Title: Nesina Tablets Specified Drug-use Survey "Type 2 Diabetes Mellitus: Combination Therapy With Hypoglycemic Drug (Insulin Preparation or Rapid-acting Insulin Secretagogues, Etc)"

NCT Number: NCT02221284

Protocol Approve Date: 02-Jun-2017

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.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

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

Nesina Tablets Specified Drug-use Survey "Type 2 Diabetes Mellitus: Combination Therapy With Hypoglycemic Drug (Insulin Preparation or Rapid-acting Insulin Secretagogues, Etc)"

Version	**Sixth version**
Creation date	**June 2, 2017**
Sponsor	**Takeda Pharmaceutical Company Limited.**

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1.0 Background

Nesina tablets (hereinafter, Nesina) are dipeptidyl peptidase-4inhibitors (hereinafter, DPP-4inhibitors) and oral hypoglycemic drugs mainly characterized by glucose level-dependent insulin secretion promotion via a GLP-1 increase and pancreas protection. Since oral hypoglycemic drugs have been generally used for a long period in patients and since multiple hypoglycemic drugs may be used simultaneously, it is important that long-term results of oral hypoglycemic drugs should be obtained from a daily clinical practice. The Specified Drug-use Survey of Nesina has been conducted in type 2 diabetes mellitus patients who have had an inadequate response to diet/exercise therapies only or diet/exercise therapies plus α-glucosidase inhibitors, thiazolidines, sulfonylureas, or biguanides. In the future, the specified drug-use survey of complication with Nesina and insulin preparations and insulin secretagogues is also expected to be conducted.

Therefore, the Nesina Tablets Specified Drug-use Survey "Type 2 Diabetic Patients Receiving Combination Therapy With a Hypoglycemic Agent (e.g., Insulin Preparations or Rapid-acting Insulin Secretagogues)" (hereinafter, this survey) is planned aiming to evaluate the safety and efficacy of Nesina when administered for 1 year in type 2 diabetic patients who have had an inadequate response to hypoglycemic agents (e.g., insulin preparations, rapid-acting insulin secretagogues) in addition to dietary/exercise therapy in daily medical practice.

This survey is conducted according to the relevant regulatory requirements including the GPSP ordinance.

2.0 Objectives

This survey is designed to evaluate the safety and efficacy of long-term use of alogliptin tablets (Nesina Tablets) in type 2 diabetic patients who have had an inadequate response to hypoglycemic agents (e.g., insulin preparations or rapid-acting insulin secretagogues)* in addition to dietary/exercise therapy in daily medical practice.

*Hypoglycemic agents which have not been used in the past Nesina Specified Drug-use Survey (i.e., other than α-glucosidase inhibitors, thiazolidines, sulfonylureas, and biguanides)

3.0 Number of Planned Participants and the Rationales

3.1 Number of Planned Participants

1,000 participants

3.2 Rationales

The Specified Drug-use Survey of Nesina has been conducted in type 2 diabetes mellitus patients who have had an inadequate response to diet/exercise therapies only or diet/exercise therapies plus α-glucosidase inhibitors, thiazolidines, sulfonylureas, or biguanides. In the future, the specified drug-use survey of complication with Nesina and insulin preparations and insulin

secretagogues is also expected to be conducted.

Therefore, the planned participants was established as 1,000 to collect as many as participants who receive a long-term complication therapy with Nesina and these hypoglycemic agents (e.g., insulin preparations, rapid-acting insulin secretagogues).

In the pooled tabulation of participants in the past Nesina Specified Drug-use Survey (as of November 30, 2013; Safety Analysis Set, 10,025 participants), the proportion of participants was as follows: elderly, 58.0%; renal impairment participants, 15.1%; and hepatic impairment participants, 13.3%. By establishment of the planned participants of 1,000 in this survey, data will be collected from approximately 600 elderly participants, approximately 150 renal impairment participants, and approximately 100 hepatic impairment participants. This establishment is not based on the statistical evidence.

4.0 Patients for Survey

Patients with type 2 diabetes mellitus. However, participants must meet the inclusion criteria and none of the exclusion criteria, described below. Refer to the Precaution in the package insert.

4.1 Inclusion Criteria

Patients who meet the following criterion are included in this survey:

Patients who have had an inadequate response to the following medications/therapies:

- Use of one hypoglycemic agent such as insulin preparations and rapid-acting insulin secretagogues, excluding other types of hypoglycemic agents (e.g., α-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides)*, in addition to dietary/exercise therapy

  *For use of Nesina Tablets in combination with these agents, a specified drug-use survey is currently ongoing.

4.2 Exclusion Criteria

Patients who meet any of the following criteria are excluded from this survey:

Patients with contraindications for Nesina Tablets

(1) Those with severe ketosis, in a state of diabetic coma or precoma, or with type 1 diabetes mellitus [Quickly rectifying hyperglycemia with administration of intravenous fluid or insulin is essential in these patients; therefore, administration of Nesina Tablets is not appropriate.]

(2) Those with severe infections, before or after surgery, or with serious trauma [Controlling blood glucose with an injection of insulin is desirable for these patients; therefore, administration of Nesina Tablets is not appropriate.]

(3) Those with a history of hypersensitivity to any of the ingredients of Nesina Tablets

5.0 Dosage and Administration

For adults, 25 mg of alogliptin is usually administered orally once daily. Refer to the Precaution

in the package insert. For renal impairment patients, refer to the Precaution with Respect to Dosage and Administration in the package insert.

6.0 Number of Scheduled Sites by Department

Internal medicine or other department: Approximately 200 sites

7.0 Methods

7.1 Observation period

12 months

7.2 Request for Sites and Agreement

The survey is conducted using the paper survey sheet. Before asking survey, the parson in charge of medical information in Takeda Pharmaceutical Company Limited. (Hereinafter, Takeda MRs) will fully explain to the Investigator about the objectives, details, and methods of this survey, based on “Request for Cooperation of Specified Drug-use Survey,” “Summary for Survey,” “Patient Enrollment Sheet (sample),” and “Survey Sheet (sample)” and will finalize written agreement with survey sites to ask requests for surveillance within the specified period.

7.3 Patient Enrollment Methods patients

This survey is conducted by Fax using Central Enrollment System. The Investigator will enroll patients for whom Nesina was prescribed after the start date of agreement with a survey site, by faxing to the Central Enrollment Center (refer to Section 12.2) the “Patient Enrollment Sheet” including the information regarding patient enrollment (refer to Section 9.1) before 14 days after the Nesina prescription date (define the prescription date as “0 day” and one day after the prescription date as “1 day”). Patients for whom Nesina prescription is scheduled cannot be enrolled earlier. The participant who assessed as ineligible for the survey for any reason cannot be enrolled in the survey. The Investigator will enroll a new participant using the “Patient Enrollment Sheet” supplied by the Takeda MR. The Takeda MR will supply for the Investigator the survey sheet issued after the Central Enrollment Center enrolled the participant.

7.4 Creation and Submission of Survey Sheet

The Investigator will create the survey sheet for all enrolled participants and submit it to the Takeda around within 1 month after the end of the observation period. If Nesina administration cannot be confirmed, specify it (do not specify other columns).

For participants who early discontinue treatment with Nesina during the observation period for any reason, the Investigator will create the survey sheet for him/her and submit it to the Takeda around within 1 month after the end of necessary observation. However, for participants who early discontinue treatment with Nesina due to an adverse event, the Investigator will continue

observation even after treatment discontinuation, wherever possible, until the adverse event resolve or is resolving and will create the survey sheet and submit it to the Takeda.

7.5 Measures for Development of Serious Adverse Events

In case of development of a serious adverse event in the observation period, the Investigator will immediately contact the parson in charge in Takeda Pharmaceutical Company Limited. (person in charge in Takeda). If the person in charge in Takeda requests additional detailed information, the Investigator will provide it.

8.0 Scheduled Period

Survey period: June 2014 to June 30, 2017

Patient enrollment period: June 2014 to June 30, 2016*

*Even if Nesina is prescribed before June 30 2016, the patients cannot be enrolled (fax of the Patient Enrollment Sheet) after July 1 2016.

In case that the enrolled participants reach the scheduled number of participants in the survey before June 30 2016, the enrollment will close earlier than the scheduled patient enrollment period. If patient enrollment period is shorten, the survey period will be also changed according to the shorten period.

9.0 Matters to be Surveyed

The Investigator will describe the data described below in the Patient Enrollment Sheet and the survey sheet. The schedule of this survey is shown in the Appendix.

9.1 Description Details in Patient Enrollment Sheet

1) Matters to be surveyed

Name of survey site, name of the investigator who describe in the Patient Enrollment Sheet, Nesina prescription date, Patient ID Number, patient initial, sex, birth date, inclusion criteria assessment, and exclusion criteria assessment

2) Survey period

At patient enrollment

9.2 Description Items in Survey Sheet

9.2.1 Front Cover of Survey Sheet

Last description date in the survey sheet and name of the Investigator who described the survey sheet

9.2.2 Patient Demographics

1) Matters to be surveyed

Diagnosis period of type 2 diabetes mellitus, category of clinical practice, disposition of hypersensitivity (yes/no and detail), concurrent disease (yes/no and detail), past medical

history (yes/no and detail), height, smoking history, drinking history, presence or absence of serum creatinine within 1 month after the start of Nesina treatment, serum creatinine level (if serum creatinine present), and severity of renal impairment and rationale for the assessment (if serum creatinine absent).

2) Survey period

At the start of Nesina treatment

9.2.3 Details of Treatment

1) Matters to be surveyed

Details of Nesina treatment (daily dose, administration period, and reason for discontinuation), and status of concomitant medications (hypoglycemic agents*) (yes/no, drug name, daily dose, route of administration, administration period, and objective of administration)

*Hypoglycemic agents which are discontinued within 3 months prior to Nesina treatment are included.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.4 Compliance with Nesina and Compliance with Diet/Exercise Therapy

1) Matters to be surveyed

Compliance with Nesina* and compliance with diet/exercise therapy**

*Criteria for assessment of compliance with Nesina

1. ≥ 90% (A participant won't miss administration, or even if he/she missed administration, the frequency is twice or three times a month.)
2. ≥ 70% (A participant missed administration once or twice weekly.)
3. ≥ 50% (A participant missed administration three times a week.)
4. < 50% (A participant missed administration four times or more a week.)

**Criteria for assessment of compliance with diet/exercise therapy

1. ≥ 90% (A participant complied as instructed.)
2. ≥ 70% (A participant mostly complied as instructed.)
3. ≥ 50% (A participant did not complied well as instructed.)
4. < 50% (A participant did not mostly complied as instructed.)
5. Not performed
6. Unknown

2) Survey period

At the start of Nesina treatment (compliance with diet/exercise therapy only), 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5 Laboratory/Observation Parameters

9.2.5.1 Vital Signs

1) Laboratory/observation parameters

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

2) Survey period

Each time point at the start of Nesina treatment, 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5.2 Laboratory Values

1) Laboratory parameters

HbA1c (NGSP value, same hereafter), fasting glucose, fasting insulin, fasting glucagon, fasting triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, serum creatinine, BUN, urinary albumin (corrected by creatinine), AST, ALT, γ-GTP, ALP, total bilirubin, amylase, and lipase

2) Survey period

Each time point at the start of Nesina treatment, 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5.3 Electrocardiography

1) Observation Parameters

Electrocardiograms (assessment and findings)

2) Survey period

Each time point from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.5.4 Tests for Waist Circumference, Coronary Arteriosclerosis, and Arteriosclerosis

1) Observation Parameters

Tests for waist circumference,* coronary arteriosclerosis and arteriosclerosis** (e.g., pulse wave velocity, cardio-ankle vascular index, intima-media thickness, intra-vascular ultrasound)

*Measure the waist diameter during light expiration at standing position and at the level of the navel. If the lower deviation of the navel occurs because of significant abdominal fat accumulation, measure the waist diameter at the level of the midpoint between the inferior rib border and anterior superior iliac spine.

**Any methods can be used. In principle, however, use the same methods for each test. If there are no

devices for measurement, the tests can be omitted.

2) Survey period

Each time point from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.5.5 Other Parameters

1) Observation parameters

Pregnancy during the observation period (yes or no) (females only)

In case of pregnancy in the observation period, the Investigator will immediately contact the person in charge in Takeda. The Investigator will provide detailed information (including the information until the delivery, as possible, such as preterm delivery) using the separate pregnancy sheet after the request from the person in charge in Takeda.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.6 Adverse Event

1) Matters to be surveyed

Presence or absence of adverse events (refer to Table 1), term of adverse events, onset date, seriousness and the reason (refer to Table 2), presence or absence of Nesina discontinuation, outcome assessment date, outcome, and causal relationship to Nesina* (refer to Table 3).

If the outcome is assessed as Not resolved or Unknown and if the causal relationship cannot be assessed, the participant will be followed up, wherever possible.

The detailed information (e.g., clinical course, laboratory tests for diagnosis) will be collected as possible for development of hypoglycemia, acute pancreatitis, renal impairment / jaundice, skin disorder including oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme, rhabdomyolysis, intestinal obstruction, interstitial pneumonia, angioedema, infection, malignant tumor, pemphigoid, and cardiovascular system-related event (e.g., symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death)

*If the causal relationship to Nesina is assessed as Not related, collect the rationales for assessment. If the relationship is assessed as Not assessable, collected the reason for Not assessable.

Note) Matters that should be considered for adverse events

Abnormal exacerbation of the target disease, i.e., worsening beyond expected natural clinical course, is defined as an adverse event; however, the expected worsening is not defined as an adverse vent.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

Table 1 Definition of adverse event

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

The following events will be handled as adverse events:

- Symptoms present in infants breastfed by a Nesina taking mother
- Symptoms present in children who received the relevant drug
- Symptoms due to occupational exposure to the relevant drug
- Symptoms due to counterfeit medications of the legitimate medicinal products manufactured by Takeda
- Unfavorable symptoms present in the patient who received the relevant drug, known by a lawsuit or other legal actions

Table 2 Criteria for severity assessment

An event which meet any of the following criteria will be assessed as "Serious:"

1. Results in death (death).
2. Is life-threatening (potential death threat).
3. Requires inpatient hospitalization or prolongation of existing hospitalization (admission / prolonged hospitalization).
4. Results in persistent or significant disability/incapacity (disability).
5. Is a congenital anomaly/birth defect (congenital anomaly).
6. Other significant medical conditions which do not meet the above criteria 1 to 5. Events listed in the "Takeda Medically Significant AE List are included in this section criteria.

