		○							
Patient enrollment	Date of prescription of this drug	○							
	Subject Identification Number	○							
	Patient Initials	○							
	Sex	○							
	Age	○							
	Inclusion/exclusion criteria	○							
	Usage of alogliptin benzoate and metformin hydrochloride immediately before use of this drug	○							
Patient background	Time of the diagnosis of type 2 diabetes mellitus		○						
	Inpatient/outpatient category		○						
	Hypersensitive diathesis		○						
	Concurrent diseases		○						
	Medical history		○						
	Height		○						
	History of smoking		○						
	History of alcohol consumption		○						
	Status of occupation		○						
	Status of treatment compliance with alogliptin benzoate and metformin hydrochloride within 3 months before the start of treatment with this drug		○						
Treatment details etc.	Detailed use of this drug		←	○	→				○
	Detailed use of concomitant drugs (for diabetes mellitus and other conditions)		←	○	→				○
	Treatment compliance status for this drug			○	○	○	○	○	○
	Concomitant drugs: number of doses per day and number of tablets per day		○	○	○	○	○	○	○
Assessments	Pulse rate, blood pressure, body weight		○	○	○	○	○	○	○
	Laboratory tests • HbA1c • Fasting blood glucose • Fasting insulin • Fasting glucagon • Fasting triglyceride • Total cholesterol • HDL cholesterol • LDL cholesterol • Serum creatinine • BUN • Urinary albumin • AST • ALT • Gamma-GTP • ALP • LDH • Total bilirubin • Amylase • Lipase • Lactic acid		○	○	○	○	○	○	○
	Electrocardiogram		○					○	○
	Waist circumference		○					○	○
	Tests related to coronary arteries and arteriosclerosis		○					○	○
	Any pregnancy (women only)		←		→	○	←	→	○
	Adverse events monitoring		←		→	○	←	→	○

○: Performed (Data from tests and observations in the routine clinical setting will be recorded if they were performed within the respective allowable time periods. Data from tests and observations at discontinuation of treatment will be entered within the allowable time period.)

← ○ → Performed throughout the period

Appendix 2 Takeda Medically Significant AE List

General
Malignancy
Endotoxic shock
Sepsis
Transmission of an infectious agent by a medicinal product

Blood and lymphatic System
Bone marrow failure
Disseminated Intravascular Coagulation
Haemolytic anaemia
Thrombotic Thrombocytopenic Purpura

Cardiovascular System
Cardiac arrest
Cardiac failure
Cardiomyopathy acute
Malignant hypertension
Myocardial infarction
Ventricular arrhythmias

Endocrine System
Adrenal crisis

Gastrointestinal System
Acute pancreatitis
GI haemorrhage
GI perforation
GI obstruction
Necrotising colitis
Peritonitis

Hepatobiliary System
Acute hepatic failure
Fulminant hepatitis

Urinary System
Acute renal failure

Immune system
Anaphylaxis
Progressive multifocal leukoencephalopathy (PML)
Transplant rejection

Musculoskeletal System
Rhabdomyolysis

Nervous System
Cerebrovascular accident
Coma
Convulsive seizures
Hyperthermia malignant
Macular oedema
Meningoencephalitis
Neuroleptic malignant syndrome
Suicidal behaviour

Reproductive System
Abortion
Uterine perforation

Respiratory System
Acute respiratory failure
Pulmonary hypertension
Pulmonary thromboembolism

Skin and subcutaneous tissue
Toxic epidermal necrolysis
Stevens-Johnson syndrome

Protocol for Specified Drug-Use Survey of INISYNC Combination Tablets "Survey on long-term use in type 2 diabetes mellitus patients with renal or hepatic impairment or advanced age"

Survey Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol Number	**Alogliptin-Met-5003**
Version Number	**Version 2**
Date of Preparation	**November 9, 2016**

Table of Contents

1.0 Background

Drugs to treat type 2 diabetes mellitus are likely used over a long time in the routine clinical setting. Inisync Combination Tablets (hereinafter referred to as "this drug") contain two active ingredients: alogliptin benzoate (brand name, Nesina Tablets) and metformin hydrochloride. Long-term combination use of these drugs in the routine clinical setting was previously investigated in a specified drug-use survey. However, clinical trial data were limited on the safety and efficacy of this drug in patients with renal impairment, patients with hepatic impairment and elderly patients, and therefore data in these patient populations are designated as part of "important missing information" in the risk management plan for this drug. Thus, with a focus particularly on these patient populations, the present specified drug-use survey (hereinafter referred to as "this survey") has been planned to investigate the long-term safety and efficacy of this drug used in the routine clinical setting in type 2 diabetes mellitus patients with renal or hepatic impairment or advanced age.

This survey will be conducted in compliance with the Ministerial Ordinance on Good Post-Marketing Study Practice (GPSP) and relevant regulatory requirements.

2.0 Objectives

This survey aims to evaluate the long-term safety and efficacy of this drug in type 2 diabetes mellitus patients with renal impairment (mild), hepatic impairment (mild or moderate), or advanced age (≥65 years) in the routine clinical setting. In addition, this survey will enroll as many as possible patients who were switched from alogliptin 25 mg and metformin hydrochloride 500 mg (ie, 250 mg twice daily) in combination as a prior medication, to examine the relationship between the efficacy and improvement in medication adherence by the switching to this combination product in those who were taking alogliptin benzoate and metformin hydrochloride in combination.

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

600 subjects (including 300 subjects with hepatic impairment)

3.2 Rationale

Among the important identified risks and important potential risks of this drug, the following were reported in the alogliptin + metformin QD group (alogliptin 25 mg plus metformin hydrochloride 500 mg once daily) of Study SYR-322-MET/CCT-001: infection-related adverse events (26.3%, 40/152 subjects), gastrointestinal symptom-related adverse events (9.9%, 15/152 subjects), lactic acidosis-related adverse events (1.3%, 2/152 subjects), and hepatic function disorder-related adverse events (0.7%, 1/152 subjects). Based on these data, the incidence in this survey can be assumed to be ≥0.7% for such events among the important identified risks and important potential risks of this drug.

Assuming a Poisson distribution for the number of such events occurring in this survey, and with a sample size of 300 each for patients with renal impairment, patients with hepatic impairment, and elderly patients, adverse events occurring with an incidence of ≥0.7% in one of the patient subpopulations can be detected in at least one patient with a probability of ≥87%. Thus, with this sample size, the events reported in Study SYR-322-MET/CCT-001 and designated as important identified risks and important potential risks of this drug would be evaluable to a reasonable extent. For events occurring with a lower incidence, overall safety assessment will be performed based on information not only from this survey but also from other sources including spontaneous reports and literature in particular.

