CONFIDENTIAL

SYNOPSIS

Name of finished product: Shingrix for Intramuscular Injection

Name of active substance: Varicella-zoster virus gE antigen 50 μg

Title: Shingrix for Intramuscular Injection Drug Use Investigation

OBJECTIVES

Primary Objective
To assess the presence or absence of issues and concerns regarding safety of Shingrix for Intramuscular Injection (hereinafter referred to as "Shingrix") under practical use conditions.

Secondary Objectives:
N/A

Other Objectives:
N/A

STUDY POPULATION
The target population of this investigation is individuals to receive Shingrix for the first time to prevent herpes zoster, for which Shingrix is indicated.

METHODOLOGY
Primary data collection, single cohort study, the percentage of subjects with ADRs

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.

RESULTS

ADRs were reported in 6,406 of the 7,707 subjects in the safety analysis set of the drug use investigation, and the percentage of subjects with ADRs was 83.1% (6,406/7,707). By MedDRA SOC, ADRs classified under the "General disorders and administration site conditions" (82.6%, 6,365/7,707) were observed in the highest percentage of subjects, followed by those under the "Musculoskeletal and connective tissue disorders" (41.0%, 3,161/7,707) and the "Nervous system disorders" (33.3%, 2,564/7,707). The most commonly reported ADR was "vaccination site pain" (78.8%, 6,070/7,707), followed by "vaccination site swelling" (54.4%, 4,191/7,707) and "vaccination site erythema" (52.8%, 4,070/7,707). Serious ADRs were reported in 0.1% (5/7,707) of the 7,707 subjects in the safety analysis set. Reported serious ADRs were "rheumatoid arthritis," "melaena," "retinal haemorrhage," "internal haemorrhage," and "hallucination" (0.0%, 1/7,707 each), and their outcomes were "resolving" or "resolved." The percentages of subjects with solicited and unsolicited AEs that cannot be ruled out as being related to this vaccine in the 7,707 subjects in the safety analysis set were 83.0% (6,394/7,707) and 9.8% (754/7,707), respectively. Examination of the incidence proportion of ADRs by severity indicated that the incidence proportion of Grade 3 ADRs in the 7,707 subjects in the safety analysis set was 11.6% (896/7,707). According to a pooled analysis of the global phase III study (StudyZOSTER-002, ZOSTER-028, ZOSTER-039, ZOSTER-041, ZOSTER-006, ZOSTER-022, ZOSTER-026), all of which were completed by the time of approval, the percentage of subjects with local and systemic solicited adverse events in the Shingrix group of the analysis set was 81.9% (5,360/6,544) and 53.1% (3,471/6,536), respectively (Attached Form 2-1). And the percentage of subjects with unsolicited adverse events that cannot be ruled out as being related to this vaccine was 31.4% (5,133/16,337) (Attached Form 2-2). Although a direct comparison is not feasible due to differences in subject characteristics and investigation method, the percentage of subjects with solicited and unsolicited adverse events that cannot be ruled out as being related to this vaccine in this investigation (83.0%, 6,394/7,707 and 9.8%, 754/7,707, respectively) were not higher than that of subjects with ADRs in the Shingrix group in the above pooled analysis of the global phase III studies (ZOSTER-002, ZOSTER-028, ZOSTER-039, ZOSTER-041, ZOSTER-006, ZOSTER-022, ZOSTER-026).The most commonly reported ADRs in this investigation (such as "vaccination site pain," "vaccination site swelling," "vaccination site erythema," "fatigue," "myalgia," "pyrexia," "headache," and "chills") were similar to those reported by the time of approval. Compared with the pre-approval data, no new safety concerns were identified regarding the incidence and types of ADRs reported in this investigation.

In addition, the time to onset of ADRs after vaccination with Shingrix was measured for each vaccination. After the first vaccination, 6,158 of the 7,707 doses in the safety analysis set (for the first vaccination) reported ADRs; regarding the solicited AEs that cannot be ruled out as being related to this vaccine, 85.5% (5,249/6,137) of the subjects with ADRs experienced the ADRs on Day 1 (the day of vaccination), and 99.0% (6,075/6,137) by Day 2. With respect to ADRs classified as unsolicited AEs, 91.5% (496/542) were observed by Day 7. The time to onset of ADRs after the second vaccination showed a similar trend to that after the first vaccination, and no other notable trends were observed.

