Title: NINLARO Capsules Drug Use-Results Survey (All-Case Surveillance)
"Relapsed/Refractory Multiple Myeloma"

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

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

Drug Use-Results Survey Protocol

NINLARO Capsules Drug Use-Results Survey

(All-Case Surveillance)

“Relapsed/Refractory Multiple Myeloma”

Survey sponsor	**Takeda Pharmaceutical Company Limited**
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[redacted]

1.0 BACKGROUND

Information about the safety of NINLARO capsules (hereinafter, “NINLARO”) in Japanese patients at the time of marketing approval is limited. Therefore, it is important to swiftly collect post-marketing safety information and provide the field of clinical practice with such information.

Having this as a background, all-case surveillance (hereinafter, “this survey”) is conducted in all cases administered NINLARO as an additional pharmacovigilance activity from the time of marketing, in order to evaluate the safety of the drug in patients with relapsed/refractory multiple myeloma in daily clinical practice.

This survey is conducted in accordance with relevant regulatory requirements including the GPSP Ordinance.

2.0 PURPOSE

To evaluate the safety of NINLARO in patients with relapsed/refractory multiple myeloma in daily clinical practice.

3.0 SCHEDULED NUMBER OF CASES AND RATIONALE

3.1 SCHEDULED NUMBER OF CASES

Total of 480 cases with relapsed/refractory multiple myeloma

3.2 RATIONALE

The clinical study results of NINLARO suggested that the incidence of skin disorder of Grade 3 or higher may be high in Japanese and clinical management such as dose adjustment may be crucial. It was therefore decided that a certain number of cases should be collected to evaluate skin disorder of Grade 3 or higher.

The second interim analysis result of a global Phase 3 clinical study (C16010 study) revealed that skin disorder of Grade 3 or higher occurred in 17 cases (4.7%) in the NINLARO group in up to 6 cycles. For similar examination in the all-case surveillance, 15 or more cases with skin disorder of Grade 3 or higher are required. To observe 15 or more cases with skin disorder of Grade 3 or higher in up to 6 cycles with a 95% probability, approximately 462 cases are required for this survey. Hence, the scheduled number of cases was set to be 480.

It is estimated that, if 480 cases are collected, it will be possible to observe 48 or more cases with thrombocytopenia (Grade 3 or higher), 21 or more cases with severe gastrointestinal disorder (Grade 3 or higher), 64 or more cases with peripheral nerve disorder (3 or more cases of Grade 3 or higher), and 44 or more cases with infections (Grade 3 or higher) in up to 6 cycles with a 95% probability.

4.0 PATIENTS TO BE SURVEYED

All the multiple myeloma patients on whom NINLARO has been administered should be surveyed.

5.0 DOSAGE AND ADMINISTRATION

In combination therapy with lenalidomide and dexamethasone, the usual adult dosage for oral administration is 4 mg as ixazomib, in the fasting state, once a day, once a week for 3 weeks (Days 1, 8, and 15), with a 13-day washout period (Days 16 through 28). This 4-week cycle will be repeated. The dose may be reduced appropriately according to the patient's condition. When administering the drug, refer to the Precautions listed in the package insert.

6.0 SCHEDULED NUMBER OF MEDICAL INSTITUTIONS BY CLINICAL DEPARTMENT

The survey should be conducted at all the medical institutions (including hematology department) in which NINLARO is used (estimated to be approximately 300 medical institutions).

7.0 METHOD

7.1 OBSERVATION PERIOD

Period from the start of NINLARO to after 6 cycles (4 weeks per cycle)

* Rationale for observation period

The second interim analysis (with the median number of treatment cycles in the NINLARO group: 17.0) of a global Phase 3 clinical study (C16010 study) revealed that adverse events had occurred in up to 6 cycles in 94% of the subjects in the NINLARO group who had continued 12 or more treatment cycles. Based on these results, it is considered that a number of subjects experienced some sort of adverse events in up to 6 cycles after the start of NINLARO and that, in relation to the events defined as important survey item, the initial onset of the event was generally observed in up to 6 cycles and the adverse events showed no tendency to increase in long-term administration of more than 6 cycles. Thus, the observation period was set to be the period from the start of NINLARO to after 6 cycles, considering that the safety profile of NINLARO should be confirmed generally in up to 6 cycles.

7.2 REQUEST TO AND CONTRACT WITH MEDICAL INSTITUTIONS

Paper-based survey sheets should be used. The person in charge from Takeda Pharmaceutical Company Limited (hereinafter, “Takeda’s person in charge”) should request medical institutions to conduct the survey on the premise that a written contract should be concluded with the institution. It is determined that Takeda’s person in charge should preliminary obtain a written agreement from the investigator which ensures the following (2) has been fully understood, and in principle deliver NINLARO after the contract is concluded. However, in case NINLARO is delivered/administered out of necessity before the contract is concluded, such cases should be retrospectively investigated and all cases that NINLARO is going to be administered should be surveyed.