From the viewpoint of patient accrual, patients with hepatic impairment will be the most difficult subpopulation to be accrued in this survey, based on the accrual rates in a previously conducted specified drug-use survey of Nesina Tablets in type 2 diabetes mellitus patients with concomitant use of a biguanide, which also enrolled patients with renal impairment, patients with hepatic impairment, and elderly patients. Thus, in order to ensure that patients with hepatic impairment in particular are adequately enrolled in this survey, the accrual target is set to "300 patients with hepatic impairment". When this target is reached, in light of the extent of overlapping of the subpopulations in the above-mentioned Nesina Tablets specified drug-use survey, approximately 300 patients with renal impairment and approximately 300 elderly patients would have been accrued.

Also, with a total sample size of ≥600 in this survey, improvement in patient convenience by switching to this combination product from alogliptin benzoate and metformin hydrochloride in combination would be evaluable to a reasonable extent.

4.0 Target Patient Population

This survey will be conducted in patients with type 2 diabetes mellitus for whom combination therapy with alogliptin benzoate and metformin hydrochloride is appropriate in the opinion of a physician, and who fulfill the following inclusion criteria and who do not meet the following exclusion criteria. The PRECAUTIONS section of the package insert for this drug should also be referenced.

4.1 Inclusion Criteria

Subjects should meet one or more of the following:

(1) Have renal impairment (mild)
(2) Have hepatic impairment (mild or moderate)
(3) Elderly (aged ≥65 years)

4.2 Exclusion Criteria

Subjects who meet the following criterion will be excluded:

Patients with any contraindication for this drug

5.0 Dosage and Administration

The usual adult dosage of this drug is 1 tablet (ie, 25 mg of alogliptin and 500 mg of metformin hydrochloride) once daily orally immediately before a meal or after a meal. The package insert for this drug should be referenced.

6.0 Planned Number of Survey Sites by Specialty Department

Approximately 120 sites, including department of internal medicine

7.0 Methods

7.1 Duration of Observation

12 months

7.2 Data Collection Method

Data will be collected using a web-based electronic data capture system ([CCI]).

7.3 Patient Enrollment Method

Patients will be enrolled using a centralized registration method via [CCI].

7.4 Case Report Form (Electronic) Completion and Electronic Signature

The survey physician or designee* will enter data on patient background, treatment details, etc. into [CCI] promptly after the end of observation at 12 months of treatment with this drug, and the survey physician will enter an electronic signature. If administration of this drug could not be confirmed, the fact of this should be entered (no other data are required).

For patients who discontinued treatment with this drug for certain reasons during the course of the observation period, the survey physician or designee will enter data on patient background, treatment details, etc. into [CCI] promptly after the end of required observations, and the survey physician will enter an electronic signature. However, for patients who discontinued treatment with this drug because of onset of an adverse event, even after the discontinuation of this drug the survey physician will continue observation as far as possible up to resolution or improvement of the adverse event. The survey physician or designee will then enter the observation result into [CCI], and the survey physician will enter an electronic signature.

*: The survey physician's designee must be a person who belongs to the medical institution (this includes a dispatched CRC or any other person with a signed consignment contract with the medical institution). Before the survey physician's designee can perform data

entry to CCI, the principal survey physician (ie, a person designated under contract at each survey site [medical institution or department] who is responsible for the conduct of the survey at the survey site) will prepare a written record (any format) of the designation and the date of designation and, after signing (or affixing name with seal), submit it to the person in charge of Takeda Pharmaceutical Company Limited (hereinafter referred to as "Takeda personnel").

8.0 Planned Survey Period

Survey period: February 2017 to June 30, 2019

Patient enrollment period: February 2017 to June 30, 2018 Note)

Note) Even if this drug is prescribed by June 30, 2018, no patient enrollment (via CCI) will be acceptable on or after July 1, 2018.

If the total number of patients enrolled in this survey reached the planned sample size before June 30, 2018, patient enrolment will be closed before the end of the patient enrollment period. If the patient enrollment period is shortened, the survey period will also be changed according to the shortened enrollment period.

9.0 Informed Consent

Prior to enrollment of a patient in this survey, the survey physician will obtain written consent of the patient or the patient's legally acceptable representative. Patients who provided consent will be assigned the subject identification numbers.

10.0 Survey Variables

The survey physician or designee will enter data on the following variables into CCI. The survey schedule is shown in Appendix 1.

10.1 Patient Enrollment

1) Survey variables

Date of prescription of this drug, subject identification number, patient initials, sex, age, assessment against the inclusion criteria (ie, the patient has renal impairment*1 [mild], hepatic impairment*2 [mild or moderate], or advanced age [≥65 years]), assessment against the exclusion criteria (ie, the patient does not have any contraindication for this drug), status of medication with alogliptin benzoate and metformin hydrochloride (presence or absence of concomitant use as alogliptin 25 mg and metformin hydrochloride 500 mg [250 mg BID]) immediately before use of this drug

As a guide to severity assessment of renal impairment and hepatic impairment, the following tables should be referenced.

*1: Severity classification of renal impairment

Severity of renal impairment	eGFR (mL/min/1.73m^2)	Serum creatinine (mg/dL) *	Creatinine clearance (Ccr, mL/min)
Mild	≥60 to <90	Male: >0.90 to ≤1.4 Female: >0.77 to ≤1.2	≥50 to ≤80
Moderate	≥30 to <60	Male: >1.4 to ≤2.4 Female: >1.2 to ≤2.0	≥30 to <50
Severe or end-stage renal disease	<30	Male: >2.4 Female: >2.0	<30

For end-stage renal disease, time of the measurement relative to a hemodialysis session is disregarded.

*: Estimated values corresponding to the Ccr (for persons who are aged 60 years and weigh 65 kg)
Adapted from the "Precautions related to Dosage and Administration" section of Nesina Tablets package insert (see Cockcroft DW, et al. Nephron 1976; 16: 31-41)

*2: Severity classification of hepatic impairment

Severity of hepatic impairment	Mild	Moderate	Severe
Total bilirubin (mg/dL)	≥1.6 to <3.0	≥3.0 to <10	≥10
AST or ALT (U/L)	≥50 to <100	≥100 to <500	≥500
ALP	≥1.25 × ULN to <2.5 × ULN	≥2.5 × ULN to <5 × ULN	≥5 × ULN
Gamma-GTP	≥1.5 × ULN	-	-
LDH	≥1.5 × ULN	-	-
Manifestations	-	Jaundice, hepatomegaly, pain in the right hypochondrium, hepatic steatosis	Bleeding tendency, disturbed consciousness and other signs of hepatic failure (fulminant hepatitis), liver cirrhosis, liver tumor, persistent jaundice over ≥6 months

ULN: Upper limit of normal of the study site

Adapted from Criteria for Seriousness/Severity Grading of Adverse Drug Reactions (Notification No. 80 of the Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated June 29, 1992)

2) Time of data collection

At enrollment of the patient

10.2 Patient Background

1) Survey variables

Time of the diagnosis of type 2 diabetes mellitus, inpatient/outpatient category, hypersensitive diathesis (presence or absence, and details), concurrent diseases (presence or absence, and details), medical history (presence or absence, and details), height, history of smoking, history of alcohol consumption, status of occupation (presence or absence), status

of treatment compliance with alogliptin benzoate and metformin hydrochloride within 3 months before the start of treatment with this drug*[3]

*3: Assessed using a scale from 0% to 100% in increments of 5%.