In order to examine factors affecting the onset of ADRs, univariate and multivariate logistic regression analyses were performed by subject characteristics in the 7,707 subjects in the safety analysis set. The results of the multivariate analysis indicated that "age 1" (< 15 years, ≥ 15 years and < 50 years, ≥ 50 years and < 65 years, ≥ 65 years and < 75 years, and ≥ 75 years) and "underlying disease" met the criteria: the point estimate was > 2 or < 0.5 for the adjusted odds ratio in the incidence proportion of ADRs by subject characteristics and the asymptotic 95% confidence interval does not exceed 1. Regarding "age 1", The incidence proportion of ADRs

was lower in the age group "≥ 75 years" than in the age group "≥ 50 and < 65 years" (point estimate of adjusted odds ratio, 0.448; 95% confidence interval, 0.381-0.527). The percentages of subjects with solicited AEs such as "vaccination site pain," "vaccination site swelling," "vaccination site erythema", "fatigue" and "pyrexia" were lower in the age group "≥ 75 years" than in the age group "≥ 50 years and < 65 years." It is known that the occurrence of adverse reactions after vaccination is influenced by multiple factors such as the characteristics of the recipient and the vaccine, and the method of administration [Hervé, 2019], among which age is considered one of the particularly important factors. It is reported that the inflammatory immune response in the acute phase after vaccination is reduced in elderly people [Yousfi, 2005], and this may have been a factor in the lower percentage of subjects with ADRs in the age group "≥ 75 years." Regarding "underlying disease", the percentage of subjects with ADRs was higher in those with underlying diseases than in those without (point estimate of adjusted odds ratio, 2.099; 95% confidence interval, 1.821-2.419). The percentages of subjects with solicited AEs such as "vaccination site pain," "vaccination site swelling," and "vaccination site erythema" were higher in those with underlying diseases than in those without. The most commonly reported underlying diseases in the safety analysis set of this investigation included "hypertension" (22.2%, 1,710/7,707), "dyslipidaemia" in (9.0%, 691/7,707), and "rheumatoid arthritis" (6.9%, 530/7,707). A prior study of ADRs to COVID vaccination among individuals with one of these most commonly reported comorbidities, rheumatoid arthritis and among those with systemic lupus erythematosus found they were at higher risk of vaccination site pain, swelling, and redness after COVID-19 vaccination than healthy individuals [Bartels, 2021]. In fact, the percentage of ADRs in subjects with comorbid rheumatoid arthritis was found to be as high as 90.4% (479/530) in this investigation. Therefore, the higher percentage of ADRs in subjects with underlying diseases might be considered partly attributable to the fact that vaccination site reactions in the acute phase after vaccination with Shingrix were commonly reported in patients with autoimmune diseases such as rheumatoid arthritis. But another report suggests that the occurrence of adverse events after COVID-19 vaccination is unrelated to the presence or absence of underlying conditions [Frankenthal, 2025]. The exact reason was unclear. In this investigation, 2 subjects were reported to use immune checkpoint inhibitors (atezolizumab and durvalumab), a therapy for which safety of Shingrix could not be sufficiently evaluated by the time of approval. Although ADRs were reported in both subjects, no new concerns were identified regarding the safety of Shingrix in individuals receiving immune checkpoint inhibitors.

In this investigation, the incidence proportions of ADRs associated with "shock and anaphylaxis" and "potential immune-mediated disease" were examined as AEs or ADRs of special interest. In the 7,707 subjects in the safety analysis set, ADRs associated with "shock and anaphylaxis" were reported in 55 subjects (0.7%, 55/7,707). The most commonly reported ADRs included "rash" (0.3%, 21/7,707), "urticaria" (0.2%, 15/7,707), and "eczema" (0.1%, 9/7,707), in descending order of frequency. No serious ADRs were reported. The outcomes of all ADRs associated with "shock and anaphylaxis" were "resolved" or "resolving" except for one with unknown outcome. According to a pooled analysis of the global phase III study in subjects aged ≥ 50 years (Study ZOSTER-006) and the global phase III study in subjects aged ≥ 70 years (Study ZOSTER-022), both of which were completed by the time of approval, in the Shingrix group, unsolicited AEs within MedDRA SMQ for "hypersensitivity" (narrow) occurring within 30 days after vaccination were reported in 2.6% (380/14,645) of the subjects, whereas AEs within MedDRA SMQ for "anaphylactic reaction" (narrow) were reported in 0.0% (1/14,645). Although a direct comparison is not feasible due to differences in subject characteristics, investigation method and assessment method, the percentage of subjects with ADRs associated with "shock and anaphylaxis" in this investigation was lower at 0.7% (55/7,707) when compared with that of subjects reported by the time of approval; no new concerns were identified regarding the incidence, types, or outcomes of ADRs associated with "shock and anaphylaxis" in this investigation.

