2. ABSTRACT

- **Title**

Long Term Post Marketing Specified Drug Use Result Survey for Repatha Subcutaneous Injection

- **Keywords**

Repatha subcutaneous injection, evolocumab, post marketing specified drug use result survey, familial hypercholesterolemia, hypercholesterolemia

- **Rationale and Background**

In the Japan new drug application (J-NDA) for evolocumab, safety and effectiveness data on about 700 Japanese patients, including 145 patients who were followed for up to 12 months (52 weeks) were shown. The post marketing surveillance (PMS) provided data from the real-world use of evolocumab in Japanese patients to supplement the data in the J-NDA. The Japan risk management plan (J-RMP) includes this survey as a part of post-marketing pharmacovigilance activities.

- **Research Question and Objectives**

The survey was conducted to obtain the safety and effectiveness information of the product in the real-world use of evolocumab in Japan.

- Primary Objectives

  The primary objectives of survey were to 1) determine the incidence of AEs and ADRs (ADRs: AEs for which causal relation to evolocumab cannot be ruled out) among patients receiving evolocumab for up to 2 years (104 weeks) and percent change in LDL-C from baseline to 12W, and 2) identify and describe patient characteristics (eg, demographics, medical history) associated with the safety and effectiveness of evolocumab therapy for the patients with familial hypercholesterolemia (FH) (heterozygous or homozygous) and hypercholesterolemia (HC) in the post-marketing real-world medical practice.

- Secondary Objective

  None.

- Hypothesis(es)/Estimation

  There was no formal hypothesis to be tested. Instead, the proposed survey provided descriptive data on real-world use of evolocumab and AE occurrence in Japan.

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- **Study Design**

A non-interventional (observational) survey in post-marketing setting without a comparator arm

- **Setting**

The planned enrollment period for this survey was 4 years from the launch of evolocumab. The enrollment was initiated from 21 April 2016, the launch of evolocumab in Japan, and the enrollment period was extended due to a lack of progress in patient enrollment. Among those who were enrolled by 31 October 2020, a total of 3739 patients were finally included in the data collection.

The survey period planned for 6 years from the launch of evolocumab was extended during the survey, therefore the data collection was finally completed on 20 April 2023, and the data cleaning was finished on 18 July 2023.

- **Patients and Study Size, Including Dropouts**

Patients with FH and HC who had not previously used evolocumab

Both the following conditions must be met.

- Had high risk factors for cardiovascular events
- Did not adequately respond to HMG-CoA reductase inhibitors (hereinafter, “statin”) or were not suitable for statin therapy

To collect 3000 patients with 2-year observation period, at least 3300 patients were planned to be enrolled. Actually, 3765 patients were enrolled during the survey period.

- **Data Source(s) and Methods**

The original source for the data collected in this survey was the patient medical records. Referring to the original source, the investigators entered and submitted the data into the electronic case report form (eCRF) via the electronic data capture (hereinafter, “EDC”) system provided by Amgen K.K.

- **Results**
- Summary of analysis set disposition

CRFs were collected from 3739 of 3765 patients enrolled. A total of 3724 patients were included in the safety analysis set, excluding 15 patients. Of those, 1615 patients with heterozygous familial hypercholesterolemia (hereinafter, “HeFH”), 91 patients with homozygous familial hypercholesterolemia (hereinafter, “HoFH”), and 1091 patients with HC were included in the efficacy analysis set 1; and 1342 patients with HeFH, 41

patients with HoFH, and 988 patients with HC were included in the efficacy analysis set 2. In the survey, the efficacy analysis set 1 was defined as patients in the safety analysis set who used this drug for the approved indication and whose low-density lipoprotein cholesterol (hereinafter, "LDL-C") levels before and after treatment with evolocumab were available and the efficacy analysis set 2 was defined as patients in the efficacy analysis set 1 who received this drug and statin at the approved dosage and administration.

- Patient characteristic

Of 3724 patients in the safety analysis set, "males" were 66.2% (2465 patients) and "females" were 33.8% (1259 patients). Age was "< 15 years" in 0.1% (4 patients), "≥ 15 years and < 65 years" in 48.4% (1803 patients), "≥ 65 years" in 51.5% (1917 patients), and "≥ 75 years" in 20.8% (774 patients). Medical history of coronary artery disease was "no" in 19.0% (707 patients) and "yes" in 79.9% (2974 patients). Statin therapy at baseline was "no" in 11.3% (420 patients) and "yes" in 88.7% (3304 patients). High-intensity statin therapy was "no" in 19.8% (737 patients) and "yes" in 80.2% (2987 patients).

- Safety

Reported AEs that were not assessed as "not related" by the physicians, including "unknown" and "not specified," were regarded as ADRs. AEs assessed as "serious" by the physicians were regarded as serious AEs (SAE).