2) Time of data collection

At initiation of treatment with this drug

10.3 Treatment Details

1) Survey variables

Detailed use of this drug (therapy start date, therapy end date, and reason for discontinuation [if applicable]), detailed use of concomitant drugs*[4] (for the treatment of diabetes mellitus) (presence or absence, if present, name of the drug, daily dose, and therapy dates), detailed use of concomitant drugs (for other conditions than diabetes mellitus) (presence or absence, if present, name of the drug, reason for use)

*4: Including antidiabetic medication discontinued within 3 months before use of this drug (Also, alogliptin benzoate and metformin hydrochloride used before this drug will be investigated.)

2) Time of data collection

From initiation of treatment with this drug until 12 months later (or discontinuation of treatment)

10.4 Treatment Compliance Status for this Drug, and Daily Dosing Frequency and Number of Tablets for Concomitant Drugs

1) Survey variables

The status of treatment compliance with this drug will be assessed using a scale from 0% to 100% in increments of 5%.

Also regarding concomitant drugs (for the treatment of diabetes mellitus or other conditions), the maximum number of doses administered per day and the maximum number of tablets administered per day will be investigated at each time of data collection.

2) Time of data collection

At initiation of treatment with this drug (except treatment compliance status for this drug), and 1, 3, 6, 9, and 12 months later (or discontinuation of treatment)

10.5 Items of Tests and Observations

Data from tests and observations in the routine clinical setting, if performed at the respective time of data collection, will be entered.

10.5.1 Vital Signs

1) Items of tests and observations

Pulse rate, blood pressure (systolic /diastolic), body weight

2) Time of data collection

At initiation of treatment with this drug, and 1, 3, 6, 9, and 12 months later (or discontinuation of treatment), if performed

10.5.2 Laboratory Tests

1) Test variables

HbA1c, fasting blood glucose, fasting insulin, fasting glucagon, fasting triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, serum creatinine, BUN, urinary albumin (urine albumin/creatinine ratio), AST, ALT, gamma-GTP, ALP, LDH, total bilirubin, amylase, lipase, lactic acid

2) Time of data collection

At initiation of treatment with this drug, and 1, 3, 6, 9, and 12 months later (or discontinuation of treatment), if performed

10.5.3 Electrocardiogram

1) Test variable

Electrocardiogram (assessment)

2) Time of data collection

At initiation of treatment with this drug and 12 months later (or discontinuation of treatment), if performed

10.5.4 Waist Circumference and Testing Related to Coronary Arteries and Arteriosclerosis

1) Test variables

Waist circumference*5, testing related to coronary arteries and arteriosclerosis*6 (eg, pulse wave velocity , blood pressure pulse wave test, cervical artery ultrasound, intravascular ultrasound)

*5: Measured at the patient's umbilicus level in a standing position at gentle exhalation. However, in patients with marked fat accumulation with downward deviation of the umbilicus, the waist circumference will be measured at the level of the midpoint between the lowest rib and the anterior superior iliac spine.

*6: Any testing method is allowed, but in principle the same method should be used throughout the individual time points of evaluation. The testing may be omitted if no testing device is available.

2) Time of data collection

At initiation of treatment with this drug and 12 months later (or discontinuation of treatment), if performed

10.5.5 Other Items of Observation

1) Observation item(s)

Presence or absence of pregnancy during the observation (only in women)

2) Time of data collection

From initiation of treatment with this drug until 12 months later (or discontinuation of treatment)

10.6 Adverse Events

1) Survey variables

Presence or absence of adverse events (see Table 1), adverse event term, date of onset, seriousness and reason for the assessment as serious (see Table 2), reason for discontinuation of this drug, outcome assessment date, outcome, causal relationship to this drug*[7] (see Table 3)

If the event outcome is "Not resolved" or "Unknown", and if the causal relationship is "Unassessable", the event should be followed as far as possible.

If onset of any of the following is reported as an adverse event, detailed information should be collected as needed: lactic acidosis, hypoglycemia, acute pancreatitis, hepatic function disorder or jaundice, severe skin disorder such as oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme, rhabdomyolysis, intestinal obstruction, interstitial pneumonia, angioedema, gastrointestinal symptom, infection, malignant tumor, pemphigoid, cardiovascular event (eg, symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death).

*7: If the causal relationship to this drug is "Not related", the basis for the assessment should be collected. If the causal relationship to this drug is "Unassessable", the reason should be collected.

Note) Special guidance about reporting of adverse events:

Abnormal worsening of the target disease, eg, outside the predictable range of the natural course of the disease, is regarded as an adverse event.

2) Time of data collection

From initiation of treatment with this drug until 12 months later (or discontinuation of treatment)

Table 1 Definition of an Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Table 2 Criteria for Serious Adverse Events

An adverse event is assessed as "serious" if it results in any of the following outcomes:

1. results in death (Death),
2. is life-threatening (Life-threatening),
3. requires hospitalization or prolongation of existing hospitalization (Hospitalization/Prolongation of hospitalization),
4. results in persistent or significant disability/incapacity (Disability),
5. leads to a congenital anomaly or birth defect (Congenital anomaly), or
6. is any other important medical event that does not 1 to 5 above.

Note: Also, any reported adverse events consistent with the "Takeda Medically Significant AE List" (Appendix 2) will be handled as serious adverse events by Takeda Pharmaceutical Company Limited.

Table 3 Assessment of the Causal Relationship Between an Adverse Event and this Drug

Causality classification	Definition
Related	An adverse event that follows a temporal sequence from administration of this drug (including the course after withdrawal of the drug), or for which there is at least reasonable possibility of involvement of this drug and its causal role cannot be ruled out, although factors other than the drug, such as the primary disease, concurrent diseases, concomitant drugs or concurrent treatments, may also be responsible.
Not related	An adverse event that does not follow a temporal sequence from administration of this drug or that can be explained reasonably by other factors, such as the primary disease, concurrent diseases, concomitant drugs or concurrent treatments.
Unassessable	The causality cannot be assessed because of insufficiency of required information, such as temporal sequence of the event onset relative to administration of this drug (including the course after withdrawal of the drug), primary disease, concurrent diseases, concomitant drugs, and concurrent treatments.

11.0 Analytical Items and Methods

11.1 Statistical Analysis Plan

A statistical analysis plan will be prepared before data lock. The statistical analysis plan will provide definitions of the analytical items and details of the analytical methods.

11.2 Analysis Sets

Analyses will be performed in two types of analysis sets: "Safety Analysis Set" and "Efficacy Analysis Set."

11.3 Disposition of Patients

Number of patients enrolled in the survey, number of patients with collected case report forms, numbers of patients evaluated for the safety and efficacy, number of patients excluded from analyses and reasons for exclusion, etc. will be summarized.

11.4 Patient Background

Patient background data such as sex, age, duration of type 2 diabetes mellitus, and concurrent diseases will be summarized.