<u>Takeda Medically Significant AE List</u>

• Acute respiratory failure / acute respiratory distress syndrome (ARDS)	• Anaphylactic shock
• Torsade de pointes / ventricular fibrillation / ventricular tachycardia	• Acute renal failure
• Malignant hypertension	• Pulmonary hypertension
• Convulsive seizure (including convulsion and epilepsy)	• Pulmonary fibrosis (including interstitial pneumonia)
• Agranulocytosis	• Malignant syndrome / malignant hyperthermia
• Aplastic anemia	• Spontaneous abortion / stillbirth and fetal death
• Toxic epidermal necrolysis /	• Spread of infection via drug or suspected spread

oculomucocutaneous syndrome (Stevens-Johnson syndrome) • Hepatic necrosis • Endotoxic shock or suspected endotoxic shock ・Acute hepatic failure

Table 3 Criteria for causality assessment between adverse events and Nesina

Assessment	Assessment criterion
Related	Temporally correlation (including the post-treatment clinical course) present. Or an adverse event that may have been caused by the primary disease, concurrent disease, concomitant medication, or other factor including concomitant procedures, but also suggested to be caused by the relevant drug.
Not related	No temporally correlation with the relevant drug. Or an adverse event presumably caused by the primary disease, concurrent disease, concomitant medication, or other factor.
Not assessable	Lack of information for assessment of temporal correlation (including the post-treatment clinical course), the primary disease, concurrent disease, concomitant medication, other factor, etc.

10.0 Analysis Parameters and Methods

10.1 Patient Component Parameters

The following will be tabulated: number of enrolled participants, number of survey sheet collected participants, number of the Safety Analysis Set, number of the Efficacy Analysis Set, and number of patients excluded from analysis and the reason for exclusion, etc.

10.2 Patient Demographics

Patient demographics including sex, age, disease period, hypersensitivity predisposition, and concurrent disease will be tabulated.

10.3 Details of Treatment

The following will be tabulated: status of Nesina treatment, status of concomitant medications, and compliance with Nesina treatment, etc.

10.4 Safety Parameters

The items described below will be tabulated in the Safety Analysis Set. Adverse events will be coded using the MedDRA/J and summarized by Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Occurrence of Adverse Events

For adverse events reported in the observation period, the type and causal relationship to Nesina will be tabulated.

10.4. 2 Factors Probably Affecting Safety

For adverse drug reactions reported in the observation period, the frequency of patient demographics (e.g., sex, age), details of treatment (e.g., status of Nesina, and status of concomitant medications) will be stratified.

10.5 Efficacy Parameters

The following will be tabulated in the Efficacy Analysis Set:

10.5.1 Change in HbA1c

HbA1c test values and the corresponding change from baseline at each testing time point (i.e., test value at each testing time point − test value at baseline) will be tabulated. In addition, the objective glycemic control achievement rate at each testing time point will be tabulated.

10.5.2 Changes in Laboratory Test Values

Test values (fasting blood glucose level, fasting insulin level, HOMA-R,* and HOMA-β*) and the corresponding changes from baseline at each testing time point (i.e., test value at each testing time point − test value at baseline) will be tabulated.

*HOMA-R: Fasting insulin × Fasting glucose / 405

**HOMA-β: (Fasting insulin × 360) / (Fasting glucose − 63)

10.5.3 Factors Probably Affecting Efficacy

For the changes in HbA1c and glycemic control achievement rate at 12 months after the start of treatment, the following will be stratified: patient demographics (e.g., sex, age, HbA1c at the start of Nesina treatment) and details of treatment (e.g., status of Nesina treatment, status of concomitant medications).

10.6 Parameters in Patients with Special Demographics

The safety and efficacy of Nesina will be stratified in elderly patients or patients with hepatic/renal impairment.

11.0 Registration of Survey Data

Takeda Pharmaceutical Company Limited. will register the survey information in the following open websites before the start of this survey.

- Japan Pharmaceutical Information Center-Clinical Trials Information
- Clinical trial registration system of National Institute of Health (US): ClinicalTrials.gov

12.0 Organizations

12.1 Manager

Takeda Pharmaceutical Company Limited.

PPD

12.2 Central Enrollment Center

PPD

13.0 CRO

PPD

14.0 Other Necessary Matters

14.1 Protocol Revision

During the survey period, the protocol can be reviewed and revised, if the following are necessary to be changed after monitored: the survey progress, adverse drug reactions / serious adverse drug reactions unexpected from the Precautions, increased frequency of specified adverse drug reactions (yes or no), and parameter appropriateness. During the survey period, if partly changes of dosage and administration and indications are approved, the protocol revision will be also considered and performed as necessary.

14.2 Measures for Issues or Questions

If any question about the safety or efficacy is arisen, data will be investigated and the relevant persons will take measures for the question.

Appendix Observation Schedule

Parameter \ Survey period		Observation period						
		At patient enrollment	At start of treatment	1 months after treatment	3 months after treatment	6 months after treatment	12 months after treatment	At treatment discontinuation
Patient enrollment	Nesina prescription date	○						
	Patient ID Number	○						
	Patients initial	○						
	Sex	○						
	Birth date	○						
	Assessment of inclusion criteria / exclusion criteria	○						
At patient demographics	Diagnosis period of type 2 diabetes mellitus		○					
	Category of clinical practice		○					
	Hypersensitivity predisposition		○					
	Concurrent disease		○					
	Past medical history		○					
	Height		○					
	Smoking history		○					
	Drinking history		○					
	Presence or absence of serum creatinine within 1 month after the start of Nesina treatment, serum creatinine level (if serum creatinine present), and severity of renal impairment and rationale for the assessment (if serum creatinine absent).		○					
Details of treatment, etc	Status of Nesina treatment		←	―	○	―	→	○
	Status of concomitant medication treatment (hypoglycemic agents* / other than hypoglycemic agents)		←	―	○	―	→	○
	Status of compliance with Nesina			○	○	○	○	○
	Status of compliance with diet/exercise therapy		○	○	○	○	○	○
Laboratory/Observation Parameters, etc	Pulse rate, blood pressure		○	○	○	○	○	○
	Weight		○	○	○	○	○	○
	Laboratory values • HbA1c (NGSP value) • Fasting glucose • Fasting insulin • Fasting glucagon • Fasting triglyceride • Total cholesterol • HDL-cholesterol • LDL-cholesterol • Serum creatinine • BUN • Urinary albumin (corrected by creatinine) • AST • ALT • γ-GTP • ALP • Total bilirubin • Amylase • Lipase		○	○	○	○	○	○
	Electrocardiogram		○				○	○
	Waist circumference		○				○	○
	Tests for coronary arteriosclerosis and arteriosclerosis		○				○	○
	Pregnancy (yes or no) (females only)		←	―	○	―	→	○
	Adverse event		←	―	○	―	→	○

○ To be performed

←　○　→ To be performed throughout the period

*Including hypoglycemic agents discontinued within 3 months before the start of Nesina treatment

Protocol for

Nesina Tablets Specified Drug-use Survey "Type 2 Diabetes Mellitus: Combination Therapy With Hypoglycemic Drug (Insulin Preparation or Rapid-acting Insulin Secretagogues, Etc)"

Version	**Fifth version**
Creation date	**November 9, 2016**
Sponsor	**Takeda Pharmaceutical Company Limited.**

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observation even after treatment discontinuation, wherever possible, until the adverse event resolve or is resolving and will create the survey sheet and submit it to the Takeda.

7.5 Measures for Development of Serious Adverse Events

In case of development of a serious adverse event in the observation period, the Investigator will immediately contact the parson in charge in Takeda Pharmaceutical Company Limited. (person in charge in Takeda). If the person in charge in Takeda requests additional detailed information, the Investigator will provide it.

8.0 Scheduled Period

Survey period: June 2014 to June 30, 2017

Patient enrollment period: June 2014 to June 30, 2016*

*Even if Nesina is prescribed before June 30 2016, the patients cannot be enrolled (fax of the Patient Enrollment Sheet) after July 1 2016.

In case that the enrolled participants reach the scheduled number of participants in the survey before June 30 2016, the enrollment will close earlier than the scheduled patient enrollment period. If patient enrollment period is shorten, the survey period will be also changed according to the shorten period.

9.0 Matters to be Surveyed

The Investigator will describe the data described below in the Patient Enrollment Sheet and the survey sheet. The schedule of this survey is shown in the Appendix.

9.1 Description Details in Patient Enrollment Sheet

1) Matters to be surveyed

Name of survey site, name of the investigator who describe in the Patient Enrollment Sheet, Nesina prescription date, Patient ID Number, patient initial, sex, birth date, inclusion criteria assessment, and exclusion criteria assessment

2) Survey period

At patient enrollment

9.2 Description Items in Survey Sheet

9.2.1 Front Cover of Survey Sheet

Last description date in the survey sheet and name of the Investigator who described the survey sheet

9.2.2 Patient Demographics

1) Matters to be surveyed

Diagnosis period of type 2 diabetes mellitus, category of clinical practice, disposition of hypersensitivity (yes/no and detail), concurrent disease (yes/no and detail), past medical history (yes/no and detail), height, smoking history, drinking history, presence or absence of

serum creatinine within 1 month after the start of Nesina treatment, serum creatinine level (if serum creatinine present), and severity of renal impairment and rationale for the assessment (if serum creatinine absent).

2) Survey period

At the start of Nesina treatment

9.2.3 Details of Treatment

1) Matters to be surveyed

Details of Nesina treatment (daily dose, administration period, and reason for discontinuation), and status of concomitant medications (hypoglycemic agents*) (yes/no, drug name, daily dose, route of administration, administration period, and objective of administration)

*Hypoglycemic agents which are discontinued within 3 months prior to Nesina treatment are included.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.4 Compliance with Nesina and Compliance with Diet/Exercise Therapy

1) Matters to be surveyed

Compliance with Nesina* and compliance with diet/exercise therapy**

*Criteria for assessment of compliance with Nesina

1. ≥ 90% (A participant won't miss administration, or even if he/she missed administration, the frequency is twice or three times a month.)
2. ≥ 70% (A participant missed administration once or twice weekly.)
3. ≥ 50% (A participant missed administration three times a week.)
4. < 50% (A participant missed administration four times or more a week.)

**Criteria for assessment of compliance with diet/exercise therapy

1. ≥ 90% (A participant complied as instructed.)
2. ≥ 70% (A participant mostly complied as instructed.)
3. ≥ 50% (A participant did not complied well as instructed.)
4. < 50% (A participant did not mostly complied as instructed.)
5. Not performed
6. Unknown

2) Survey period

At the start of Nesina treatment (compliance with diet/exercise therapy only), 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5 Laboratory/Observation Parameters

9.2.5.1 Vital Signs

1) Laboratory/observation parameters

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

2) Survey period

Each time point at the start of Nesina treatment, 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5.2 Laboratory Values

1) Laboratory parameters

HbA1c (NGSP value, same hereafter), fasting glucose, fasting insulin, fasting glucagon, fasting triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, serum creatinine, BUN, urinary albumin (corrected by creatinine), AST, ALT, γ-GTP, ALP, total bilirubin, amylase, and lipase

2) Survey period

Each time point at the start of Nesina treatment, 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5.3 Electrocardiography

1) Observation Parameters

Electrocardiograms (assessment and findings)

2) Survey period

Each time point from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.5.4 Tests for Waist Circumference, Coronary Arteriosclerosis, and Arteriosclerosis

1) Observation Parameters

Tests for waist circumference,* coronary arteriosclerosis and arteriosclerosis** (e.g., pulse wave velocity, cardio-ankle vascular index, intima-media thickness, intra-vascular ultrasound)

*Measure the waist diameter during light expiration at standing position and at the level of the navel. If the lower deviation of the navel occurs because of significant abdominal fat accumulation, measure the waist diameter at the level of the midpoint between the inferior rib border and anterior superior iliac spine.

**Any methods can be used. In principle, however, use the same methods for each test. If there are no devices for measurement, the tests can be omitted.

2) Survey period

Each time point from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.5.5 Other Parameters

1) Observation parameters

Pregnancy during the observation period (yes or no) (females only)

In case of pregnancy in the observation period, the Investigator will immediately contact the person in charge in Takeda. The Investigator will provide detailed information (including the information until the delivery, as possible, such as preterm delivery) using the separate pregnancy sheet after the request from the person in charge in Takeda.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.6 Adverse Event

1) Matters to be surveyed

Presence or absence of adverse events (refer to Table 1), term of adverse events, onset date, seriousness and the reason (refer to Table 2), presence or absence of Nesina discontinuation, outcome assessment date, outcome, and causal relationship to Nesina* (refer to Table 3).

If the outcome is assessed as Not resolved or Unknown and if the causal relationship cannot be assessed, the participant will be followed up, wherever possible.

The detailed information (e.g., clinical course, laboratory tests for diagnosis) will be collected as possible for development of hypoglycemia, acute pancreatitis, renal impairment / jaundice, skin disorder including oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme, rhabdomyolysis, intestinal obstruction, interstitial pneumonia, angioedema, infection, malignant tumor, pemphigoid, and cardiovascular system-related event (e.g., symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death)

*If the causal relationship to Nesina is assessed as Not related, collect the rationales for assessment. If the relationship is assessed as Not assessable, collected the reason for Not assessable.

Note) Matters that should be considered for adverse events

Abnormal exacerbation of the target disease, i.e., worsening beyond expected natural clinical course, is defined as an adverse event; however, the expected worsening is not defined as an adverse vent.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment

discontinuation)

Table 1 Definition of adverse event

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

The following events will be handled as adverse events:

• Symptoms present in infants breastfed by a Nesina taking mother

• Symptoms present in children who received the relevant drug

• Symptoms due to occupational exposure to the relevant drug

• Symptoms due to counterfeit medications of the legitimate medicinal products manufactured by Takeda

• Unfavorable symptoms present in the patient who received the relevant drug, known by a lawsuit or other legal actions

Table 2 Criteria for severity assessment

An event which meet any of the following criteria will be assessed as "Serious:"

1. Results in death (death).
2. Is life-threatening (potential death threat).
3. Requires inpatient hospitalization or prolongation of existing hospitalization (admission / prolonged hospitalization).
4. Results in persistent or significant disability/incapacity (disability).
5. Is a congenital anomaly/birth defect (congenital anomaly).
6. Other significant medical conditions which do not meet the above criteria 1 to 5. Events listed in the "Takeda Medically Significant AE List are included in this section criteria.

