Clinical Study Protocol

NCT Number: NCT05882279

Title: Evaluation of the Effectiveness of Risk Minimization Measures: A survey among pharmacists to assess the impact of the RMP material for patients on promoting the proper use of NINLARO in Japan

Study Number: C16065

Document Version and Date: Version 1.0 / 20-Apr-2023

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

NON-INTERVENTIONAL SAFETY STUDY PROTOCOL

Study title: Evaluation of the Effectiveness of Risk Minimization Measures: A survey among pharmacists to assess the impact of the RMP material for patients on promoting the proper use of NINLARO in Japan

Study number: C16065

Version number: Version 1.0 (20 April 2023)

Ethics statement: This study will be conducted in compliance with the protocol, the Declaration of Helsinki, International Society for Pharmacoepidemiology Guidelines for Good Epidemiology Practices, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guidelines for Methodological Standards in Pharmacoepidemiology, Good Pharmacovigilance Practices, and all applicable regulatory requirements.

Signature page

Study title: Evaluation of the Effectiveness of Risk Minimization Measures: A survey among pharmacists to assess the impact of the RMP material for patients on promoting the proper use of NINLARO in Japan

Study number: C16065

Version number: Version 1.0 (20 April 2023)

MAH (Marketing Authorization Holder):

Role	Head of Safety Management, Global Patient Safety Evaluation Japan	**Printed Name**	[redacted] Director, Global Patient Safety Evaluation Japan, Takeda Development Center Japan Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome Chuo-ku, Osaka 540-8645, Japan
Signature		**Date (DD-MMM-YYYY)**	

EU and UK QPPV:

Role	European Union (EU) Qualified Person responsible for PV (QPPV) and UK (United Kingdom) QPPV	**Printed Name**	[redacted] Global Patient Safety Evaluation Takeda Belgium NV Leonardo da Vincilaan 7, 1930

			Zaventem, Belgium
Signature		**Date (DD-MMM-YYYY)**	

Study information

Title	Evaluation of the Effectiveness of Risk Minimization Measures: A survey among pharmacists to assess the impact of the RMP material for patients on promoting the proper use of NINLARO in Japan
Protocol number	C16065
Protocol version identifier	1.0
Date of last version of protocol	Not Applicable
EU PAS register number	TBD
Active substance	ixazomib citrate (ATC code: L01XG03)
Medicinal product	NINLARO 2.3 mg hard capsules NINLARO 3 mg hard capsules NINLARO 4 mg hard capsules
Product reference	Not Applicable
Procedure number	Not Applicable
Joint PASS	No
Research question and objectives	The overall research question is to investigate whether the RMP material for patients (dosing instruction), which is defined as an additional risk minimization measure in J-RMP, is utilized for the proper use of NINLARO. Primary Objective: To assess the frequency of pharmacists who have provided patients with the contents of the RMP material for patients Secondary Objective: • To assess the frequency of pharmacists who have obtained the RMP material for patients • To evaluate the depth of understanding of proper usage of NINLARO among pharmacists
Country(-ies) of study	Japan
Author	Global Patient Safety Evaluation Japan, Takeda Development Center Japan
Marketing authorization holder(s)	TAKEDA PHARMACEUTICAL COMPANY LIMITED 1-1, Doshomachi 4-chome Chuo-ku, Osaka 540-8645, JAPAN

MAH Contact Person	[redacted] Director, Global Patient Safety Evaluation Japan, Takeda Development Center Japan Takeda Pharmaceutical Company Limited [redacted]

TABLE OF CONTENTS

1.0 LIST OF ABBREVIATIONS

Abbreviations	Definition
ADR	adverse drug reaction
AE	adverse event
CCDS	Company Core Data Sheet
HCP	healthcare professional
IRD	ixazomib, lenalidomide and dexamethasone
PI	proteasome inhibitor
PQC	product quality complaint
RMP	risk management plan
rrMM	relapsed/refractory multiple myeloma
SAE	serious adverse event
SOP	standard operating procedure
SSR	special situation report