11.5 Treatment Details

Detailed use of this drug and concomitant drugs will be summarized.

11.6 Treatment Compliance Status, and Daily Dosing Frequency and Number of Tablets for Concomitant Drugs

Treatment compliance status will be summarized for alogliptin benzoate and metformin hydrochloride within 3 months before use of this drug, and also for this drug at each time of data collection. Also regarding concomitant drugs (for the treatment of diabetes mellitus and other conditions), the maximum number of doses administered per day and the maximum number of tablets administered per day will be summarized.

11.7 Safety Data

The following data will be summarized using the safety analysis set. Adverse events will be coded using the MedDRA/J, and summarized by Preferred Term (PT) and System Organ Class (SOC).

11.7.1 Adverse Event Profile

Adverse events occurring during the observation period will be summarized using frequency distribution by event type, time to onset, seriousness, causal relationship to this drug, etc.

11.7.2 Factors Likely Affecting the Safety

Adverse drug reactions occurring during the observation period will be summarized using frequency distribution, with stratification of patients according to background factors (eg, sex, age, presence or absence of renal impairment, presence or absence of hepatic impairment) and treatment details (eg, detailed use of this drug).

11.8 Efficacy data

The following data will be summarized using the efficacy analysis set.

11.8.1 HbA1c over time

The HbA1c level and change (value at the respective time after initiation of treatment

minus baseline value) at each time point of evaluation will be summarized.

11.8.2 Fasting blood glucose over time

The fasting blood glucose level and change (value at the respective time after initiation of treatment minus baseline value) at each time point of evaluation will be summarized.

11.8.3 Fasting insulin over time

The fasting insulin level and change (value at the respective time after initiation of treatment minus baseline value) at each time point of evaluation will be summarized.

11.8.4 Factors likely affecting the efficacy

A subgroup analysis will be performed on change in HbA1c etc., with stratification of patients according to background factors (eg, sex, age, presence or absence of renal impairment, presence or absence of hepatic impairment, baseline HbA1c level) and treatment details (eg, detailed use of this drug). In addition, among the patients with no change in the dose of alogliptin benzoate and metformin hydrochloride between before and after the switching to this drug, and no change in the dose of any antidiabetic medication during the treatment with this drug, the treatment compliance status between before and after the use of this drug and change in HbA1c will be summarized, and the relationship between medication adherence and change in HbA1c will be analyzed. In this analysis, in order to minimize influence of other factors than reductions in the number of tablets per day and the number of doses per day by switching to this drug among factors likely contributing to medication adherence, subgroup analyses according to such other factors etc. will be used to characterize the relationship between medication adherence and change in HbA1c as far as possible.

11.8.5 Factors Likely Affecting Medication Adherence

Regarding change in the medication adherence, in order to minimize influence of other factors than reductions in the number of tablets administered per day and the number of doses per day by switching to this drug among factors likely contributing to medication adherence, subgroup analyses according to such other factors etc. will be used to characterize the influence of this drug on the medication adherence.

11.9 Special Patient Populations

For each of the subpopulations of patients with renal impairment, patients with hepatic impairment, and elderly patients in this survey, a similar analysis to Sections 10.1 to 10.8.3 will be performed.

12.0 Informed Consent Form and Patient Consent

The informed consent form contains the description as to how the patients' personal

information and medical information are used in this survey. The informed consent form also describes the survey overview, the freedom of patients to withdraw from the survey at any time without providing a reason without any disadvantages in treatment.

The survey physician will provide a potential survey subject (or legally acceptable representative) with explanation about this survey as provided in the informed consent form. If of the patient (or legally acceptable representative) agrees to participate in this survey, he/she (or legally acceptable representative) will sign and date the informed consent form. The survey physician will retain the original of the signed informed consent form.

13.0 Registration of Survey Information

Before initiation of this survey, information on this survey will be registered with the following website.

- Japan Pharmaceutical Information Center (JAPIC) Clinical Trials Information

14.0 Administrative Structure

14.1 Chief Administrator

Post-marketing Survey Chief Administrator
Takeda Pharmaceutical Company Limited

15.0 Trustees

PPD

16.0 Other Necessary Items

16.1 Amendments to the Protocol

During the survey period, monitoring will be performed regarding the progress of the survey, occurrence of adverse drug reactions unexpected from the PRECAUTIONS and serious adverse drug reactions, any increase in the incidence of particular adverse drug reactions, validity of the survey variables, etc., and the protocol will be reviewed and amended as necessary. If any partial change to the DOSAGE AND ADMINISTRATION, INDICATIONS, etc. is approved during the survey period, whether or not the protocol should be amended will be examined, and the protocol will be amended as necessary.

16.2 Actions to be Taken in Response to Detection of any Issues or Concerns

Whenever an issue is found regarding the safety or efficacy, the data will be investigated in detail, and necessary actions will be determined.

Appendix 1 Observation Schedule

Survey variables \ Time of data collection		Observation period							
		Enrollment	Start of treatment	1 month	3 months	6 months	9 months	12 months	Discontinuation of treatment
Scheduled day in the survey		-	0	30	90	180	270	360	-
Allowable window (day) (earliest to latest)		-	−30 to 0	1 to 60	61 to 136	137 to 226	227 to 316	317 to 456	-
Informed consent		○							
Patient enrollment	Date of prescription of this drug	○							
	Subject Identification Number	○							
	Patient Initials	○							
	Sex	○							
	Age	○							
	Inclusion/exclusion criteria	○							
	Usage of alogliptin benzoate and metformin hydrochloride immediately before use of this drug	○							
Patient background	Time of the diagnosis of type 2 diabetes mellitus		○						
	Inpatient/outpatient category		○						
	Hypersensitive diathesis		○						
	Concurrent diseases		○						
	Medical history		○						
	Height		○						
	History of smoking		○						
	History of alcohol consumption		○						
	Status of occupation		○						
	Status of treatment compliance with alogliptin benzoate and metformin hydrochloride within 3 months before the start of treatment with this drug		○						
Treatment details etc.	Detailed use of this drug		←	○	→				○
	Detailed use of concomitant drugs (for diabetes mellitus and other conditions)		←	○	→				○
	Treatment compliance status for this drug			○	○	○	○	○	○
	Concomitant drugs: number of doses per day and number of tablets per day		○	○	○	○	○	○	○
Assessments	Pulse rate, blood pressure, body weight		○	○	○	○	○	○	○
	Laboratory tests • HbA1c • Fasting blood glucose • Fasting insulin • Fasting glucagon • Fasting triglyceride • Total cholesterol • HDL cholesterol • LDL cholesterol • Serum creatinine • BUN • Urinary albumin • AST • ALT • Gamma-GTP • ALP • LDH • Total bilirubin • Amylase • Lipase • Lactic acid		○	○	○	○	○	○	○
	Electrocardiogram		○					○	○
	Waist circumference		○					○	○
	Tests related to coronary arteries and arteriosclerosis		○					○	○
	Any pregnancy (women only)		←		→	○	←	→	○
	Adverse events monitoring		←		→	○	←	→	○

○: Performed (Data from tests and observations in the routine clinical setting will be recorded if they were performed within the respective allowable time periods. Data from tests and observations at discontinuation of treatment will be entered within the allowable time period.)

