Title: Post-Marketing Surveillance Study on NesinaAct Tablet®

NCT Number: NCT04980014

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STATISTICAL ANALYSIS PLAN

Post-Marketing Surveillance Study on NesinaAct Tablet®
Use Among Type 2 Diabetes Mellitus Patients in Korea

Product Name : NesinaAct Tablet®

Protocol No. : Alogliptin-Pio-5002

Version : V6.0

Effective Date : 19-OCT-2020

Approvals

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Revisions

DATE OF REVISION	INDICATION REVISION	REASON FOR CHANGE	AUTHOR NAME
02-SEP-2016	2.3.1 Inclusion criteria	To reflect starting dose	PPD
	Appendix 1. Mock up TLFs	To reflect updated title	
07-MAR-2018	List of abbreviations	Add abbreviation	PPD
	3.1 Safety Analysis Sets	Add exclusion criteria from Safety Analysis Set	
	4.2 Safety Endpoint	Add comment about visit window more clearly like Effectiveness Endpoint did	
	6. StatisticalAnalysis Method	Add AE analysis of the local product document form	
	6.1 Composition of Subjects	Modify the text for the same as Protocol	
	6.2 Subject Characteristics	Modify the text for the same as Protocol and CRF.	
	6.3 Effectiveness Analyses	Add analysis for long-term F/U patients	
	6.4.2 Adverse Events by Preferred Terms	Add analysis for long-term F/U patients and for unexpected SAE/Serious ADR(SADR) of safety assessment analysis items	
	Appendix 1. Mock up TLFs	To reflect updated title	
20-DEC -2018	6.4 Safety Analyses	Add summary analysis for AE	PPD
	6.4.2 Adverse Events by Preferred Terms	Add AE analysis of the local product document form	
	6.4.3 Adverse Events by Period	Add analysis for AE by period	
	Appendix 1. Mock up TLFs	To reflect updated title	
10-MAY -2019	3.1 Safety Analysis Sets	Reflect updated guidelines	PPD
	3.2 Effectiveness Analysis Sets	Add effectiveness analysis criteria	
	6.2 Subject Characteristics	Add analysis condition	

19-OCT-2020	6.4.1 Adverse Events by Subject Characteristics	To modify of phrase	PPD
	Appendix 1. Mock up TLFs	To reflect updated title	

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List of abbreviations

ADR	:	Adverse Drug Reaction
AE	:	Adverse Event
BMI	:	Body Mass Index
CRF	:	Case Report Form
MFDS	:	Ministry of Food and Drug Safety
PMS	:	Post Marketing Surveillance
SADR	:	Serious Adverse Drug Reaction
SAE	:	Serious Adverse Event
SAP	:	Statistical Analysis Plan
SAS	:	Statistical Analysis System
T2DM	:	Type 2 Diabetes Mellitus
WHOART	:	World Health Organization Adverse Reactions Terminology

1. Study Objective

This surveillance is to evaluate the safety and effectiveness of NesinaAct therapy in real-world setting for its approved indications.

1.1 Primary Objective

The primary objective of this surveillance is to estimate the proportion of all adverse events (AEs) including serious adverse events (SAEs) and serious adverse drug reactions (SADRs) in patients who are treated for type 2 diabetes mellitus under NesinaAct therapy with a dose of 12.5/30mg, 12.5/15mg, 25/30mg, 25/15mg (alogliptin/pioglitazone) once daily by physicians in the real-world clinical practice setting over a period of 26 weeks.

① Serious AEs (SAEs) and Serious ADRs (SADRs)
② Unexpected AEs and ADRs that are not mentioned in precautions.
③ ADRs that are already known.
④ Non-serious Adverse Drug Reaction (ADR)
⑤ Other safety-related information (influence upon laboratory values, etc.)