ADRs were observed in 5.50% (205/3724 patients) included in the safety analysis set. The most common ADRs (≥ 5 patients) were "injection site erythema" (0.43%; 16 patients), "myalgia" (0.38%; 14 patients), "injection site pain," "malaise" (0.35%; 13 patients each), "hepatic function abnormal" (0.32%; 12 patients), "pruritus," "blood creatine phosphokinase increased" (0.30%; 11 patients each), "rash," "injection site swelling" (0.27%; 10 patients each), "angina pectoris" (0.16%; 6 patients), "diarrhoea," "injection site pruritus," and "low density lipoprotein decreased" (0.13%; 5 patients each).

Serious ADRs were observed in 0.51% (19/3724 patients) included in the safety analysis set. Serious ADRs were "angina pectoris" (0.08%; 3 patients), "cerebral infarction," "rhabdomyolysis" (0.05%; 2 patients each), "Graves' disease," "aortic dissection," "arteriosclerosis," "Behcet's syndrome," "vasculitis," "iliac artery stenosis," "peripheral arterial occlusive disease," "pulmonary alveolar haemorrhage," "mechanical

ileus," "myalgia," "renal impairment," "acute kidney injury," "asthenia," "sudden death," "blood creatine phosphokinase increased," and "hepatic enzyme increased" (0.03%; 1 patient each). Serious ADRs with an outcome of "death" were reported in 2 patients: "sudden death" and "cerebral infarction" in 1 patient each.

Patient characteristic factors affecting the safety were investigated and significant differences were found in the incidence of ADRs for medical history of allergy and statin therapy at baseline.

Based on the J-RMP, the important identified risks, important potential risks and important missing information were set in the safety specification items in this survey.

No important identified risks were specified for evolocumab in the J-RMP.

Hypersensitivity and immunogenicity were identified as important potential risks in the J-RMP. ADRs related to hypersensitivity were reported in 0.99% (37/3724 patients) and none of them were serious. No ADRs related to immunogenicity were reported.

As important missing information, the incidence of ADRs in patients with HoFH (including pediatrics), elderly patients (≥ 75 years), patients with hepatic impairment, patients with hepatitis C virus (HCV) infection, and patients with long-term use (including effects of LDL-C < 40 mg/dL [< 1.0 mmol/L]) was calculated.

ADRs were reported in 6.48% (7/108 patients) of patients with HoFH (including pediatrics). The ADRs were "hepatic function abnormal" (1.85%; 2 patients), "nausea," "drug eruption," "erythema," "pain in extremity," "injection site erythema," "injection site swelling," and "aspartate aminotransferase increased" (0.93%; 1 patient each). None of them were serious. Of patients with HoFH, 4 were pediatric and 1 of them had ADRs.

ADRs were reported in 4.91% (38/774 patients) of elderly patients (age ≥ 75 years). The ADRs were "malaise" (0.52%; 4 patients), "pruritus," "rash," "myalgia" (0.39%; 3 patients each), "angina pectoris," "drug eruption," "urticaria" (0.26%; 2 patients each), "diabetes mellitus," "decreased appetite," "depression," "insomnia," "cerebral infarction," "dysarthria," "headache," "memory impairment," "peripheral coldness," "peripheral arterial occlusive disease," "dysphonia," "abdominal pain," "diarrhoea," "vomiting," "mechanical ileus," "faeces soft," "dry skin," "back pain," "rhabdomyolysis," "chromaturia," "renal impairment," "pain," "alanine aminotransferase increased," "aspartate aminotransferase increased," "blood creatine phosphokinase increased,"

"low density lipoprotein decreased," "low density lipoprotein increased," "weight decreased," and "subdural haematoma" (0.13%; 1 patient each). Serious ADRs were reported in 6 patients: "rhabdomyolysis," "renal impairment," "mechanical ileus," "angina pectoris," "cerebral infarction," and "peripheral arterial occlusive disease" in 1 patient each. There were no notable differences in the incidence of ADRs among elderly (age ≥ 75 years) patients (4.91%; 38/774 patients), adult (age ≥ 15 to < 65 years) patients (5.32%; 96/1803 patients) and elderly (age ≥ 65 to < 75 years) patients (6.12%; 70/1143 patients).

