Title: Nesina Tablets Special Drug Use Surveillance: Mild Type 2 Diabetes Mellitus

NCT Number: NCT01964963

Protocol Approve Date: 02-Mar-2017

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

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

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

Protocol for

Nesina Tablets Special Drug Use Surveillance: Mild Type 2 Diabetes Mellitus

Version	**Fifth version**
Creation date	**March 2, 2017**
Sponsor	**Takeda Pharmaceutical Company Limited.**

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1.0 Surveillance Background

The goal of diabetes mellitus treatment is to maintain patients' QOLs as those in healthy people and to secure their lifetimes through management for a favorable blood glucose level for a long time. In particular, early drug treatment is considered important for patients with mild type 2 diabetes mellitus, which maintains a favorable blood glucose level and inhibits the diabetes progress, along with prevention of microangiopathy.

As an oral drug started to be administered early to patients with mild type 2 diabetes mellitus, the desirable drug should have a low risk of hypoglycemia, be well tolerable, and not exhaust pancreatic function.

DPP-4 inhibitors selectively inhibit DPP-4, increase blood GLP-1 levels, and prompt the pancreas to secrete insulin in a glucose level-dependent manner. Taken together, DPP-4 inhibitors are expected to be highly effective for patients with mild type 2 diabetes mellitus.

As a DPP-4 inhibitor, Nesina tablets (generic name: alogliptin benzoate) are confirmed to be highly effective and safe when administered alone and combined with various oral diabetic drugs in clinical studies conducted in Japan. The following are approved indications for Nesina:

Indications for Nesina tablets

Type 2 diabetes mellitus

However, this indication is limited only for patients who had an insufficient response to the following therapies:

(1) Only diet and exercise therapies.
(2) α-glucosidase inhibitors used in addition to diet and exercise therapies.
(3) Thiazolidines used in addition to diet and exercise therapies.
(4) Sulfonylureas used in addition to diet and exercise therapies.
(5) Biguanides used in addition to diet and exercise therapies.

However, the efficacy and safety of Nesina has not been well evaluated for patients with mild type 2 diabetes mellitus because Nesina tablets have been administered to type 2 diabetes mellitus patients with HbA1c of ≥ 6.5% (for patients treated with sulfonylureas, HbA1c of ≥ 7.0%) in clinical studies conducted before drug approval.

Therefore, this Special Drug Use Surveillance (hereinafter, the Surveillance) was planned to evaluate the long-term safety and efficacy of Nesina tablets (hereinafter, Nesina) for patients with mild type 2 diabetes mellitus patients in a daily clinical practice.

2.0 Objectives of Surveillance

To examine the safety and efficacy of long-term treatment with alogliptin (Nesina) in patients with mild type 2 diabetes mellitus in the routine clinical setting.

3.0 Number of Planned Patients for Surveillance and the Rationales

3.1 Number of Planned Patients for Surveillance

20000 patients

3.2 Rationales

According to database of 16 hospitals in Japan, supplied by PPD., of 142358 patients documented as visited from October to December 2010, 15141 were patients with type 2 diabetes mellitus. Of these, 4165 patients had HbA1c (JDS) of ≤ 7.0%, which were the target population in this Surveillance. For patients with indications for Nesina, in addition, 1864 patients (70.4%) received only diet and exercise therapies (no diabetic drugs); 226 patients (8.5%) received α-glucosidase inhibitors; 175 patients (6.6%) received thiazolidines; 273 patients (10.3%) received sulfonylureas; 109 patients (4.1%) received biguanides (each drug was administered alone).

In order to identify adverse drug reactions with a frequency of ≥ 0.5% using ≥ a 95% confidence level, 600 patients will be required. Assuming that the proportion of drugs in patients with mild type 2 diabetes mellitus is same as the above, if data in 20000 patients with mild type 2 diabetes mellitus are collected in this Surveillance, 14084 patients will be required for Nesina treatment alone; 1708 patients will be required for combination with α-glucosidase inhibitors; 1322 patients will be required for combination with thiazolidines; 2063 patients will be required for combination with sulfonylureas; 824 patients will be required for combination with biguanides. Since any combination can identify the adverse drug reactions with a frequency of ≥ 0.5% using ≥ a 95% confidence level, the number of planned patients for surveillance was established as 20000.

4.0 Patients for Surveillance

Patients with mild type 2 diabetes mellitus will be evaluated for this Surveillance. However, patients must meet the inclusion criteria and none of the exclusion criteria, described below. Refer to the Precaution with Respect to Indication in the package insert.

4.1 Inclusion Criteria

Patients who meet the following criterion will be included in this Surveillance:

(1) Patients with HbA1c (JDS value) ≤7.0% at the time of enrolment (within 3 months before initiation of Nesina therapy)

* Regardless of the use of antidiabetic medication

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from this Surveillance:

(1) Patients with severe ketosis, diabetic coma or precoma, or type 1 diabetes mellitus

(2) Patients with severe infection, pre- or post-operative patients, or patients with serious traumatic injury

(3) Patients with a history of hypersensitivity to any ingredient of Nesina

5.0 Dosage and Administration for Patients to be Surveyed

The usual adult dose of alogliptin is 25 mg administered orally once daily. Refer to the Precaution with Respect to Dosage and Administration in the package insert.

6.0 Number of To-be Survey Sites by Department

Internal medicine or other department: Approximately 1000 sites

7.0 Survey Methods

7.1 Observation Period

The observation period will be 36 months after the start date of Nesina treatment.

If Nesina treatment is discontinued for any reason, the survey will be ended at the discontinuation.

7.2 Request for Sites and Agreement

This surveillance will be conducted using the electronic data collection system via web (CCI Before asking survey, MRs of Takeda Takeda Pharmaceutical Company Limited. (Hereinafter, Takeda MRs) will fully explain to the Investigator about the objectives, details, handling methods for CCI and handling of electronic signature, user ID, and passwords, based on "Request for Cooperation of Special Drug Use Surveillance," "Summary for Surveillance," "Entry Screen Images," and "Brief Manual for Handling of CCI and will finalize written agreement with survey sites to ask requests for surveillance within the specified period.

7.3 Methods for Registration of Patients to be Surveyed

This Surveillance will be conducted using Central Registration System with CCI The Investigator will enter registration data on CCI (refer to Section 9.1) for patients who start Nesina treatment after the start date of agreement with a survey site, before 14 days after the start date of Nesina treatment (define the start date of treatment as "0 day" and one day after the start date of treatment as "1 day").

7.4 Entry on Survey Sheet (Electronic) and Electronic Signature

The Investigator will enter patient demographic data and details of treatment on CCI at each data entry time point (at the start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after the start of Nesina treatment or treatment discontinuation). In addition, the Investigator will sign electronically on the survey sheet in CCI for "Patient Demographic Data and Details of Treatment by 12 Months of Treatment" after 12 months of treatment and for Patient Demographic Data and Details of Treatment by 36 Months of Treatment" after 36 months of treatment.

For patients who discontinue treatment with Nesina during the observation period for any reason, the Investigator will enter the patient demographic data and details of treatment on CCI and will sign electronically in the survey sheet around within 1 month after the end of necessary observation. However, for patients who discontinue treatment with Nesina due to an adverse event, the Investigator will continue observation after treatment discontinuation, wherever possible, until the adverse event resolve or is resolving and will enter the observation results on CCI as well as sign electronically in the survey sheet.
In case that additional survey is required after Takeda checked the details, Takeda will ask request for re-survey on CCI The Investigator will check the details of request for re-survey and enter the re-survey results on CCI as well as sign electronically in the survey sheet.

7.5 Measures for Development of Adverse Events

In case of development of an adverse event, the Investigator will contact the person in charge of Takeda Pharmaceutical Company Limited (hereinafter, the person in charge of Takeda). If the person in charge of Takeda requests additional detailed information, the Investigator will provide it.

8.0 Scheduled Survey Period

Survey period: July 2011 to July 31, 2017
Patient registration period: July 2011 to July 31, 2013[Note)]
Due date for entry of "Patient Data and Details of Treatment by 12 Months of Treatment:" August 31, 2014
Due date for entry of "Patient Data and Details of Treatment by 36 Months of Treatment:" July 31, 2017

[Note)] Patients who will be treated with Nesina by July 31, 2013 can be registered.
In case that the registered patients reach the scheduled number of patients to be surveyed before July 31 2013, the registration will close earlier than scheduled.

9.0 Matters to be Surveyed

The Investigator will enter data of the parameters described below on CCI The schedule of this surveillance is shown in the Appendix.

9.1 Patient Registration Data

1) Matters to be surveyed
Start date of Nesina treatment, Patient ID Number, patient initial, sex, birth date, HbA1c (JDS) within 3 months prior to Nesina treatment, inclusion criteria assessment, and exclusion criteria assessment

2) Survey period
At patient registration

9.2 Survey sheet: patient demographic data

1) Matters to be surveyed

Diagnosis period of type 2 diabetes mellitus, height, practice category (at the start of survey), presence or absence of pregnancy (females only), pregnancy week (if applicable), severity of renal impairment, rationale for assessment of the severity of renal impairment, concurrent disease, prior medical history, alcohol history, smoking history, and presence or absence of dietary intervention / exercise intervention

2) Survey period

At the start of Nesina treatment

9.3 Survey sheet: details of treatment

1) Matters to be surveyed

Details of Nesina treatment (daily dose and administration period), status of end of Nesina treatment, reason for Nesina discontinuation (if applicable), details of other diabetic drug treatment* (drug name, daily dose, route of administration, and administration period), and status of concomitant medications (other than diabetic drugs) (drug name, route of administration, administration period, and objectives of administration)

* Diabetic drugs which are discontinued within 3 months prior to Nesina treatment are included.