1.2 Secondary Objective

The secondary objectives of this surveillance are to monitor in this cohort of patients from baseline to endpoint (at 26 weeks):

- HbA1c
- Fasting serum glucose
- Lipid profile
- Body weight
- Blood Pressure

2. Study Design

2.1 Study Period

NesinaAct has been approved for marketing by Ministry of Food and Drug Safety on 24 October 2014 and has been designated to conduct the PMS to 30 May 2019, according to the examination period of Nesina™ Tab, a single agent.

2.2 Expected Number of Subjects

In accordance with the guidelines provided by the MFDS (Ministry of Food and Drug Safety), at least 600 subjects will be enrolled. Subjects will be enrolled by a continuous registration method.
In this PMS, all patients taking NesinaAct for more than 26 weeks shall be categorized into long-term use subjects, and at least 50% (300 subjects) of long-term use subjects shall be secured among subjects of safety evaluation.

2.3 Study Population

2.3.1 Inclusion criteria

NesinaAct will be given to Type 2 Diabetes Mellitus subjects aged 19 years old or older who sign and date a written, informed consent form and who are eligible for the combination of Alogliptin and Pioglitazone as an adjunct to diet and exercise to improve glycemic control and with one of the following criteria:

① For subjects inadequately controlled on diet and exercise [Start taking 25/15mg NesinaAct]
② For subjects inadequately controlled on metformin alone (In case of adding the Nesina Act in patients that were prescribed single therapy before baseline (within 12 weeks), It will assess the Safety analysis set) [Start taking metformin and 25/15mg NesinaAct]
③ For subject inadequately controlled on pioglitazone alone (In case of adding the Nesina Act in patients that were prescribed single therapy before baseline (within 12 weeks), It will assess the Safety analysis set) [According to the current therapy, start taking 25/15mg or 25/30mg NesinaAct]
④ For subject inadequately controlled on metformin and pioglitazone combination therapy [According to the current therapy, start taking metformin and 25/15mg or 25/30mg NesinaAct]

⑤ For subject switching from alogliptin co-administered with pioglitazone [Start taking alogliptin and pioglitazone with an existing dosage]

2.3.2 Exclusion criteria

① Patients treated with NesinaAct outside of the locally approved label in Korea
② Patients with contraindication for the use of NesinaAct (as described in the Korean product label)

2.4 Study Method

To reach the number of contracted cases, each investigator will sequentially enroll the first subject who meets the inclusion and exclusion criteria and who receives NesinaAct for the first time under the approval label by MFDS after the effective agreement date.

3. Analysis Sets

3.1 Safety Analysis Sets

Safety analysis set includes subjects who were treated with NesinaAct at least once and completed the follow-up※ for safety.

※ The following Guideline on Standards for re-examination for new drugs, etc of MFDS(Chapter III, no. 3)

Composition of subjects:

The composition of subjects shall be presented with rule for estimation of the number of subjects whose CRFs were collected, the number of subjects of safety evaluation*, the number of subjects of efficacy evaluation, the number of dropouts and the reason etc.

* The number of subjects of safety evaluation: Cases who have been administered study medication once at least, and safety follow up has been made.

Based on 'rules for estimation of each number of safety evaluation cases', the following local regulation and Guideline on Standards for re-examination for new drugs, etc※ of MFDS, non-safety analysis set are excluded from the safety analysis set:

※ Guideline on Standards for re-examination for new drugs, etc (Chapter III, no. 3)
Patient Population for Surveillance:

A. Patients planned to receive a drug under surveillance by investigator's medical judgment shall be subject.
B. Subject who do not use within approved range shall not be included in the subject in principal.
   ※ However, if data of subject whose use is beyond approved range is collected, perform analysis as a separate item.
C. Describe actual selection methods of subject in detail.