<u>Takeda Medically Significant AE List</u>

• Acute respiratory failure / acute respiratory distress syndrome (ARDS)	• Anaphylactic shock
• Torsade de pointes / ventricular fibrillation / ventricular tachycardia	• Acute renal failure
• Malignant hypertension	• Pulmonary hypertension
• Convulsive seizure (including convulsion and epilepsy)	• Pulmonary fibrosis (including interstitial pneumonia)
• Agranulocytosis	• Malignant syndrome / malignant hyperthermia
• Aplastic anemia	• Spontaneous abortion / stillbirth and fetal death
• Toxic epidermal necrolysis / oculomucocutaneous syndrome (Stevens-Johnson	• Spread of infection via drug or suspected spread

syndrome)

• Hepatic necrosis • Endotoxic shock or suspected endotoxic shock

・Acute hepatic failure

Table 3 Criteria for causality assessment between adverse events and Nesina

Assessment	Assessment criterion
Related	Temporally correlation (including the post-treatment clinical course) present. Or an adverse event that may have been caused by the primary disease, concurrent disease, concomitant medication, or other factor including concomitant procedures, but also suggested to be caused by the relevant drug.
Not related	No temporally correlation with the relevant drug. Or an adverse event presumably caused by the primary disease, concurrent disease, concomitant medication, or other factor.
Not assessable	Lack of information for assessment of temporal correlation (including the post-treatment clinical course), the primary disease, concurrent disease, concomitant medication, other factor, etc.

10.0 Analysis Parameters and Methods

10.1 Patient Component Parameters

The following will be tabulated: number of enrolled participants, number of survey sheet collected participants, number of the Safety Analysis Set, number of the Efficacy Analysis Set, and number of patients excluded from analysis and the reason for exclusion, etc.

10.2 Patient Demographics

Patient demographics including sex, age, disease period, hypersensitivity predisposition, and concurrent disease will be tabulated.

10.3 Details of Treatment

The following will be tabulated: status of Nesina treatment, status of concomitant medications, and compliance with Nesina treatment, etc.

10.4 Safety Parameters

The items described below will be tabulated in the Safety Analysis Set. Adverse events will be coded using the MedDRA/J and summarized by Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Occurrence of Adverse Events

For adverse events reported in the observation period, the type and causal relationship to Nesina will be tabulated.

10.4. 2 Factors Probably Affecting Safety

For adverse drug reactions reported in the observation period, the frequency of patient demographics (e.g., sex, age), details of treatment (e.g., status of Nesina, and status of concomitant medications) will be stratified.

10.5 Efficacy Parameters

The following will be tabulated in the Efficacy Analysis Set:

10.5.1 Change in HbA1c

HbA1c test values and the corresponding change from baseline at each testing time point (i.e., test value at each testing time point − test value at baseline) will be tabulated. In addition, the objective glycemic control achievement rate at each testing time point will be tabulated.

10.5.2 Changes in Laboratory Test Values

Test values (fasting blood glucose level, fasting insulin level, HOMA-R,* and HOMA-β*) and the corresponding changes from baseline at each testing time point (i.e., test value at each testing time point − test value at baseline) will be tabulated.

*HOMA-R: Fasting insulin × Fasting glucose / 405

**HOMA-β: (Fasting insulin × 360) / (Fasting glucose − 63)

10.5.3 Factors Probably Affecting Efficacy

For the changes in HbA1c and glycemic control achievement rate at 12 months after the start of treatment, the following will be stratified: patient demographics (e.g., sex, age, HbA1c at the start of Nesina treatment) and details of treatment (e.g., status of Nesina treatment, status of concomitant medications).

10.6 Parameters in Patients with Special Demographics

The safety and efficacy of Nesina will be stratified in elderly patients or patients with hepatic/renal impairment.

11.0 Registration of Survey Data

Takeda Pharmaceutical Company Limited. will register the survey information in the following open websites before the start of this survey.

- Japan Pharmaceutical Information Center-Clinical Trials Information
- Clinical trial registration system of National Institute of Health (US): ClinicalTrials.gov

12.0 Organizations

12.1 Manager

Takeda Pharmaceutical Company Limited.

PPD

12.2 Central Enrollment Center

PPD

13.0 CRO

PPD

14.0 Other Necessary Matters

14.1 Protocol Revision

During the survey period, the protocol can be reviewed and revised, if the following are necessary to be changed after monitored: the survey progress, adverse drug reactions / serious adverse drug reactions unexpected from the Precautions, increased frequency of specified adverse drug reactions (yes or no), and parameter appropriateness. During the survey period, if partly changes of dosage and administration and indications are approved, the protocol revision will be also considered and performed as necessary.

14.2 Measures for Issues or Questions

If any question about the safety or efficacy is arisen, data will be investigated and the relevant persons will take measures for the question.

Appendix Observation Schedule

Parameter \ Survey period		Observation period						
		At patient enrollment	At start of treatment	1 months after treatment	3 months after treatment	6 months after treatment	12 months after treatment	At treatment discontinuation
Patient enrollment	Nesina prescription date	○						
	Patient ID Number	○						
	Patients initial	○						
	Sex	○						
	Birth date	○						
	Assessment of inclusion criteria / exclusion criteria	○						
At patient demographics	Diagnosis period of type 2 diabetes mellitus		○					
	Category of clinical practice		○					
	Hypersensitivity predisposition		○					
	Concurrent disease		○					
	Past medical history		○					
	Height		○					
	Smoking history		○					
	Drinking history		○					
	Presence or absence of serum creatinine within 1 month after the start of Nesina treatment, serum creatinine level (if serum creatinine present), and severity of renal impairment and rationale for the assessment (if serum creatinine absent).		○					
Details of treatment, etc.	Status of Nesina treatment		←	―	○	―	→	○
	Status of concomitant medication treatment (hypoglycemic agents* / other than hypoglycemic agents)		←	―	○	―	→	○
	Status of compliance with Nesina			○	○	○	○	○
	Status of compliance with diet/exercise therapy		○	○	○	○	○	○
Laboratory/Observation Parameters, etc	Pulse rate, blood pressure		○	○	○	○	○	○
	Weight		○	○	○	○	○	○
	Laboratory values • HbA1c (NGSP value) • Fasting glucose • Fasting insulin • Fasting glucagon • Fasting triglyceride • Total cholesterol • HDL-cholesterol • LDL-cholesterol • Serum creatinine • BUN • Urinary albumin (corrected by creatinine) • AST • ALT • γ-GTP • ALP • Total bilirubin • Amylase • Lipase		○	○	○	○	○	○
	Electrocardiogram		○				○	○
	Waist circumference		○				○	○
	Tests for coronary arteriosclerosis and arteriosclerosis		○				○	○
	Pregnancy (yes or no) (females only)		←	―	○	―	→	○
	Adverse event		←	―	○	―	→	○

○ : To be performed

←　○　→: To be performed throughout the period

*Including hypoglycemic agents discontinued within 3 months before the start of Nesina treatment

Protocol for

Nesina Tablets Specified Drug-use Survey "Type 2 Diabetes Mellitus: Combination Therapy With Hypoglycemic Drug (Insulin Preparation or Rapid-acting Insulin Secretagogues, Etc)"

Version	**Fourth version**
Creation date	**February 1, 2016**
Sponsor	**Takeda Pharmaceutical Company Limited.**

1.0 Background

Nesina tablets (hereinafter, Nesina) are dipeptidyl peptidase-4inhibitors (hereinafter, DPP-4inhibitors) and oral hypoglycemic drugs mainly characterized by glucose level-dependent insulin secretion promotion via a GLP-1 increase and pancreas protection. Since oral hypoglycemic drugs have been generally used for a long period in patients and since multiple hypoglycemic drugs may be used simultaneously, it is important that long-term results of oral hypoglycemic drugs should be obtained from a daily clinical practice. The Specified Drug-use Survey of Nesina has been conducted in type 2 diabetes mellitus patients who have had an inadequate response to diet/exercise therapies only or diet/exercise therapies plus α-glucosidase inhibitors, thiazolidines, sulfonylureas, or biguanides. In the future, the specified drug-use survey of complication with Nesina and insulin preparations and insulin secretagogues is also expected to be conducted.

Therefore, the Nesina Tablets Specified Drug-use Survey "Type 2 Diabetic Patients Receiving Combination Therapy With a Hypoglycemic Agent (e.g., Insulin Preparations or Rapid-acting Insulin Secretagogues)" (hereinafter, this survey) is planned aiming to evaluate the safety and efficacy of Nesina when administered for 1 year in type 2 diabetic patients who have had an inadequate response to hypoglycemic agents (e.g., insulin preparations, rapid-acting insulin secretagogues) in addition to dietary/exercise therapy in daily medical practice.

This survey is conducted according to the relevant regulatory requirements including the GPSP ordinance.

2.0 Objectives

This survey is designed to evaluate the safety and efficacy of long-term use of alogliptin tablets (Nesina Tablets) in type 2 diabetic patients who have had an inadequate response to hypoglycemic agents (e.g., insulin preparations or rapid-acting insulin secretagogues)* in addition to dietary/exercise therapy in daily medical practice.

*Hypoglycemic agents which have not been used in the past Nesina Specified Drug-use Survey (i.e., other than α-glucosidase inhibitors, thiazolidines, sulfonylureas, and biguanides)

3.0 Number of Planned Participants and the Rationales

3.1 Number of Planned Participants

1,000 participants

3.2 Rationales

The Specified Drug-use Survey of Nesina has been conducted in type 2 diabetes mellitus patients who have had an inadequate response to diet/exercise therapies only or diet/exercise therapies plus α-glucosidase inhibitors, thiazolidines, sulfonylureas, or biguanides. In the future, the specified drug-use survey of complication with Nesina and insulin preparations and insulin

secretagogues is also expected to be conducted.

Therefore, the planned participants was established as 1,000 to collect as many as participants who receive a long-term complication therapy with Nesina and these hypoglycemic agents (e.g., insulin preparations, rapid-acting insulin secretagogues).

In the pooled tabulation of participants in the past Nesina Specified Drug-use Survey (as of November 30, 2013; Safety Analysis Set, 10,025 participants), the proportion of participants was as follows: elderly, 58.0%; renal impairment participants, 15.1%; and hepatic impairment participants, 13.3%. By establishment of the planned participants of 1,000 in this survey, data will be collected from approximately 600 elderly participants, approximately 150 renal impairment participants, and approximately 100 hepatic impairment participants. This establishment is not based on the statistical evidence.

4.0 Patients for Survey

Patients with type 2 diabetes mellitus. However, participants must meet the inclusion criteria and none of the exclusion criteria, described below. Refer to the Precaution in the package insert.

4.1 Inclusion Criteria

Patients who meet the following criterion are included in this survey:

Patients who have had an inadequate response to the following medications/therapies:

- Use of one hypoglycemic agent such as insulin preparations and rapid-acting insulin secretagogues, excluding other types of hypoglycemic agents (e.g., α-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides)*, in addition to dietary/exercise therapy

  *For use of Nesina Tablets in combination with these agents, a specified drug-use survey is currently ongoing.

4.2 Exclusion Criteria

Patients who meet any of the following criteria are excluded from this survey:

Patients with contraindications for Nesina Tablets

(1) Those with severe ketosis, in a state of diabetic coma or precoma, or with type 1 diabetes mellitus [Quickly rectifying hyperglycemia with administration of intravenous fluid or insulin is essential in these patients; therefore, administration of Nesina Tablets is not appropriate.]

(2) Those with severe infections, before or after surgery, or with serious trauma [Controlling blood glucose with an injection of insulin is desirable for these patients; therefore, administration of Nesina Tablets is not appropriate.]

(3) Those with a history of hypersensitivity to any of the ingredients of Nesina Tablets

5.0 Dosage and Administration

For adults, 25 mg of alogliptin is usually administered orally once daily. Refer to the Precaution

in the package insert. For renal impairment patients, refer to the Precaution with Respect to Dosage and Administration in the package insert.

6.0 Number of Scheduled Sites by Department

Internal medicine or other department: Approximately 200 sites

7.0 Methods

7.1 Observation period

12 months

7.2 Request for Sites and Agreement

The survey is conducted using the paper survey sheet. Before asking survey, the parson in charge of medical information in Takeda Pharmaceutical Company Limited. (Hereinafter, Takeda MRs) will fully explain to the Investigator about the objectives, details, and methods of this survey, based on “Request for Cooperation of Specified Drug-use Survey,” “Summary for Survey,” “Patient Enrollment Sheet (sample),” and “Survey Sheet (sample)” and will finalize written agreement with survey sites to ask requests for surveillance within the specified period.

7.3 Patient Enrollment Methods patients

This survey is conducted by Fax using Central Enrollment System. The Investigator will enroll patients for whom Nesina was prescribed after the start date of agreement with a survey site, by faxing to the Central Enrollment Center (refer to Section 12.2) the “Patient Enrollment Sheet” including the information regarding patient enrollment (refer to Section 9.1) before 14 days after the Nesina prescription date (define the prescription date as “0 day” and one day after the prescription date as “1 day”). Patients for whom Nesina prescription is scheduled cannot be enrolled earlier. The participant who assessed as ineligible for the survey for any reason cannot be enrolled in the survey. The Investigator will enroll a new participant using the “Patient Enrollment Sheet” supplied by the Takeda MR. The Takeda MR will supply for the Investigator the survey sheet issued after the Central Enrollment Center enrolled the participant.

7.4 Creation and Submission of Survey Sheet

The Investigator will create the survey sheet for all enrolled participants and submit it to the Takeda around within 1 month after the end of the observation period. If Nesina administration cannot be confirmed, specify it (do not specify other columns).

For participants who early discontinue treatment with Nesina during the observation period for any reason, the Investigator will create the survey sheet for him/her and submit it to the Takeda around within 1 month after the end of necessary observation. However, for participants who early discontinue treatment with Nesina due to an adverse event, the Investigator will continue

observation even after treatment discontinuation, wherever possible, until the adverse event resolve or is resolving and will create the survey sheet and submit it to the Takeda.

7.5 Measures for Development of Serious Adverse Events

In case of development of a serious adverse event in the observation period, the Investigator will immediately contact the parson in charge in Takeda Pharmaceutical Company Limited. (person in charge in Takeda). If the person in charge in Takeda requests additional detailed information, the Investigator will provide it.

8.0 Scheduled Period

Survey period: June 2014 to June 30, 2017

Patient enrollment period: June 2014 to June 30, 2016*

*Even if Nesina is prescribed before June 30 2016, the patients cannot be enrolled (fax of the Patient Enrollment Sheet) after July 1 2016.