2) Survey period

Period from the start of Nesina treatment to 36 months after treatment (or treatment discontinuation)

9.4 Laboratory/Observation Parameters

1) Matters to be surveyed

HbA1c (JDS, international standard value, or NGSP), fasting glucose, fasting insulin, fasting triglyceride, total cholesterol," HDL-cholesterol, LDL-cholesterol, weight, and blood pressure

2) Survey period

At the start of Nesina treatment, 3 months , 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months of treatment (or treatment discontinuation)

9.5 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), procedures related to Nesina, outcome, causal relationship to Nesina (refer to Table 3), presence or absence of diabetic complication (diabetic retinopathy, diabetic neuropathy, or diabetic nephropathy), change over time in clinically important laboratory values related to adverse events

If the outcome is assessed as Not resolved or Unknown and if the causal relationship cannot

be assessed, the patient will be followed up, wherever possible. The detailed information (clinical course, laboratory tests for diagnosis, etc.) will be collected as possible for development of hypoglycemia, tumor, pancreatitis, edema, angioedema-related symptom, immune system disorder, skin disorder and subcutaneous tissue disorder, cardiovascular system event (symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death, etc.)

2) Survey period

Period from the start of Nesina treatment to 36 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 in infants breastfed by a Nesina taking mother • Symptoms in children who received the relevant drug • Symptoms in patients who received the relevant drug at a higher dose than approved or who took by themselves

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. (e.g., bronchospasm and the like, requiring a short-term intensive care in an emergency room and the like)

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

Table 3 Criteria for causality assessment between adverse events and Nesina

Assessment	Assessment criterion
Related (Suspectedly related)	Temporally evident 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 (Unlikely related)	No temporally evident 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 registered patients, number of survey sheet (electronic) collected patients, number of survey completer, number of survey discontinuations and the reason for discontinuation, 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

The following patient demographics will be tabulated: age, sex, disease period, severity of renal impairment (including severity) (yes or no), concurrent disease, past medical history, alcohol history, smoking history, etc.

10.3 Details of Treatment

The following will be tabulated: status of Nesina treatment, status of concomitant medications (including the status of diabetic drugs at the start of 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 and summarized by Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Occurrence of Adverse Drug Reactions

The type, seriousness, onset period, and the like for adverse drug reactions reported in the observation period 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., age, sex), 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 Changes in HbA1c over Time

The HbA1c values at each time point and the changes (values at each time point − values at the start of Nesina treatment) will be tabulated. The achieving percent in glycemic control for HbA1c will be tabulated for each time point.

10.5.2 Factors Probably Affecting Efficacy

For the changes in HbA1c and the achieving percent in glycemic control for HbA1c at 36 months after the start of treatment, the following will be stratified: patients demographics

(e.g., age, sex, 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

For the safety and efficacy in patients with moderate or higher renal impairment, the relationship between the severity of renal impairment and Nesina doses (each will be stratified) will be thoroughly evaluated.

10.7 Interim Analysis

After 1-year observation period is completed in all patients, the interim analysis for the parameters described in Sections 10.1 to 10.6 will be performed to confirm the early safety and efficacy of Nesina in patients with mild type 2 diabetes mellitus, based on the data entered in "Patient Data and Details of Treatment by 12 Months of Treatment."

11.0 Surveillance Organizations

11.1 Investigator

PPD Takeda Pharmaceutical Company Limited.

12.0 Name and address of CRO and Scope of the CRO Task

PPD

13.0 Other Necessary Matters

13.1 Revision of the Protocol

During the surveillance period, the protocol can be reviewed and revised, if the following are necessary to be changed after monitored: the survey progress, number of dropouts, development of 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 surveillance period, if partly changes of dosage and administration and indications are approved, the protocol revision will be also considered and performed as necessary.

13.2 Measures for Issues or Questions

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

Appendix Surveillance Schedule

Parameters \ Survey/data entry time point		Observation period									
		At patient registration	At start of treatment	3 months after treatment	6 months after treatment	12 months after treatment	18 months after treatment	24 months after treatment	30 months after treatment	36 months after treatment	At treatment discontinuation
Patient registration data	Start date of Nesina treatment	○									
	Patient ID Number	○									
	Patients initial	○									
	Sex	○									
	Birth date	○									
	HbA1c within 3 months prior to Nesina treatment	○									
	Inclusion criteria / exclusion criteria	○									
Patient demographic data	Diagnosis period of type 2 diabetes mellitus		○								
	Height		○								
	Category of clinical practice (at start of survey)		○								
	Pregnancy (yes or no) (females only)		○								
	Week of pregnancy (if applicable)		○								
	Severity of renal impairment		○								
	Rationale for severity assessment of renal impairment		○								
	Concurrent disease		○								
	Past medical history		○								
	Alcohol history		○								
	Smoking history		○								
	Dietary/exercise intervention (yes or no)		○								
Details of treatment	Status of Nesina treatment		←○→								○
	Status of other diabetic drug		←○→								○
	Status of concomitant medication (other than diabetic drugs)		←○→								○
Laboratory/Observation Parameters, etc	Laboratory values • HbA1c (JDS, international standard value, or NGSP) • Fasting glucose • Fasting insulin • Fasting triglyceride • Total cholesterol • HDL-cholesterol • LDL-cholesterol		○	○	○	○	○	○	○	○	○
	Weight		○	○	○	○	○	○	○	○	○
	Blood pressure		○	○	○	○	○	○	○	○	○
	Adverse event		←○→								○

○ Performed

←○→ Performed throughout the period

* Including the diabetic drugs discontinued within 3 months prior to the start of Nesina

Protocol for

Nesina Tablets Special Drug Use Surveillance: Mild Type 2 Diabetes Mellitus

Version	**Fourth version**
Creation date	**June 30, 2016**
Sponsor	**Takeda Pharmaceutical Company Limited.**

Table of Contents

1.0 Surveillance Background

The goal of diabetes mellitus treatment is to maintain patients' QOLs as those in healthy people and to secure their lifetimes through management for a favorable blood glucose level for a long time. In particular, early drug treatment is considered important for patients with mild type 2 diabetes mellitus, which maintains a favorable blood glucose level and inhibits the diabetes progress, along with prevention of microangiopathy.

As an oral drug started to be administered early to patients with mild type 2 diabetes mellitus, the desirable drug should have a low risk of hypoglycemia, be well tolerable, and not exhaust pancreatic function.

DPP-4 inhibitors selectively inhibit DPP-4, increase blood GLP-1 levels, and prompt the pancreas to secrete insulin in a glucose level-dependent manner. Taken together, DPP-4 inhibitors are expected to be highly effective for patients with mild type 2 diabetes mellitus.

As a DPP-4 inhibitor, Nesina tablets (generic name: alogliptin benzoate) are confirmed to be highly effective and safe when administered alone and combined with various oral diabetic drugs in clinical studies conducted in Japan. The following are approved indications for Nesina:

Indications for Nesina tablets

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However, this indication is limited only for patients who had an insufficient response to the following therapies:

(1) Only diet and exercise therapies.
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2.0 Objectives of Surveillance

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3.0 Number of Planned Patients for Surveillance and the Rationales

3.1 Number of Planned Patients for Surveillance

20000 patients

3.2 Rationales

According to database of 16 hospitals in Japan, supplied by PPD of 142358 patients documented as visited from October to December 2010, 15141 were patients with type 2 diabetes mellitus. Of these, 4165 patients had HbA1c (JDS) of ≤ 7.0%, which were the target population in this Surveillance. For patients with indications for Nesina, in addition, 1864 patients (70.4%) received only diet and exercise therapies (no diabetic drugs); 226 patients (8.5%) received α-glucosidase inhibitors; 175 patients (6.6%) received thiazolidines; 273 patients (10.3%) received sulfonylureas; 109 patients (4.1%) received biguanides (each drug was administered alone).

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4.0 Patients for Surveillance

Patients with mild type 2 diabetes mellitus will be evaluated for this Surveillance. However, patients must meet the inclusion criteria and none of the exclusion criteria, described below. Refer to the Precaution with Respect to Indication in the package insert.

4.1 Inclusion Criteria

Patients who meet the following criterion will be included in this Surveillance:

(1) Patients with HbA1c (JDS value) ≤7.0% at the time of enrolment (within 3 months before initiation of Nesina therapy)

* Regardless of the use of antidiabetic medication

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from this Surveillance:

(1) Patients with severe ketosis, diabetic coma or precoma, or type 1 diabetes mellitus

(2) Patients with severe infection, pre- or post-operative patients, or patients with serious traumatic injury

(3) Patients with a history of hypersensitivity to any ingredient of Nesina

5.0 Dosage and Administration for Patients to be Surveyed

The usual adult dose of alogliptin is 25 mg administered orally once daily. Refer to the Precaution with Respect to Dosage and Administration in the package insert.

6.0 Number of To-be Survey Sites by Department

Internal medicine or other department: Approximately 1000 sites

7.0 Survey Methods

7.1 Observation Period

The observation period will be 36 months after the start date of Nesina treatment.

If Nesina treatment is discontinued for any reason, the survey will be ended at the discontinuation.