Non-safety analysis set is as follows:

(1) Subjects who have consented prior to the contract.
(2) Subjects who have been administered NesinaAct prior to the contract date
(3) Subjects who have been administered NesinaAct prior to the consent.
(4) Subjects who have taken NesinaAct prior to enrollment into the study
※ This study is carried out with 'Continuous Surveillance Method'
Continuous Surveillance Method:
A method that surveillance doctor needs to insert all the number of subject continuously from subject of the first dose after start of surveillance to subjects of referral on the surveillance table.
(5) Subjects who violated inclusion/exclusion criteria (see section 2.3)
※ Guideline on Standards for re-examination for new drugs, etc (Chapter III, no. 3 Patient Population for Surveillance) (refer to 3.1)

3.2 Effectiveness Analysis Sets

Effectiveness analysis set includes subjects who have completed NesinaAct treatment for more than 13 weeks and have performed Final effectiveness assessment according to the investigator's clinical discretion.

Among safety assessment cases, a case will be included as an effectiveness assessment case when effectiveness assessment can be performed.

Based on 'rules for estimation of number of effectiveness assessment cases', the following cases are excluded from the effectiveness analysis set:

(1) Subjects who excluded from safety analysis set
(2) Final effectiveness assessment is missing
(3) Final effectiveness assessment is "Assessment impossible"
(4) Subjects who administrated NesinaAct less than 13 weeks(91 days)

4. Endpoint

4.1 Effectiveness Endpoint

- Effectiveness proportion of the final effectiveness assessment(Effective: 'Improved', Ineffective : 'Unchanged' or 'Worsened')
- HbA1c at baseline, 13 and 26 weeks* after initiating NesinaAct
- Fasting Plasma Glucose at baseline, 13 and 26 weeks* after initiating NesinaAct
- Lipid profile at baseline, 13 and 26 weeks* after initiating NesinaAct

* In case that the date for Lab Test is collected, analysis includes subjects who only came to fit the window visit (Visit 2 (13weeks ± 2weeks), Visit 3 (26weeks ± 2weeks)).

4.2 Safety Endpoint

- Body weight at baseline, 13 and 26 weeks after initiating NesinaAct
- Blood Pressure at baseline,13 and 26 weeks* after initiating NesinaAct
- All adverse events

* In case that the date for Lab Test is collected, analysis includes subjects who only came to fit the window visit (Visit 2 (13weeks ± 2weeks), Visit 3 (26weeks ± 2weeks)).

5. Assessment criteria of Endpoint

5.1 Effectiveness Endpoint

Effectiveness will be determined through improvement in Fasting blood glucose or HbA1c, Lipid profile. Final effectiveness assessment will be evaluated at 26 weeks (or stop date of treatment) after the start of therapy.

The final effectiveness assessment 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 NesinaAct was discontinued before 13 weeks

5.2 Safety Endpoint

- All AEs that occurred on NesinaAct treatment or within 30 days after the end of the treatment.

6. Statistical Analysis Method

- Each statistical analysis will be carried out with SAS Software version 9.4 or more recent version.
- For descriptive statistics, mean, standard deviation, minimum and maximum will be calculated for continuous variables, and frequency and percentage for categorical variables.
- Data including sign of inequality such as "≥20", ">20" will be excluded from analysis.
- If applicable, all test statistics will be the results of two-sided tests with the statistical significant level 0.05.
- The followings shall be included only in re-examination report.
  - Analysis by type of medical history/concurrent medical conditions, pre-treatment history for T2DM, concomitant medication for T2DM, concomitant medication for other than T2DM
  - Preferred terms of Serious AE/Serious ADR, unexpected AE/ADR according to the proportion of AE in the local product document.