In case that the enrolled participants reach the scheduled number of participants in the survey before June 30 2016, the enrollment will close earlier than the scheduled patient enrollment period. If patient enrollment period is shorten, the survey period will be also changed according to the shorten period.

9.0 Matters to be Surveyed

The Investigator will describe the data described below in the Patient Enrollment Sheet and the survey sheet. The schedule of this survey is shown in the Appendix.

9.1 Description Details in Patient Enrollment Sheet

1) Matters to be surveyed

Name of survey site, name of the investigator who describe in the Patient Enrollment Sheet, Nesina prescription date, Patient ID Number, patient initial, sex, birth date, inclusion criteria assessment, and exclusion criteria assessment

2) Survey period

At patient enrollment

9.2 Description Items in Survey Sheet

9.2.1 Front Cover of Survey Sheet

Last description date in the survey sheet and name of the Investigator who described the survey sheet

9.2.2 Patient Demographics

1) Matters to be surveyed

Diagnosis period of type 2 diabetes mellitus, category of clinical practice, disposition of hypersensitivity (yes/no and detail), concurrent disease (yes/no and detail), past medical history (yes/no and detail), height, smoking history, drinking history, presence or absence of

serum creatinine within 1 month after the start of Nesina treatment, serum creatinine level (if serum creatinine present), and severity of renal impairment and rationale for the assessment (if serum creatinine absent).

2) Survey period

At the start of Nesina treatment

9.2.3 Details of Treatment

1) Matters to be surveyed

Details of Nesina treatment (daily dose, administration period, and reason for discontinuation), and status of concomitant medications (hypoglycemic agents*) (yes/no, drug name, daily dose, route of administration, administration period, and objective of administration)

*Hypoglycemic agents which are discontinued within 3 months prior to Nesina treatment are included.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.4 Compliance with Nesina and Compliance with Diet/Exercise Therapy

1) Matters to be surveyed

Compliance with Nesina* and compliance with diet/exercise therapy**

*Criteria for assessment of compliance with Nesina

1. ≥ 90% (A participant won't miss administration, or even if he/she missed administration, the frequency is twice or three times a month.)
2. ≥ 70% (A participant missed administration once or twice weekly.)
3. ≥ 50% (A participant missed administration three times a week.)
4. < 50% (A participant missed administration four times or more a week.)

**Criteria for assessment of compliance with diet/exercise therapy

1. ≥ 90% (A participant complied as instructed.)
2. ≥ 70% (A participant mostly complied as instructed.)
3. ≥ 50% (A participant did not complied well as instructed.)
4. < 50% (A participant did not mostly complied as instructed.)
5. Not performed
6. Unknown

2) Survey period

At the start of Nesina treatment (compliance with diet/exercise therapy only), 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5 Laboratory/Observation Parameters

9.2.5.1 Vital Signs

1) Laboratory/observation parameters

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

2) Survey period

Each time point at the start of Nesina treatment, 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5.2 Laboratory Values

1) Laboratory parameters

HbA1c (NGSP value, same hereafter), fasting glucose, fasting insulin, fasting glucagon, fasting triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, serum creatinine, BUN, urinary albumin (corrected by creatinine), AST, ALT, γ-GTP, ALP, total bilirubin, amylase, and lipase

2) Survey period

Each time point at the start of Nesina treatment, 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5.3 Electrocardiography

1) Observation Parameters

Electrocardiograms (assessment and findings)

2) Survey period

Each time point from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.5.4 Tests for Waist Circumference, Coronary Arteriosclerosis, and Arteriosclerosis

1) Observation Parameters

Tests for waist circumference,* coronary arteriosclerosis and arteriosclerosis** (e.g., pulse wave velocity, cardio-ankle vascular index, intima-media thickness, intra-vascular ultrasound)

*Measure the waist diameter during light expiration at standing position and at the level of the navel. If the lower deviation of the navel occurs because of significant abdominal fat accumulation, measure the waist diameter at the level of the midpoint between the inferior rib border and anterior superior iliac spine.

**Any methods can be used. In principle, however, use the same methods for each test. If there are no devices for measurement, the tests can be omitted.

2) Survey period

Each time point from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.5.5 Other Parameters

1) Observation parameters

Pregnancy during the observation period (yes or no) (females only)

In case of pregnancy in the observation period, the Investigator will immediately contact the person in charge in Takeda. The Investigator will provide detailed information (including the information until the delivery, as possible, such as preterm delivery) using the separate pregnancy sheet after the request from the person in charge in Takeda.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.6 Adverse Event

1) Matters to be surveyed

Presence or absence of adverse events (refer to Table 1), term of adverse events, onset date, seriousness and the reason (refer to Table 2), presence or absence of Nesina discontinuation, outcome assessment date, outcome, and causal relationship to Nesina* (refer to Table 3).

If the outcome is assessed as Not resolved or Unknown and if the causal relationship cannot be assessed, the participant will be followed up, wherever possible.

The detailed information (e.g., clinical course, laboratory tests for diagnosis) will be collected as possible for development of hypoglycemia, acute pancreatitis, renal impairment / jaundice, skin disorder including oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme, rhabdomyolysis, intestinal obstruction, interstitial pneumonia, angioedema, infection, malignant tumor, and cardiovascular system-related event (e.g., symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death)

*If the causal relationship to Nesina is assessed as Not related, collect the rationales for assessment. If the relationship is assessed as Not assessable, collected the reason for Not assessable.

Note) Matters that should be considered for adverse events

Abnormal exacerbation of the target disease, i.e., worsening beyond expected natural clinical course, is defined as an adverse event; however, the expected worsening is not defined as an adverse vent.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment

discontinuation)

Table 1 Definition of adverse event

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

The following events will be handled as adverse events:

• Symptoms present in infants breastfed by a Nesina taking mother

• Symptoms present in children who received the relevant drug

• Symptoms due to occupational exposure to the relevant drug

• Symptoms due to counterfeit medications of the legitimate medicinal products manufactured by Takeda

• Unfavorable symptoms present in the patient who received the relevant drug, known by a lawsuit or other legal actions

Table 2 Criteria for severity assessment

An event which meet any of the following criteria will be assessed as "Serious:"

1. Results in death (death).
2. Is life-threatening (potential death threat).
3. Requires inpatient hospitalization or prolongation of existing hospitalization (admission / prolonged hospitalization).
4. Results in persistent or significant disability/incapacity (disability).
5. Is a congenital anomaly/birth defect (congenital anomaly).
6. Other significant medical conditions which do not meet the above criteria 1 to 5. Events listed in the "Takeda Medically Significant AE List are included in this section criteria.

<u>Takeda Medically Significant AE List</u>

• Acute respiratory failure / acute respiratory distress syndrome (ARDS)	• Anaphylactic shock
• Torsade de pointes / ventricular fibrillation / ventricular tachycardia	• Acute renal failure
• Malignant hypertension	• Pulmonary hypertension
• Convulsive seizure (including convulsion and epilepsy)	• Pulmonary fibrosis (including interstitial pneumonia)
• Agranulocytosis	• Malignant syndrome / malignant hyperthermia
• Aplastic anemia	• Spontaneous abortion / stillbirth and fetal death

• Toxic epidermal necrolysis / oculomucocutaneous syndrome (Stevens-Johnson syndrome) • Hepatic necrosis ・Acute hepatic failure	• Spread of infection via drug or suspected spread • Endotoxic shock or suspected endotoxic shock

Table 3 Criteria for causality assessment between adverse events and Nesina

Assessment	Assessment criterion
Related	Temporally correlation (including the post-treatment clinical course) present. Or an adverse event that may have been caused by the primary disease, concurrent disease, concomitant medication, or other factor including concomitant procedures, but also suggested to be caused by the relevant drug.
Not related	No temporally correlation with the relevant drug. Or an adverse event presumably caused by the primary disease, concurrent disease, concomitant medication, or other factor.
Not assessable	Lack of information for assessment of temporal correlation (including the post-treatment clinical course), the primary disease, concurrent disease, concomitant medication, other factor, etc.

10.0 Analysis Parameters and Methods

10.1 Patient Component Parameters

The following will be tabulated: number of enrolled participants, number of survey sheet collected participants, number of the Safety Analysis Set, number of the Efficacy Analysis Set, and number of patients excluded from analysis and the reason for exclusion, etc.

10.2 Patient Demographics

Patient demographics including sex, age, disease period, hypersensitivity predisposition, and concurrent disease will be tabulated.

10.3 Details of Treatment

The following will be tabulated: status of Nesina treatment, status of concomitant medications, and compliance with Nesina treatment, etc.

10.4 Safety Parameters

The items described below will be tabulated in the Safety Analysis Set. Adverse events will be coded using the MedDRA/J and summarized by Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Occurrence of Adverse Events

For adverse events reported in the observation period, the type and causal relationship to Nesina will be tabulated.

10.4. 2 Factors Probably Affecting Safety

For adverse drug reactions reported in the observation period, the frequency of patient demographics (e.g., sex, age), details of treatment (e.g., status of Nesina, and status of concomitant medications) will be stratified.

10.5 Efficacy Parameters

The following will be tabulated in the Efficacy Analysis Set:

10.5.1 Change in HbA1c

HbA1c test values and the corresponding change from baseline at each testing time point (i.e., test value at each testing time point − test value at baseline) will be tabulated. In addition, the objective glycemic control achievement rate at each testing time point will be tabulated.

10.5.2 Changes in Laboratory Test Values

Test values (fasting blood glucose level, fasting insulin level, HOMA-R,* and HOMA-β*) and the corresponding changes from baseline at each testing time point (i.e., test value at each testing time point − test value at baseline) will be tabulated.

*HOMA-R: Fasting insulin × Fasting glucose / 405

**HOMA-β: (Fasting insulin × 360) / (Fasting glucose − 63)

10.5.3 Factors Probably Affecting Efficacy

For the changes in HbA1c and glycemic control achievement rate at 12 months after the start of treatment, the following will be stratified: patient demographics (e.g., sex, age, HbA1c at the start of Nesina treatment) and details of treatment (e.g., status of Nesina treatment, status of concomitant medications).

10.6 Parameters in Patients with Special Demographics

The safety and efficacy of Nesina will be stratified in elderly patients or patients with hepatic/renal impairment.

11.0 Registration of Survey Data

Takeda Pharmaceutical Company Limited. will register the survey information in the following open websites before the start of this survey.

- Japan Pharmaceutical Information Center-Clinical Trials Information
- Clinical trial registration system of National Institute of Health (US): ClinicalTrials.gov

12.0 Organizations

12.1 Manager

Takeda Pharmaceutical Company Limited.

PPD

12.2 Central Enrollment Center

PPD

13.0 CRO

PPD

14.0 Other Necessary Matters

14.1 Protocol Revision

During the survey period, the protocol can be reviewed and revised, if the following are necessary to be changed after monitored: the survey progress, adverse drug reactions / serious adverse drug reactions unexpected from the Precautions, increased frequency of specified adverse drug reactions (yes or no), and parameter appropriateness. During the survey period, if partly changes of dosage and administration and indications are approved, the protocol revision will be also considered and performed as necessary.

14.2 Measures for Issues or Questions

If any question about the safety or efficacy is arisen, data will be investigated and the relevant persons will take measures for the question.

Appendix Observation Schedule

Parameter \ Survey period		Observation period						
		At patient enrollment	At start of treatment	1 months after treatment	3 months after treatment	6 months after treatment	12 months after treatment	At treatment discontinuation
Patient enrollment	Nesina prescription date	○						
	Patient ID Number	○						
	Patients initial	○						
	Sex	○						
	Birth date	○						
	Assessment of inclusion criteria / exclusion criteria	○						
At patient demographics	Diagnosis period of type 2 diabetes mellitus		○					
	Category of clinical practice		○					
	Hypersensitivity predisposition		○					
	Concurrent disease		○					
	Past medical history		○					
	Height		○					
	Smoking history		○					
	Drinking history		○					
	Presence or absence of serum creatinine within 1 month after the start of Nesina treatment, serum creatinine level (if serum creatinine present), and severity of renal impairment and rationale for the assessment (if serum creatinine absent).		○					
Details of treatment, etc	Status of Nesina treatment		←	―	○	―	→	○
	Status of concomitant medication treatment (hypoglycemic agents* / other than hypoglycemic agents)		←	―	○	―	→	○
	Status of compliance with Nesina			○	○	○	○	○
	Status of compliance with diet/exercise therapy		○	○	○	○	○	○
Laboratory/Observation Parameters, etc	Pulse rate, blood pressure		○	○	○	○	○	○
	Weight		○	○	○	○	○	○
	Laboratory values • HbA1c (NGSP value) • Fasting glucose • Fasting insulin • Fasting glucagon • Fasting triglyceride • Total cholesterol • HDL-cholesterol • LDL-cholesterol • Serum creatinine • BUN • Urinary albumin (corrected by creatinine) • AST • ALT • γ-GTP • ALP • Total bilirubin • Amylase • Lipase		○	○	○	○	○	○
	Electrocardiogram		○				○	○
	Waist circumference		○				○	○
	Tests for coronary arteriosclerosis and arteriosclerosis		○				○	○
	Pregnancy (yes or no) (females only)		←	―	○	―	→	○
	Adverse event		←	―	○	―	→	○

○ To be performed

←— ○ —→ To be performed throughout the period

*Including hypoglycemic agents discontinued within 3 months before the start of Nesina treatment

Protocol for

Nesina Tablets Specified Drug-use Survey "Type 2 Diabetes Mellitus: Combination Therapy With Hypoglycemic Drug (Insulin Preparation or Rapid-acting Insulin Secretagogues, Etc)"

Version	**Third version**
Creation date	**November 27, 2015**
Sponsor	**Takeda Pharmaceutical Company Limited.**

Table of Contents

1.0 Background

Nesina tablets (hereinafter, Nesina) are dipeptidyl peptidase-4inhibitors (hereinafter, DPP-4inhibitors) and oral hypoglycemic drugs mainly characterized by glucose level-dependent insulin secretion promotion via a GLP-1 increase and pancreas protection. Since oral hypoglycemic drugs have been generally used for a long period in patients and since multiple hypoglycemic drugs may be used simultaneously, it is important that long-term results of oral hypoglycemic drugs should be obtained from a daily clinical practice. The Specified Drug-use Survey of Nesina has been conducted in type 2 diabetes mellitus patients who have had an inadequate response to diet/exercise therapies only or diet/exercise therapies plus α-glucosidase inhibitors, thiazolidines, sulfonylureas, or biguanides. In the future, the specified drug-use survey of complication with Nesina and insulin preparations and insulin secretagogues is also expected to be conducted.