7.2 Request for Sites and Agreement

This surveillance will be conducted using the electronic data collection system via web CCI. Before asking survey, MRs of Takeda Takeda Pharmaceutical Company Limited. (Hereinafter, Takeda MRs) will fully explain to the Investigator about the objectives, details, handling methods for CCI and handling of electronic signature, user ID, and passwords, based on "Request for Cooperation of Special Drug Use Surveillance," "Summary for Surveillance," "Entry Screen Images," and "Brief Manual for Handling of CCI and will finalize written agreement with survey sites to ask requests for surveillance within the specified period.

7.3 Methods for Registration of Patients to be Surveyed

This Surveillance will be conducted using Central Registration System with CCI The Investigator will enter registration data on CCI (refer to Section 9.1) for patients who start Nesina treatment after the start date of agreement with a survey site, before 14 days after the start date of Nesina treatment (define the start date of treatment as "0 day" and one day after the start date of treatment as "1 day").

7.4 Entry on Survey Sheet (Electronic) and Electronic Signature

The Investigator will enter patient demographic data and details of treatment on CCI at each data entry time point (at the start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after the start of Nesina treatment or treatment discontinuation). In addition, the Investigator will sign electronically on the survey sheet in CCI for "Patient Demographic Data and Details of Treatment by 12 Months of Treatment" after 12 months of treatment and for Patient Demographic Data and Details of Treatment by 36 Months of Treatment" after 36 months of treatment.

For patients who discontinue treatment with Nesina during the observation period for any reason, the Investigator will enter the patient demographic data and details of treatment on CCI and will sign electronically in the survey sheet around within 1 month after the end of necessary observation. However, for patients who discontinue treatment with Nesina due to an adverse event, the Investigator will continue observation after treatment discontinuation, wherever possible, until the adverse event resolve or is resolving and will enter the observation results on CCI as well as sign electronically in the survey sheet.
In case that additional survey is required after Takeda checked the details, Takeda will ask request for re-survey on CCI The Investigator will check the details of request for re-survey and enter the re-survey results on CCI as well as sign electronically in the survey sheet.

7.5 Measures for Development of Adverse Events

In case of development of an adverse event, the Investigator will contact the person in charge of Takeda Pharmaceutical Company Limited (hereinafter, the person in charge of Takeda). If the person in charge of Takeda requests additional detailed information, the Investigator will provide it.

8.0 Scheduled Survey Period

Survey period: July 2011 to July 31, 2017
Patient registration period: July 2011 to July 31, 2013[Note)]
Due date for entry of "Patient Data and Details of Treatment by 12 Months of Treatment:" August 31, 2014
Due date for entry of "Patient Data and Details of Treatment by 36 Months of Treatment:" February 28, 2017

[Note)] Patients who will be treated with Nesina by July 31, 2013 can be registered.
In case that the registered patients reach the scheduled number of patients to be surveyed before July 31 2013, the registration will close earlier than scheduled.

9.0 Matters to be Surveyed

The Investigator will enter data of the parameters described below on CCI The schedule of this surveillance is shown in the Appendix.

9.1 Patient Registration Data

1) Matters to be surveyed

Start date of Nesina treatment, Patient ID Number, patient initial, sex, birth date, HbA1c (JDS) within 3 months prior to Nesina treatment, inclusion criteria assessment, and exclusion criteria assessment

2) Survey period

At patient registration

9.2 Survey sheet: patient demographic data

1) Matters to be surveyed

Diagnosis period of type 2 diabetes mellitus, height, practice category (at the start of survey), presence or absence of pregnancy (females only), pregnancy week (if applicable), severity of renal impairment, rationale for assessment of the severity of renal impairment, concurrent disease, prior medical history, alcohol history, smoking history, and presence or absence of dietary intervention / exercise intervention

2) Survey period

At the start of Nesina treatment

9.3 Survey sheet: details of treatment

1) Matters to be surveyed

Details of Nesina treatment (daily dose and administration period), status of end of Nesina treatment, reason for Nesina discontinuation (if applicable), details of other diabetic drug treatment* (drug name, daily dose, route of administration, and administration period), and status of concomitant medications (other than diabetic drugs) (drug name, route of administration, administration period, and objectives of administration)

* Diabetic drugs which are discontinued within 3 months prior to Nesina treatment are included.

2) Survey period

Period from the start of Nesina treatment to 36 months after treatment (or treatment discontinuation)

9.4 Laboratory/Observation Parameters

1) Matters to be surveyed

HbA1c (JDS, international standard value, or NGSP), fasting glucose, fasting insulin, fasting triglyceride, total cholesterol," HDL-cholesterol, LDL-cholesterol, weight, and blood pressure

2) Survey period

At the start of Nesina treatment, 3 months , 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months of treatment (or treatment discontinuation)

9.5 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), procedures related to Nesina, outcome, causal relationship to Nesina (refer to Table 3), presence or absence of diabetic complication (diabetic retinopathy, diabetic neuropathy, or diabetic nephropathy), change over time in clinically important laboratory values related to adverse events

If the outcome is assessed as Not resolved or Unknown and if the causal relationship cannot

be assessed, the patient will be followed up, wherever possible. The detailed information (clinical course, laboratory tests for diagnosis, etc.) will be collected as possible for development of hypoglycemia, tumor, pancreatitis, edema, angioedema-related symptom, immune system disorder, skin disorder and subcutaneous tissue disorder, cardiovascular system event (symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death, etc.)

2) Survey period

Period from the start of Nesina treatment to 36 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 in infants breastfed by a Nesina taking mother • Symptoms in children who received the relevant drug • Symptoms in patients who received the relevant drug at a higher dose than approved or who took by themselves

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. (e.g., bronchospasm and the like, requiring a short-term intensive care in an emergency room and the like)

Takeda Medically Significant AE List

- Acute respiratory failure / acute respiratory distress syndrome (ARDS)
- Torsade de pointes / ventricular fibrillation / ventricular tachycardia
- Malignant hypertension
- Convulsive seizure (including convulsion and epilepsy)
- Agranulocytosis
- Aplastic anemia
- Toxic epidermal necrolysis / oculomucocutaneous syndrome (Stevens-Johnson syndrome)
- Hepatic necrosis
- Acute hepatic failure
- Anaphylactic shock
- Acute renal failure
- Pulmonary hypertension
- Pulmonary fibrosis (including interstitial pneumonia)
- Malignant syndrome / malignant hyperthermia
- Spontaneous abortion / stillbirth and fetal death
- 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 (Suspectedly related)	Temporally evident 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 (Unlikely related)	No temporally evident 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 registered patients, number of survey sheet (electronic) collected patients, number of survey completer, number of survey discontinuations and the reason for discontinuation, 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

The following patient demographics will be tabulated: age, sex, disease period, severity of renal impairment (including severity) (yes or no), concurrent disease, past medical history, alcohol history, smoking history, etc.

10.3 Details of Treatment

The following will be tabulated: status of Nesina treatment, status of concomitant medications (including the status of diabetic drugs at the start of 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 and summarized by Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Occurrence of Adverse Drug Reactions

The type, seriousness, onset period, and the like for adverse drug reactions reported in the observation period 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., age, sex), 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 Changes in HbA1c over Time

The HbA1c values at each time point and the changes (values at each time point − values at the start of Nesina treatment) will be tabulated. The achieving percent in glycemic control for HbA1c will be tabulated for each time point.

10.5.2 Factors Probably Affecting Efficacy

For the changes in HbA1c and the achieving percent in glycemic control for HbA1c at 36 months after the start of treatment, the following will be stratified: patients demographics

(e.g., age, sex, 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

For the safety and efficacy in patients with moderate or higher renal impairment, the relationship between the severity of renal impairment and Nesina doses (each will be stratified) will be thoroughly evaluated.

10.7 Interim Analysis

After 1-year observation period is completed in all patients, the interim analysis for the parameters described in Sections 10.1 to 10.6 will be performed to confirm the early safety and efficacy of Nesina in patients with mild type 2 diabetes mellitus, based on the data entered in "Patient Data and Details of Treatment by 12 Months of Treatment."

11.0 Surveillance Organizations

11.1 Investigator

PPD Takeda Pharmaceutical Company Limited.

12.0 Name and address of CRO and Scope of the CRO Task

PPD

13.0 Other Necessary Matters

13.1 Revision of the Protocol

During the surveillance period, the protocol can be reviewed and revised, if the following are necessary to be changed after monitored: the survey progress, number of dropouts, development of 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 surveillance period, if partly changes of dosage and administration and indications are approved, the protocol revision will be also considered and performed as necessary.