← ○ → Performed throughout the period

Appendix 2 Takeda Medically Significant AE List

General
Malignancy
Endotoxic shock
Sepsis
Transmission of an infectious agent by a medicinal product

Blood and lymphatic System
Bone marrow failure
Disseminated Intravascular Coagulation
Haemolytic anaemia
Thrombotic Thrombocytopenic Purpura

Cardiovascular System
Cardiac arrest
Cardiac failure
Cardiomyopathy acute
Malignant hypertension
Myocardial infarction
Ventricular arrhythmias

Endocrine System
Adrenal crisis

Gastrointestinal System
Acute pancreatitis
GI haemorrhage
GI perforation
GI obstruction
Necrotising colitis
Peritonitis

Hepatobiliary System
Acute hepatic failure
Fulminant hepatitis

Urinary System
Acute renal failure

Immune system
Anaphylaxis
Progressive multifocal leukoencephalopathy (PML)
Transplant rejection

Musculoskeletal System
Rhabdomyolysis

Nervous System
Cerebrovascular accident
Coma
Convulsive seizures
Hyperthermia malignant
Macular oedema
Meningoencephalitis
Neuroleptic malignant syndrome
Suicidal behaviour

Reproductive System
Abortion
Uterine perforation

Respiratory System
Acute respiratory failure
Pulmonary hypertension
Pulmonary thromboembolism

Skin and subcutaneous tissue
Toxic epidermal necrolysis
Stevens-Johnson syndrome

Protocol for Specified Drug-Use Survey of INISYNC Combination Tablets "Survey on long-term use in type 2 diabetes mellitus patients with renal or hepatic impairment or advanced age"

Survey Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol Number	**Alogliptin-Met-5003**
Version Number	**Version 1**
Date of Preparation	**October 11, 2016**

Table of Contents

1.0 Background

Drugs to treat type 2 diabetes mellitus are likely used over a long time in the routine clinical setting. Inisync Combination Tablets (hereinafter referred to as "this drug") contain two active ingredients: alogliptin benzoate (brand name, Nesina Tablets) and metformin hydrochloride. Long-term combination use of these drugs in the routine clinical setting was previously investigated in a specified drug-use survey. However, clinical trial data were limited on the safety and efficacy of this drug in patients with renal impairment, patients with hepatic impairment and elderly patients, and therefore data in these patient populations are designated as part of "important missing information" in the risk management plan for this drug. Thus, with a focus particularly on these patient populations, the present specified drug-use survey (hereinafter referred to as "this survey") has been planned to investigate the long-term safety and efficacy of this drug used in the routine clinical setting in type 2 diabetes mellitus patients with renal or hepatic impairment or advanced age.

This survey will be conducted in compliance with the Ministerial Ordinance on Good Post-Marketing Study Practice (GPSP) and relevant regulatory requirements.

2.0 Objectives

This survey aims to evaluate the long-term safety and efficacy of this drug in type 2 diabetes mellitus patients with renal impairment (mild), hepatic impairment (mild or moderate), or advanced age (≥65 years) in the routine clinical setting. In addition, this survey will enroll as many as possible patients who were switched from alogliptin 25 mg and metformin hydrochloride 500 mg (ie, 250 mg twice daily) in combination as a prior medication, to examine the relationship between the efficacy and improvement in medication adherence by the switching to this combination product in those who were taking alogliptin benzoate and metformin hydrochloride in combination.

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

600 subjects (including 300 subjects with hepatic impairment)

3.2 Rationale

Among the important identified risks and important potential risks of this drug, the following were reported in the alogliptin + metformin QD group (alogliptin 25 mg plus metformin hydrochloride 500 mg once daily) of Study SYR-322-MET/CCT-001: infection-related adverse events (26.3%, 40/152 subjects), gastrointestinal symptom-related adverse events (9.9%, 15/152 subjects), lactic acidosis-related adverse events (1.3%, 2/152 subjects), and hepatic function disorder-related adverse events (0.7%, 1/152 subjects). Based on these data, the incidence in this survey can be assumed to be ≥0.7% for such events among the important identified risks and important potential risks of this drug.

Assuming a Poisson distribution for the number of such events occurring in this survey, and with a sample size of 300 each for patients with renal impairment, patients with hepatic impairment, and elderly patients, adverse events occurring with an incidence of ≥0.7% in one of the patient subpopulations can be detected in at least one patient with a probability of ≥87%. Thus, with this sample size, the events reported in Study SYR-322-MET/CCT-001 and designated as important identified risks and important potential risks of this drug would be evaluable to a reasonable extent. For events occurring with a lower incidence, overall safety assessment will be performed based on information not only from this survey but also from other sources including spontaneous reports and literature in particular.

From the viewpoint of patient accrual, patients with hepatic impairment will be the most difficult subpopulation to be accrued in this survey, based on the accrual rates in a previously conducted specified drug-use survey of Nesina Tablets in type 2 diabetes mellitus patients with concomitant use of a biguanide, which also enrolled patients with renal impairment, patients with hepatic impairment, and elderly patients. Thus, in order to ensure that patients with hepatic impairment in particular are adequately enrolled in this survey, the accrual target is set to "300 patients with hepatic impairment". When this target is reached, in light of the extent of overlapping of the subpopulations in the above-mentioned Nesina Tablets specified drug-use survey, approximately 300 patients with renal impairment and approximately 300 elderly patients would have been accrued.

Also, with a total sample size of ≥600 in this survey, improvement in patient convenience by switching to this combination product from alogliptin benzoate and metformin hydrochloride in combination would be evaluable to a reasonable extent.

4.0 Target Patient Population

This survey will be conducted in patients with type 2 diabetes mellitus for whom combination therapy with alogliptin benzoate and metformin hydrochloride is appropriate in the opinion of a physician, and who fulfill the following inclusion criteria and who do not meet the following exclusion criteria. The PRECAUTIONS section of the package insert for this drug should also be referenced.

4.1 Inclusion Criteria

Subjects should meet one or more of the following:

(1) Have renal impairment (mild)
(2) Have hepatic impairment (mild or moderate)
(3) Elderly (aged ≥65 years)

4.2 Exclusion Criteria

Subjects who meet the following criterion will be excluded:

Patients with any contraindication for this drug

5.0 Dosage and Administration

The usual adult dosage of this drug is 1 tablet (ie, 25 mg of alogliptin and 500 mg of metformin hydrochloride) once daily orally immediately before a meal or after a meal. The package insert for this drug should be referenced.

6.0 Planned Number of Survey Sites by Specialty Department

Approximately 120 sites, including department of internal medicine

7.0 Methods

7.1 Duration of Observation

12 months

7.2 Data Collection Method

Data will be collected using a web-based electronic data capture system ([CCI]).

