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# Post Marketing Surveillance Protocol for Nesina® Tablet

## 「Monotherapy or Combination Therapy in Type 2 Diabetic Patients」



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**Compound:** Nesina Tab.(Alogliptin Benzoate)

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# 1. Background

Nesina Tablet is therapy used to help control glucose in patients with type 2 diabetes, which is featured by its mechanism of action by inhibiting dipeptidyl peptidase-4(hereafter, DPP-4) of inactivating glucagon-like peptide-1(hereafter, GLP-1), one of incretin hormones, leading to elevated blood level of GLP-1 and promoting insulin secretion in the pancrease in a glucose level-dependent way. The clinical uses of oral anti-hyperglycemic agents require a long term by their nature, and accordingly, before anything else, it is important to obtain broad use information in actual clinical practices. In this aspect, this Post Marketing Surveillance(hereafter, the PMS) was planned to collect 3,000 patients over a 6 year re-examination period of 31 May 2013 –30 May 2019 for the purpose of examining safety and efficacy of Alogliptin (active ingredient of Nesina) in monotherapy or combination therapy of Nesina Tab under routine clinical practices in type 2 diabetic patients.

As provided in Clause 3, Article 6 of the Standards for Re-examination of New Drugs, etc., 3,000 subjects will be composed by integrating the number of subjects collected from the Nesina Tab. PMS and the NesinaMet (alogliptin-metformin fixed dose combination(FDC)) Tab. PMS.

# 2. Objective

To examine the following conditions that may appear at single or combined administration of Nesina Tab. in accordance with the approved label directions.

① Serious Adverse Event(SAE)·Adverse Drug Reaction(SADR)

- Causing death or life-threatening
- Requiring hospitalization or extension of hospitalization
- Causing continuous or significant disability or dysfunction
- Causing congenital malformation or abnormality
- Other medically significant event *

* This section includes the [Takeda Medically Significant Adverse Event List]. For details, see Section 7.8 Safety Assessment.

② Unexpected AE and ADR that are not reflected upon the Precautions

③ ADRs that are already known

④ Non-serious Adverse Drug Reaction

⑤ Other safety·efficacy related information

# 3. Planned Number of Patients and Grounds for Setting

## 3.1 PLANNED NUMBER OF PATIENTS

According to the Ministry of Food and Drug Safety(MFDS) Notification, 3,000 patients using single or

combination regimen of alogliptin are to be enrolled, and 3,000 enrolled patients in total will be collected from the Nesina Tab. PMS and the NesinaMet Tab. PMS together.

The objective of the MFDS re-examination system is to reconfirm the clinical usefulness of the product through collecting, reviewing, identifying, and verifying the safety and efficacy information about the product in general practice for 3,000 patients during 6 years re-examination period in accordance with the guidelines provided by the MFDS (Ministry of Food and Drug Safety).

Subjects will be enrolled by a continuous registration method. Subjects who agree to participate in this study will sign the Informed Consent Form. Discontinuation of treatment will be determined by a patient's willingness to continue treatment and the investigator's discretion. The reason for discontinued treatment will be documented in CRF(if applicable).

Subjects can also discontinue participation in this study anytime without providing reason, during the surveillance. The major criteria of subject's discontinuation to participate will be documented by Investigators. Also we will endeavor to ensure that subject's visit of all stages are performed in accordance with protocol.

### 3.2 Grounds for setting

Minimum sample size of 3,000 subjects was decided based on the requirements for re-examination of new drugs, etc. by the MFDS or regulatory authorities. In this PMS, for any reason, the number of subjects to be enrolled will be determined even in consideration of subjects to be excluded from the safety analysis set, and the number of subjects in the safety analysis set as collected from the Nesina Tab. PMS and the NesinaMet Tab. PMS will be 3,000 at least.

## 4. Subject

Patients will be enrolled by a continuous registration method. Patients who agree to participate in this study will sign the Informed Consent Form. Discontinuation of treatment will be determined by a patient's willingness to continue treatment and the investigator's discretion. The reason for discontinued treatment will be documented. Patients can also withdraw their consent to participate in this study.