13.2 Measures for Issues or Questions

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

Appendix Surveillance Schedule

Survey/data entry time point / Parameters		Observation period									
		At patient registration	At start of treatment	3 months after treatment	6 months after treatment	12 months after treatment	18 months after treatment	24 months after treatment	30 months after treatment	36 months after treatment	At treatment discontinuation
Patient registration data	Start date of Nesina treatment	○									
	Patient ID Number	○									
	Patients initial	○									
	Sex	○									
	Birth date	○									
	HbA1c within 3 months prior to Nesina treatment	○									
	Inclusion criteria / exclusion criteria	○									
Patient demographic data	Diagnosis period of type 2 diabetes mellitus		○								
	Height		○								
	Category of clinical practice (at start of survey)		○								
	Pregnancy (yes or no) (females only)		○								
	Week of pregnancy (if applicable)		○								
	Severity of renal impairment		○								
	Rationale for severity assessment of renal impairment		○								
	Concurrent disease		○								
	Past medical history		○								
	Alcohol history		○								
	Smoking history		○								
	Dietary/exercise intervention (yes or no)		○								
Details of treatment	Status of Nesina treatment		←○→								○
	Status of other diabetic drug		←○→								○
	Status of concomitant medication (other than diabetic drugs)		←○→								○
Laboratory/Observation Parameters, etc	Laboratory values • HbA1c (JDS, international standard value, or NGSP) • Fasting glucose • Fasting insulin • Fasting triglyceride • Total cholesterol • HDL-cholesterol • LDL-cholesterol		○	○	○	○	○	○	○	○	○
	Weight		○	○	○	○	○	○	○	○	○
	Blood pressure		○	○	○	○	○	○	○	○	○
	Adverse event		←○→								○

○ Performed

←○→ Performed throughout the period

* Including the diabetic drugs discontinued within 3 months prior to the start of Nesina

Protocol for

Nesina Tablets Special Drug Use Surveillance: Mild Type 2 Diabetes Mellitus

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

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1.0 Surveillance Background

The goal of diabetes mellitus treatment is to maintain patients' QOLs as those in healthy people and to secure their lifetimes through management for a favorable blood glucose level for a long time. In particular, early drug treatment is considered important for patients with mild type 2 diabetes mellitus, which maintains a favorable blood glucose level and inhibits the diabetes progress, along with prevention of microangiopathy.

As an oral drug started to be administered early to patients with mild type 2 diabetes mellitus, the desirable drug should have a low risk of hypoglycemia, be well tolerable, and not exhaust pancreatic function.

DPP-4 inhibitors selectively inhibit DPP-4, increase blood GLP-1 levels, and prompt the pancreas to secrete insulin in a glucose level-dependent manner. Taken together, DPP-4 inhibitors are expected to be highly effective for patients with mild type 2 diabetes mellitus.

As a DPP-4 inhibitor, Nesina tablets (generic name: alogliptin benzoate) are confirmed to be highly effective and safe when administered alone and combined with various oral diabetic drugs in clinical studies conducted in Japan. The following are approved indications for Nesina:

Indications for Nesina tablets

Type 2 diabetes mellitus

However, this indication is limited only for patients who had an insufficient response to the following therapies:

(1) Only diet and exercise therapies.
(2) α-glucosidase inhibitors used in addition to diet and exercise therapies.
(3) Thiazolidines used in addition to diet and exercise therapies.
(4) Sulfonylureas used in addition to diet and exercise therapies.
(5) Biguanides used in addition to diet and exercise therapies.

However, the efficacy and safety of Nesina has not been well evaluated for patients with mild type 2 diabetes mellitus because Nesina tablets have been administered to type 2 diabetes mellitus patients with HbA1c of ≥ 6.5% (for patients treated with sulfonylureas, HbA1c of ≥ 7.0%) in clinical studies conducted before drug approval.

Therefore, this Special Drug Use Surveillance (hereinafter, the Surveillance) was planned to evaluate the long-term safety and efficacy of Nesina tablets (hereinafter, Nesina) for patients with mild type 2 diabetes mellitus patients in a daily clinical practice.

2.0 Objectives of Surveillance

To examine the safety and efficacy of long-term treatment with alogliptin (Nesina) in patients with mild type 2 diabetes mellitus in the routine clinical setting.

3.0 Number of Planned Patients for Surveillance and the Rationales

3.1 Number of Planned Patients for Surveillance

20000 patients

3.2 Rationales

According to database of 16 hospitals in Japan, supplied by PPD of 142358 patients documented as visited from October to December 2010, 15141 were patients with type 2 diabetes mellitus. Of these, 4165 patients had HbA1c (JDS) of ≤ 7.0%, which were the target population in this Surveillance. For patients with indications for Nesina, in addition, 1864 patients (70.4%) received only diet and exercise therapies (no diabetic drugs); 226 patients (8.5%) received α-glucosidase inhibitors; 175 patients (6.6%) received thiazolidines; 273 patients (10.3%) received sulfonylureas; 109 patients (4.1%) received biguanides (each drug was administered alone).

In order to identify adverse drug reactions with a frequency of ≥ 0.5% using ≥ a 95% confidence level, 600 patients will be required. Assuming that the proportion of drugs in patients with mild type 2 diabetes mellitus is same as the above, if data in 20000 patients with mild type 2 diabetes mellitus are collected in this Surveillance, 14084 patients will be required for Nesina treatment alone; 1708 patients will be required for combination with α-glucosidase inhibitors; 1322 patients will be required for combination with thiazolidines; 2063 patients will be required for combination with sulfonylureas; 824 patients will be required for combination with biguanides. Since any combination can identify the adverse drug reactions with a frequency of ≥ 0.5% using ≥ a 95% confidence level, the number of planned patients for surveillance was established as 20000.

4.0 Patients for Surveillance

Patients with mild type 2 diabetes mellitus will be evaluated for this Surveillance. However, patients must meet the inclusion criteria and none of the exclusion criteria, described below. Refer to the Precaution with Respect to Indication in the package insert.

4.1 Inclusion Criteria

Patients who meet the following criterion will be included in this Surveillance:

(1) Patients with HbA1c (JDS value) ≤7.0% at the time of enrolment (within 3 months before initiation of Nesina therapy)

* Regardless of the use of antidiabetic medication

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from this Surveillance:

(1) Patients with severe ketosis, diabetic coma or precoma, or type 1 diabetes mellitus

(2) Patients with severe infection, pre- or post-operative patients, or patients with serious traumatic injury

(3) Patients with a history of hypersensitivity to any ingredient of Nesina

5.0 Dosage and Administration for Patients to be Surveyed

The usual adult dose of alogliptin is 25 mg administered orally once daily. Refer to the Precaution with Respect to Dosage and Administration in the package insert.

6.0 Number of To-be Survey Sites by Department

Internal medicine or other department: Approximately 1000 sites

7.0 Survey Methods

7.1 Observation Period

The observation period will be 36 months after the start date of Nesina treatment.

If Nesina treatment is discontinued for any reason, the survey will be ended at the discontinuation.

7.2 Request for Sites and Agreement

This surveillance will be conducted using the electronic data collection system via web (CCI). Before asking survey, MRs of Takeda Takeda Pharmaceutical Company Limited. (Hereinafter, Takeda MRs) will fully explain to the Investigator about the objectives, details, handling methods for CCI and handling of electronic signature, user ID, and passwords, based on "Request for Cooperation of Special Drug Use Surveillance," "Summary for Surveillance," "Entry Screen Images," and "Brief Manual for Handling of CCI and will finalize written agreement with survey sites to ask requests for surveillance within the specified period.

7.3 Methods for Registration of Patients to be Surveyed

This Surveillance will be conducted using Central Registration System with CCI The Investigator will enter registration data on CCI (refer to Section 9.1) for patients who start Nesina treatment after the start date of agreement with a survey site, before 14 days after the start date of Nesina treatment (define the start date of treatment as "0 day" and one day after the start date of treatment as "1 day").

7.4 Entry on Survey Sheet (Electronic) and Electronic Signature

The Investigator will enter patient demographic data and details of treatment on CCI at each data entry time point (at the start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after the start of Nesina treatment or treatment discontinuation). In addition, the Investigator will sign electronically on the survey sheet in CCI for "Patient Demographic Data and Details of Treatment by 12 Months of Treatment" after 12 months of treatment and for Patient Demographic Data and Details of Treatment by 36 Months of Treatment" after 36 months of treatment.

For patients who discontinue treatment with Nesina during the observation period for any reason, the Investigator will enter the patient demographic data and details of treatment on CCI and will sign electronically in the survey sheet around within 1 month after the end of necessary observation. However, for patients who discontinue treatment with Nesina due to an adverse event, the Investigator will continue observation after treatment discontinuation, wherever possible, until the adverse event resolve or is resolving and will enter the observation results on CCI as well as sign electronically in the survey sheet.
In case that additional survey is required after Takeda checked the details, Takeda will ask request for re-survey on CCI The Investigator will check the details of request for re-survey and enter the re-survey results on CCI as well as sign electronically in the survey sheet.

7.5 Measures for Development of Adverse Events

In case of development of an adverse event, the Investigator will contact the person in charge of Takeda Pharmaceutical Company Limited (hereinafter, the person in charge of Takeda). If the person in charge of Takeda requests additional detailed information, the Investigator will provide it.

8.0 Scheduled Survey Period

Survey period: July 2011 to January 31, 2017
Patient registration period: July 2011 to July 31, 2013[Note)]
Due date for entry of "Patient Data and Details of Treatment by 12 Months of Treatment:" August 31, 2014
Due date for entry of "Patient Data and Details of Treatment by 36 Months of Treatment:" August 31, 2016

[Note)] Patients who will be treated with Nesina by July 31, 2013 can be registered.
In case that the registered patients reach the scheduled number of patients to be surveyed before July 31 2013, the registration will close earlier than scheduled.

9.0 Matters to be Surveyed

The Investigator will enter data of the parameters described below on CCI The schedule of this surveillance is shown in the Appendix.

