Protocol No. 212853

Shingrix for intramuscular injection
Drug Use Investigation

Protocol

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Contents

1. Objectives

To assess the presence or absence of issues and concerns related to safety of Shingrix under practical use conditions.

2. Safety Specification

Safety specification in this investigation are as follows;

- Shock and anaphylaxis
- Potential Immune-Mediated Disease (pIMD)

3. Target Population

Persons vaccinated with Shingrix for the first time, for the purpose of preventing zoster.

4. Target number of subjects

1. Target sample size
   15,000 dose (over 7,500 subjects): To obtain data of 15,000 doses of vaccination, addition of subjects will be discussed as necessary.
2. Rationale
   To collect more safety information in Japanese, this investigation targets to collect data of 15,000 dose (more than 7,500 subjects). From the data of 15,000 dose, this investigation have a power of 95% to detect at least one and more cases of unspecified adverse events with an incidence of 0.02% at vaccination.

5. Investigation Period

Investigation Period: From August 2020 to March 2025

Observation period: 30-day period after each dose (day of vaccination designated as Day 1) for each subject.

Registration Period: From August 2020 to June 2024

Registration may be terminated prior to the expiration, if the planned number of doses of vaccination is achieaved earlier.

6. Number of Investigational Sites by department

Medical institutes, mainly internal medicine, where agreed to be participate in this investigation (approximately 1,000 sites)

7. Investigation Methods

This is prospective investigation. The enrolment of subject and data collection will be operated via Electronic Data Capture (hereinafter referred to as EDC) system.

1. Proposal for investigation and contract with investigational site
   1) At the medical institutions where Shingrix has been already introduced and delivered, medical representative (MR) explain the objectives, target population, investigation items and methods to the physicians and ask for their participation to this investigation.
   2) If the physician agrees to participate to this investigation, a written contract will be concluded with the head of the medical institute (e.g., hospital director) before the start of investigation at the investigational site.
2. Obtaining informed consent

Investigator give a full explanation to vaccinated person (and/or person's representative) of information regarding participation in this investigation and publication of the study results using Informed Consent Form(ICF), and obtain his/her (and/or person's representative's) signature or name/seal and date of consent. Once a informed concent is obtained from vaccinated person (and/or person's representative), investigator put that information into the Enrollment form by marking in a checkbox for "Yes, informed concent is obtained". The obrained ICF will not be submitted to MR.

If vaccinated person (and/or person's representative) withdraw his/her consent during the study period, investigator report it in written form.

3. Enrolment of investigational subject

   This investigation will be conducted with central registration style.

   1） Before Shingrix immunization, investigator ask person expected to be vaccinated to fill in pre-immunization questionnaire as usual, and judge whether the person is adequate for immunization based on the questionnaire and interview.
   2） Investigator inoculate Shingrix to the person who is adequate for vaccination.
   3） Investigator give a Health observation form to the vaccinated person who agreed to be participate to this investigation (hereinafter referred to as subject), and ask her/him to write down any symptom or any changes of physical condition they had during 30 days observation period after immunization.
   4） Investigator register the subject by inputing required information into EDC system within eight days after initial vaccination with Shingrix (day of vaccination designated as Day 1).
   5） Investigator will terminate the registration once as many subjects as contracted have been registered, or when the registration period has ended.

4. Data collection and data entry into EDC system.

   1） Investigator input data of investigation items, i.e. subject background etc.
   2） At the visit after the 30-day observation period following each vaccination (day of vaccination designated as Day 1), the investigator make sure whether post-vaccination adverse events are presence or not and its details if any, by checking the Health observation form and/or interviewing from subject under routine clinical practice.
   3） If there is no visit by subject or no Health observation form is sent back to investigator, the investigator try to obtain safety information by phone or some other way, as possible.
   4） Investigator input and send data of investigation items obtained after observation period via EDC system.

8. Investigation items

Investigator collect following investigation items as possible under routine clinical practice, and input data into EDC system.

1. Information on the medical institute

   Name of the medical institute, name of the department, name of the investigator

2. Subject Information

   Identification number (number for management in each site), sex, year of birth or age at the time of the initial vaccinationSubject

3. Background

Experience of zoster vaccine immunization, whether applicable for “Individuals who require careful administration” in package insert, underlying disease (including allergy for drug and food), medical history, presence/absence of immune-abnormality [underlying disease relating to immune-abnormality, past-medications (drug thought to be affecting immunity and, the period of dose), past therapies (therapy thought to be affecting immunity, and the period of therapy)]