In addition, among subjects enrolled in the NesinaMet Tab. PMS, only subjects who have been administered NesinaMet Tab. identically to the label of Nesina Tab. are integrated in this PMS. Relevant label indication of NesinaMet Tab. is as follows:

① The case of no prior history of antidiabetic medication and may not achieve adequate glycemic control with single therapy

② The case of inadequate glycemic control with metformin single therapy

③ Combination therapy with pioglitazone and this drug in case of inadequate glycemic control with metformin and pioglitazone combination therapy

④ Combination therapy with insulin and this drug in case of inadequate glycemic control with metformin and insulin combination therapy

Besides, as labeled for NesinaMet Tab., there is 'substitution of alogliptin-metformin combination regimen', but the subject has already been being administered Nesina Tab. and the data have not been collected for safety of the subject taking the study drug for the first time, and thus the subject is to be excluded from integrated analysis with this PMS.

## 4.1 Inclusion Criteria

The study should enroll adults aged 19 years or older who are diagnosed with T2DM(Type 2 Diabetes Mellitus) who correspond to one of the followings and are initiating treatment with Nesina Tab for the first time as an adjunct to diet and exercise to improve glycemic control;

① Monotherapy Nesina

② Combination therapy with the surveillance drug (Nesina) in case of inadequate glycemic control with metformin or sulfonylurea or thiazolidinedione single therapy

③ Combination therapy with the surveillance drug (Nesina) in case of inadequate glycemic control with thiazolidinedione and metformin combination therapy

④ Combination therapy with the surveillance drug (Nesina) in case of inadequate glycemic control with insulin(single therapy or combination with metformin) therapy

⑤ Combination therapy with metformin in patients who have no prior history of antidiabetic medication and may not achieve adequate glycemic control with monotherapy Nesina

## 4.2 Exclusion Criteria

① Patients treated with Nesina Tab outside of the locally approved label in Korea

② Patients with contraindication for the use of Nesina (as described in the Korean product label)

## 4.3 Special population

Children(aged under 12 years), elderly(65 years or older), pregnant women, patients with renal impairment, and patients with hepatic impairment shall be categorized into specific subjects, and once data of such subjects are collected, their safety and efficacy shall be analyzed additionally.

## 4.4 Long-term use subjects(for more than 26 weeks)

In this PMS, all patients taking the drug for more than 26 weeks shall be categorized into long-term use subjects, and their safety and efficacy shall be analyzed. Among subjects of safety evaluation, at least 50% of long-term use subjects shall be secured.

### 4.5 Other subjects

If patients excluded from safety analysis are collected, such as in off-label use cases, any AE occurring during the PMS period shall be additionally checked or separately analysed as the per needed.

## 5. Expected PMS Period

As required for any new medicine approved by MFDS, safety and efficacy are evaluated in the setting of routine practice during the re-examination period of 6 years from the approval date.

① Re-examination period: 31 May 2013 –30 May 2019 (6 years)

② Re-examination application period: 31 May 2019 – 30 August 2019

If there is safety information of the study drug which is to be collected additionally after the planned re-examination period, relevant safety information will be reported to the MFDS or regulatory authorities.

## 6. Data Source/Data Collection Process

Takeda will select more than about 200 medical institutions including relevant departments of University hospitals, general hospitals and clinics where the surveillance drug is mainly prescribed and where staff who has expertise in treatment of type 2 diabetic patients can sufficiently fulfill the objectives of the surveillance and request for surveillance after signing a written contract. The investigators will be qualified representative physicians who provide care to patients with type 2 diabetes mellitus.

Adult patients with type 2 diabetes mellitus who are initiating Nesina for the first time and taking Nesina at least once as indicated by the MFDS will be included. Patients will be treated as part of routine practice at Korean healthcare centers by accredited physicians.

Each investigator will sequentially enroll patients who are initiating Nesina Tab for the first time until the target number of patients per center is reached. The treatment with Nesina and study population should comply with the recommendations written in the local product information at the timing of enrollment (as the local product information may change).

Each patient will be followed for 26 weeks. Data will be collected at 13 weeks and 26 weeks after enrollment during standard of care office visits. Physician's follow up safety assessments can be conducted by mail, phone calls, or e-mail. All patients will be evaluated for safety during Nesina use and for 30 days after their last dose to confirm the safety profile of Nesina under routine, daily practice or to learn of previously unsuspected adverse reactions. The decision about the duration and closure of treatment is solely at the decision of the treating physician with agreement of the patient.

Investigators will use an eCRF(electronic Case Report Form). Therefore, if the investigator records the enrolled patient's data on the eCRF during the surveillance and the surveillance is completed, the eCRF will be delivered to Takeda and the department in charge of data management. The person in charge of this surveillance will check entries in the eCRF and, if necessary, request re-inquiry.