9.1 Patient Registration Data

1) Matters to be surveyed
Start date of Nesina treatment, Patient ID Number, patient initial, sex, birth date, HbA1c (JDS) within 3 months prior to Nesina treatment, inclusion criteria assessment, and exclusion criteria assessment

2) Survey period
At patient registration

9.2 Survey sheet: patient demographic data

1) Matters to be surveyed

Diagnosis period of type 2 diabetes mellitus, height, practice category (at the start of survey), presence or absence of pregnancy (females only), pregnancy week (if applicable), severity of renal impairment, rationale for assessment of the severity of renal impairment, concurrent disease, prior medical history, alcohol history, smoking history, and presence or absence of dietary intervention / exercise intervention

2) Survey period

At the start of Nesina treatment

9.3 Survey sheet: details of treatment

1) Matters to be surveyed

Details of Nesina treatment (daily dose and administration period), status of end of Nesina treatment, reason for Nesina discontinuation (if applicable), details of other diabetic drug treatment* (drug name, daily dose, route of administration, and administration period), and status of concomitant medications (other than diabetic drugs) (drug name, route of administration, administration period, and objectives of administration)

* Diabetic drugs which are discontinued within 3 months prior to Nesina treatment are included.

2) Survey period

Period from the start of Nesina treatment to 36 months after treatment (or treatment discontinuation)

9.4 Laboratory/Observation Parameters

1) Matters to be surveyed

HbA1c (JDS, international standard value, or NGSP), fasting glucose, fasting insulin, fasting triglyceride, total cholesterol," HDL-cholesterol, LDL-cholesterol, weight, and blood pressure

2) Survey period

At the start of Nesina treatment, 3 months , 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months of treatment (or treatment discontinuation)

9.5 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), procedures related to Nesina, outcome, causal relationship to Nesina (refer to Table 3), presence or absence of diabetic complication (diabetic retinopathy, diabetic neuropathy, or diabetic nephropathy), change over time in clinically important laboratory values related to adverse events

If the outcome is assessed as Not resolved or Unknown and if the causal relationship cannot

be assessed, the patient will be followed up, wherever possible. The detailed information (clinical course, laboratory tests for diagnosis, etc.) will be collected as possible for development of hypoglycemia, tumor, pancreatitis, edema, angioedema-related symptom, immune system disorder, skin disorder and subcutaneous tissue disorder, cardiovascular system event (symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death, etc.)

2) Survey period

Period from the start of Nesina treatment to 36 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 in infants breastfed by a Nesina taking mother • Symptoms in children who received the relevant drug • Symptoms in patients who received the relevant drug at a higher dose than approved or who took by themselves

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. (e.g., bronchospasm and the like, requiring a short-term intensive care in an emergency room and the like)

Takeda Medically Significant AE List

- Acute respiratory failure / acute respiratory distress syndrome (ARDS)
- Torsade de pointes / ventricular fibrillation / ventricular tachycardia
- Malignant hypertension
- Convulsive seizure (including convulsion and epilepsy)
- Agranulocytosis
- Aplastic anemia
- Toxic epidermal necrolysis / oculomucocutaneous syndrome (Stevens-Johnson syndrome)
- Hepatic necrosis
- Acute hepatic failure
- Anaphylactic shock
- Acute renal failure
- Pulmonary hypertension
- Pulmonary fibrosis (including interstitial pneumonia)
- Malignant syndrome / malignant hyperthermia
- Spontaneous abortion / stillbirth and fetal death
- 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 (Suspectedly related)	Temporally evident 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 (Unlikely related)	No temporally evident 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 registered patients, number of survey sheet (electronic) collected patients, number of survey completer, number of survey discontinuations and the reason for discontinuation, 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

The following patient demographics will be tabulated: age, sex, disease period, severity of renal impairment (including severity) (yes or no), concurrent disease, past medical history, alcohol history, smoking history, etc.

10.3 Details of Treatment

The following will be tabulated: status of Nesina treatment, status of concomitant medications (including the status of diabetic drugs at the start of 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 and summarized by Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Occurrence of Adverse Drug Reactions

The type, seriousness, onset period, and the like for adverse drug reactions reported in the observation period 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., age, sex), 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 Changes in HbA1c over Time

The HbA1c values at each time point and the changes (values at each time point − values at the start of Nesina treatment) will be tabulated. The achieving percent in glycemic control for HbA1c will be tabulated for each time point.

10.5.2 Factors Probably Affecting Efficacy

For the changes in HbA1c and the achieving percent in glycemic control for HbA1c at 36 months after the start of treatment, the following will be stratified: patients demographics

(e.g., age, sex, 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

For the safety and efficacy in patients with moderate or higher renal impairment, the relationship between the severity of renal impairment and Nesina doses (each will be stratified) will be thoroughly evaluated.

10.7 Interim Analysis

After 1-year observation period is completed in all patients, the interim analysis for the parameters described in Sections 10.1 to 10.6 will be performed to confirm the early safety and efficacy of Nesina in patients with mild type 2 diabetes mellitus, based on the data entered in "Patient Data and Details of Treatment by 12 Months of Treatment."

11.0 Surveillance Organizations

11.1 Investigator

PPD Takeda Pharmaceutical Company Limited.

12.0 Name and address of CRO and Scope of the CRO Task

PPD

13.0 Other Necessary Matters

13.1 Revision of the Protocol

During the surveillance period, the protocol can be reviewed and revised, if the following are necessary to be changed after monitored: the survey progress, number of dropouts, development of 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 surveillance period, if partly changes of dosage and administration and indications are approved, the protocol revision will be also considered and performed as necessary.

13.2 Measures for Issues or Questions

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

Appendix Surveillance Schedule

Survey/data entry time point / Parameters		Observation period									
		At patient registration	At start of treatment	3 months after treatment	6 months after treatment	12 months after treatment	18 months after treatment	24 months after treatment	30 months after treatment	36 months after treatment	At treatment discontinuation
Patient registration data	Start date of Nesina tablets	X									
	Patient ID Number	X									
	Patients initial	X									
	Sex	X									
	Birth date	X									
	HbA1c within 3 months prior to Nesina treatment	X									
	Inclusion criteria / exclusion criteria	X									
Patient demographic data	Diagnosis period of type 2 diabetes mellitus		X								
	Height		X								
	Category of clinical practice (at start of survey)		X								
	Pregnancy (yes or no) (females only)		X								
	Week of pregnancy (if applicable)		X								
	Severity of renal impairment		X								
	Rationale for severity assessment of renal impairment		X								
	Concurrent disease		X								
	Past medical history		X								
	Alcohol history		X								
	Smoking history		X								
	Dietary/exercise intervention (yes or no)		X								
Details of treatment	Status of Nesina tablet treatment		←				X				→
	Other diabetic drug		←				X				→
	Concomitant medication (other than diabetic drugs)		←				X				→
Laboratory/Observation Parameters, etc	Laboratory values • HbA1c (JDS, international standard value, or NGSP) • Fasting glucose • Fasting insulin • Fasting triglyceride • Total cholesterol • HDL-cholesterol • LDL-cholesterol		X	X	X	X	X	X	X	X	X
	Weight		X	X	X	X	X	X	X	X	X
	Blood pressure		X	X	X	X	X	X	X	X	X
	Adverse event		←				X				→

Protocol for

Nesina Tablets Special Drug Use Surveillance: Mild Type 2 Diabetes Mellitus

Version	**Second version**
Creation date	**February 24, 2012**
Sponsor	**Takeda Pharmaceutical Company Limited.**

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1.0 Surveillance Background

The goal of diabetes mellitus treatment is to maintain patients' QOLs as those in healthy people and to secure their lifetimes through management for a favorable blood glucose level for a long time. In particular, early drug treatment is considered important for patients with mild type 2 diabetes mellitus, which maintains a favorable blood glucose level and inhibits the diabetes progress, along with prevention of microangiopathy.

As an oral drug started to be administered early to patients with mild type 2 diabetes mellitus, the desirable drug should have a low risk of hypoglycemia, be well tolerable, and not exhaust pancreatic function.

DPP-4 inhibitors selectively inhibit DPP-4, increase blood GLP-1 levels, and prompt the pancreas to secrete insulin in a glucose level-dependent manner. Taken together, DPP-4 inhibitors are expected to be highly effective for patients with mild type 2 diabetes mellitus.

As a DPP-4 inhibitor, Nesina tablets (generic name: alogliptin benzoate) are confirmed to be highly effective and safe when administered alone and combined with various oral diabetic drugs in clinical studies conducted in Japan. The following are approved indications for Nesina:

Indications for Nesina tablets

Type 2 diabetes mellitus

However, this indication is limited only for patients who had an insufficient response to the following therapies:

(1) Only diet and exercise therapies.
(2) α-glucosidase inhibitors used in addition to diet and exercise therapies.
(3) Thiazolidines used in addition to diet and exercise therapies.
(4) Sulfonylureas used in addition to diet and exercise therapies.
(5) Biguanides used in addition to diet and exercise therapies.

However, the efficacy and safety of Nesina has not been well evaluated for patients with mild type 2 diabetes mellitus because Nesina tablets have been administered to type 2 diabetes mellitus patients with HbA1c of ≥ 6.5% (for patients treated with sulfonylureas, HbA1c of ≥ 7.0%) in clinical studies conducted before drug approval.

Therefore, this Special Drug Use Surveillance (hereinafter, the Surveillance) was planned to evaluate the long-term safety and efficacy of Nesina tablets (hereinafter, Nesina) for patients with mild type 2 diabetes mellitus patients in a daily clinical practice.