2.0 RESPONSIBLE PARTIES

Sponsor

TAKEDA PHARMACEUTICAL COMPANY LIMITED
1-1, Doshomachi 4-chome Chuo-ku, Osaka 540-8645, JAPAN

Principal Investigator:

[redacted]

Director, Global Patient Safety Evaluation Japan, Takeda Development Center Japan

Takeda Pharmaceutical Company Limited

[redacted]

Co-investigator:

[redacted]

Subcontractor on survey implementation

Medilead, Inc.
Tokyo Opera City Tower, 24F 3-20-2 Nishishinjuku, Shinjuku-ku, Tokyo 163-1424 JAPAN

3.0 ABSTRACT

Title

Evaluation of the Effectiveness of Risk Minimization Measures: A survey among pharmacists to assess the impact of the RMP material for patients on promoting the proper use of NINLARO in Japan

Rationale and background

Ixazomib (NINLARO) is an oral, highly selective, and reversible proteasome inhibitor (PI). Ixazomib preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome. Ixazomib is administered as a citrate ester, designated ixazomib citrate. Ixazomib citrate, a prodrug, rapidly hydrolyses under physiological conditions to its biologically active form, ixazomib.

Ixazomib is approved in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed/refractory multiple myeloma (rrMM) in a total of 72 countries worldwide as of 19 Nov 2022. In Japan, ixazomib is approved in combination with lenalidomide and dexamethasone for the indications of rrMM was approved on 30 Mar 2017 and was launched under the name of NINLARO on 24 May 2017.Each drug is dosed with different dosing schedules as follows:

- Ixazomib is dosed on Days 1, 8, 15 of a 28-day treatment cycle.
- Lenalidomide is dosed on Days 1 through 21 of a 28-day treatment cycle.
- Dexamethasone is dosed on Days 1, 8, 15, and 22 of a 28-day treatment cycle.

Overdose of ixazomib in combination with lenalidomide and dexamethasone (IRD therapy) has been reported in sponsored clinical trials, Investigator-Initiated Sponsored Research studies, and post-marking phase. Some of the overdoses have been associated with serious adverse events including multiple organ failure and death. Based on the safety signal evaluation of accidental overdose, overdose was endorsed as an identified risk of ixazomib. To minimize the risk of overdose, it is essential to ensure providers and patients understand the importance of adhering to the prescribed dosing schedule. The risk of overdose is described in Company Core Data Sheet (CCDS). As part of RMP in Japan (J-RMP), Takeda created the RMP material for patients to instruct the dosing of IRD therapy and has been distributed to patients via healthcare professional (HCP)s since its launch in Japan, in May 2017.

This web survey is planned to assess the effectiveness of distributed RMP material in prevention of ixazomib overdose in Japanese clinical practice.

Research question and objectives

The overall research question is to investigate whether the RMP material for patients (dosing instruction), which is defined as an additional risk minimization measure in J-RMP, is utilized for the proper use of NINLARO.

Primary Objective:

To assess the frequency of pharmacists who have provided patients with the contents of the RMP material for patients

Secondary Objective:

- To assess the frequency of pharmacists who have obtained the RMP material for patients
- To evaluate the depth of understanding of proper usage of NINLARO among pharmacists

Study design

This web-based survey is intended for pharmacists who have instructed the dosing of IRD therapy to patients with rrMM. The survey will be self-administered via the web (i.e., the Internet). The questionnaires will be provided in Japanese.

Population

As most IRD therapy are prescribed as in-hospital prescriptions in Japan, in-hospital pharmacists are mainly involved in the explanation of how to take NINLARO in IRD therapy.

Pharmacists included in Nikkei Research Access Panel, active in clinical practice, and with valid contact details who meet the inclusion criteria, as listed in Section 8.2.2, will be randomly selected to participate in the survey.

Inclusion criteria

The survey will be conducted among pharmacists meeting the following inclusion criteria:

- Pharmacists who belong to hospitals prescribing NINLARO
- Pharmacists who have instructed the dosing of NINLARO in IRD therapy to patients

Exclusion criteria

None

Variables

In order to address the study objectives, the following information will be collected:

- Information on participating pharmacists (work experience, specialty)
- Information on hospitals where pharmacists are working (hospital type, number of beds/pharmacists, specialty)
- Information on the status of providing patients with the contents of the RMP material for patients
- Information on recollection of having obtained the RMP material for patients
- Information on pharmacists' awareness of the proper use of NINLARO
- Information on preferences for materials, etc.