Patients' medical records and laboratory test results will be data sources in this study.

Only in the case that the laboratory test is done as part of standard of care practice and the data are available will the data be collected for this study.

## 7. Item of PMS

The Investigator will enter the patient information corresponding to the following items in eCRF.

### 7.1 Information on Patient Enrollment

① Site Information: Name of Site, Name of Department, Name of Investigator

② Patient Information : Initial of Patient , Number of Patient, Signed date of Informed Consent Form

③ Demographic Information: Gender, Date of Birth, Pregnant/Nursing (only for women), Type of Treatment(Outpatient/Hospitalization), Height, Weight

④ Inclusion/Exclusion Criteria

### 7.2 Medical History of Patient

① Diagnosed date of T2DM

② Renal Impairment(Including Severity)

③ Concurrent disease : Hepatic Impairment, Allergy, Cardiovascular disease, Cancer, Pancreatitis and Others

④ Drinking and Smoking

### 7.3 Administration of Nesina Tab

① Start Date/Stop Date

② Daily Dose

③ Daily dose frequency

④ Reason for dose modification/discontinuation

### 7.4 Pre-treatment/Concomitant Medication

① Pre-treatments for T2DM for 12weeks prior to Nesina treatment

② Concomitant Medications prescribed during Nesina treatment

- Presence/Absence of Concomitant Medication
- Product Name/Generic name
- Daily Dose and Frequency
- Route of Administration
- Start Date/Stop Date(or Continuation)

- Purpose of Administration(such as Treatment(for T2DM and Concurrent disease), Adverse Event and Prevention)

## 7.5 Compliance Status

① Nesina Tab Compliance [*1] at 13 and 26 weeks after initiating Nesina

② Diet Therapy & Exercise Therapy [*2] at before and 13 and 26 weeks after initiating Nesina

*1 Treatment compliance status evaluation criteria

1. Taking properly as directed (90% or more taken：never forgetting to take the drug or if forgetting, just 2-3 days per month)
2. Taking mostly as directed (70% or more taken：forgetting to take the drug 1-2 day(s) per week)
3. Not taking properly as directed (50% or more taken：forgetting to take the drug 3 days per week)
4. Little taking as directed (Less than 50% taken：forgetting to take the drug 4 days or more per week)

*2 Diet therapy･exercise therapy compliance status evaluation criteria

1. Conducting properly as directed (90% or more conducted)
2. Conducting mostly as directed (70% or more conducted)
3. Not conducting properly as directed (50% or more conducted)
4. Little conducting as directed (less than 50% conducted)
5. Not conducting or compliance status unknown

## 7.6 Efficacy related Laboratory Data

① HbA1c at baseline and 13 and 26 weeks after initiating Nesina

② Fasting Plasma Glucose at baseline and 13 and 26 weeks after initiating Nesina

However, in case a relevant test has not been performed at 13 weeks and 26 weeks, please collect data within 2 weeks before and after 13 weeks and 26 weeks.

## 7.7 Abnormal change in Laboratory data

Laboratory tests are not mandatory because of the non-interventional nature of this study. Check “Absence” on the eCRF if testing is not performed or there is no significant abnormal change after initiating Nesina.

If laboratory result collected, record the following in detail.

- Presence/Absence of Significant abnormal change in laboratory result
- Date of test before Nesina Tab administration
- Date of test after Nesina Tab administration

- Result of the laboratory test
- Unit of tested item
- Normal range of tested item
- Investigator's remarks.

## 7.8 Safety Assessment

All AEs that occurred on the surveillance drug treatment or within 30 days after the end of the treatment, whether or not related to the drug, will be recorded. The safety assessment should include all undesirable changes of medical findings (including a clinical test finding) noted during medical visits according to local practice guidelines and all AEs associated with the surveillance drug administration.

The following information should be included in the AE investigation.

- Occurrence status of AE
- Name of AE
- Onset and stop date of AE
- Severity of AE
- Seriousness of AE
- Special Interest AE
- Outcome of AE
- Causal relationship to the surveillance drug
- Causal relationship except the surveillance drug
- Actions taken to the surveillance drug due to AE
- Treatment(Yes/No)/ Details of treatment for AE
- Investigator's opinion etc.