2.0 Objectives of Surveillance

To examine the safety and efficacy of long-term treatment with alogliptin (Nesina) in patients with mild type 2 diabetes mellitus in the routine clinical setting.

3.0 Number of Planned Patients for Surveillance and the Rationales

3.1 Number of Planned Patients for Surveillance

20000 patients

3.2 Rationales

According to database of 16 hospitals in Japan, supplied by PPD of 142358 patients documented as visited from October to December 2010, 15141 were patients with type 2 diabetes mellitus. Of these, 4165 patients had HbA1c (JDS) of ≤ 7.0%, which were the target population in this Surveillance. For patients with indications for Nesina, in addition, 1864 patients (70.4%) received only diet and exercise therapies (no diabetic drugs); 226 patients (8.5%) received α-glucosidase inhibitors; 175 patients (6.6%) received thiazolidines; 273 patients (10.3%) received sulfonylureas; 109 patients (4.1%) received biguanides (each drug was administered alone).

In order to identify adverse drug reactions with a frequency of ≥ 0.5% using ≥ a 95% confidence level, 600 patients will be required. Assuming that the proportion of drugs in patients with mild type 2 diabetes mellitus is same as the above, if data in 20000 patients with mild type 2 diabetes mellitus are collected in this Surveillance, 14084 patients will be required for Nesina treatment alone; 1708 patients will be required for combination with α-glucosidase inhibitors; 1322 patients will be required for combination with thiazolidines; 2063 patients will be required for combination with sulfonylureas; 824 patients will be required for combination with biguanides. Since any combination can identify the adverse drug reactions with a frequency of ≥ 0.5% using ≥ a 95% confidence level, the number of planned patients for surveillance was established as 20000.

4.0 Patients for Surveillance

Patients with mild type 2 diabetes mellitus will be evaluated for this Surveillance. However, patients must meet the inclusion criteria and none of the exclusion criteria, described below. Refer to the Precaution with Respect to Indication in the package insert.

4.1 Inclusion Criteria

Patients who meet the following criterion will be included in this Surveillance:

(1) Patients with HbA1c (JDS value) ≤7.0% at the time of enrolment (within 3 months before initiation of Nesina therapy)

* Regardless of the use of antidiabetic medication

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from this Surveillance:

(1) Patients with severe ketosis, diabetic coma or precoma, or type 1 diabetes mellitus

(2) Patients with severe infection, pre- or post-operative patients, or patients with serious traumatic injury

(3) Patients with a history of hypersensitivity to any ingredient of Nesina

5.0 Dosage and Administration for Patients to be Surveyed

The usual adult dose of alogliptin is 25 mg administered orally once daily. Refer to the Precaution with Respect to Dosage and Administration in the package insert.

6.0 Number of To-be Survey Sites by Department

Internal medicine or other department: Approximately 1000 sites

7.0 Survey Methods

7.1 Observation Period

The observation period will be 36 months after the start date of Nesina treatment.

If Nesina treatment is discontinued for any reason, the survey will be ended at the discontinuation.

7.2 Request for Sites and Agreement

This surveillance will be conducted using the electronic data collection system via web CCI. Before asking survey, MRs of Takeda Takeda Pharmaceutical Company Limited. (Hereinafter, Takeda MRs) will fully explain to the Investigator about the objectives, details, handling methods for CCI and handling of electronic signature, user ID, and passwords, based on "Request for Cooperation of Special Drug Use Surveillance," "Summary for Surveillance," "Entry Screen Images," and "Brief Manual for Handling of CCI and will finalize written agreement with survey sites to ask requests for surveillance within the specified period.

7.3 Methods for Registration of Patients to be Surveyed

This Surveillance will be conducted using Central Registration System with CCI The Investigator will enter registration data on CCI (refer to Section 9.1) for patients who start Nesina treatment after the start date of agreement with a survey site, before 14 days after the start date of Nesina treatment (define the start date of treatment as "0 day" and one day after the start date of treatment as "1 day").

7.4 Entry on Survey Sheet (Electronic) and Electronic Signature

The Investigator will enter patient demographic data and details of treatment on CCI at each data entry time point (at the start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after the start of Nesina treatment or treatment discontinuation). In addition, the Investigator will sign electronically on the survey sheet in CCI for "Patient Demographic Data and Details of Treatment by 12 Months of Treatment" after 12 months of treatment and for Patient Demographic Data and Details of Treatment by 36 Months of Treatment" after 36 months of treatment.

For patients who discontinue treatment with Nesina during the observation period for any reason, the Investigator will enter the patient demographic data and details of treatment on CCI and will sign electronically in the survey sheet around within 1 month after the end of necessary observation. However, for patients who discontinue treatment with Nesina due to an adverse event, the Investigator will continue observation after treatment discontinuation, wherever possible, until the adverse event resolve or is resolving and will enter the observation results on CCI as well as sign electronically in the survey sheet.
In case that additional survey is required after Takeda checked the details, Takeda will ask request for re-survey on CCI The Investigator will check the details of request for re-survey and enter the re-survey results on CCI as well as sign electronically in the survey sheet.

7.5 Measures for Development of Adverse Events

In case of development of an adverse event, the Investigator will contact the Takeda MR. If the Takeda MR requests additional detailed information, the Investigator will provide it.

8.0 Scheduled Survey Period

Survey period: July 2011 to January 31, 2017
Patient registration period: July 2011 to July 31, 2013[Note)]
Due date for entry of "Patient Data and Details of Treatment by 12 Months of Treatment:" August 31, 2014
Due date for entry of "Patient Data and Details of Treatment by 36 Months of Treatment:" August 31, 2016

[Note)] Patients who will be treated with Nesina by July 31, 2013 can be registered.
In case that the registered patients reach the scheduled number of patients to be surveyed before July 31 2013, the registration will close earlier than scheduled.

9.0 Matters to be Surveyed

The Investigator will enter data of the parameters described below on CCI The schedule of this surveillance is shown in the Appendix.

9.1 Patient Registration Data

1) Matters to be surveyed

Start date of Nesina treatment, Patient ID Number, patient initial, sex, birth date, HbA1c (JDS) within 3 months prior to Nesina treatment, inclusion criteria assessment, and exclusion criteria assessment

2) Survey period

At patient registration

9.2 Survey sheet: patient demographic data

1) Matters to be surveyed

Diagnosis period of type 2 diabetes mellitus, height, practice category (at the start of survey), presence or absence of pregnancy (females only), pregnancy week (if applicable), severity of renal impairment, rationale for assessment of the severity of renal impairment, concurrent disease, prior medical history, alcohol history, smoking history, and presence or absence of dietary intervention / exercise intervention

2) Survey period

At the start of Nesina treatment

9.3 Survey sheet: details of treatment

1) Matters to be surveyed

Details of Nesina treatment (daily dose and administration period), status of end of Nesina treatment, reason for Nesina discontinuation (if applicable), details of other diabetic drug treatment* (drug name, daily dose, route of administration, and administration period), and status of concomitant medications (other than diabetic drugs) (drug name, route of administration, administration period, and objectives of administration)

* Diabetic drugs which are discontinued within 3 months prior to Nesina treatment are included.

2) Survey period

Period from the start of Nesina treatment to 36 months after treatment (or treatment discontinuation)

9.4 Laboratory/Observation Parameters

1) Matters to be surveyed

HbA1c (JDS, international standard value, or NGSP), fasting glucose, fasting insulin, fasting triglyceride, total cholesterol," HDL-cholesterol, LDL-cholesterol, weight, and blood pressure

2) Survey period

At the start of Nesina treatment, 3 months , 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months of treatment (or treatment discontinuation)

9.5 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), procedures related to Nesina, outcome, causal relationship to Nesina (refer to Table 3), presence or absence of diabetic complication (diabetic retinopathy, diabetic neuropathy, or diabetic nephropathy), change over time in clinically important laboratory values related to adverse events

If the outcome is assessed as Not resolved or Unknown and if the causal relationship cannot be assessed, the patient will be followed up, wherever possible. The detailed information (clinical course, laboratory tests for diagnosis, etc.) will be collected as possible for

development of hypoglycemia, tumor, pancreatitis, edema, angioedema-related symptom, immune system disorder, skin disorder and subcutaneous tissue disorder, cardiovascular system event (symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death, etc.)

2) Survey period

Period from the start of Nesina treatment to 36 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 in infants breastfed by a Nesina taking mother • Symptoms in children who received the relevant drug • Symptoms in patients who received the relevant drug at a higher dose than approved or who took by themselves

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. (e.g., bronchospasm and the like, requiring a short-term intensive care in an emergency room and the like)

Takeda Medically Significant AE List

- Acute respiratory failure / acute respiratory distress syndrome (ARDS)
- Torsade de pointes / ventricular fibrillation / ventricular tachycardia
- Malignant hypertension
- Convulsive seizure (including convulsion and epilepsy)
- Agranulocytosis
- Aplastic anemia
- Toxic epidermal necrolysis / oculomucocutaneous syndrome (Stevens-Johnson syndrome)
- Hepatic necrosis
- Acute hepatic failure
- Anaphylactic shock
- Acute renal failure
- Pulmonary hypertension
- Pulmonary fibrosis (including interstitial pneumonia)
- Malignant syndrome / malignant hyperthermia
- Spontaneous abortion / stillbirth and fetal death
- 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 (Suspectedly related)	Temporally evident 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 (Unlikely related)	No temporally evident 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 registered patients, number of survey sheet (electronic) collected patients, number of survey completer, number of survey discontinuations and the reason for discontinuation, 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

The following patient demographics will be tabulated: age, sex, disease period, severity of renal impairment (including severity) (yes or no), concurrent disease, past medical history, alcohol history, smoking history, etc.