(1) REQUEST FOR COOPERATION WITH THIS SURVEY

Takeda’s person in charge should request the investigator to cooperate with this survey by explaining the purpose, contents, and method of this survey (all-case surveillance, etc.) as well as information including proper use of NINLARO to him/her, in accordance with the “Request

for cooperation with the Drug Use-Results Survey," "Outline of Survey," "Patient Registration Sheet (sample)," "Survey Sheet (sample)," "Precautions and Instructions for Use," "Proper Use Guide," etc.

(2) PRELIMINARY UNDERSTANDING OF THE INVESTIGATOR

1) The medical institution has already decided to adopt NINLARO or intends to adopt NINLARO.
2) The medical institution should promptly conclude the contract for this survey.
3) The investigator should enroll patients before prescription of NINLARO or on the day of the prescription in compliance with the Outline of Survey for this survey.
4) The investigator should prepare the survey sheet for all cases administered NINLARO in compliance to the Outline of Survey for this survey.

(3) CONTRACT FOR THE SURVEY

Takeda's person in charge should, promptly after obtaining a written agreement from the investigator, conclude a written contract with the medical institution. Takeda's person in charge should bring the "Patient Registration Sheet" to the investigator.

7.3 PATIENT ENROLLMENT METHOD

The "Central Registration Method" using FAX should be used.

In this survey, the investigator prepares the "Patient Registration Sheet" for the patient to be surveyed and register the patient by sending it by FAX to the Central Registration Center (see Section 12.3) in principle before prescription of NINLARO or on the day of the prescription.

7.4 PREPARATION AND SUBMISSION OF SURVEY SHEETS

The investigator should prepare a survey sheet for the enrolled cases requiring survey sheet preparation promptly after completion of the observation period of each case, and the investigator should sign or print his/her name on and seal the sheet to submit to Takeda's person in charge. In case it cannot be confirmed that the patient has taken NINLARO, this should be included in the sheet. (Other items are not necessary.)

For cases in which NINLARO was discontinued due to some reasons in the middle of the observation period, the investigator should prepare a survey sheet promptly after the completion of necessary observation, and the investigator should sign or print his/her name on and seal the sheet to submit to Takeda's person in charge. However, for cases in which NINLARO was discontinued due to adverse events, they should be continuously observed even after the discontinuation as much as possible until the events are recovered/resolved or recovering/resolving. Then, the investigator should include the observation results in the survey sheet, and the investigator should sign or print the name on and seal the sheet.

7.5 CONFIRMATION OF ALL-CASE SURVEILLANCE

After transition to a period where preparation and submission of survey forms is not required, the physician in charge of the survey should, upon confirmation that the cases for which survey

sheets have been submitted are all those on whom NINLARO was started during the period requiring preparation and submission of the survey sheet, sign or print his/her name on and seal the "All-Case Surveillance Confirmation Form" to submit to Takeda's person in charge.

8.0 SCHEDULED PERIOD OF SURVEY

Survey period: from the date of marketing NINLARO to the time of lifting of approval conditions for all-case surveillance (planned in around March 2021)
Patient enrollment period: from the date of marketing NINLARO to the time of lifting of approval conditions for all-case surveillance Note)

Note) Time to transition from the period requiring preparation and submission of the survey sheet to the patient enrollment only period (not requiring preparation and submission of the survey sheet) should be determined with consultation with the Pharmaceuticals and Medical Devices Agency when the number of enrolled cases is estimated to reach the scheduled number of cases, based on the collection status of survey sheets and on confirmation that the targeted information can be obtained.
The number of enrolled cases is estimated to reach 480 in May 2018.

Since the number of patients enrolled has reached the planned number of 480 patients, for enrolled cases who started NINLARO by September 24, 2017 are required preparation and submission of survey sheet. Enrolled cases who started NINLARO from September 25, 2017 are not required preparation and submission of survey sheet.

Enrollment should continue until the approval conditions for all-case surveillance are lifted so that a system is maintained where survey sheets can be collected as necessary to obtain appropriate information.