- If necessary, logistic regression analysis

6.1 Composition of Subjects

- Completed number of patients
- Number of patients for safety analysis set
- Frequency of criterion for excluded from the safety analysis set
- Number of patients for effectiveness analysis
- Frequency of criterion for excluded from the effectiveness analysis set

6.2 Subject Characteristics

The following subject characteristics will be reported:

age, gender, height(baseline), weight(baseline), BMI(baseline), type of treatment, T2DM duration, concurrent disease, smoking, drinking, long-term F/U patients(≥26weeks)

The following special subject characteristics will be reported:

Elderly(65 years or older), patients with renal impairment

The following medication characteristics will be reported:

total administration period, daily dose, pre-treatment history for T2DM, concomitant medication for T2DM, concomitant medication for other than T2DM

Derived variable	Description
BMI	(Weight) / (Height)^2
T2DM duration	(Administration start date) - (First diagnosed date of T2DM) + 1
Total administration period	- (Administration period) = (administration end date)-(start date) + 1 - (Total administration period) = (Sum of administration period) If the medication is being continued at the completion of the study, last administration end date is replaced with “date of surveillance completion” in CRF section 10.

6.3 Effectiveness Analyses

Statistical analysis on effectiveness parameter will be done on effectiveness analysis set.

Frequency and percentage of Final effectiveness assessment will be calculated.

Also, Subjects who were evaluated as 'Improved' in Final effectiveness assessment shall be regarded as "Effectiveness" and 'Unchanged' and 'Worsened' as "Ineffectiveness" to get an effectiveness proportion. And effectiveness proportion and the its 95% confidence interval will be calculated using the exact method.

An effectiveness proportion shall be obtained per subject characteristics, and it shall be analyzed by categorical data analysis(Chi-square test or Fisher's Exact test). The 95% confidence interval for effectiveness proportion by subject characteristics will be calculated using the exact method.

Additionally, the change from before initiating NesinaAct to after initiating NesinaAct (Visit2, Visit3) of continuous effectiveness variable (HbA1c, fasting blood glucose, Total cholesterol, LDL-C and HDL-C) will be calculated for each patient. And the difference of continuous effectiveness variable between before initiating NesinaAct and after initiating NesinaAct (Visit2, Visit3) will be analyzed using paired t-test. For number of patients with HbA1c <7% for Visit1, Visit2 and Visit3, frequency and percentage will be calculated. It will be analyzed by considering the visit window of Visit2 (13weeks ± 2weeks), Visit3 (26weeks ± 2weeks).

In case of Long-term F/U patients, Frequency and percentage of Final effectiveness assessment from will be calculated.

Also Long-term F/U patients who were evaluated as 'Improved' in Final effectiveness assessment shall be regarded as "Effectiveness" and 'Unchanged' and 'Worsened' as "Ineffectiveness" to get an effectiveness proportion. And effectiveness proportion and the its 95% confidence interval will be calculated using the exact method.

About Long-term F/U patients likewise, the change from before initiating NesinaAct to after initiating NesinaAct (Visit2, Visit3) of continuous effectiveness variable (HbA1c, fasting blood glucose, Total cholesterol, LDL-C and HDL-C) will be calculated for each patient. And the difference of continuous effectiveness variable between before initiating NesinaAct and after initiating NesinaAct (Visit2, Visit3)

will be analyzed using paired t-test. For number of patients with HbA1c <7% for Visit1, Visit2 and Visit3, frequency and percentage will be calculated. It will be analyzed by considering the visit window of Visit2 (13weeks ± 2weeks), Visit3 (26weeks ± 2weeks).

If necessary, multivariate analysis for the impact of the effectiveness may be carried out using logistic regression analysis.

6.4 Safety Analyses

Safety analysis on safety parameter will be done on safety analysis set.

In the safety analysis set, create a summary table with AEs and the following information will be included.

- the number of subjects to whom AE occurred
- the number of AEs
- the incidence proportion of AEs and its 95% confidence interval using the exact method

Additionally, the change from before initiating NesinaAct to after initiating NesinaAct (Visit2, Visit3) of continuous safety variable (body weight, blood pressure) will be calculated for each patient. And the difference of continuous safety variable between before initiating NesinaAct and after initiating NesinaAct (Visit2, Visit3) will be analyzed using paired t-test. It will be analyzed by considering the visit window of Visit2 (13weeks ± 2weeks), Visit3 (26weeks ± 2weeks).