10.3 Details of Treatment

The following will be tabulated: status of Nesina treatment, status of concomitant medications (including the status of diabetic drugs at the start of 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 and summarized by Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Occurrence of Adverse Drug Reactions

The type, seriousness, onset period, and the like for adverse drug reactions reported in the observation period 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., age, sex), 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 Changes in HbA1c over Time

The HbA1c values at each time point and the changes (values at each time point − values at the start of Nesina treatment) will be tabulated. The achieving percent in glycemic control for HbA1c will be tabulated for each time point.

10.5.2 Factors Probably Affecting Efficacy

For the changes in HbA1c and the achieving percent in glycemic control for HbA1c at 36 months after the start of treatment, the following will be stratified: patients demographics (e.g., age, sex, 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

For the safety and efficacy in patients with moderate or higher renal impairment, the relationship between the severity of renal impairment and Nesina doses (each will be stratified) will be thoroughly evaluated.

10.7 Interim Analysis

After 1-year observation period is completed in all patients, the interim analysis for the parameters described in Sections 10.1 to 10.6 will be performed to confirm the early safety and efficacy of Nesina in patients with mild type 2 diabetes mellitus, based on the data entered in “Patient Data and Details of Treatment by 12 Months of Treatment.”

11.0 Surveillance Organizations

11.1 Investigator

PPD Takeda Pharmaceutical Company Limited.

PPD

11.2 Medical Expert

PPD

12.0 Name and address of CRO and Scope of the CRO Task

PPD

13.0 Other Necessary Matters

13.1 Revision of the Protocol

During the surveillance period, the protocol can be reviewed and revised, if the following are necessary to be changed after monitored: the survey progress, number of dropouts, development of 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 surveillance period, if partly changes of dosage and

administration and indications are approved, the protocol revision will be also considered and performed as necessary.

13.2 Measures for Issues or Questions

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

Appendix Surveillance Schedule

Parameters		Survey/data entry time point: At patient registration	At start of treatment	3 months after treatment	6 months after treatment	12 months after treatment	18 months after treatment	24 months after treatment	30 months after treatment	36 months after treatment	At treatment discontinuation
		Observation period									
Patient registration data	Start date of Nesina tablets	X									
	Patient ID Number	X									
	Patients initial	X									
	Sex	X									
	Birth date	X									
	HbA1c within 3 months prior to Nesina treatment	X									
	Inclusion criteria / exclusion criteria	X									
Patient demographic data	Diagnosis period of type 2 diabetes mellitus		X								
	Height		X								
	Category of clinical practice (at start of survey)		X								
	Pregnancy (yes or no) (females only)		X								
	Week of pregnancy (if applicable)		X								
	Severity of renal impairment		X								
	Rationale for severity assessment of renal impairment		X								
	Concurrent disease		X								
	Past medical history		X								
	Alcohol history		X								
	Smoking history		X								
	Dietary/exercise intervention (yes or no)		X								
Details of treatment	Status of Nesina tablet treatment		← X →								
	Other diabetic drug		← X →								
	Concomitant medication (other than diabetic drugs)		← X →								
Laboratory/Observation Parameters, etc	Laboratory values • HbA1c (JDS, international standard value, or NGSP) • Fasting glucose • Fasting insulin • Fasting triglyceride • Total cholesterol • HDL-cholesterol • LDL-cholesterol		X	X	X	X	X	X	X	X	X
	Weight		X	X	X	X	X	X	X	X	X
	Blood pressure		X	X	X	X	X	X	X	X	X
	Adverse event		← X →								

Protocol for

Nesina Tablets Special Drug Use Surveillance: Mild Type 2 Diabetes Mellitus

Version	**First version**
Creation date	**June 22, 2011**
Sponsor	**Takeda Pharmaceutical Company Limited.**

Table of Contents

1.0 Surveillance Background

The goal of diabetes mellitus treatment is to maintain patients' QOLs as those in healthy people and to secure their lifetimes through management for a favorable blood glucose level for a long time. In particular, early drug treatment is considered important for patients with mild type 2 diabetes mellitus, which maintains a favorable blood glucose level and inhibits the diabetes progress, along with prevention of microangiopathy.

As an oral drug started to be administered early to patients with mild type 2 diabetes mellitus, the desirable drug should have a low risk of hypoglycemia, be well tolerable, and not exhaust pancreatic function.

DPP-4 inhibitors selectively inhibit DPP-4, increase blood GLP-1 levels, and prompt the pancreas to secrete insulin in a glucose level-dependent manner. Taken together, DPP-4 inhibitors are expected to be highly effective for patients with mild type 2 diabetes mellitus.

As a DPP-4 inhibitor, Nesina tablets (generic name: alogliptin benzoate) are confirmed to be highly effective and safe when administered alone and combined with various oral diabetic drugs in clinical studies conducted in Japan. The following are approved indications for Nesina:

Indications for Nesina tablets

Type 2 diabetes mellitus

However, this indication is limited only for patients who had an insufficient response to the following therapies:

(1) Only diet and exercise therapies.
(2) α-glucosidase inhibitors used in addition to diet and exercise therapies.
(3) Thiazolidines used in addition to diet and exercise therapies.
(4) Sulfonylureas used in addition to diet and exercise therapies.
(5) Biguanides used in addition to diet and exercise therapies.

However, the efficacy and safety of Nesina has not been well evaluated for patients with mild type 2 diabetes mellitus because Nesina tablets have been administered to type 2 diabetes mellitus patients with HbA1c of ≥ 6.5% (for patients treated with sulfonylureas, HbA1c of ≥ 7.0%) in clinical studies conducted before drug approval.

Therefore, this Special Drug Use Surveillance (hereinafter, the Surveillance) was planned to evaluate the long-term safety and efficacy of Nesina tablets (hereinafter, Nesina) for patients with mild type 2 diabetes mellitus patients in a daily clinical practice.

2.0 Objectives of Surveillance

To examine the safety and efficacy of long-term treatment with alogliptin (Nesina) in patients with mild type 2 diabetes mellitus in the routine clinical setting.

3.0 Number of Planned Patients for Surveillance and the Rationales

3.1 Number of Planned Patients for Surveillance

20000 patients

3.2 Rationales

According to database of 16 hospitals in Japan, supplied by PPD of 142358 patients documented as visited from October to December 2010, 15141 were patients with type 2 diabetes mellitus. Of these, 4165 patients had HbA1c (JDS) of ≤ 7.0%, which were the target population in this Surveillance. For patients with indications for Nesina, in addition, 1864 patients (70.4%) received only diet and exercise therapies (no diabetic drugs); 226 patients (8.5%) received α-glucosidase inhibitors; 175 patients (6.6%) received thiazolidines; 273 patients (10.3%) received sulfonylureas; 109 patients (4.1%) received biguanides (each drug was administered alone).

In order to identify adverse drug reactions with a frequency of ≥ 0.5% using ≥ a 95% confidence level, 600 patients will be required. Assuming that the proportion of drugs in patients with mild type 2 diabetes mellitus is same as the above, if data in 20000 patients with mild type 2 diabetes mellitus are collected in this Surveillance, 14084 patients will be required for Nesina treatment alone; 1708 patients will be required for combination with α-glucosidase inhibitors; 1322 patients will be required for combination with thiazolidines; 2063 patients will be required for combination with sulfonylureas; 824 patients will be required for combination with biguanides. Since any combination can identify the adverse drug reactions with a frequency of ≥ 0.5% using ≥ a 95% confidence level, the number of planned patients for surveillance was established as 20000.

4.0 Patients for Surveillance

Patients with mild type 2 diabetes mellitus will be evaluated for this Surveillance. However, patients must meet the inclusion criteria and none of the exclusion criteria, described below. Refer to the Precaution with Respect to Indication in the package insert.

4.1 Inclusion Criteria

Patients who meet the following criterion will be included in this Surveillance:

(1) Patients with HbA1c (JDS value) ≤7.0% at the time of enrolment (within 3 months before initiation of Nesina therapy)

* Regardless of the use of antidiabetic medication

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from this Surveillance:

(1) Patients with severe ketosis, diabetic coma or precoma, or type 1 diabetes mellitus

(2) Patients with severe infection, pre- or post-operative patients, or patients with serious traumatic injury

(3) Patients with a history of hypersensitivity to any ingredient of Nesina

5.0 Dosage and Administration for Patients to be Surveyed

The usual adult dose of alogliptin is 25 mg administered orally once daily. Refer to the Precaution with Respect to Dosage and Administration in the package insert.

6.0 Number of To-be Survey Sites by Department

Internal medicine or other department: Approximately 1000 sites

7.0 Survey Methods

7.1 Observation Period

The observation period will be 36 months after the start date of Nesina treatment.

If Nesina treatment is discontinued for any reason, the survey will be ended at the discontinuation.

7.2 Request for Sites and Agreement

This surveillance will be conducted using the electronic data collection system via web [CCI redacted] Before asking survey, MRs of Takeda Takeda Pharmaceutical Company Limited. (Hereinafter, Takeda MRs) will fully explain to the Investigator about the objectives, details, handling methods for [CCI redacted], and handling of electronic signature, user ID, and passwords, based on "Request for Cooperation of Special Drug Use Surveillance," "Summary for Surveillance," "Entry Screen Images," and "Brief Manual for Handling of [CCI redacted] and will finalize written agreement with survey sites to ask requests for surveillance within the specified period.