Therefore, the Nesina Tablets Specified Drug-use Survey "Type 2 Diabetic Patients Receiving Combination Therapy With a Hypoglycemic Agent (e.g., Insulin Preparations or Rapid-acting Insulin Secretagogues)" (hereinafter, this survey) is planned aiming to evaluate the safety and efficacy of Nesina when administered for 1 year in type 2 diabetic patients who have had an inadequate response to hypoglycemic agents (e.g., insulin preparations, rapid-acting insulin secretagogues) in addition to dietary/exercise therapy in daily medical practice.

This survey is conducted according to the relevant regulatory requirements including the GPSP ordinance.

2.0 Objectives

This survey is designed to evaluate the safety and efficacy of long-term use of alogliptin tablets (Nesina Tablets) in type 2 diabetic patients who have had an inadequate response to hypoglycemic agents (e.g., insulin preparations or rapid-acting insulin secretagogues)* in addition to dietary/exercise therapy in daily medical practice.

*Hypoglycemic agents which have not been used in the past Nesina Specified Drug-use Survey (i.e., other than α-glucosidase inhibitors, thiazolidines, sulfonylureas, and biguanides)

3.0 Number of Planned Participants and the Rationales

3.1 Number of Planned Participants

1,000 participants

3.2 Rationales

The Specified Drug-use Survey of Nesina has been conducted in type 2 diabetes mellitus patients who have had an inadequate response to diet/exercise therapies only or diet/exercise therapies plus α-glucosidase inhibitors, thiazolidines, sulfonylureas, or biguanides. In the future, the specified drug-use survey of complication with Nesina and insulin preparations and insulin

secretagogues is also expected to be conducted.

Therefore, the planned participants was established as 1,000 to collect as many as participants who receive a long-term complication therapy with Nesina and these hypoglycemic agents (e.g., insulin preparations, rapid-acting insulin secretagogues).

In the pooled tabulation of participants in the past Nesina Specified Drug-use Survey (as of November 30, 2013; Safety Analysis Set, 10,025 participants), the proportion of participants was as follows: elderly, 58.0%; renal impairment participants, 15.1%; and hepatic impairment participants, 13.3%. By establishment of the planned participants of 1,000 in this survey, data will be collected from approximately 600 elderly participants, approximately 150 renal impairment participants, and approximately 100 hepatic impairment participants. This establishment is not based on the statistical evidence.

4.0 Patients for Survey

Patients with type 2 diabetes mellitus. However, participants must meet the inclusion criteria and none of the exclusion criteria, described below. Refer to the Precaution in the package insert.

4.1 Inclusion Criteria

Patients who meet the following criterion are included in this survey:

Patients who have had an inadequate response to the following medications/therapies:

- Use of one hypoglycemic agent such as insulin preparations and rapid-acting insulin secretagogues, excluding other types of hypoglycemic agents (e.g., α-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides)*, in addition to dietary/exercise therapy

  *For use of Nesina Tablets in combination with these agents, a specified drug-use survey is currently ongoing.

4.2 Exclusion Criteria

Patients who meet any of the following criteria are excluded from this survey:

Patients with contraindications for Nesina Tablets

(1) Those with severe ketosis, in a state of diabetic coma or precoma, or with type 1 diabetes mellitus [Quickly rectifying hyperglycemia with administration of intravenous fluid or insulin is essential in these patients; therefore, administration of Nesina Tablets is not appropriate.]

(2) Those with severe infections, before or after surgery, or with serious trauma [Controlling blood glucose with an injection of insulin is desirable for these patients; therefore, administration of Nesina Tablets is not appropriate.]

(3) Those with a history of hypersensitivity to any of the ingredients of Nesina Tablets

5.0 Dosage and Administration

For adults, 25 mg of alogliptin is usually administered orally once daily. Refer to the Precaution

in the package insert. For renal impairment patients, refer to the Precaution with Respect to Dosage and Administration in the package insert.

6.0 Number of Scheduled Sites by Department

Internal medicine or other department: Approximately 200 sites

7.0 Methods

7.1 Observation period

12 months

7.2 Request for Sites and Agreement

The survey is conducted using the paper survey sheet. Before asking survey, the parson in charge of medical information in Takeda Pharmaceutical Company Limited. (Hereinafter, Takeda MRs) will fully explain to the Investigator about the objectives, details, and methods of this survey, based on “Request for Cooperation of Specified Drug-use Survey,” “Summary for Survey,” “Patient Enrollment Sheet (sample),” and “Survey Sheet (sample)” and will finalize written agreement with survey sites to ask requests for surveillance within the specified period.

7.3 Patient Enrollment Methods patients

This survey is conducted by Fax using Central Enrollment System. The Investigator will enroll patients for whom Nesina was prescribed after the start date of agreement with a survey site, by faxing to the Central Enrollment Center (refer to Section 12.2) the “Patient Enrollment Sheet” including the information regarding patient enrollment (refer to Section 9.1) before 14 days after the Nesina prescription date (define the prescription date as “0 day” and one day after the prescription date as “1 day”). Patients for whom Nesina prescription is scheduled cannot be enrolled earlier. The participant who assessed as ineligible for the survey for any reason cannot be enrolled in the survey. The Investigator will enroll a new participant using the “Patient Enrollment Sheet” supplied by the Takeda MR. The Takeda MR will supply for the Investigator the survey sheet issued after the Central Enrollment Center enrolled the participant.

7.4 Creation and Submission of Survey Sheet

The Investigator will create the survey sheet for all enrolled participants and submit it to the Takeda around within 1 month after the end of the observation period. If Nesina administration cannot be confirmed, specify it (do not specify other columns).

For participants who early discontinue treatment with Nesina during the observation period for any reason, the Investigator will create the survey sheet for him/her and submit it to the Takeda around within 1 month after the end of necessary observation. However, for participants who early discontinue treatment with Nesina due to an adverse event, the Investigator will continue

observation even after treatment discontinuation, wherever possible, until the adverse event resolve or is resolving and will create the survey sheet and submit it to the Takeda.

7.5 Measures for Development of Serious Adverse Events

In case of development of a serious adverse event in the observation period, the Investigator will immediately contact the Takeda MR. If the Takeda MR requests additional detailed information, the Investigator will provide it.

8.0 Scheduled Period

Survey period: June 2014 to February 28, 2017

Patient enrollment period: June 2014 to February 29, 2016*

*Even if Nesina is prescribed before February 29 2016, the patients cannot be enrolled (fax of the Patient Enrollment Sheet) after March 1 2016.

In case that the enrolled participants reach the scheduled number of participants in the survey before February 29 2016, the enrollment will close earlier than the scheduled patient enrollment period. If patient enrollment period is shorten, the survey period will be also changed according to the shorten period.

9.0 Matters to be Surveyed

The Investigator will describe the data described below in the Patient Enrollment Sheet and the survey sheet. The schedule of this survey is shown in the Appendix.

9.1 Description Details in Patient Enrollment Sheet

1) Matters to be surveyed

Name of survey site, name of the investigator who describe in the Patient Enrollment Sheet, Nesina prescription date, Patient ID Number, patient initial, sex, birth date, inclusion criteria assessment, and exclusion criteria assessment

2) Survey period

At patient enrollment

9.2 Description Items in Survey Sheet

9.2.1 Front Cover of Survey Sheet

Last description date in the survey sheet and name of the Investigator who described the survey sheet

9.2.2 Patient Demographics

1) Matters to be surveyed

Diagnosis period of type 2 diabetes mellitus, category of clinical practice, disposition of hypersensitivity (yes/no and detail), concurrent disease (yes/no and detail), past medical history (yes/no and detail), height, smoking history, drinking history, presence or absence of serum creatinine within 1 month after the start of Nesina treatment, serum creatinine level (if

serum creatinine present), and severity of renal impairment and rationale for the assessment (if serum creatinine absent).

2) Survey period

At the start of Nesina treatment

9.2.3 Details of Treatment

1) Matters to be surveyed

Details of Nesina treatment (daily dose, administration period, and reason for discontinuation), and status of concomitant medications (hypoglycemic agents*) (yes/no, drug name, daily dose, route of administration, administration period, and objective of administration)

*Hypoglycemic agents which are discontinued within 3 months prior to Nesina treatment are included.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.4 Compliance with Nesina and Compliance with Diet/Exercise Therapy

1) Matters to be surveyed

Compliance with Nesina* and compliance with diet/exercise therapy**

*Criteria for assessment of compliance with Nesina

1. ≥ 90% (A participant won't miss administration, or even if he/she missed administration, the frequency is twice or three times a month.)
2. ≥ 70% (A participant missed administration once or twice weekly.)
3. ≥ 50% (A participant missed administration three times a week.)
4. < 50% (A participant missed administration four times or more a week.)

**Criteria for assessment of compliance with diet/exercise therapy

1. ≥ 90% (A participant complied as instructed.)
2. ≥ 70% (A participant mostly complied as instructed.)
3. ≥ 50% (A participant did not complied well as instructed.)
4. < 50% (A participant did not mostly complied as instructed.)
5. Not performed
6. Unknown

2) Survey period

At the start of Nesina treatment (compliance with diet/exercise therapy only), 1 month, 3

months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5 Laboratory/Observation Parameters

9.2.5.1 Vital Signs

1) Laboratory/observation parameters

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

2) Survey period

Each time point at the start of Nesina treatment, 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5.2 Laboratory Values

1) Laboratory parameters

HbA1c (NGSP value, same hereafter), fasting glucose, fasting insulin, fasting glucagon, fasting triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, serum creatinine, BUN, urinary albumin (corrected by creatinine), AST, ALT, γ-GTP, ALP, total bilirubin, amylase, and lipase

2) Survey period

Each time point at the start of Nesina treatment, 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5.3 Electrocardiography

1) Observation Parameters

Electrocardiograms (assessment and findings)

2) Survey period

Each time point from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.5.4 Tests for Waist Circumference, Coronary Arteriosclerosis, and Arteriosclerosis

1) Observation Parameters

Tests for waist circumference,* coronary arteriosclerosis and arteriosclerosis** (e.g., pulse wave velocity, cardio-ankle vascular index, intima-media thickness, intra-vascular ultrasound)

*Measure the waist diameter during light expiration at standing position and at the level of the navel. If the lower deviation of the navel occurs because of significant abdominal fat accumulation, measure the waist diameter at the level of the midpoint between the inferior rib border and anterior superior iliac spine.

**Any methods can be used. In principle, however, use the same methods for each test. If there are no devices for measurement, the tests can be omitted.

2) Survey period

Each time point from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.5.5 Other Parameters

1) Observation parameters

Pregnancy during the observation period (yes or no) (females only)

In case of pregnancy in the observation period, the Investigator will immediately contact the Takeda MR. The Investigator will provide detailed information (including the information until the delivery, as possible, such as preterm delivery) using the separate pregnancy sheet after the request from the Takeda MR.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.6 Adverse Event

1) Matters to be surveyed

Presence or absence of adverse events (refer to Table 1), term of adverse events, onset date, seriousness and the reason (refer to Table 2), presence or absence of Nesina discontinuation, outcome assessment date, outcome, and causal relationship to Nesina* (refer to Table 3).

If the outcome is assessed as Not resolved or Unknown and if the causal relationship cannot be assessed, the participant will be followed up, wherever possible.

The detailed information (e.g., clinical course, laboratory tests for diagnosis) will be collected as possible for development of hypoglycemia, acute pancreatitis, renal impairment / jaundice, skin disorder including oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme, rhabdomyolysis, intestinal obstruction, interstitial pneumonia, angioedema, infection, malignant tumor, and cardiovascular system-related event (e.g., symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death)

*If the causal relationship to Nesina is assessed as Not related, collect the rationales for assessment. If the relationship is assessed as Not assessable, collected the reason for Not assessable.

Note) Matters that should be considered for adverse events

Abnormal exacerbation of the target disease, i.e., worsening beyond expected natural clinical course, is defined as an adverse event; however, the expected worsening is not defined as an adverse vent.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

Table 1 Definition of adverse event

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

The following events will be handled as adverse events:

• Symptoms present in infants breastfed by a Nesina taking mother

• Symptoms present in children who received the relevant drug

• Symptoms due to occupational exposure to the relevant drug

• Symptoms due to counterfeit medications of the legitimate medicinal products manufactured by Takeda

• Unfavorable symptoms present in the patient who received the relevant drug, known by a lawsuit or other legal actions

Table 2 Criteria for severity assessment

An event which meet any of the following criteria will be assessed as "Serious:"

1. Results in death (death).
2. Is life-threatening (potential death threat).
3. Requires inpatient hospitalization or prolongation of existing hospitalization (admission / prolonged hospitalization).
4. Results in persistent or significant disability/incapacity (disability).
5. Is a congenital anomaly/birth defect (congenital anomaly).
6. Other significant medical conditions which do not meet the above criteria 1 to 5. Events listed in the "Takeda Medically Significant AE List are included in this section criteria.

<u>Takeda Medically Significant AE List</u>

• Acute respiratory failure / acute respiratory distress syndrome (ARDS)	• Anaphylactic shock
• Torsade de pointes / ventricular fibrillation / ventricular tachycardia	• Acute renal failure
• Malignant hypertension	• Pulmonary hypertension
• Convulsive seizure (including convulsion and epilepsy)	• Pulmonary fibrosis (including interstitial pneumonia)
• Agranulocytosis	• Malignant syndrome / malignant hyperthermia
• Aplastic anemia	• Spontaneous abortion / stillbirth and fetal death
• Toxic epidermal necrolysis / oculomucocutaneous syndrome (Stevens-Johnson syndrome)	• Spread of infection via drug or suspected spread

• Hepatic necrosis ・Acute hepatic failure	• Endotoxic shock or suspected endotoxic shock

Table 3 Criteria for causality assessment between adverse events and Nesina

Assessment	Assessment criterion
Related	Temporally correlation (including the post-treatment clinical course) present. Or an adverse event that may have been caused by the primary disease, concurrent disease, concomitant medication, or other factor including concomitant procedures, but also suggested to be caused by the relevant drug.
Not related	No temporally correlation with the relevant drug. Or an adverse event presumably caused by the primary disease, concurrent disease, concomitant medication, or other factor.
Not assessable	Lack of information for assessment of temporal correlation (including the post-treatment clinical course), the primary disease, concurrent disease, concomitant medication, other factor, etc.

10.0 Analysis Parameters and Methods

10.1 Patient Component Parameters

The following will be tabulated: number of enrolled participants, number of survey sheet collected participants, number of the Safety Analysis Set, number of the Efficacy Analysis Set, and number of patients excluded from analysis and the reason for exclusion, etc.