*Causality should be determined as follows:*

① Certain: it has reasonable temporal relationship with the drug, and it cannot be explained with either drugs or chemical agents. Clinically acceptable response is shown at the drug discontinuation as well as it shows decisive response pharmaceutically or phenomenological when the drug resumes as necessary.

② Probable/likely: it has reasonable temporal relationship with the drug, and it is not likely caused by other drugs or chemical agents or concomitant diseases. Also clinically acceptable response is shown at the drug discontinuation (no information about resumption)

③ Possible: it has reasonable temporal relationship with the drug, but it can be explained with other drugs or chemical agents or accompanied diseases. It has insufficient or unclear information about drug discontinuation.

④ Unlikely: it is a temporary case which does not seem to have causal relationship with the administration or use of the drug, and it can be reasonably explained with other drugs or chemical agents or underlying diseases.

⑤ Conditional/unclassified: there is a need to get more data for proper evaluation of causality of event. The investigator is reviewing the additional data of event.

⑥ Unassessible/unclassifiable: there is not enough or conflicting information so the investigator cannot make evaluation or confirmation.

⑦ Not applicable.

*The severity of AE will be determined according to the following criteria:*

① Mild: there are self-aware or objective symptoms, but they do not interrupt daily life. The treatment can be continued without dose adjustment.

② Moderate: interruption in daily life is recognized. Dose adjustment or additional treatment is required due to the adverse event.

③ Severe: daily life cannot be managed with the symptom. The administration of the drug should be discontinued due to significant adverse event.

*The outcome of AE will be determined according to the following criteria:*

① Recovered

② Recovering

③ Not recovered

④ Recovered with sequela

⑤ Unknown

⑥ Lethal injury

⑦ Death likely related to Adverse Event

⑧ Death not related to Adverse Event

*The SAE will be determined according to the following criteria:*

① Causing death or life-threatening

② Requiring hospitalization or extension of hospitalization

③ Causing continuous or significant disability or dysfunction

④ Causing congenital malformation or abnormality

⑤ Other medically significant event *

*「Takeda Medically Significant AE List」 is included in this clause. (for example, bronchospasm requiring short-term intensive treatment at emergency room.)

**Takeda Medically significant AE List**

**Terms**

| **General** | **Hepatobiliary System** |
|---|---|
| Malignancy | Acute hepatic failure |
| Endotoxic shock | Fulminant hepatitis |
| Sepsis | **Immune system** |
| Transmission of an infectious agent by a med icinal product | Anaphylaxis |
| Necrotic Conditions including Gangrene | Progressive multifocal leukoencephalopathy (PML) |
| **Blood and lymphatic System** | Transplant rejection |
| Bone marrow failure | **Musculoskeletal System** |
| Disseminated Intravascular Coagulation | Rhabdomyolysis |
| Thrombotic Thrombocytopenic Purpura | **Nervous System** |
| Acquired hemoglobinopathy | Cerebrovascular accident |
| Hemolysis | Coma |
| **Cardiovascular System** | Convulsive seizures |
| Cardiac arrest | Hyperthermia malignant |
| Cardiac failure | Macular oedema |
| Cardiomyopathy acute | Psychosis |
| Malignant hypertension | Meningoencephalitis |
| Ventricular arrhythmias | Neuroleptic malignant syndrome |
| Embolisms and Infarctions | Suicidal behaviour |
| Dissection and Rupture of Important Vessels | **Reproductive System** |
| **Endocrine System** | Abortion |
| Adrenal crisis | Uterine perforation |
| **Gastrointestinal System** | **Respiratory System** |
| Acute pancreatitis | Acute respiratory failure |
| GI haemorrhage | Pulmonary hypertension |
| GI perforation | **Skin and subcutaneous tissue** |
| GI obstruction | Toxic epidermal necrolysis |
| Necrotising colitis | Stevens-Johnson syndrome |
| Peritonitis | **Urinary System** |

| | |
|---|---|
| | Acute renal failure |

All SAEs which start during the study and are not resolved by the end of the observational period should be followed until resolved if possible.

**Special Interest AEs**

A Special Interest Adverse Event (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

*Pancreatitis*

This is an adverse event of special interest for alogliptin.

Study drug should be interrupted immediately if any of the following circumstances occur at any time during treatment:

If pancreatitis is suspected

Serum amylase ≥2 x ULN

Serum lipase ≥2 x ULN.