7.3 Patient Enrollment Method

Patients will be enrolled using a centralized registration method via [CCI].

7.4 Case Report Form (Electronic) Completion and Electronic Signature

The survey physician or designee* will enter data on patient background, treatment details, etc. into [CCI] promptly after the end of observation at 12 months of treatment with this drug, and the survey physician will enter an electronic signature. If administration of this drug could not be confirmed, the fact of this should be entered (no other data are required).

For patients who discontinued treatment with this drug for certain reasons during the course of the observation period, the survey physician or designee will enter data on patient background, treatment details, etc. into [CCI] promptly after the end of required observations, and the survey physician will enter an electronic signature. However, for patients who discontinued treatment with this drug because of onset of an adverse event, even after the discontinuation of this drug the survey physician will continue observation as far as possible up to resolution or improvement of the adverse event. The survey physician or designee will then enter the observation result into [CCI], and the survey physician will enter an electronic signature.

*: The survey physician's designee must be a person who belongs to the medical institution (this includes a dispatched CRC or any other person with a signed consignment contract with the medical institution). Before the survey physician's designee can perform data

entry to CCI, the principal survey physician (ie, a person designated under contract at each survey site [medical institution or department] who is responsible for the conduct of the survey at the survey site) will prepare a written record (any format) of the designation and the date of designation and, after signing (or affixing name with seal), submit it to the person in charge of Takeda Pharmaceutical Company Limited (hereinafter referred to as "Takeda personnel").

8.0 Planned Survey Period

Survey period: February 2017 to June 30, 2019

Patient enrollment period: February 2017 to June 30, 2018 Note)

Note) Even if this drug is prescribed by June 30, 2018, no patient enrollment (via CCI) will be acceptable on or after July 1, 2018.

If the total number of patients enrolled in this survey reached the planned sample size before June 30, 2018, patient enrolment will be closed before the end of the patient enrollment period. If the patient enrollment period is shortened, the survey period will also be changed according to the shortened enrollment period.

9.0 Informed Consent

Prior to enrollment of a patient in this survey, the survey physician will obtain written consent of the patient or the patient's legally acceptable representative. Patients who provided consent will be assigned the subject identification numbers.

10.0 Survey Variables

The survey physician or designee will enter data on the following variables into CCI. The survey schedule is shown in Appendix 1.

10.1 Patient Enrollment

1) Survey variables

Date of prescription of this drug, subject identification number, patient initials, sex, age, assessment against the inclusion criteria (ie, the patient has renal impairment*1 [mild], hepatic impairment*2 [mild or moderate], or advanced age [≥65 years]), assessment against the exclusion criteria (ie, the patient does not have any contraindication for this drug), status of medication with alogliptin benzoate and metformin hydrochloride (presence or absence of concomitant use as alogliptin 25 mg and metformin hydrochloride 500 mg [250 mg BID]) immediately before use of this drug

As a guide to severity assessment of renal impairment and hepatic impairment, the following tables should be referenced.

*1: Severity classification of renal impairment

Severity of renal impairment	eGFR (mL/min/1.73m^2)	Serum creatinine (mg/dL) *	Creatinine clearance (Ccr, mL/min)
Mild	≥60 to <90	Male: >0.90 to ≤1.4 Female: >0.77 to ≤1.2	≥50 to ≤80
Moderate	≥30 to <60	Male: >1.4 to ≤2.4 Female: >1.2 to ≤2.0	≥30 to <50
Severe or end-stage renal disease	<30	Male: >2.4 Female: >2.0	<30

For end-stage renal disease, time of the measurement relative to a hemodialysis session is disregarded.

*: Estimated values corresponding to the Ccr (for persons who are aged 60 years and weigh 65 kg)
Adapted from the "Precautions related to Dosage and Administration" section of Nesina Tablets package insert (see Cockcroft DW, et al. Nephron 1976; 16: 31-41)

*2: Severity classification of hepatic impairment

Severity of hepatic impairment	Mild	Moderate	Severe
Total bilirubin (mg/dL)	≥1.6 to <3.0	≥3.0 to <10	≥10
AST or ALT (U/L)	≥50 to <100	≥100 to <500	≥500
ALP	≥1.25 × ULN to <2.5 × ULN	≥2.5 × ULN to <5 × ULN	≥5 × ULN
Gamma-GTP	≥1.5 × ULN	-	-
LDH	≥1.5 × ULN	-	-
Manifestations	-	Jaundice, hepatomegaly, pain in the right hypochondrium, hepatic steatosis	Bleeding tendency, disturbed consciousness and other signs of hepatic failure (fulminant hepatitis), liver cirrhosis, liver tumor, persistent jaundice over ≥6 months

ULN: Upper limit of normal of the study site

Adapted from Criteria for Seriousness/Severity Grading of Adverse Drug Reactions (Notification No. 80 of the Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated June 29, 1992)

2) Time of data collection

At enrollment of the patient

10.2 Patient Background

1) Survey variables

Time of the diagnosis of type 2 diabetes mellitus, inpatient/outpatient category, hypersensitive diathesis (presence or absence, and details), concurrent diseases (presence or absence, and details), medical history (presence or absence, and details), height, history of smoking, history of alcohol consumption, status of occupation (presence or absence), status

of treatment compliance with alogliptin benzoate and metformin hydrochloride within 3 months before the start of treatment with this drug*[3]

*3: Assessed using a scale from 0% to 100% in increments of 5%.

2) Time of data collection

At initiation of treatment with this drug

10.3 Treatment Details

1) Survey variables

Detailed use of this drug (therapy start date, therapy end date, and reason for discontinuation [if applicable]), detailed use of concomitant drugs*[4] (for the treatment of diabetes mellitus) (presence or absence, if present, name of the drug, daily dose, and therapy dates), detailed use of concomitant drugs (for other conditions than diabetes mellitus) (presence or absence, if present, name of the drug, reason for use)

*4: Including antidiabetic medication discontinued within 3 months before use of this drug (Also, alogliptin benzoate and metformin hydrochloride used before this drug will be investigated.)

2) Time of data collection

From initiation of treatment with this drug until 12 months later (or discontinuation of treatment)

10.4 Treatment Compliance Status for this Drug, and Daily Dosing Frequency and Number of Tablets for Concomitant Drugs

1) Survey variables

The status of treatment compliance with this drug will be assessed using a scale from 0% to 100% in increments of 5%.

Also regarding concomitant drugs (for the treatment of diabetes mellitus or other conditions), the maximum number of doses administered per day and the maximum number of tablets administered per day will be investigated at each time of data collection.

2) Time of data collection

At initiation of treatment with this drug (except treatment compliance status for this drug), and 1, 3, 6, 9, and 12 months later (or discontinuation of treatment)

10.5 Items of Tests and Observations

Data from tests and observations in the routine clinical setting, if performed at the respective time of data collection, will be entered.