10.2 Patient Demographics

Patient demographics including sex, age, disease period, hypersensitivity predisposition, and concurrent disease will be tabulated.

10.3 Details of Treatment

The following will be tabulated: status of Nesina treatment, status of concomitant medications, and compliance with Nesina treatment, etc.

10.4 Safety Parameters

The items described below will be tabulated in the Safety Analysis Set. Adverse events will be coded using the MedDRA/J and summarized by Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Occurrence of Adverse Events

For adverse events reported in the observation period, the type and causal relationship to Nesina will be tabulated.

10.4. 2 Factors Probably Affecting Safety

For adverse drug reactions reported in the observation period, the frequency of patient demographics (e.g., sex, age), details of treatment (e.g., status of Nesina, and status of concomitant medications) will be stratified.

10.5 Efficacy Parameters

The following will be tabulated in the Efficacy Analysis Set:

10.5.1 Change in HbA1c

HbA1c test values and the corresponding change from baseline at each testing time point (i.e., test value at each testing time point − test value at baseline) will be tabulated. In addition, the objective glycemic control achievement rate at each testing time point will be tabulated.

10.5.2 Changes in Laboratory Test Values

Test values (fasting blood glucose level, fasting insulin level, HOMA-R,* and HOMA-β*) and the corresponding changes from baseline at each testing time point (i.e., test value at each testing time point − test value at baseline) will be tabulated.

*HOMA-R: Fasting insulin × Fasting glucose / 405

**HOMA-β: (Fasting insulin × 360) / (Fasting glucose − 63)

10.5.3 Factors Probably Affecting Efficacy

For the changes in HbA1c and glycemic control achievement rate at 12 months after the start of treatment, the following will be stratified: patient demographics (e.g., sex, age, HbA1c at the start of Nesina treatment) and details of treatment (e.g., status of Nesina treatment, status of concomitant medications).

10.6 Parameters in Patients with Special Demographics

The safety and efficacy of Nesina will be stratified in elderly patients or patients with hepatic/renal impairment.

11.0 Registration of Survey Data

Takeda Pharmaceutical Company Limited. will register the survey information in the following open websites before the start of this survey.

- Japan Pharmaceutical Information Center-Clinical Trials Information
- Clinical trial registration system of National Institute of Health (US): Clinical Trials.gov

12.0 Organizations

12.1 Manager

Takeda Pharmaceutical Company Limited.

PPD

12.2 Central Enrollment Center

PPD

13.0 CRO

PPD

14.0 Other Necessary Matters

14.1 Protocol Revision

During the survey period, the protocol can be reviewed and revised, if the following are necessary to be changed after monitored: the survey progress, adverse drug reactions / serious adverse drug reactions unexpected from the Precautions, increased frequency of specified adverse drug reactions (yes or no), and parameter appropriateness. During the survey period, if partly changes of dosage and administration and indications are approved, the protocol revision will be also considered and performed as necessary.

14.2 Measures for Issues or Questions

If any question about the safety or efficacy is arisen, data will be investigated and the relevant persons will take measures for the question.

Appendix Observation Schedule

	Survey period / Parameter	Observation period						
		At patient enrollment	At start of treatment	1 months after treatment	3 months after treatment	6 months after treatment	12 months after treatment	At treatment discontinuation
Patient enrollment	Nesina prescription date	○						
	Patient ID Number	○						
	Patients initial	○						
	Sex	○						
	Birth date	○						
	Inclusion criteria / exclusion criteria	○						
At patient demographics	Diagnosis period of type 2 diabetes mellitus		○					
	Category of clinical practice		○					
	Hypersensitivity predisposition		○					
	Concurrent disease		○					
	Past medical history		○					
	Height		○					
	Smoking history		○					
	Drinking history		○					
	Presence or absence of serum creatinine within 1 month after the start of Nesina treatment, serum creatinine level (if serum creatinine present), and severity of renal impairment and rationale for the assessment (if serum creatinine absent).		○					
Details of treatment, etc	Status of Nesina treatment		←	―	○	→		○
	Status of concomitant medication treatment (hypoglycemic agents* / other than hypoglycemic agents)		←	―	○	→		○
	Status of compliance with Nesina			○	○	○	○	○
	Status of compliance with diet/exercise therapy		○	○	○	○	○	○
Laboratory/Observation Parameters, etc	Pulse rate, blood pressure		○	○	○	○	○	○
	Weight		○	○	○	○	○	○
	Laboratory values • HbA1c (NGSP value) • Fasting glucose • Fasting insulin • Fasting glucagon • Fasting triglyceride • Total cholesterol • HDL-cholesterol • LDL-cholesterol • Serum creatinine • BUN • Urinary albumin (corrected by creatinine) • AST • ALT • γ-GTP • ALP • Total bilirubin • Amylase • Lipase		○	○	○	○	○	○
	Electrocardiogram		○				○	○
	Waist circumference		○				○	○
	Tests for coronary arteriosclerosis and arteriosclerosis		○				○	○
	Pregnancy (yes or no) (females only)		←	―	○	→		○
	Adverse event		←	―	○	→		○

○ : To be performed

←— ○ —→ : To be performed throughout the period

*Including hypoglycemic agents discontinued within 3 months before the start of Nesina treatment

Protocol for

Nesina Tablets Specified Drug-use Survey "Type 2 Diabetes Mellitus: Combination Therapy With Hypoglycemic Drug (Insulin Preparation or Rapid-acting Insulin Secretagogues, Etc)"

Version	**Second version**
Creation date	**April 1, 2015**
Sponsor	**Takeda Pharmaceutical Company Limited.**

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1.0 Background

Nesina tablets (hereinafter, Nesina) are dipeptidyl peptidase-4inhibitors (hereinafter, DPP-4inhibitors) and oral hypoglycemic drugs mainly characterized by glucose level-dependent insulin secretion promotion via a GLP-1 increase and pancreas protection. Since oral hypoglycemic drugs have been generally used for a long period in patients and since multiple hypoglycemic drugs may be used simultaneously, it is important that long-term results of oral hypoglycemic drugs should be obtained from a daily clinical practice. The Specified Drug-use Survey of Nesina has been conducted in type 2 diabetes mellitus patients who have had an inadequate response to diet/exercise therapies only or diet/exercise therapies plus α-glucosidase inhibitors, thiazolidines, sulfonylureas, or biguanides. In the future, the specified drug-use survey of complication with Nesina and insulin preparations and insulin secretagogues is also expected to be conducted.

Therefore, the Nesina Tablets Specified Drug-use Survey "Type 2 Diabetic Patients Receiving Combination Therapy With a Hypoglycemic Agent (e.g., Insulin Preparations or Rapid-acting Insulin Secretagogues)" (hereinafter, this survey) is planned aiming to evaluate the safety and efficacy of Nesina when administered for 1 year in type 2 diabetic patients who have had an inadequate response to hypoglycemic agents (e.g., insulin preparations, rapid-acting insulin secretagogues) in addition to dietary/exercise therapy in daily medical practice.

This survey is conducted according to the relevant regulatory requirements including the GPSP ordinance.

2.0 Objectives

This survey is designed to evaluate the safety and efficacy of long-term use of alogliptin tablets (Nesina Tablets) in type 2 diabetic patients who have had an inadequate response to hypoglycemic agents (e.g., insulin preparations or rapid-acting insulin secretagogues)* in addition to dietary/exercise therapy in daily medical practice.

*Hypoglycemic agents which have not been used in the past Nesina Specified Drug-use Survey (i.e., other than α-glucosidase inhibitors, thiazolidines, sulfonylureas, and biguanides)

3.0 Number of Planned Participants and the Rationales

3.1 Number of Planned Participants

1,000 participants

3.2 Rationales

The Specified Drug-use Survey of Nesina has been conducted in type 2 diabetes mellitus patients who have had an inadequate response to diet/exercise therapies only or diet/exercise therapies plus α-glucosidase inhibitors, thiazolidines, sulfonylureas, or biguanides. In the future, the specified drug-use survey of complication with Nesina and insulin preparations and insulin

secretagogues is also expected to be conducted.

Therefore, the planned participants was established as 1,000 to collect as many as participants who receive a long-term complication therapy with Nesina and these hypoglycemic agents (e.g., insulin preparations, rapid-acting insulin secretagogues).

In the pooled tabulation of participants in the past Nesina Specified Drug-use Survey (as of November 30, 2013; Safety Analysis Set, 10,025 participants), the proportion of participants was as follows: elderly, 58.0%; renal impairment participants, 15.1%; and hepatic impairment participants, 13.3%. By establishment of the planned participants of 1,000 in this survey, data will be collected from approximately 600 elderly participants, approximately 150 renal impairment participants, and approximately 100 hepatic impairment participants. This establishment is not based on the statistical evidence.

4.0 Patients for Survey

Patients with type 2 diabetes mellitus. However, participants must meet the inclusion criteria and none of the exclusion criteria, described below. Refer to the Precaution in the package insert.

4.1 Inclusion Criteria

Patients who meet the following criterion are included in this survey:

Patients who have had an inadequate response to the following medications/therapies:

- Use of one hypoglycemic agent such as insulin preparations and rapid-acting insulin secretagogues, excluding other types of hypoglycemic agents (e.g., α-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides)*, in addition to dietary/exercise therapy

  *For use of Nesina Tablets in combination with these agents, a specified drug-use survey is currently ongoing.

4.2 Exclusion Criteria

Patients who meet any of the following criteria are excluded from this survey:

Patients with contraindications for Nesina Tablets

(1) Those with severe ketosis, in a state of diabetic coma or precoma, or with type 1 diabetes mellitus [Quickly rectifying hyperglycemia with administration of intravenous fluid or insulin is essential in these patients; therefore, administration of Nesina Tablets is not appropriate.]

(2) Those with severe infections, before or after surgery, or with serious trauma [Controlling blood glucose with an injection of insulin is desirable for these patients; therefore, administration of Nesina Tablets is not appropriate.]

(3) Those with a history of hypersensitivity to any of the ingredients of Nesina Tablets

5.0 Dosage and Administration

For adults, 25 mg of alogliptin is usually administered orally once daily. Refer to the Precaution

in the package insert. For renal impairment patients, refer to the Precaution with Respect to Dosage and Administration in the package insert.

6.0 Number of Scheduled Sites by Department

Internal medicine or other department: Approximately 200 sites

7.0 Methods

7.1 Observation period

12 months

7.2 Request for Sites and Agreement

The survey is conducted using the paper survey sheet. Before asking survey, the parson in charge of medical information in Takeda Pharmaceutical Company Limited. (Hereinafter, Takeda MRs) will fully explain to the Investigator about the objectives, details, and methods of this survey, based on “Request for Cooperation of Specified Drug-use Survey,” “Summary for Survey,” “Patient Enrollment Sheet (sample),” and “Survey Sheet (sample)” and will finalize written agreement with survey sites to ask requests for surveillance within the specified period.

7.3 Patient Enrollment Methods patients

This survey is conducted by Fax using Central Enrollment System. The Investigator will enroll patients for whom Nesina was prescribed after the start date of agreement with a survey site, by faxing to the Central Enrollment Center (refer to Section 12.2) the “Patient Enrollment Sheet” including the information regarding patient enrollment (refer to Section 9.1) before 14 days after the Nesina prescription date (define the prescription date as “0 day” and one day after the prescription date as “1 day”). Patients for whom Nesina prescription is scheduled cannot be enrolled earlier. The participant who assessed as ineligible for the survey for any reason cannot be enrolled in the survey. The Investigator will enroll a new participant using the “Patient Enrollment Sheet” supplied by the Takeda MR. The Takeda MR will supply for the Investigator the survey sheet issued after the Central Enrollment Center enrolled the participant.

7.4 Creation and Submission of Survey Sheet

The Investigator will create the survey sheet for all enrolled participants and submit it to the Takeda around within 1 month after the end of the observation period. If Nesina administration cannot be confirmed, specify it (do not specify other columns).

For participants who early discontinue treatment with Nesina during the observation period for any reason, the Investigator will create the survey sheet for him/her and submit it to the Takeda around within 1 month after the end of necessary observation. However, for participants who early discontinue treatment with Nesina due to an adverse event, the Investigator will continue

observation even after treatment discontinuation, wherever possible, until the adverse event resolve or is resolving and will create the survey sheet and submit it to the Takeda.

7.5 Measures for Development of Serious Adverse Events

In case of development of a serious adverse event in the observation period, the Investigator will immediately contact the parson in charge in Takeda Pharmaceutical Company Limited. (person in charge in Takeda). If the person in charge in Takeda requests additional detailed information, the Investigator will provide it.

8.0 Scheduled Period

Survey period: June 2014 to November 30, 2016

Patient enrollment period: June 2014 to November 30, 2015*

*Even if Nesina is prescribed before November 30 2015, the patients cannot be enrolled (fax of the Patient Enrollment Sheet) after December 1 2015.

In case that the enrolled participants reach the scheduled number of participants in the survey before November 30 2015, the enrollment will close earlier than the scheduled patient enrollment period. If patient enrollment period is shorten, the survey period will be also changed according to the shorten period.

9.0 Matters to be Surveyed

The Investigator will describe the data described below in the Patient Enrollment Sheet and the survey sheet. The schedule of this survey is shown in the Appendix.

9.1 Description Details in Patient Enrollment Sheet

1) Matters to be surveyed

Name of survey site, name of the investigator who describe in the Patient Enrollment Sheet, Nesina prescription date, Patient ID Number, patient initial, sex, birth date, inclusion criteria assessment, and exclusion criteria assessment

2) Survey period

At patient enrollment

9.2 Description Items in Survey Sheet

9.2.1 Front Cover of Survey Sheet

Last description date in the survey sheet and name of the Investigator who described the survey sheet

9.2.2 Patient Demographics

1) Matters to be surveyed

Diagnosis period of type 2 diabetes mellitus, category of clinical practice, disposition of hypersensitivity (yes/no and detail), concurrent disease (yes/no and detail), past medical history (yes/no and detail), height, smoking history, drinking history, presence or absence of

serum creatinine within 1 month after the start of Nesina treatment, serum creatinine level (if serum creatinine present), and severity of renal impairment and rationale for the assessment (if serum creatinine absent).