9.0 SURVEY ITEMS

The investigator should include the following items in the Patient Registration Sheet and Survey Sheet. The schedule of this survey is indicated in [redacted]

9.1 ITEMS TO BE INCLUDED IN THE PATIENT REGISTRATION SHEET

1) Survey items

Name of the medical institution, name of the physician who filled out the Patient Registration Sheet, prescription date of NINLARO, patient identification number, patient's initials, gender, age, name of diagnosis, condition

2) Survey period

At the time of patient enrollment

9.2 ITEMS TO BE INCLUDED IN THE SURVEY SHEET

9.2.1 Survey sheet cover

Last entry date (month day, year) of the survey sheet, name of the physician who filled out the survey sheet

9.2.2 Patient characteristics

1) Survey items

Time of diagnosis of multiple myeloma (time of initial onset), type of multiple myeloma, clinical stage (ISS), IMWG diagnostic criteria, ECOG Performance Status, therapeutic category, virus testing, hepatic function disorder (presence/absence and details), renal function disorder (presence/absence and details), complications (presence/absence and details), medical history (presence/absence and details), height, weight, treatment of multiple myeloma before the start of NINLARO (presence/absence and details: pharmacotherapy, radiotherapy, hematopoietic stem cell transplant)

2) Survey period

At the start of NINLARO

9.2.3 Treatment

1) Survey items

Administration status of NINLARO/lenalidomide, and dexamethasone (date of starting the cycle, single dose, presence/absence of adjustment of single dose, treatment compliance status), confirmation of continuation/discontinuation of NINLARO, administration status of drugs used to prevent recurrence of infections and herpes zoster (presence/absence and name of the drug, duration of administration)

2) Survey period

Period from the start of NINLARO to after 6 cycles (or to the discontinuation of NINLARO)

9.2.4 Observation items

1) Observation items

Presence/absence of pregnancy during the observation period (for women only)

2) Survey period

Period from the start of NINLARO to after 6 cycles (or to the discontinuation of NINLARO)

9.2.5 Adverse events

1) Survey items

Presence/absence of adverse events (see Table 1), name of the adverse event*, date of onset, CTCAE Grade (worst grade and its date), seriousness and its reasons (see Table 2), treatment for the event (presence/absence and details), outcome assessment date, outcome, causal relationship with NINLARO** (see Table 3), changes in laboratory tests related to adverse events

If the outcome has been assessed to be not recovered/not resolved, follow-up surveillance should be conducted as much as possible.

* For peripheral nerve disorder, indicate symptoms of peripheral nerve disorder

** If NINLARO is assessed to be not related, obtain the rationale for assessment.

Note) Items to be concerned regarding adverse events

Abnormal exacerbation of the target disease, or exacerbation beyond the expected natural history of the disease should be considered as an adverse event.

Table 1 Definition of adverse events

An adverse event (AE) refers to any unfavorable medical event that has occurred to a patient administered with a drug. AEs do not necessarily refer to only events whose causal relationship with the administration of the drug is clear. In other words, AEs are any unfavorable events or unintended signs (including abnormalities in laboratory test results), or symptoms or diseases occurring when a drug is administered, in which presence/absence of the causal relationship with the drug administered does not matter.

Table 2 Assessment criteria for seriousness

1. Results in death (death) 2. Life-threatening (risk of death) "Life-threatening" indicates cases where a patient was at risk of death when the relevant event occurred. It does not mean a hypothetical indication that had the event been severer the patient would have died. 3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization) 4. Results in persistent or significant disability or incapacity (disorder) 5. Congenital anomaly/birth defect (congenital anomaly) 6. May not be immediately life-threatening or lead to death or hospitalization but requires treatments to prevent the outcomes such as the above 1 to 5, or places patients at risk.

* Note that Takeda Pharmaceutical Company Limited will consider an adverse event listed on the "Takeda Medically Significant AE List" ([redacted]) as a serious adverse event if such event is reported.

Table 3 Assessment criteria for the causal relationship between adverse events and NINLARO

Assessment	Assessment criteria
Related	An adverse event in which there is a temporal relationship with the drug (including the time lapse after the discontinuation) or whose causal relationship cannot be ruled out because there is at least a reasonable possibility that the drug is involved, despite other suspected factors such as underlying diseases, complications, concomitant drugs, and concomitant treatment.

Not related	An adverse event in which there is no temporal relationship with the drug or which can be very likely caused by other factors such as underlying diseases, complications, concomitant drugs, and concomitant treatment.

2) Important survey items

Detailed information on the following events, considered as important survey items, will be collected as much as possible if they occur.