If any of the circumstances described above occur during the study, the investigator must complete the AE/SAE Case Report Form [(e)CRF] page, a Pancreatitis Adverse Event of Special Interest Form and report it to Takeda within 24 hours of first onset or notification of the event. The investigator will determine if the subject has a diagnosis of pancreatitis. If yes, full details of the event should be obtained and recorded.

*Hypersensitivity reactions*

This is an adverse event of special interest for alogliptin.

If any of the subject experiences a hypersensitivity reaction during the study, the investigator must complete the AE/SAE Case Report Form [(e)CRF] page, a Hypersensitivity reactions Adverse Event of Special Interest Form and report it to Takeda within 24 hours of first onset or notification of the event. The investigator will determine if the subject has a diagnosis of hypersensitivity reaction. If yes, full details of the event should be obtained and recorded.

*Liver Function Test Abnormalities*

This is an adverse event of special interest for alogliptin.

If the subject is experiencing symptoms or if the liver test is abnormal (as defined below), the abnormality should be documented as an adverse event, and a Liver Function Test Abnormality (LFTA) Form completed. If the event meets serious criteria, the SAE (e)CRF page must be completed within 24 hours of first onset or notification of the event;

ALT or AST ≥3 times ULN in conjunction with a bilirubin >2 times ULN

ALT or AST >5 times ULN for more than 2 weeks
ALT or AST ≥3 times ULN with the appearance of fatigue, nausea, vomiting, upper right-quadrant tenderness, fever, rash or eosinophilia.

In each of these instances, the patient should be followed to a satisfactory conclusion (ie, until the adverse event resolves, the laboratory value returns to baseline, or the condition becomes stable).

*NOTE: All SAEs which start during the study and are not resolved by the end of the observational period should be followed until resolved if possible.*

### 7.9 Effectiveness Assessment (Overall improvement)

Efficacy will be determined through improvement in HbA1c or fasting plasma glucose. Final assessment will be performed at 26 weeks after the start of therapy.

The final Effectiveness assessment by investigator's subjective medical consideration will be characterized according to the classification criteria below:

① Improved: signs and symptoms are significantly improved

② Unchanged: improvement in signs and symptoms is not significant or there is no change in signs and symptoms

③ Worsened: signs and symptoms are worsened

④ Assessment impossible: assessment is impossible because the surveillance drug was discontinued before 13 weeks

'Improved' will be analyzed as valid, and 'Unchanged' and 'Worsened' will be analyzed as invalid.

## 8. Statistical Analysis

### 8.1 Composition of subjects

Lists of planned number of patients, completed number of patients, number of patients for safety analysis set, and number of patients for efficacy analysis set will be presented like following;

- Planned(Agreed) subjects includes patients agreed for surveillance by written contract with investigator
- Completed subjects includes patients whose eCRFs are retrieved after completion of surveillance
- Safety analysis set includes patients who were treated with the surveillance drug at least once and completed the follow-up for safety
- Efficacy analysis set includes patients who have completed the surveillance drug treatment for more than 13 weeks and have performed overall assessment according to the investigator's clinical discretion.

Also, subjects integrated from the NesinaMet Tab. PMS described in '4. Subjects' above shall be

included in safety evaluation in this PMS and analyzed in the same way but shall be excluded from efficacy evaluation.

### 8.2 Subject demographic data analysis

All background data such as patient demographics, diagnosis, pre-treatment for T2DM, complications and concomitant medications, administration period and dosage of Nesina tablet will be expressed in descriptive statistics. For continuous data, mean, standard deviation, minimum value, maximum value, and median shall be obtained, and for categorical data, frequency and percentage shall be obtained.

### 8.3 Safety and Efficacy Analysis

Statistical analyses will be of explorative and descriptive nature. Safety and efficacy data will be further analyzed using logistic regression to identify the factors that may affect the safety and efficacy of Nesina Tab(eg, sex, age, complication, concomitant medication, duration of Nesina Tab). In the efficacy analysis set, frequency and percentage of efficacy parameters (HbA1C change, patients to reach <7% of HbA1C, Fasting Blood Glucose change and Overall effectiveness) will be summarized. In safety analysis set, AEs, ADRs, serious AEs/ADRs, and unexpected AEs/ADRs will be categorized into SOC(System Organ Class) and PT(Preferred Term) of WHO ART, these will be prepared in a list, and each incidence rate will be calculated. The incidence rate and effective rate of AEs between each demographic characteristic will be compared using chi-square test or Fischer's exact test as subgroup analysis. Safety analysis for special population (eg, child, geriatric patients, pregnant women, patients with renal or hepatic impairment) included in this study will be performed. According to the MFDS guidelines for all adverse events reported during re-examination period, the incidence rate and effective rate shall be analyzed, and 95% confidence interval provided.