10.5.1 Vital Signs

1) Items of tests and observations

Pulse rate, blood pressure (systolic /diastolic), body weight

2) Time of data collection

At initiation of treatment with this drug, and 1, 3, 6, 9, and 12 months later (or discontinuation of treatment), if performed

10.5.2 Laboratory Tests

1) Test variables

HbA1c, fasting blood glucose, fasting insulin, fasting glucagon, fasting triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, serum creatinine, BUN, urinary albumin (urine albumin/creatinine ratio), AST, ALT, gamma-GTP, ALP, LDH, total bilirubin, amylase, lipase, lactic acid

2) Time of data collection

At initiation of treatment with this drug, and 1, 3, 6, 9, and 12 months later (or discontinuation of treatment), if performed

10.5.3 Electrocardiogram

1) Test variable

Electrocardiogram (assessment)

2) Time of data collection

At initiation of treatment with this drug and 12 months later (or discontinuation of treatment), if performed

10.5.4 Waist Circumference and Testing Related to Coronary Arteries and Arteriosclerosis

1) Test variables

Waist circumference*5, testing related to coronary arteries and arteriosclerosis*6 (eg, pulse wave velocity , blood pressure pulse wave test, cervical artery ultrasound, intravascular ultrasound)

*5: Measured at the patient's umbilicus level in a standing position at gentle exhalation. However, in patients with marked fat accumulation with downward deviation of the umbilicus, the waist circumference will be measured at the level of the midpoint between the lowest rib and the anterior superior iliac spine.

*6: Any testing method is allowed, but in principle the same method should be used throughout the individual time points of evaluation. The testing may be omitted if no testing device is available.

2) Time of data collection

At initiation of treatment with this drug and 12 months later (or discontinuation of treatment), if performed

10.5.5 Other Items of Observation

1) Observation item(s)

Presence or absence of pregnancy during the observation (only in women)

2) Time of data collection

From initiation of treatment with this drug until 12 months later (or discontinuation of treatment)

10.6 Adverse Events

1) Survey variables

Presence or absence of adverse events (see Table 1), adverse event term, date of onset, seriousness and reason for the assessment as serious (see Table 2), reason for discontinuation of this drug, outcome assessment date, outcome, causal relationship to this drug*[7] (see Table 3)

If the event outcome is "Not resolved" or "Unknown", and if the causal relationship is "Unassessable", the event should be followed as far as possible.

If onset of any of the following is reported as an adverse event, detailed information should be collected as needed: lactic acidosis, hypoglycemia, acute pancreatitis, hepatic function disorder or jaundice, severe skin disorder such as oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme, rhabdomyolysis, intestinal obstruction, interstitial pneumonia, angioedema, gastrointestinal symptom, infection, malignant tumor, cardiovascular event (eg, symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death).

*7: If the causal relationship to this drug is "Not related", the basis for the assessment should be collected. If the causal relationship to this drug is "Unassessable", the reason should be collected.

Note) Special guidance about reporting of adverse events:

Abnormal worsening of the target disease, eg, outside the predictable range of the natural course of the disease, is regarded as an adverse event.

2) Time of data collection

From initiation of treatment with this drug until 12 months later (or discontinuation of treatment)

Table 1 Definition of an Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Table 2 Criteria for Serious Adverse Events

An adverse event is assessed as "serious" if it results in any of the following outcomes:

1. results in death (Death),
2. is life-threatening (Life-threatening),
3. requires hospitalization or prolongation of existing hospitalization (Hospitalization/Prolongation of hospitalization),
4. results in persistent or significant disability/incapacity (Disability),
5. leads to a congenital anomaly or birth defect (Congenital anomaly), or
6. is any other important medical event that does not 1 to 5 above.

Note: Also, any reported adverse events consistent with the "Takeda Medically Significant AE List" (Appendix 2) will be handled as serious adverse events by Takeda Pharmaceutical Company Limited.

Table 3 Assessment of the Causal Relationship Between an Adverse Event and this Drug

Causality classification	Definition
Related	An adverse event that follows a temporal sequence from administration of this drug (including the course after withdrawal of the drug), or for which there is at least reasonable possibility of involvement of this drug and its causal role cannot be ruled out, although factors other than the drug, such as the primary disease, concurrent diseases, concomitant drugs or concurrent treatments, may also be responsible.
Not related	An adverse event that does not follow a temporal sequence from administration of this drug or that can be explained reasonably by other factors, such as the primary disease, concurrent diseases, concomitant drugs or concurrent treatments.
Unassessable	The causality cannot be assessed because of insufficiency of required information, such as temporal sequence of the event onset relative to administration of this drug (including the course after withdrawal of the drug), primary disease, concurrent diseases, concomitant drugs, and concurrent treatments.

11.0 Analytical Items and Methods

11.1 Statistical Analysis Plan

A statistical analysis plan will be prepared before data lock. The statistical analysis plan will provide definitions of the analytical items and details of the analytical methods.

11.2 Analysis Sets

Analyses will be performed in two types of analysis sets: "Safety Analysis Set" and "Efficacy Analysis Set."

11.3 Disposition of Patients

Number of patients enrolled in the survey, number of patients with collected case report forms, numbers of patients evaluated for the safety and efficacy, number of patients excluded from analyses and reasons for exclusion, etc. will be summarized.

11.4 Patient Background

Patient background data such as sex, age, duration of type 2 diabetes mellitus, and concurrent diseases will be summarized.

11.5 Treatment Details

Detailed use of this drug and concomitant drugs will be summarized.

11.6 Treatment Compliance Status, and Daily Dosing Frequency and Number of Tablets for Concomitant Drugs

Treatment compliance status will be summarized for alogliptin benzoate and metformin hydrochloride within 3 months before use of this drug, and also for this drug at each time of data collection. Also regarding concomitant drugs (for the treatment of diabetes mellitus and other conditions), the maximum number of doses administered per day and the maximum number of tablets administered per day will be summarized.

11.7 Safety Data

The following data will be summarized using the safety analysis set. Adverse events will be coded using the MedDRA/J, and summarized by Preferred Term (PT) and System Organ Class (SOC).

11.7.1 Adverse Event Profile

Adverse events occurring during the observation period will be summarized using frequency distribution by event type, time to onset, seriousness, causal relationship to this drug, etc.

11.7.2 Factors Likely Affecting the Safety

Adverse drug reactions occurring during the observation period will be summarized using frequency distribution, with stratification of patients according to background factors (eg, sex, age, presence or absence of renal impairment, presence or absence of hepatic impairment) and treatment details (eg, detailed use of this drug).

11.8 Efficacy data

The following data will be summarized using the efficacy analysis set.

11.8.1 HbA1c over time

The HbA1c level and change (value at the respective time after initiation of treatment

minus baseline value) at each time point of evaluation will be summarized.

11.8.2 Fasting blood glucose over time

The fasting blood glucose level and change (value at the respective time after initiation of treatment minus baseline value) at each time point of evaluation will be summarized.

11.8.3 Fasting insulin over time

The fasting insulin level and change (value at the respective time after initiation of treatment minus baseline value) at each time point of evaluation will be summarized.