7.3 Methods for Registration of Patients to be Surveyed

This Surveillance will be conducted using Central Registration System with [CCI redacted]. The Investigator will enter registration data on [CCI redacted] (refer to Section 9.1) for patients who start Nesina treatment after the start date of agreement with a survey site, before 14 days after the start date of Nesina treatment (define the start date of treatment as "0 day" and one day after the start date of treatment as "1 day").

7.4 Entry on Survey Sheet (Electronic) and Electronic Signature

The Investigator will enter patient demographic data and details of treatment on [CCI redacted] at each data entry time point (at the start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after the start of Nesina treatment or treatment discontinuation). In addition, the Investigator will sign electronically on the survey sheet in [CCI redacted] for "Patient Demographic Data and Details of Treatment by 12 Months of Treatment" after 12 months of treatment and for Patient Demographic Data and Details of Treatment by 36 Months of Treatment" after 36 months of treatment.

For patients who discontinue treatment with Nesina during the observation period for any reason, the Investigator will enter the patient demographic data and details of treatment on CCI and will sign electronically in the survey sheet around within 1 month after the end of necessary observation. However, for patients who discontinue treatment with Nesina due to an adverse event, the Investigator will continue observation after treatment discontinuation, wherever possible, until the adverse event resolve or is resolving and will enter the observation results on CCI as well as sign electronically in the survey sheet.
In case that additional survey is required after Takeda checked the details, Takeda will ask request for re-survey on CCI. The Investigator will check the details of request for re-survey and enter the re-survey results on CCI as well as sign electronically in the survey sheet.

7.5 Measures for Development of Adverse Events

In case of development of an adverse event, the Investigator will contact the Takeda MR. If the Takeda MR requests additional detailed information, the Investigator will provide it.

8.0 Scheduled Survey Period

Survey period: July 2011 to January 31, 2017
Patient registration period: July 2011 to July 31, 2013[Note)]
Due date for entry of "Patient Data and Details of Treatment by 12 Months of Treatment:" August 31, 2014
Due date for entry of "Patient Data and Details of Treatment by 36 Months of Treatment:" August 31, 2016

[Note)] Patients who will be treated with Nesina by July 31, 2013 can be registered.
In case that the registered patients reach the scheduled number of patients to be surveyed before July 31 2013, the registration will close earlier than scheduled.

9.0 Matters to be Surveyed

The Investigator will enter data of the parameters described below on CCI The schedule of this surveillance is shown in the Appendix.

9.1 Patient Registration Data

1) Matters to be surveyed

Start date of Nesina treatment, Patient ID Number, patient initial, sex, birth date, HbA1c (JDS) within 3 months prior to Nesina treatment, inclusion criteria assessment, and exclusion criteria assessment

2) Survey period

At patient registration

9.2 Survey sheet: patient demographic data

1) Matters to be surveyed

Diagnosis period of type 2 diabetes mellitus, height, practice category (at the start of survey), presence or absence of pregnancy (females only), pregnancy week (if applicable), severity of renal impairment, rationale for assessment of the severity of renal impairment, concurrent disease, prior medical history, alcohol history, smoking history, and presence or absence of dietary intervention / exercise intervention

2) Survey period

At the start of Nesina treatment

9.3 Survey sheet: details of treatment

1) Matters to be surveyed

Details of Nesina treatment (daily dose and administration period), status of end of Nesina treatment, reason for Nesina discontinuation (if applicable), details of other diabetic drug treatment* (drug name, daily dose, route of administration, and administration period), and status of concomitant medications (other than diabetic drugs) (drug name, route of administration, administration period, and objectives of administration)

* Diabetic drugs which are discontinued within 3 months prior to Nesina treatment are included.

2) Survey period

Period from the start of Nesina treatment to 36 months after treatment (or treatment discontinuation)

9.4 Laboratory/Observation Parameters

1) Matters to be surveyed

HbA1c (JDS or international standard value), fasting glucose, fasting insulin, fasting triglyceride, total cholesterol," HDL-cholesterol, LDL-cholesterol, weight, and blood pressure

2) Survey period

At the start of Nesina treatment, 3 months , 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months of treatment (or treatment discontinuation)

9.5 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), procedures related to Nesina, outcome, causal relationship to Nesina (refer to Table 3), presence or absence of diabetic complication (diabetic retinopathy, diabetic neuropathy, or diabetic nephropathy), change over time in clinically important laboratory values related to adverse events

If the outcome is assessed as Not resolved or Unknown and if the causal relationship cannot be assessed, the patient will be followed up, wherever possible. The detailed information (clinical course, laboratory tests for diagnosis, etc.) will be collected as possible for

development of hypoglycemia, tumor, pancreatitis, edema, angioedema-related symptom, immune system disorder, skin disorder and subcutaneous tissue disorder, cardiovascular system event (symptomatic coronary artery disease, cerebrovascular disorder, arteriosclerosis obliterans, cardiovascular death, sudden death, etc.)

2) Survey period

Period from the start of Nesina treatment to 36 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 in infants breastfed by a Nesina taking mother • Symptoms in children who received the relevant drug • Symptoms in patients who received the relevant drug at a higher dose than approved or who took by themselves

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. (e.g., bronchospasm and the like, requiring a short-term intensive care in an emergency room and the like)

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

Table 3 Criteria for causality assessment between adverse events and Nesina

Assessment	Assessment criterion
Related (Suspectedly related)	Temporally evident 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 (Unlikely related)	No temporally evident 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 registered patients, number of survey sheet (electronic) collected patients, number of survey completer, number of survey discontinuations and the reason for discontinuation, 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

The following patient demographics will be tabulated: age, sex, disease period, severity of renal impairment (including severity) (yes or no), concurrent disease, past medical history, alcohol history, smoking history, etc.

10.3 Details of Treatment

The following will be tabulated: status of Nesina treatment, status of concomitant medications (including the status of diabetic drugs at the start of 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 and summarized by Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Occurrence of Adverse Drug Reactions

The type, seriousness, onset period, and the like for adverse drug reactions reported in the observation period 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., age, sex), 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 Changes in HbA1c over Time

The HbA1c values at each time point and the changes (values at each time point − values at the start of Nesina treatment) will be tabulated. The achieving percent in glycemic control for HbA1c will be tabulated for each time point.

10.5.2 Factors Probably Affecting Efficacy

For the changes in HbA1c and the achieving percent in glycemic control for HbA1c at 36 months after the start of treatment, the following will be stratified: patients demographics

(e.g., age, sex, 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

For the safety and efficacy in patients with moderate or higher renal impairment, the relationship between the severity of renal impairment and Nesina doses (each will be stratified) will be thoroughly evaluated.

10.7 Interim Analysis

After 1-year observation period is completed in all patients, the interim analysis for the parameters described in Sections 10.1 to 10.6 will be performed to confirm the early safety and efficacy of Nesina in patients with mild type 2 diabetes mellitus, based on the data entered in "Patient Data and Details of Treatment by 12 Months of Treatment."

11.0 Surveillance Organizations

11.1 Investigator

PPD Takeda Pharmaceutical Company Limited.

PPD

11.2 Medical Expert

PPD

12.0 Name and address of CRO and Scope of the CRO Task

PPD

13.0 Other Necessary Matters

13.1 Revision of the Protocol

During the surveillance period, the protocol can be reviewed and revised, if the following are necessary to be changed after monitored: the survey progress, number of dropouts, development of 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 surveillance period, if partly changes of dosage and administration and indications are approved, the protocol revision will be also considered and performed as necessary.

13.2 Measures for Issues or Questions

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

Appendix Surveillance Schedule

Parameters \ Survey/data entry time point		Observation period									
		At patient registration	At start of treatment	3 months after treatment	6 months after treatment	12 months after treatment	18 months after treatment	24 months after treatment	30 months after treatment	36 months after treatment	At treatment discontinuation
Patient registration data	Start date of Nesina tablets	X									
	Patient ID Number	X									
	Patients initial	X									
	Sex	X									
	Birth date	X									
	HbA1c within 3 months prior to Nesina treatment	X									
	Inclusion criteria / exclusion criteria	X									
Patient demographic data	Diagnosis period of type 2 diabetes mellitus		X								
	Height		X								
	Category of clinical practice (at start of survey)		X								
	Pregnancy (yes or no) (females only)		X								
	Week of pregnancy (if applicable)		X								
	Severity of renal impairment		X								
	Rationale for severity assessment of renal impairment		X								
	Concurrent disease		X								
	Past medical history		X								
	Alcohol history		X								
	Smoking history		X								
	Dietary/exercise intervention (yes or no)		X								
Details of treatment	Status of Nesina tablet treatment		← X →								
	Other diabetic drug		← X →								
	Concomitant medication (other than diabetic drugs)		← X →								
Laboratory/Observation Parameters, etc	Laboratory values • HbA1c (JDS or international standard value) • Fasting glucose • Fasting insulin • Fasting triglyceride • Total cholesterol • HDL-cholesterol • LDL-cholesterol		X	X	X	X	X	X	X	X	X
	Weight		X	X	X	X	X	X	X	X	X
	Blood pressure		X	X	X	X	X	X	X	X	X
	Adverse event		← X →								