## 9. Other Requirements

### 9.1 Amendment of plan

Need for amendment of the plan shall be examined based on new knowledge obtained from the course of this PMS, and if necessary, the plan shall be amended. Also, if partial change in the administration & dosage or indications is approved during this PMS, need for amendment of this plan shall be examined, and if necessary, and it shall be amended. In case of amendment of the plan, except for a little change, amendment plan shall be submitted to the Ministry of Food and Drug Safety in advance.

### 9.2 Measures when problem or doubt is identified

If an unexpected ADR or SAE appeared or frequency of AE sharply increased, or a safety and efficacy problem is found compared to before marketing, execution of special investigation shall be examined to verify the significance.

# 10. Adverse Event Definitions

Adverse Event(AE) means any and all undesirable or unintended signs(including abnormal clinical laboratory values), symptoms, or diseases that are incurred when the drug is administered, and is not related to causal relationship with the drug.

Adverse Drug Reaction(ADR) means a harmful and unintended reaction resulting from usual administration and use of the drug, whose causal relationship with the drug cannot be excluded, and if causal relationship with the drug is unknown among AEs reported spontaneously, it is regarded as ADR.

Unexpected ADR means an ADR with difference in the nature or severity, specificity, or the outcome, compared to the product licensure/notification of the drug.

All AEs that are to be incurred in all patients who have been administered Nesina Tab once at least shall be recorded irrespective of causal relationship with the drug. Information on AEs shall be collected by patient's spontaneous report, telephone or finding by the investigator at an additional visit, and physical and laboratory examination, etc.

Even if medical conditions and diseases being present prior to administration of Nesina Tab were worsened after starting to administer the drug, they shall be decided as AEs.

## 10.1 Serious Adverse Event Collection and Reporting

Following the patient's written consent to participate in the study, all SAEs, whether or not related to Nesina Tab under study, must be collected, and SAE term, onset/stop date, severity, causal relationship to Nesina Tab, causal relationship except with Nesina Tab due to AE, action taken, etc. should be captured on the eCRF Safety Assessment Page.

SAEs must be individually recorded on the SAE Report Form presented by MFDS and reported to Takeda Pharmaceuticals Korea Co., Ltd within 24 hours to comply with regulatory requirements. A form should be completed for any event where doubt exists regarding its status of seriousness.

All SAEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to : Notification of Serious Adverse Events to Takeda Pharmaceuticals Korea Co., Ltd.

| **24 /7 SAE Hotline** | |
|---|---|
| Phone Number | PPD |
| Fax Number | |
| **For SAE Reporting,**<br>**please E-MAIL the completed SAE Report Form to Takeda within 24 HOURS of first awareness** | |

Even if the investigator is aware of additional information or FU information on SAE, he/she should report to the sponsor within 24 hours.

### 10.2 Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of the study.

Non-serious adverse events must be also recorded in the eCRF Safety Assessment page. Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of the Nesina Tab under study and for those present at the end of the study, as appropriate.

### 10.3 Pregnancy Reporting

If the patient becomes pregnant during drug treatment or within 30 days after the end of treatment, the administration of the drug under study should be immediately discontinued and the subject should be terminated early from the study. Once the investigator confirms that the subject becomes pregnant during drug treatment or within 30 days after the end of treatment, pregnancy related information will be collected after obtaining the ICF for the use of pregnancy information from the subject. Takeda Pregnancy Notification Form should be completed and should be reported to Safety Staff of Takeda Pharmaceuticals Korea Co., Ltd within 24 hours of his/her awareness. In addition, if the partner (spouse) of the male subject is also reported to have a pregnancy during drug treatment or within 30 days after the end of treatment, pregnancy related information will be collected after obtaining the ICF for the use of pregnancy information from the partner (spouse) of the subject. Takeda Pregnancy Notification Form should be completed and should be reported to Safety Staff of Takeda Pharmaceuticals Korea Co., Ltd within 24 hours of his/her awareness. The investigator should provide follow up information to Takeda Pharmaceuticals Korea Co., Ltd during the pregnancy and until delivery or the end of the pregnancy.

## 11. Appendix

**Appendix 1. Case Report Form**