If necessary, multivariate analysis for the impact of the safety may be carried out using logistic regression analysis.

6.4.1 Adverse Events by Subject Characteristics

For the AE(s) according to the subject characteristics in the safety assessment population:

- The number of subjects to whom AE occurred and the number of AEs will be calculated.
- The incidence proportion of AEs will be analyzed by Chi-square test or Fisher's exact test and its 95% confidence interval will be calculated using the exact method.

6.4.2 Adverse Events by Preferred Terms

All AEs recorded in the CRF will be classified by body organs and terms under the classification standard of WHOART terms, and all AEs excluding the AEs whose causal relation with NesinaAct is 'Unlikely' shall be treated as AEs whose causal relation cannot be excluded (hereafter "Adverse Drug Reaction(ADR)").

① The number of subjects and the number of unexpected AE/ADR, SAE/Serious ADR (SADR), unexpected SAE/Serious ADR (SADR) and AE/ADR will be calculated according to the preferred terms. Also, the incidence proportion and its 95% confidence interval using the exact method will be estimated.

② For long-term F/U patients, the number of subjects and the number of unexpected AE/ADR, SAE/Serious ADR (SADR), unexpected SAE/Serious ADR (SADR) and AE/ADR will be calculated according to the preferred terms. Also, the incidence proportion and its 95% confidence interval using the exact method will be estimated.

③ The subject of unexpected AE/ADR, SAE/Serious ADR (SADR), unexpected SAE/Serious ADR (SADR), AE/ADR, renal impairment and elderly will be listed.

④ For non-safety analysis sets, the number of subjects and the number of unexpected AE/ADR, SAE/Serious ADR (SADR), unexpected SAE/Serious ADR (SADR) and AE/ADR will be calculated according to the preferred terms. Also, the incidence proportion and its 95% confidence interval using the exact method will be estimated.

⑤ For non-safety analysis sets, the subject of unexpected AE/ADR, SAE/Serious ADR (SADR), unexpected SAE/Serious ADR (SADR) and AE/ADR will be listed.

⑥ The number of AE according to the special interest, severity, outcome, causality relationship with NesinaAct, causality relationship other than NesinaAct, action taken, treatment will be calculated.

⑦ All AEs will be classified into the preferred terms according to the special interest, severity, outcome, causality relationship with NesinaAct, causality relationship other than NesinaAct, action taken, treatment. Also, the number of each AE will be calculated.

⑧ Preferred terms of unexpected AE/ADR, SAE/Serious ADR (SADR) will be presented respectively according to the proportion of AE in the local product document in re-examination report.

Note: Unexpected AE/ADR will be classified by medical review and with reference to the local SRSD. Terms already included in the SRSD are classified as 'expected'. All other terms will be classified as 'expected' or 'unexpected' by medical review.

6.4.3 Adverse Events by Period

In re-examination report, create a summary table with AEs for each period* and the following information will be included.

- the number of subjects to whom AE occurred
- the number of AEs
- the incidence proportion of AEs and its 95% confidence interval using the exact method

Derived variable	Description
*period(category)	The period from the first administration to the occurrence of AE (Date of Onset) – (Administration start date) +1 - Category: 1) 91 days (13 weeks) or below 2) 92 days ~ 182 days (26 weeks) 3) 183 days ~ 273 days (39 weeks) 4) 274 days ~ 364 days (52 weeks) 5) Over 364 days (52 weeks)If the date of the administration start date is incomplete but some of the dates could be identified, the period will be classified into each category for categorical analysis

By period, the number of subjects and the number of expected AE/ADR, unexpected AE/ADR and AE/ADR will be calculated according to the preferred terms. Also, the incidence proportion and its 95% confidence interval using the exact method will be estimated.

Appendix 1. Mock up TLFs

See "NesinAct_SAP(V6.0)_Mock up TLFs.docx"