Data sources

The survey is a primary data collection among pharmacists who have instructed the NINLARO dosing for IRD therapy to patients.

Study size

The sample size of 300 pharmacists was set. When n = 300, the width of the two-sided 95% confidence interval of the response ratio in the binary response questionnaire will be ± 5.7% at the maximum.

Data analyses

Demographics and other baseline characteristics of participants will be summarized.

For each question, the number and/or percentage of participants who responded for each answer option is calculated. Cross-tabulations are also performed between participants' backgrounds and/or questions, as appropriate.

Milestones

Start of data collection	June 2023
End of data collection	June 2023
Study results	July 2023

4.0 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	20 April 2023	N/A	N/A	Initial protocol

5.0 MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	June 2023	<date>	<text>
End of data collection	June 2023	<date>	<text>
Registration in the EU PAS register	May 2023	<date>	<date>
Study results	July 2023	<date>	<text>

6.0 RATIONALE AND BACKGROUND

Ixazomib is an oral, highly selective, and reversible PI. Ixazomib preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome. Ixazomib is administered as a citrate ester, designated ixazomib citrate. Ixazomib citrate, a prodrug, rapidly hydrolyses under physiological conditions to its biologically active form, ixazomib.

Ixazomib is approved in combination with lenalidomide and dexamethasone for the treatment of patients with rrMM in a total of 72 countries worldwide as of 19 Nov 2022. In Japan, ixazomib is approved in combination with lenalidomide and dexamethasone for the indications of rrMM was approved on 30 Mar 2017 and was launched under the name of NINLARO on 24 May 2017. Each drug is dosed with different dosing schedules as follows.

- Ixazomib is dosed on Days 1, 8, 15 of a 28-day treatment cycle.
- Lenalidomide is dosed on Days 1 through 21 of a 28-day treatment cycle.
- Dexamethasone is dosed on Days 1, 8, 15, and 22 of a 28-day treatment cycle.

Overdose of ixazomib in combination with lenalidomide and dexamethasone(IRD therapy) has been reported in sponsored clinical trials, Investigator-Initiated Sponsored Research studies, and post-market. Some of the overdoses have been associated with serious adverse events including multiple organ failure and death. Based on the safety signal evaluation of accidental overdose, overdose was endorsed as an identified risk of ixazomib. To minimize the risk of overdose, it is essential to ensure providers and patients understand the importance of adhering to the prescribed dosing schedule. The risk of overdose is described in CCDS. Takeda created the RMP material for patients to instruct the dosing of IRD therapy and has been distributed to patients via HCPs since the launch in Japan, in May 2017.

This web survey is planned to assess the effectiveness of distributed RMP material in prevention of ixazomib overdose in Japanese clinical practice.

7.0 RESEARCH QUESTION AND OBJECTIVES

The overall research question is to investigate whether the RMP material for patients (dosing instruction), which is defined as an additional risk minimization measure in J-RMP, is utilized for the proper use of NINLARO.

Primary Objective:

To assess the frequency of pharmacists who have provided patients with the contents of the RMP material for patients

Secondary Objective:

- To assess the frequency of pharmacists who have received the RMP material for patients
- To evaluate the depth of understanding of the proper use of NINLARO among pharmacists

8.0 RESEARCH METHODS

8.1 STUDY DESIGN

This web-based survey is intended for pharmacists who have instructed the dosing of IRD therapy to patients with rrMM. The survey will be self-administered via the web (i.e., the Internet). The questionnaires will be provided in Japanese.

8.2 SETTING

8.2.1 Study population

As most IRD therapy are prescribed as in-hospital prescriptions in Japan, in-hospital pharmacists are mainly involved in the explanation of how to take NINLARO in IRD therapy.

Pharmacists included in Nikkei Research Access Panel, active in clinical practice, and with valid contact details who meet the inclusion criteria, as listed in Section 8.2.2, will be randomly selected to participate in the survey.