11.8.4 Factors likely affecting the efficacy

A subgroup analysis will be performed on change in HbA1c etc., with stratification of patients according to background factors (eg, sex, age, presence or absence of renal impairment, presence or absence of hepatic impairment, baseline HbA1c level) and treatment details (eg, detailed use of this drug). In addition, among the patients with no change in the dose of alogliptin benzoate and metformin hydrochloride between before and after the switching to this drug, and no change in the dose of any antidiabetic medication during the treatment with this drug, the treatment compliance status between before and after the use of this drug and change in HbA1c will be summarized, and the relationship between medication adherence and change in HbA1c will be analyzed. In this analysis, in order to minimize influence of other factors than reductions in the number of tablets per day and the number of doses per day by switching to this drug among factors likely contributing to medication adherence, subgroup analyses according to such other factors etc. will be used to characterize the relationship between medication adherence and change in HbA1c as far as possible.

11.8.5 Factors Likely Affecting Medication Adherence

Regarding change in the medication adherence, in order to minimize influence of other factors than reductions in the number of tablets administered per day and the number of doses per day by switching to this drug among factors likely contributing to medication adherence, subgroup analyses according to such other factors etc. will be used to characterize the influence of this drug on the medication adherence.

11.9 Special Patient Populations

For each of the subpopulations of patients with renal impairment, patients with hepatic impairment, and elderly patients in this survey, a similar analysis to Sections 10.1 to 10.8.3 will be performed.

12.0 Informed Consent Form and Patient Consent

The informed consent form contains the description as to how the patients' personal

information and medical information are used in this survey. The informed consent form also describes the survey overview, the freedom of patients to withdraw from the survey at any time without providing a reason without any disadvantages in treatment.

The survey physician will provide a potential survey subject (or legally acceptable representative) with explanation about this survey as provided in the informed consent form. If of the patient (or legally acceptable representative) agrees to participate in this survey, he/she (or legally acceptable representative) will sign and date the informed consent form. The survey physician will retain the original of the signed informed consent form.

13.0 Registration of Survey Information

Before initiation of this survey, information on this survey will be registered with the following website.

- Japan Pharmaceutical Information Center (JAPIC) Clinical Trials Information

14.0 Administrative Structure

14.1 Chief Administrator

Post-marketing Survey Chief Administrator
Takeda Pharmaceutical Company Limited

15.0 Trustees

16.0 Other Necessary Items

16.1 Amendments to the Protocol

During the survey period, monitoring will be performed regarding the progress of the survey, occurrence of adverse drug reactions unexpected from the PRECAUTIONS and serious adverse drug reactions, any increase in the incidence of particular adverse drug reactions, validity of the survey variables, etc., and the protocol will be reviewed and amended as necessary. If any partial change to the DOSAGE AND ADMINISTRATION, INDICATIONS, etc. is approved during the survey period, whether or not the protocol should be amended will be examined, and the protocol will be amended as necessary.

16.2 Actions to be Taken in Response to Detection of any Issues or Concerns

Whenever an issue is found regarding the safety or efficacy, the data will be investigated in detail, and necessary actions will be determined.

Appendix 1 Observation Schedule

Survey variables \ Time of data collection		Observation period							
		Enrollment	Start of treatment	1 month	3 months	6 months	9 months	12 months	Discontinuation of treatment
Scheduled day in the survey		-	0	30	90	180	270	360	-
Allowable window (day) (earliest to latest)		-	−30 to 0	1 to 60	61 to 136	137 to 226	227 to 316	317 to 456	-
Informed consent		○							
Patient enrollment	Date of prescription of this drug	○							
	Subject Identification Number	○							
	Patient Initials	○							
	Sex	○							
	Age	○							
	Inclusion/exclusion criteria	○							
	Usage of alogliptin benzoate and metformin hydrochloride immediately before use of this drug	○							
Patient background	Time of the diagnosis of type 2 diabetes mellitus		○						
	Inpatient/outpatient category		○						
	Hypersensitive diathesis		○						
	Concurrent diseases		○						
	Medical history		○						
	Height		○						
	History of smoking		○						
	History of alcohol consumption		○						
	Status of occupation		○						
	Status of treatment compliance with alogliptin benzoate and metformin hydrochloride within 3 months before the start of treatment with this drug		○						
Treatment details etc.	Detailed use of this drug		←	○	→				○
	Detailed use of concomitant drugs (for diabetes mellitus and other conditions)		←	○	→				○
	Treatment compliance status for this drug			○	○	○	○	○	○
	Concomitant drugs: number of doses per day and number of tablets per day		○	○	○	○	○	○	○
Assessments	Pulse rate, blood pressure, body weight		○	○	○	○	○	○	○
	Laboratory tests • HbA1c • Fasting blood glucose • Fasting insulin • Fasting glucagon • Fasting triglyceride • Total cholesterol • HDL cholesterol • LDL cholesterol • Serum creatinine • BUN • Urinary albumin • AST • ALT • Gamma-GTP • ALP • LDH • Total bilirubin • Amylase • Lipase • Lactic acid		○	○	○	○	○	○	○
	Electrocardiogram		○					○	○
	Waist circumference		○					○	○
	Tests related to coronary arteries and arteriosclerosis		○					○	○
	Any pregnancy (women only)		←		→	○	←	→	○
	Adverse events monitoring		←		→	○	←	→	○

○: Performed (Data from tests and observations in the routine clinical setting will be recorded if they were performed within the respective allowable time periods. Data from tests and observations at discontinuation of treatment will be entered within the allowable time period.)

← ○ → Performed throughout the period

Appendix 2 Takeda Medically Significant AE List

General
Malignancy
Endotoxic shock
Sepsis
Transmission of an infectious agent by a medicinal product

Blood and lymphatic System
Bone marrow failure
Disseminated Intravascular Coagulation
Haemolytic anaemia
Thrombotic Thrombocytopenic Purpura

Cardiovascular System
Cardiac arrest
Cardiac failure
Cardiomyopathy acute
Malignant hypertension
Myocardial infarction
Ventricular arrhythmias

Endocrine System
Adrenal crisis

Gastrointestinal System
Acute pancreatitis
GI haemorrhage
GI perforation
GI obstruction
Necrotising colitis
Peritonitis

Hepatobiliary System
Acute hepatic failure
Fulminant hepatitis

Urinary System
Acute renal failure

Immune system
Anaphylaxis
Progressive multifocal leukoencephalopathy (PML)
Transplant rejection

Musculoskeletal System
Rhabdomyolysis

Nervous System
Cerebrovascular accident
Coma
Convulsive seizures
Hyperthermia malignant
Macular oedema
Meningoencephalitis
Neuroleptic malignant syndrome
Suicidal behaviour

Reproductive System
Abortion
Uterine perforation

Respiratory System
Acute respiratory failure
Pulmonary hypertension
Pulmonary thromboembolism

Skin and subcutaneous tissue
Toxic epidermal necrolysis
Stevens-Johnson syndrome