ADRs were reported in 4.79% (35/730 patients) of patients with hepatic dysfunction. The ADRs reported in patients with hepatic dysfunction were "hepatic function abnormal," "myalgia" (0.55%; 4 patients each), "injection site swelling" (0.41%; 3 patients), "hyperuricaemia," "diarrhoea," "pruritus," "malaise," "blood creatine phosphokinase increased" (0.27%; 2 patients each), "anaphylactic reaction," "dizziness," "headache," "angina pectoris," "iliac artery stenosis," "dyspepsia," "nausea," "drug eruption," "erythema," "pain in extremity," "renal impairment," "acute kidney injury," "injection site erythema," "injection site haemorrhage," "injection site pain," "injection site pruritus," "injection site warmth," "sudden death," "alanine aminotransferase increased," "aspartate aminotransferase increased," "blood pressure increased," "blood triglycerides increased," "gamma-glutamyltransferase increased," "low density lipoprotein decreased," "low density lipoprotein increased," and "hepatic enzyme increased" (0.14%; 1 patient each). Serious ADRs were reported in 5 patients: "renal impairment," "sudden death," "acute kidney injury," "iliac artery stenosis," and "angina pectoris" in 1 patient each. On the other hand, ADRs were reported in 5.72% of patients without hepatic dysfunction. As a result of investigating factors affecting the incidence of ADRs, there was no significant difference between the incidence of ADRs in patients with and without hepatic dysfunction at baseline.

Hepatitis C did not occur in any of the 3724 patients in the safety analysis set. Of 3724 patients in the safety analysis set, 32 were tested positive for HCV and 6.25% (2/32 patients) of them had ADRs. ADRs reported in patients with an HCV-positive result were "cerebral infarction," "arteriosclerosis," and "renal impairment" (3.13%; 1 patient each); no hepatic dysfunction or laboratory abnormalities related to hepatic functions were reported. Serious ADRs were reported in 1 patient: "cerebral infarction" and "arteriosclerosis."

Of the 3724 patients in the safety analysis set, the incidence of ADRs was 3.94% (89/2260 patients) in the subset of patients with a minimum post-baseline LDL-C < 40 mg/dL and 3.46% (46/1330 patients) in those with < 25 mg/dL; there was no notable difference in types of ADRs compared with those in patients with ≥ 40 mg/dL.

- Efficacy

The percent change in LDL-C from baseline to Week 12 (mean ± standard deviation [SD]; the same applies hereinafter) was −58.2 ± 27.4% in the efficacy analysis set 1. Percent changes by diagnosis were −55.9 ± 28.8% in patients with HeFH, −45.7 ± 28.2% in patients with HoFH, and −63.3 ± 23.7% in patients with HC. Baseline LDL-C levels were 146.3 ± 54.0 mg/dL, 188.3 ± 78.3 mg/dL, and 111.5 ± 42.8 mg/dL, respectively.

Patient characteristic factors affecting the efficacy were investigated and significant differences were found in the target LDL-C achievement rates for sex, diagnosis, medical history of coronary artery disease, diabetes mellitus + impaired glucose intolerance, chronic kidney disease (hereinafter, “CKD”), hypertension, high-intensity statin therapy, and non-medicine therapy (therapeutic exercise).

- **Discussion**

The incidence of ADRs (5.50%; 205/3724 patients) in this survey was lower than in clinical studies conducted at the time of approval, with no events showing an increasing trend. In addition, the incidence of serious ADRs (0.51%; 19/3724 patients) in this survey was lower than that in the clinical studies at the time of approval, with no events showing an increasing trend.

Among ADRs reported in the safety specification items, the incidence of ADRs related to hypersensitivity was lower than that related to hypersensitivity in the clinical studies at the time of approval, with no events showing an increasing trend.

The incidence of ADRs in patients with HoFH in this survey was lower than that in patients for HoFH in the clinical studies at the time of approval, with no events showing an increasing trend.

There were no notable differences in the incidence and type of ADRs between adults (≥ 15 years and < 65 years) (5.32%; 96/1803 patients) and elderly patients (≥ 65 years and < 75 years) (6.12%; 70/1143 patients) among elderly patients ≥ 75 years of age (4.91%; 38/774 patients).

There was no significant difference between the incidence of ADRs in patients with and without hepatic dysfunction at baseline.

Hepatitis C did not occur in patients in the safety analysis set, and there were no hepatic dysfunction or laboratory abnormalities related to hepatic functions in HCV-positive patients.

As a result of examining incidence of ADRs by minimum post-baseline LDL-C was discussed to investigate the safety of long-term use (including the effects of LDL-C $<$ 40 mg/dL [$<$ 1.0 mmol/L]), there was no notable difference in types of ADRs between those groups. As with the results of clinical studies conducted at the time of approval, there was no notable trend in the minimum post-baseline LDL-C level and the incidence of ADRs.

Percent changes in LDL-C from baseline at Week 12 after the start of treatment in the efficacy analysis set decreased by approximately 50% in all patient groups, it was considered that evolocumab showed good efficacy in patients with FH and HC.

As mentioned above, there is currently no new knowledge regarding the safety and effectiveness of evolocumab, and the benefit-risk balance of evolocumab with respect to the approved indications is considered favorable.

- **Marketing Authorization Holder(s)**

Amgen K.K.

- **Names and Affiliations of Principal Investigators**

There was no principal investigator for this survey.