2) Survey period

At the start of Nesina treatment

9.2.3 Details of Treatment

1) Matters to be surveyed

Details of Nesina treatment (daily dose, administration period, and reason for discontinuation), and status of concomitant medications* (hypoglycemic agents) (yes/no, drug name, daily dose, route of administration, administration period, and objective of administration)

*Hypoglycemic agents which are discontinued within 3 months prior to Nesina treatment are included.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.4 Compliance with Nesina and Compliance with Diet/Exercise Therapy

1) Matters to be surveyed

Compliance with Nesina* and compliance with diet/exercise therapy**

*Criteria for assessment of compliance with Nesina

1. ≥ 90% (A participant won't miss administration, or even if he/she missed administration, the frequency is twice or three times a month.)
2. ≥ 70% (A participant missed administration once or twice weekly.)
3. ≥ 50% (A participant missed administration three times a week.)
4. < 50% (A participant missed administration four times or more a week.)

**Criteria for assessment of compliance with diet/exercise therapy

1. ≥ 90% (A participant complied as instructed.)
2. ≥ 70% (A participant mostly complied as instructed.)
3. ≥ 50% (A participant did not complied well as instructed.)
4. < 50% (A participant did not mostly complied as instructed.)
5. Not performed
6. Unknown

2) Survey period

At the start of Nesina treatment (compliance with diet/exercise therapy only), 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5 Laboratory/Observation Parameters

9.2.5.1 Vital Signs

1) Laboratory/observation parameters

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

2) Survey period

Each time point at the start of Nesina treatment, 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5.2 Laboratory Values

1) Laboratory parameters

HbA1c (NGSP value, same hereafter), fasting glucose, fasting insulin, fasting glucagon, fasting triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, serum creatinine, BUN, urinary albumin (corrected by creatinine), AST, ALT, γ-GTP, ALP, total bilirubin, amylase, and lipase

2) Survey period

Each time point at the start of Nesina treatment, 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5.3 Electrocardiography

1) Observation Parameters

Electrocardiograms (assessment and findings)

2) Survey period

Each time point from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.5.4 Tests for Waist Circumference, Coronary Arteriosclerosis, and Arteriosclerosis

1) Observation Parameters

Tests for waist circumference,* coronary arteriosclerosis and arteriosclerosis** (e.g., pulse wave velocity, cardio-ankle vascular index, intima-media thickness, intra-vascular ultrasound)

*Measure the waist diameter during light expiration at standing position and at the level of the navel. If the lower deviation of the navel occurs because of significant abdominal fat accumulation, measure the waist diameter at the level of the midpoint between the inferior rib border and anterior superior iliac spine.

**Any methods can be used. In principle, however, use the same methods for each test. If there are no devices for measurement, the tests can be omitted.

2) Survey period

Each time point from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.5.5 Other Parameters

1) Observation parameters

Pregnancy during the observation period (yes or no) (females only)

In case of pregnancy in the observation period, the Investigator will immediately contact the person in charge in Takeda. The Investigator will provide detailed information (including the information until the delivery, as possible, such as preterm delivery) using the separate pregnancy sheet after the request from the person in charge in Takeda.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.6 Adverse Event

1) Matters to be surveyed

Presence or absence of adverse events (refer to Table 1), term of adverse events, onset date, seriousness and the reason (refer to Table 2), presence or absence of Nesina discontinuation, outcome assessment date, outcome, and causal relationship to Nesina* (refer to Table 3).

If the outcome is assessed as Not resolved or Unknown and if the causal relationship cannot be assessed, the participant will be followed up, wherever possible.

The detailed information (e.g., clinical course, laboratory tests for diagnosis) will be collected as possible for development of hypoglycemia, acute pancreatitis, renal impairment / jaundice, skin disorder including oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme, rhabdomyolysis, intestinal obstruction, interstitial pneumonia, angioedema, infection, malignant tumor, and cardiovascular system-related event (e.g., symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death)

*If the causal relationship to Nesina is assessed as Not related, collect the rationales for assessment. If the relationship is assessed as Not assessable, collected the reason for Not assessable.

Note) Matters that should be considered for adverse events

Abnormal exacerbation of the target disease, i.e., worsening beyond expected natural clinical course, is defined as an adverse event; however, the expected worsening is not defined as an adverse vent.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment

discontinuation)

Table 1 Definition of adverse event

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

The following events will be handled as adverse events:

• Symptoms present in infants breastfed by a Nesina taking mother

• Symptoms present in children who received the relevant drug

• Symptoms due to occupational exposure to the relevant drug

• Symptoms due to counterfeit medications of the legitimate medicinal products manufactured by Takeda

Table 2 Criteria for severity assessment

An event which meet any of the following criteria will be assessed as "Serious:"

1. Results in death (death).
2. Is life-threatening (potential death threat).
3. Requires inpatient hospitalization or prolongation of existing hospitalization (admission / prolonged hospitalization).
4. Results in persistent or significant disability/incapacity (disability).
5. Is a congenital anomaly/birth defect (congenital anomaly).
6. Other significant medical conditions which do not meet the above criteria 1 to 5. Events listed in the "Takeda Medically Significant AE List are included in this section criteria.

<u>Takeda Medically Significant AE List</u>

• Acute respiratory failure / acute respiratory distress syndrome (ARDS)	• Anaphylactic shock
• Torsade de pointes / ventricular fibrillation / ventricular tachycardia	• Acute renal failure
• Malignant hypertension	• Pulmonary hypertension
• Convulsive seizure (including convulsion and epilepsy)	• Pulmonary fibrosis (including interstitial pneumonia)
• Agranulocytosis	• Malignant syndrome / malignant hyperthermia
• Aplastic anemia	• Spontaneous abortion / stillbirth and fetal death
• Toxic epidermal necrolysis / oculomucocutaneous syndrome (Stevens-Johnson syndrome)	• Spread of infection via drug or suspected spread
• Hepatic necrosis	• Endotoxic shock or suspected endotoxic shock
・Acute hepatic failure	

Table 3 Criteria for causality assessment between adverse events and Nesina

Assessment	Assessment criterion
Related	Temporally correlation (including the post-treatment clinical course) present. Or an adverse event that may have been caused by the primary disease, concurrent disease, concomitant medication, or other factor including concomitant procedures, but also suggested to be caused by the relevant drug.
Not related	No temporally correlation with the relevant drug. Or an adverse event presumably caused by the primary disease, concurrent disease, concomitant medication, or other factor.
Not assessable	Lack of information for assessment of temporal correlation (including the post-treatment clinical course), the primary disease, concurrent disease, concomitant medication, other factor, etc.

10.0 Analysis Parameters and Methods

10.1 Patient Component Parameters

The following will be tabulated: number of enrolled participants, number of survey sheet collected participants, number of the Safety Analysis Set, number of the Efficacy Analysis Set, and number of patients excluded from analysis and the reason for exclusion, etc.

10.2 Patient Demographics

Patient demographics including sex, age, disease period, hypersensitivity predisposition, and concurrent disease will be tabulated.

10.3 Details of Treatment

The following will be tabulated: status of Nesina treatment, status of concomitant medications, and compliance with Nesina treatment, etc.

10.4 Safety Parameters

The items described below will be tabulated in the Safety Analysis Set. Adverse events will be coded using the MedDRA/J and summarized by Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Occurrence of Adverse Events

For adverse events reported in the observation period, the type and causal relationship to Nesina will be tabulated.

10.4. 2 Factors Probably Affecting Safety

For adverse drug reactions reported in the observation period, the frequency of patient demographics (e.g., sex, age), details of treatment (e.g., status of Nesina, and status of

concomitant medications) will be stratified.

10.5 Efficacy Parameters

The following will be tabulated in the Efficacy Analysis Set:

10.5.1 Change in HbA1c

HbA1c test values and the corresponding change from baseline at each testing time point (i.e., test value at each testing time point − test value at baseline) will be tabulated. In addition, the objective glycemic control achievement rate at each testing time point will be tabulated.

10.5.2 Changes in Laboratory Test Values

Test values (fasting blood glucose level, fasting insulin level, HOMA-R,* and HOMA-β*) and the corresponding changes from baseline at each testing time point (i.e., test value at each testing time point − test value at baseline) will be tabulated.

*HOMA-R: Fasting insulin × Fasting glucose / 405

**HOMA-β: (Fasting insulin × 360) / (Fasting glucose − 63)

10.5.3 Factors Probably Affecting Efficacy

For the changes in HbA1c and glycemic control achievement rate at 12 months after the start of treatment, the following will be stratified: patient demographics (e.g., sex, age, HbA1c at the start of Nesina treatment) and details of treatment (e.g., status of Nesina treatment, status of concomitant medications).

10.6 Parameters in Patients with Special Demographics

The safety and efficacy of Nesina will be stratified in elderly patients or patients with hepatic/renal impairment.

11.0 Registration of Survey Data

Takeda Pharmaceutical Company Limited. will register the survey information in the ClinicalTrials.gov and an open website (JAPIC-CTI*) before the start of this survey.

*Japan Pharmaceutical Information Center-Clinical Trials Information

12.0 Organizations

12.1 Manager

Takeda Pharmaceutical Company Limited.

PPD

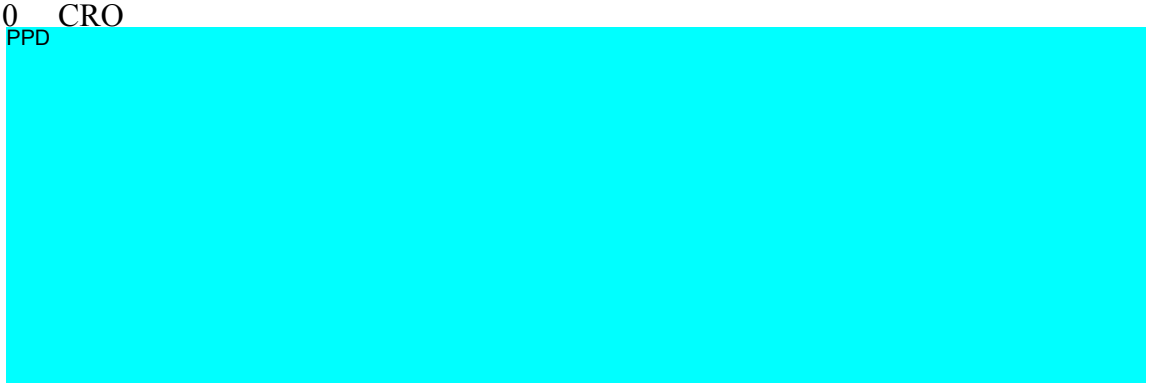
12.2 Central Enrollment Center

PPD

PPD

13.0 CRO

PPD



14.0 Other Necessary Matters

14.1 Protocol Revision

During the survey period, the protocol can be reviewed and revised, if the following are necessary to be changed after monitored: the survey progress, adverse drug reactions / serious adverse drug reactions unexpected from the Precautions, increased frequency of specified adverse drug reactions (yes or no), and parameter appropriateness. During the survey period, if partly changes of dosage and administration and indications are approved, the protocol revision will be also considered and performed as necessary.

14.2 Measures for Issues or Questions

If any question about the safety or efficacy is arisen, data will be investigated and the relevant persons will take measures for the question.

Appendix Observation Schedule

Parameter \ Survey period		Observation period						
		At patient enrollment	At start of treatment	1 months after treatment	3 months after treatment	6 months after treatment	12 months after treatment	At treatment discontinuation
Patient enrollment	Nesina prescription date	○						
	Patient ID Number	○						
	Patients initial	○						
	Sex	○						
	Birth date	○						
	Inclusion criteria / exclusion criteria	○						
At patient demographics	Diagnosis period of type 2 diabetes mellitus		○					
	Category of clinical practice		○					
	Hypersensitivity predisposition		○					
	Concurrent disease		○					
	Past medical history		○					
	Height		○					
	Smoking history		○					
	Drinking history		○					
	Presence or absence of serum creatinine within 1 month after the start of Nesina treatment, serum creatinine level (if serum creatinine present), and severity of renal impairment and rationale for the assessment (if serum creatinine absent).		○					
Details of treatment, etc	Status of Nesina treatment		←———	———	○	———	———→	○
	Status of concomitant medication treatment (hypoglycemic agents / other than hypoglycemic agents)		←———	———	○	———	———→	○
	Status of compliance with Nesina			○	○	○	○	○
	Status of compliance with diet/exercise therapy		○	○	○	○	○	○
Laboratory/Observation Parameters, etc	Pulse rate, blood pressure		○	○	○	○	○	○
	Weight		○	○	○	○	○	○
	Laboratory values • HbA1c (NGSP value) • Fasting glucose • Fasting insulin • Fasting glucagon • Fasting triglyceride • Total cholesterol • HDL-cholesterol • LDL-cholesterol • Serum creatinine • BUN • Urinary albumin (corrected by creatinine) • AST • ALT • γ-GTP • ALP • Total bilirubin • Amylase • Lipase		○	○	○	○	○	○
	Electrocardiogram		○				○	○
	Waist circumference		○				○	○
	Tests for coronary arteriosclerosis and arteriosclerosis		○				○	○
	Pregnancy (yes or no) (females only)		←———	———	○	———	———→	○
	Adverse event		←———	———	○	———	———→	○

○ : To be performed

←——○——→ : To be performed throughout the period

Protocol for

Nesina Tablets Specified Drug-use Survey "Type 2 Diabetes Mellitus: Combination Therapy With Hypoglycemic Drug (Insulin Preparation or Rapid-acting Insulin Secretagogues, Etc)"

Version	**First version**
Creation date	**May 7, 2014**
Sponsor	**Takeda Pharmaceutical Company Limited.**

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1.0 Background

Nesina tablets (hereinafter, Nesina) are dipeptidyl peptidase-4inhibitors (hereinafter, DPP-4inhibitors) and oral hypoglycemic drugs mainly characterized by glucose level-dependent insulin secretion promotion via a GLP-1 increase and pancreas protection. Since oral hypoglycemic drugs have been generally used for a long period in patients and since multiple hypoglycemic drugs may be used simultaneously, it is important that long-term results of oral hypoglycemic drugs should be obtained from a daily clinical practice. The Specified Drug-use Survey of Nesina has been conducted in type 2 diabetes mellitus patients who have had an inadequate response to diet/exercise therapies only or diet/exercise therapies plus α-glucosidase inhibitors, thiazolidines, sulfonylureas, or biguanides. In the future, the specified drug-use survey of complication with Nesina and insulin preparations and insulin secretagogues is also expected to be conducted.

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This survey is conducted according to the relevant regulatory requirements including the GPSP ordinance.

2.0 Objectives

This survey is designed to evaluate the safety and efficacy of long-term use of alogliptin tablets (Nesina Tablets) in type 2 diabetic patients who have had an inadequate response to hypoglycemic agents (e.g., insulin preparations or rapid-acting insulin secretagogues)* in addition to dietary/exercise therapy in daily medical practice.