8.2.2 Inclusion criteria

The survey will be conducted among pharmacists meeting the following inclusion criteria:

- Pharmacists who belong to hospitals prescribing NINLARO
- Pharmacists who have instructed the dosing of NINLARO in IRD therapy to patients

8.2.3 Exclusion criteria

None

8.2.4 Recruitment Process

Recruitment will be conducted as follows:

- Based on the information from the Nikkei Research Access Panel, pharmacists working in hospitals with experience in prescribing NINLARO will be invited to participate in the survey via e-mail and portal site, in accordance with local requirements. The survey background and objectives, the contact information for questions, the intended use of data, and the proposed compensation will be explained to the pharmacists at this step.
- If the pharmacists agree to participate in the survey, they will access the link for the web questionnaire and answer it following the instructions. If the questionnaire is started but not yet completed, the pharmacist will be sent a reminder by e-mail.

8.3 VARIABLES

In order to address the study objectives, the following information will be collected (all questionnaires using options):

- Information on participating pharmacists
  - Work experience
  - Specialty (with or without licenses related to cancer therapy)
- Information on hospitals where pharmacists are working
  - Hospital type
  - Number of beds
  - Number of pharmacists
  - Specialty (with or without cancer central hospitals designation)
- Information on the status of providing patients with the contents of the RMP material for patients
  - Status of providing patients with NINLARO dosing schedule
  - For pharmacists who provide patients with NINLARO dosing schedule, materials that have been used for explanation
- Information on recollection of having obtained the RMP material for patients
- Information on pharmacists' awareness of the proper use of NINLARO
  - Understanding of the proper NINLARO dosing schedule
  - Understanding of the importance of providing NINLARO dosing schedule
- Information on preferences for materials, etc.
  - Self-perceived awareness of RMP for NINLARO
  - Factors to look for in materials for patient
  - Preferred media (paper / electronic)

8.4 DATA SOURCES

The survey is a primary data collection among pharmacists who have instructed the NINLARO dosing for IRD therapy to patients. Sampling will be done based on the information from Nikkei Research Access Panel. Potential respondents will be invited to participate in the survey via e-mail and portal site, in accordance with local requirements. If the pharmacists agree to participate in the survey, they will access the link for the web questionnaire in the e-mail or "my page" on the portal site and answer the questionnaire following the instructions. The data will be collected in a web questionnaire, which will be filled in by the participating pharmacist.

8.5 STUDY SIZE

The sample size (the targeted final analysis set) of 300 pharmacists was set. When n = 300, the width of the two-sided 95% confidence interval of the response rate in the binary response questionnaire will be ± 5.7% at the maximum.

8.6 DATA MANAGEMENT

Data collection will be carried out by Medilead, Inc. via web questionnaire in accordance with their applicable standard operating procedures (SOPs). Collected data will be entered and stored in a secure server for this survey. The statistical analysis will be conducted using ASSUM.

8.7 DATA ANALYSIS

The baseline characteristics of participants will be summarized.

For each question, the number and/or percentage of participants who responded for each answer option is calculated. Cross-tabulations are also performed between participants' backgrounds and/or questions, as appropriate.

8.8 QUALITY CONTROL

Medilead, Inc, will create the raw data set (data cleaning), cross-tabulation tables, and survey result report, according to their procedures.

8.9 LIMITATIONS OF THE RESEARCH METHODS

The potential for selection bias of pharmacists participating in a survey is an inherent bias/limitation to any study based on volunteer participation. In this study, sampling will be done based on the information from the Nikkei Research Access Panel. It doesn't include all pharmacists working in hospitals with experience in prescribing NINLARO so that the generalization and external validity of the results is restricted. In addition, participants have to be willing (and able) to answer a questionnaire online. These pharmacists may not be fully representative of the whole targeted population (1).

In terms of exposure bias, pharmacists may have potential conflicts of interest with the survey.

Recall bias is minimized through broad sampling to include respondents with varying lengths of exposure to the RMP material and having experience in prescribing NINLARO.