4. Vaccination status
   Presence or absence of vaccination, date of vaccination, lot number, route of vaccination, site of vaccination, body temperature before vaccination, symptoms before vaccination, reason of discontinue vaccination
5. Vaccines except for Shingrix inoculated during observational period
   Presence or absence of vaccines except Shingrix inoculated during observational period (including simultaneously inoculated vaccines), names of vaccines, date of vaccination and site of vaccination
6. Medication during observational period
   Presence or absence of drugs used during observational period, name of drug, duration of use, the reason for use
7. Therapy duringobservation period
   Presence or absence of therapy conducted during observation period and name and date of the therapy, the reason for conducting therapy.
8. Pregnancy / Breast-feeding
   If subject is female, presence or absence of pregnancy at the timing of vaccination and during observational period. Expected date of delivery.
   For the outcomes like birth, abortive birth, artificial abortion and adverse events etc., conduct follow up investigation of mother and baby, as possible.
9. Adverse Event
   Presence or absence of solicited/non-solicited adverse events after Shingrix vaccination.
   Name of adverse event (diagnosis or symptom), date of onset, outcome of the adverse event, date of outcome, severity (grade), seriousness, reason for seriousness, causal relationship to Shingrix, potential causative factors other than Shingrix
   1） To understand vaccine related adverse events and safety specification for Shingrix, all adverse events (diagnosis, symptom or abnormality of laboratory test etc.) after vaccination with Shingrix will be collected regardless the causal relation.
   Causal relativity to the adverse event will be assessed by investigator as “YES” or “NO” depending on presence or absence of possible reasonable cause.
   2） The adverse event which assessed YES for causal relativity will be handled as potentially “vaccine related adverse reaction”.

Solicited adverse events The following adverse events reported within 7 days after vaccination (day of vaccination designated as Day 1): Adverse events at injection site ; pain , redness and swelling Systemic adverse events; myalgia, fatigue, headache, shivering, fever and gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain) Non solicited adverse events

Adverse events other than solicited adverse events that are observed within 30 days after vaccination with Shingrix (day of vaccination designated as Day 1), including specific symptoms as above reported at least 8 days after vaccination

* If safety specification ‘Shock and anaphylaxis” or ‘Potential Immune-Mediated Disease (pIMD)” was reported, detailed information will be requested.
* In other case of adverse event, detailed information may be requested, if necessary.

9. Analytical Items and Methods

Detailed analytical plan is determined in Statistical analytice plan.

1) Analysis items
   (1) Items related to subject composition
      ① Number of subjects registered, number of subjects for whom the CRF is collected, and number of subjects for whom information is collected
      ② Number of subjects included in safety analysis, number of subject excluded from analysis, and reasons for exclusion
      ③ Number of subjects per vaccination included in safety analysis (each dose and cumulative), number of subjects per vaccination excluded from analysis, and reasons for exclusion
   (2) Items related to safety
      ① Occurrence of vaccine related adverse reaction and infections (type, severity, incidence proportion, etc.)
      ② Occurrence of safety specifications

2) Analytical methods
   (1) Safety
      Calculate incidence proportion of vaccine related adverse reaction.
   (2) Consideration of covariates
      Consideration for covariates which may relate to safety (incidence proportion of vaccine related adverse reaction) by calculation odds ratio and 95% confidence interval, figure out forest-plot if necessary.

10. Organization Structure for Implementation of the Investigation

See Appendix 5.

11. Name and address of the contractor of this investigation, and scope of contracted tasks

Scope of contracted tasks: Subject registration, data management, statistical analysis, EDC and EDC related activities, and other related operations
Contractor: CMIC Co.,Ltd
Address: 1-1-1, Shibaura, Minato-ku, Tokyo

12. Timing and rationale of milestones to evaluate of the results or report to the Pharmaceuticals and Medical Devices Agency (PMDA)

- At timing of Periodic Safety Report. We report an implementation status and result obtained in the period to PMDA to conduct a comprehensive review of safety information.
- At the timing of re-examination of Shingrix. We submit final report based on all fixed data collected in this investigation.

13. Possible additional measure and the decision criteria, which may be taken by the results of this investigation

We review Shingrix RMP at the timing of submitting Periodic Safety Report.
If problems are found from the results of this investigation during or at the end of evaluation, following items will be considered; necessity of additional safety specifications, revision of this investigation, necessity of additional risk minimization plan, and/or conduction of new drug use investigation or post-marketing clinical study if necessary.

14. Publication of the results

For the purpose of "proper use" and "safety assurance" of Shingrix, the final results of this investigation will be published, moreover interim analysis may be provided to clinical setting, if necessary. Outline of plan and result will be disclosed in GSK Clinical Study Register and ClinicalTrials.gov.

15. Other necessary items

1) Protocol Amendments
   Progress, number of drop out subjects, emergence of unknown or severe adverse events, significant incrementation of specific adverse event and propriety of investigation items are usually watched during investigation period, and in case of necessity, protocol of this investigation will be revised.
   PMDA will be notified of change to the protocol beforehand unless it is a minor change.
2) Measures to be taken when issues and concerns were detected
   Additional special drug use investigation or post-marketing clinical trial will be considered if issues or concerns were found from the results of assessment/analysis during the study period or after the completion of drug use investigation.

16. Appendix

1)	Drug Use Investigation of Shingrix Implementation Outline	Attachment 1
2)	Drug Use Investigation of Shingrix Registration Form (EDC)	Attachment 2
3)	Drug Use Investigation of Shingrix Case Report Form (EDC)	Attachment 3
4)	Drug Use Investigation of Shingrix Health Observation Form	Attachment 4
5)	Organizational structure for post-marketing surveillance	Attachment 5