- Thrombocytopenia
- Severe gastrointestinal disorder
- Skin disorder
- Peripheral nerve disorder
- Infections

* Rationale for important survey items

Among the important identified risks, important potential risks, and their related events listed in the Risk Management Plan, the events above were determined as important survey items based on the following reasons:

a) Thrombocytopenia

The profile (incidence, severity, actions to be taken, etc.) of this event occurring in Japanese patients in clinical use will be confirmed because the incidence of event related to thrombocytopenia was higher in the ixazomib group than that of the placebo group in a global Phase 3 clinical study [C16010 study].

b) Severe gastrointestinal disorder

The profile (incidence, severity, actions to be taken, etc.) of this event occurring in Japanese patients in clinical use will be confirmed because the incidence of gastrointestinal disorder was higher in the ixazomib group than that of the placebo group, and particularly severe gastrointestinal disorder was observed in many subjects in the ixazomib group in a global Phase 3 clinical study [C16010 study].

c) Skin disorder

The profile (incidence, severity, actions to be taken, etc.) of this event occurring in Japanese patients in clinical use will be confirmed because the incidence of skin disorder was higher in the ixazomib group than that of the placebo group and severe skin disorder was observed in many subjects in the ixazomib group in a global Phase 3 clinical study [C16010 study].

d) Peripheral nerve disorder

The profile (incidence, severity, etc.) of this event occurring in Japanese patients in clinical use will be confirmed because the incidence of peripheral nerve disorder was higher in the ixazomib group than that in the placebo group and the event more frequently led to withdrawal, dose-reduction, and discontinuation of the investigational drug in the global Phase 3 clinical study [C16010 study].

e) Infections

Infections were highly frequently observed in a global Phase 3 clinical study (C16010 study). The incidence of herpes infections was higher in the ixazomib group than in the placebo group. Therefore, the incidence of this event occurring in Japanese patients in clinical use and the administration status of prophylactic drugs will be confirmed.

3) Survey period

Period from the start of NINLARO to after 6 cycles (or to the discontinuation of NINLARO)

10.0 ANALYSIS ITEMS AND METHOD

10.1 ITEMS RELATED TO CASE STRUCTURE

The number of enrolled patients, number of cases whose survey sheets were collected, number of cases subject to safety evaluation, number of cases excluded from evaluation, and reasons for exclusion should be aggregated.

10.2 PATIENT CHARACTERISTICS

Patient characteristics including the gender, age, duration of multiple myeloma, and complications should be aggregated.

10.3 TREATMENT

The administration status of NINLARO, lenalidomide and dexamethasone, and administration status of drugs used to prevent recurrence of infections or herpes zoster should be aggregated.

10.4 ITEMS RELATED TO SAFETY

The following items should be aggregated in cases subject to safety evaluation. Adverse events should be rephrased using MedDRA/J and summarized in Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Incidence of adverse events

The frequencies of adverse events which occurred during the observation period should be aggregated according to the type, time of onset, seriousness, causal relationship with NINLARO.

10.4.2 Factors that may affect the safety

The frequencies of adverse reactions which occurred during the observation period should be aggregated according to the classification, such as patient characteristic factors, (age, presence/absence of renal complications, presence/absence of hepatic complications, etc.) and the administration status of NINLARO.

10.5 INTERIM ANALYSIS

In order to swiftly evaluate, analyze, and if necessary, publish the safety information obtained from this survey, cases on which safety evaluation can be conducted among those whose survey sheets were collected up to 1 year after the start of this survey will be analyzed in the same manner as Sections 10.1 through 10.4.

11.0 REGISTRATION OF SURVEY INFORMATION

Information about this survey should be registered to the following public website before the start of this survey:

- Japan Pharmaceutical Information Center-Clinical Trials Information

12.0 ORGANIZATIONAL STRUCTURE

12.1 SUPERVISOR

Supervisor of post-marketing surveys, etc.,
Takeda Pharmaceutical Company Limited

12.2 MEDICAL ADVISOR

Provides advice on preparation and revision of study protocols, preparation and revision of clinical study reports, and the conduct of the survey with medical judgment.

[redacted]

12.3 CENTRAL REGISTRATION CENTER

[redacted]

13.0 CONTRACT RESEARCH ORGANIZATION

(1) [redacted]

(2) [redacted]

(3) [redacted]

Contracted services: Data management services, “storage of records, etc.” and “conversion of adverse events, etc. into a PDF format and support for provision of related information”

14.0 OTHER NECESSARY MATTERS

14.1 REVISION OF THE PROTOCOL

During the survey period, the progress of survey, occurrence of adverse reactions and serious adverse reactions that cannot be predicted from the Precautions, presence/absence of elevated frequency of specific adverse reactions, and appropriateness of survey items should be understood, and if necessary, this Protocol should be reviewed and revised. Additionally, approval for a partial change in the Dosage and Administration or Indications is obtained during the survey period, the necessity to revise this Protocol should be discussed and the Protocol should be revised, where necessary.

14.2 ACTIONS TO BE TAKEN IF PROBLEMS AND QUESTIONS ARISE

If any problem is found in the safety, data should be reviewed to take actions.