Pharmacists will be allowed to participate only once. The format will allow for the questionnaire to be started but saved and completed at another time. Thus, stakeholder bias or unverified respondents are not applicable. A Reminder will be sent by e-mail to both non-responders and those who started but not yet completed to reduce non-response bias.

Web surveys may promote social desirability bias which refers to the tendency of pharmacists to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behavior. Social desirability can affect the validity of survey research findings regarding the knowledge

of both RMP and the proper usage of NINLARO, but the use of prepopulated items in the questionnaire could reduce this bias (2).

9.0 PROTECTION OF HUMAN SUBJECTS

The survey is non-interventional. HCP information such as name and e-mail address will not be linked in any way to the answers provided by the HCPs and all answers will be anonymous to the study sponsor. Data collected will remain absolutely confidential, and only aggregated data will be analyzed and communicated in a report.

9.1 ETHICAL AND REGULATORY CONSIDERATIONS

The survey will follow the regulatory and ethical requirements in Japan.

The objective of this study is not to influence physicians' prescribing behaviour by any means.

9.2 HCP INFORMATION AND CONFIDENTIALITY

Persons participating in the study will be informed of the targets of the investigation, the intended use of data, and recipients of these data. The answers provided will be collected in an anonymous way.

Data will be recorded in a central database and will include security elements to prevent others than authorized staff from accessing data.

10.0 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

10.1 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

10.2 SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or results in prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect
- Is a medically important event

  Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3 ADVERSE DRUG REACTIONS

An Adverse Drug Reaction (ADR) is “a response to a medicinal product which is noxious and unintended.” Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a possibility.

10.4 PRODUCT QUALITY COMPLAINTS

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, strength, purity, effectiveness, or performance of a product or device and combination product after it is released for distribution.

10.5 SPECIAL SITUATION REPORTS

A Special Situation Report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure
- Breastfeeding: Infant exposure from breast milk
- Overdose: All information of any accidental or intentional overdose
- Drug abuse, misuse, or medication errors: All information on medicinal product abuse, misuse or medication error (potential or actual)
- Gathering detailed information for AEs occurring in the pediatric or elderly population, as described in GVP Module VI
- Lack of efficacy of Takeda product
- Accidental/Occupational exposure
- Use outside the terms of the marketing authorization, also known as “off-label”

Information on the below situations, if received, should be collected and transmitted to GPSE (PV) although they are not considered special situations per GVP Module VI:

- Suspected transmission of an infectious agent: All information on a suspected (in the sense of

confirmed or potential) transmission of an infectious agent by a medicinal product.

- Use of falsified / counterfeit medicinal product
- Drug-drug interactions and drug-food interactions
- Inadvertent or accidental exposure with or without an AE

A SSR should be reported even if there is no associated AE.

10.6 COLLECTION AND NOTIFYING OF ADVERSE EVENTS, SPECIAL SITUATION REPORTS AND PRODUCT QUALITY COMPLAINTS TO TAKEDA PHARMACOVIGILANCE

Safety events spontaneously notified to the investigator(s) or research team

If during the conduct of the study the investigator(s) or a member of the research team is spontaneously informed by a HCP or patient of an SAE, AE, ADR, SSR or PQC where the event/complaint pertains to a Takeda product (or unbranded generic), such information should be notified to the relevant Takeda Pharmacovigilance department within **1 working day for fatal or life-threatening SAEs, within 4 calendar days for other SAEs, and within 7 calendar days for all other events**. As such reports are spontaneously notified, causality of any adverse events should be assumed unless there is evidence to the contrary.

- **AE reports and SSRs shall be reported to** [redacted]
- **PQCs shall be reported to** [redacted]

11.0 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study results will be submitted possibly for publication in a peer-review journal.

12.0 REFERENCES

(1) Wyatt JC. When to use web-based surveys. J Am Med Inform Assoc 2000; 7(4):426–9.

(2) Nederhof AJ. Methods of coping with social desirability bias: A review. Eur. J. Soc. Psychol. 1985; 15(3):263–80.

ANNEX 1 LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Version 1.0	20 April 2023	NINLARO_RMM Effectiveness Study_Questionnaire