*Hypoglycemic agents which have not been used in the past Nesina Specified Drug-use Survey (i.e., other than α-glucosidase inhibitors, thiazolidines, sulfonylureas, and biguanides)

3.0 Number of Planned Participants and the Rationales

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1,000 participants

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The Specified Drug-use Survey of Nesina has been conducted in type 2 diabetes mellitus patients who have had an inadequate response to diet/exercise therapies only or diet/exercise therapies plus α-glucosidase inhibitors, thiazolidines, sulfonylureas, or biguanides. In the future, the specified drug-use survey of complication with Nesina and insulin preparations and insulin

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Therefore, the planned participants was established as 1,000 to collect as many as participants who receive a long-term complication therapy with Nesina and these hypoglycemic agents (e.g., insulin preparations, rapid-acting insulin secretagogues).

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  *For use of Nesina Tablets in combination with these agents, a specified drug-use survey is currently ongoing.

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Patients who meet any of the following criteria are excluded from this survey:

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(2) Those with severe infections, before or after surgery, or with serious trauma [Controlling blood glucose with an injection of insulin is desirable for these patients; therefore, administration of Nesina Tablets is not appropriate.]

(3) Those with a history of hypersensitivity to any of the ingredients of Nesina Tablets

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For adults, 25 mg of alogliptin is usually administered orally once daily. Refer to the Precaution

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12 months

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The Investigator will create the survey sheet for all enrolled participants and submit it to the Takeda MR around within 1 month after the end of the observation period. If Nesina administration cannot be confirmed, specify it (do not specify other columns).

For participants who early discontinue treatment with Nesina during the observation period for any reason, the Investigator will create the survey sheet for him/her and submit it to the Takeda MR around within 1 month after the end of necessary observation. However, for participants who early discontinue treatment with Nesina due to an adverse event, the Investigator will

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2) Survey period

At patient enrollment

9.2 Description Items in Survey Sheet

9.2.1 Front Cover of Survey Sheet

Last description date in the survey sheet and name of the Investigator who described the survey sheet

9.2.2 Patient Demographics

1) Matters to be surveyed

Diagnosis period of type 2 diabetes mellitus, category of clinical practice, disposition of hypersensitivity (yes/no and detail), concurrent disease (yes/no and detail), past medical history (yes/no and detail), height, smoking history, drinking history, presence or absence of serum creatinine within 1 month after the start of Nesina treatment, serum creatinine level (if

serum creatinine present), and severity of renal impairment and rationale for the assessment (if serum creatinine absent).

2) Survey period

At the start of Nesina treatment

9.2.3 Details of Treatment

1) Matters to be surveyed

Details of Nesina treatment (daily dose, administration period, and reason for discontinuation), and status of concomitant medications* (hypoglycemic agents) (yes/no, drug name, daily dose, route of administration, administration period, and objective of administration)

*Hypoglycemic agents which are discontinued within 3 months prior to Nesina treatment are included.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.4 Compliance with Nesina and Compliance with Diet/Exercise Therapy

1) Matters to be surveyed

Compliance with Nesina* and compliance with diet/exercise therapy**

*Criteria for assessment of compliance with Nesina

1. ≥ 90% (A participant won't miss administration, or even if he/she missed administration, the frequency is twice or three times a month.)
2. ≥ 70% (A participant missed administration once or twice weekly.)
3. ≥ 50% (A participant missed administration three times a week.)
4. < 50% (A participant missed administration four times or more a week.)

**Criteria for assessment of compliance with diet/exercise therapy

1. ≥ 90% (A participant complied as instructed.)
2. ≥ 70% (A participant mostly complied as instructed.)
3. ≥ 50% (A participant did not complied well as instructed.)
4. < 50% (A participant did not mostly complied as instructed.)
5. Not performed
6. Unknown

2) Survey period

At the start of Nesina treatment (compliance with diet/exercise therapy only), 1 month, 3

months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5 Laboratory/Observation Parameters

9.2.5.1 Vital Signs

1) Laboratory/observation parameters

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

2) Survey period

Each time point at the start of Nesina treatment, 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5.2 Laboratory Values

1) Laboratory parameters

HbA1c (NGSP value, same hereafter), fasting glucose, fasting insulin, fasting glucagon, fasting triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, serum creatinine, BUN, urinary albumin (corrected by creatinine), AST, ALT, γ-GTP, ALP, total bilirubin, amylase, and lipase

2) Survey period

Each time point at the start of Nesina treatment, 1 month, 3 months, 6 months, and 12 months after the start of treatment (or treatment discontinuation)

9.2.5.3 Electrocardiography

1) Observation Parameters

Electrocardiograms (assessment and findings)

2) Survey period

Each time point from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.5.4 Tests for Waist Circumference, Coronary Arteriosclerosis, and Arteriosclerosis

1) Observation Parameters

Tests for waist circumference,* coronary arteriosclerosis and arteriosclerosis** (e.g., pulse wave velocity, cardio-ankle vascular index, intima-media thickness, intra-vascular ultrasound)

*Measure the waist diameter during light expiration at standing position and at the level of the navel. If the lower deviation of the navel occurs because of significant abdominal fat accumulation, measure the waist diameter at the level of the midpoint between the inferior rib border and anterior superior iliac spine.

**Any methods can be used. In principle, however, use the same methods for each test. If there are no devices for measurement, the tests can be omitted.

2) Survey period

Each time point from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.5.5 Other Parameters

1) Observation parameters

Pregnancy during the observation period (yes or no) (females only)

In case of pregnancy in the observation period, the Investigator will immediately contact the Takeda MR. The Investigator will provide detailed information (including the information until the delivery, as possible, such as preterm delivery) using the separate pregnancy sheet after the request from the Takeda MR.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

9.2.6 Adverse Event

1) Matters to be surveyed

Presence or absence of adverse events (refer to Table 1), term of adverse events, onset date, seriousness and the reason (refer to Table 2), presence or absence of Nesina discontinuation, outcome assessment date, outcome, and causal relationship to Nesina* (refer to Table 3).

If the outcome is assessed as Not resolved or Unknown and if the causal relationship cannot be assessed, the participant will be followed up, wherever possible.

The detailed information (e.g., clinical course, laboratory tests for diagnosis) will be collected as possible for development of hypoglycemia, acute pancreatitis, renal impairment / jaundice, skin disorder including oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme, rhabdomyolysis, intestinal obstruction, interstitial pneumonia, angioedema, infection, malignant tumor, and cardiovascular system-related event (e.g., symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death)

*If the causal relationship to Nesina is assessed as Not related, collect the rationales for assessment. If the relationship is assessed as Not assessable, collected the reason for Not assessable.

Note) Matters that should be considered for adverse events

Abnormal exacerbation of the target disease, i.e., worsening beyond expected natural clinical course, is defined as an adverse event; however, the expected worsening is not defined as an adverse vent.

2) Survey period

Period from the start of Nesina treatment to 12 months after treatment (or treatment discontinuation)

Table 1 Definition of adverse event

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

The following events will be handled as adverse events:

• Symptoms present in infants breastfed by a Nesina taking mother

• Symptoms present in children who received the relevant drug

• Symptoms due to occupational exposure to the relevant drug

• Symptoms due to counterfeit medications of the legitimate medicinal products manufactured by Takeda

Table 2 Criteria for severity assessment

An event which meet any of the following criteria will be assessed as "Serious:"

1. Results in death (death).
2. Is life-threatening (potential death threat).
3. Requires inpatient hospitalization or prolongation of existing hospitalization (admission / prolonged hospitalization).
4. Results in persistent or significant disability/incapacity (disability).
5. Is a congenital anomaly/birth defect (congenital anomaly).
6. Other significant medical conditions which do not meet the above criteria 1 to 5. Events listed in the "Takeda Medically Significant AE List are included in this section criteria.

Takeda Medically Significant AE List

• Acute respiratory failure / acute respiratory distress syndrome (ARDS)	• Anaphylactic shock
• Torsade de pointes / ventricular fibrillation / ventricular tachycardia	• Acute renal failure
• Malignant hypertension	• Pulmonary hypertension
• Convulsive seizure (including convulsion and epilepsy)	• Pulmonary fibrosis (including interstitial pneumonia)
• Agranulocytosis	• Malignant syndrome / malignant hyperthermia
• Aplastic anemia	• Spontaneous abortion / stillbirth and fetal death
• Toxic epidermal necrolysis / oculomucocutaneous syndrome (Stevens-Johnson syndrome)	• Spread of infection via drug or suspected spread
• Hepatic necrosis	• Endotoxic shock or suspected endotoxic shock
• Acute hepatic failure	suspected endotoxic shock

Table 3 Criteria for causality assessment between adverse events and Nesina

Assessment	Assessment criterion
Related	Temporally correlation (including the post-treatment clinical course) present. Or an adverse event that may have been caused by the primary disease, concurrent disease, concomitant medication, or other factor including concomitant procedures, but also suggested to be caused by the relevant drug.
Not related	No temporally correlation with the relevant drug. Or an adverse event presumably caused by the primary disease, concurrent disease, concomitant medication, or other factor.
Not assessable	Lack of information for assessment of temporal correlation (including the post-treatment clinical course), the primary disease, concurrent disease, concomitant medication, other factor, etc.

10.0 Analysis Parameters and Methods

10.1 Patient Component Parameters

The following will be tabulated: number of enrolled participants, number of survey sheet collected participants, number of the Safety Analysis Set, number of the Efficacy Analysis Set, and number of patients excluded from analysis and the reason for exclusion, etc.

10.2 Patient Demographics

Patient demographics including sex, age, disease period, hypersensitivity predisposition, and concurrent disease will be tabulated.

10.3 Details of Treatment

The following will be tabulated: status of Nesina treatment, status of concomitant medications, and compliance with Nesina treatment, etc.

10.4 Safety Parameters

The items described below will be tabulated in the Safety Analysis Set. Adverse events will be coded using the MedDRA/J and summarized by Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Occurrence of Adverse Events

For adverse events reported in the observation period, the type and causal relationship to Nesina will be tabulated.

10.4. 2 Factors Probably Affecting Safety

For adverse drug reactions reported in the observation period, the frequency of patient demographics (e.g., sex, age), details of treatment (e.g., status of Nesina, and status of

concomitant medications) will be stratified.

10.5 Efficacy Parameters

The following will be tabulated in the Efficacy Analysis Set:

10.5.1 Change in HbA1c

HbA1c test values and the corresponding change from baseline at each testing time point (i.e., test value at each testing time point − test value at baseline) will be tabulated. In addition, the objective glycemic control achievement rate at each testing time point will be tabulated.

10.5.2 Changes in Laboratory Test Values

Test values (fasting blood glucose level, fasting insulin level, HOMA-R,* and HOMA-β*) and the corresponding changes from baseline at each testing time point (i.e., test value at each testing time point − test value at baseline) will be tabulated.

*HOMA-R: Fasting insulin × Fasting glucose / 405

**HOMA-β: (Fasting insulin × 360) / (Fasting glucose − 63)

10.5.3 Factors Probably Affecting Efficacy

For the changes in HbA1c and glycemic control achievement rate at 12 months after the start of treatment, the following will be stratified: patient demographics (e.g., sex, age, HbA1c at the start of Nesina treatment) and details of treatment (e.g., status of Nesina treatment, status of concomitant medications).

10.6 Parameters in Patients with Special Demographics

The safety and efficacy of Nesina will be stratified in elderly patients or patients with hepatic/renal impairment.

11.0 Registration of Survey Data

Takeda Pharmaceutical Company Limited. will register the survey information in the ClinicalTrials.gov and an open website (JAPIC-CTI*) before the start of this survey.

*Japan Pharmaceutical Information Center-Clinical Trials Information

12.0 Organizations

12.1 Manager

PPD Takeda Pharmaceutical Company Limited.

PPD

12.2 Central Enrollment Center

PPD

13.0 CRO

PPD

14.0 Other Necessary Matters

14.1 Protocol Revision

During the survey period, the protocol can be reviewed and revised, if the following are necessary to be changed after monitored: the survey progress, adverse drug reactions / serious adverse drug reactions unexpected from the Precautions, increased frequency of specified adverse drug reactions (yes or no), and parameter appropriateness. During the survey period, if partly changes of dosage and administration and indications are approved, the protocol revision will be also considered and performed as necessary.

14.2 Measures for Issues or Questions

If any question about the safety or efficacy is arisen, data will be investigated and the relevant persons will take measures for the question.

Appendix Observation Schedule

Parameter	Survey period	Observation period						
		At patient enrollment	At start of treatment	1 months after treatment	3 months after treatment	6 months after treatment	12 months after treatment	At treatment discontinuation
Patient enrollment	Nesina prescription date	○						
	Patient ID Number	○						
	Patients initial	○						
	Sex	○						
	Birth date	○						
	Inclusion criteria / exclusion criteria	○						
At patient demographics	Diagnosis period of type 2 diabetes mellitus		○					
	Category of clinical practice		○					
	Hypersensitivity predisposition		○					
	Concurrent disease		○					
	Past medical history		○					
	Height		○					
	Smoking history		○					
	Drinking history		○					
	Presence or absence of serum creatinine within 1 month after the start of Nesina treatment, serum creatinine level (if serum creatinine present), and severity of renal impairment and rationale for the assessment (if serum creatinine absent).		○					
Details of treatment, etc.	Status of Nesina treatment		←	―	○	→		○
	Status of concomitant medication treatment (hypoglycemic agents / other than hypoglycemic agents)		←	―	○	→		○
	Status of compliance with Nesina			○	○	○	○	○
	Status of compliance with diet/exercise therapy		○	○	○	○	○	○
Laboratory/Observation Parameters, etc	Pulse rate, blood pressure		○	○	○	○	○	○
	Weight		○	○	○	○	○	○
	Laboratory values • HbA1c (NGSP value) • Fasting glucose • Fasting insulin • Fasting glucagon • Fasting triglyceride • Total cholesterol • HDL-cholesterol • LDL-cholesterol • Serum creatinine • BUN • Urinary albumin (corrected by creatinine) • AST • ALT • γ-GTP • ALP • Total bilirubin • Amylase • Lipase		○	○	○	○	○	○
	Electrocardiogram		○				○	○
	Waist circumference		○				○	○
	Tests for coronary arteriosclerosis and arteriosclerosis		○				○	○
	Pregnancy (yes or no) (females only)		←	―	○	→		○
	Adverse event		←	―	○	→		○

○ :To be performed

←——○——→ :To be performed throughout the period