In the 7,707 subjects in the safety analysis set, ADRs associated with "potential immune-mediated disease" were reported in 2 subjects (0.0%, 2/7,707). The most commonly reported

ADRs were “butterfly rash” and “rheumatoid arthritis” (0.0%, 1/7,707 each). In a pooled analysis of the global phase III study in subjects aged ≥ 50 years (Study ZOSTER-006) and the global phase III study in subjects aged ≥ 70 years (Study ZOSTER-022), both of which were completed by the time of approval, the “potential immune-mediated diseases” that the investigator considered to be related to vaccination were reported in 0.1% (16/14,645) of the subjects in the Shingrix group throughout the follow-up period after vaccination. Although a direct comparison is not feasible due to differences in subject characteristics, investigation method and assessment method, the percentage of subjects with ADRs associated with “potential immune-mediated disease” in this investigation was 0.0% (2/7,707), which was similar to that of subjects reported by the time of approval, and no new concerns were identified regarding the incidence, types, or outcomes of ADRs associated with “potential immune-mediated disease” in this investigation. As individuals with specific characteristics, the percentages of children (< 15 years), elderly people (≥ 65 years), pregnant and breastfeeding women, individuals with renal impairment, individuals with hepatic impairment, individuals with immune abnormalities and individuals considered to require precaution for vaccination by the investigator who experienced ADRs were examined. In the 7,707 subjects in the safety analysis set of this investigation, no use in children (< 15 years) was reported. Use in elderly people (≥ 65 years) was reported in 54.6% (4,210/7,707). The percentage of elderly subjects with ADRs was 81.4% (3,429/4,210). The percentage of elderly subjects with ADRs was 81.4% (3,429/4,210), whereas that of subjects aged < 65 years with ADRs was 85.1% (2,977/3,497); both were similar. and no new concerns were identified regarding the safety of Shingrix in elderly people. Use in women was reported in 67.6% (5,212/7,707); no use was reported in pregnant and breastfeeding women. Use in individuals with renal impairment was reported in 1.4% (110/7,707) and the percentage of subjects with renal impairment who experienced ADRs was 82.7% (91/110).The percentage of subjects with renal impairment who experienced ADRs (82.7%, 91/110) was comparable to that of subjects without renal impairment who experienced ADRs (83.1%, 6,315/7,597); no new concerns were identified regarding the safety of Shingrix in individuals with renal impairment. Use in subjects with hepatic impairment was reported in 2.2% (166/7,707) and the percentage of subjects with hepatic impairment who experienced ADRs was 85.5% (142/166). The percentage of subjects with hepatic impairment who experienced ADRs (85.5%, 142/166) was comparable to that of subjects without hepatic impairment who experienced ADRs (83.1%, 6,264/7,541); no new concerns were identified regarding the safety of Shingrix in subjects with hepatic impairment. Use in individuals with immune abnormalities was reported in 9.1% (702/7,707) and the percentage of subjects with immune abnormalities who experienced ADRs was 90.6% (636/702). As a result of the multivariate logistic regression analysis, among the 7,707 subjects in the safety analysis set, the incidence proportion rate of ADRs in the subjects with and without immune abnormalities were 90.8% (513/565) and 82.0% (5,207/6,348), respectively, and “immune abnormality” did not meet the above criteria (point estimate of adjusted odds ratio, 1.331; 95% confidence interval, 0.976-1.814). Use in individuals considered to require precaution for vaccination by the investigator was reported in 0.5% (39/7,707). As the result of the univariate logistic regression analysis, the incidence proportion rates of ADRs in those classified as "Applicable" and "Not Applicable" for individuals considered to require precaution for vaccination by the investigator were 92.3% (36/39 cases) and 83.1% (6,370/7,668 cases), respectively, and did not meet the above criteria (point estimate of unadjusted odds ratio: 2.445, 95% confidence interval: 0.752-7.950).

CONCLUSION

No new concerns were identified in the safety of Shingrix in this investigation, and it was considered unnecessary to implement new measures to ensure proper use.

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systemic lupus erythematosus and rheumatoid arthritis. *Rheumatology International*, 41: 1925-31

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