1. ABSTRACT

- **Title**

General Use Results Survey of OTEZLA in patients with oral ulcers due to Behçet's disease who have had an inadequate response to topical therapies

- **Keywords**

OTEZLA, apremilast, post-marketing surveillance, Behçet's disease

- **Rationale and Background**

Following the approval of Otezla 10 mg, 20 mg, and 30 mg tablets (hereinafter referred to by the generic name, apremilast) for the treatment of oral ulcers associated with Behçet's disease that have been inadequately controlled by topical therapies, the Pharmaceuticals and Medical Devices Agency (PMDA) indicated the need for further investigation of apremilast's safety profile under real-world conditions. Specifically, given that there is limited information on the safety of apremilast in Behçet's disease patients with oral ulcers and other major organ involvement, such as gastrointestinal lesions, and apremilast can cause gastrointestinal side effects, the Agency requested collection of safety information related to gastrointestinal disorders for Behçet's disease patients in the post-marketing setting and provision of the information to the medical community. This study was therefore planned to assess the safety of apremilast in a real-world setting.

- **Research Question and Objectives**

The objective of this study was to evaluate the safety of apremilast in actual clinical settings of use in apremilast-naive patients with oral ulcers due to Behçet's disease who have had an inadequate response to topical therapies.

- **Study Design**

This was a prospective observational cohort study of patients with oral ulcers due to Behçet's disease treated with apremilast in the post-marketing clinical setting in Japan.

- **Setting**

This study was conducted with participating medical institutions in Japan. Contracts were executed with 49 hospitals and clinics throughout Japan for the conduct of this study. Of the contracted hospitals and clinics, 34 facilities enrolled patients.

The study began on 6 July 2020, and enrollment was completed on 26 December 2022.

Data was collected for a period of 6 months on each enrolled patient unless apremilast was discontinued earlier. If apremilast was discontinued during the observation period,

data was collected up to the date of discontinuation and for 28 days following the date of discontinuation. Data collection ended on 10 October 2024, and database lock occurred on 28 February 2025.

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

Patients who received their first dose of apremilast for the following indication were eligible for this study:

  - Oral ulcers associated with Behçet's disease that have been inadequately controlled by topical therapies

The planned sample size was 100 patients. The actual number of enrolled patients exceeded this target, with 116 patients enrolled.

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

The source data for this study was the patients' medical records. Investigators entered data from the medical records into electronic Case Report Forms (eCRFs) through a post-marketing surveillance data collection system, Electronic Data Capture (EDC) provided by Amgen K.K.

- **Variables**

Patient demographics and disease characteristics, prior medications and therapies for Behçet's disease (including biologics), apremilast administration details, concomitant medications, concomitant non-pharmacological therapies, adverse events, and laboratory test results.

- **Results**

Patient composition

Of the 116 enrolled patients, CRFs were collected for 115 patients. A CRF was not collected for 1 patient due to time constraints related to the attending physician's demanding schedule. One patient was excluded from the safety analysis set as the patient did not return to the hospital after apremilast administration, resulting in 114 patients for the safety analysis.

Patient characteristics

Of the 114 patients included in the safety analysis, 39 patients (34.2%) were male, and 75 patients (65.8%) were female. Of the female patients, 1 patient (1.3%) was pregnant; the pregnancy was discovered after administration of apremilast and treatment was interrupted. No patients (0.0%) were less than 15 years, 106 patients (93.0%) were 15 years or older and younger than 65 years, and 8 patients (7.0%) were 65 years or older. Disease duration was less than 1 year in 38 patients (33.3%), 1 year or more but less

than 2 years in 8 patients (7.0%), 2 years or more but less than 5 years in 18 patients (15.8%), and 5 years or more in 46 patients (40.4%). In addition, 92 patients (80.7%) had active Behçet's disease at enrollment. A total of 23 patients (20.2%) had ileocecal ulcers or other GI lesions, and 18 patients (15.8%) had intestinal type Behçet's disease lesions.

Safety

In this study, adverse events reported by physicians were classified as adverse reactions (ARs) if the physician's causality assessment was anything other than not related (including unknown). ARs assessed by the physician as serious were classified as serious ARs.

Of the 114 patients in the safety analysis set, 63 patients (55.26%) experienced ARs. The most commonly reported ARs (≥ 5% cut off) were diarrhoea [26 patients (22.81%)], nausea [24 patients (21.05%)], and headache [11 patients (9.65%)].

Serious ARs were reported in 2 patients (1.75%): Meniere's disease and myalgia, one patient each [0.88% each]. None of the ARs had a fatal outcome.

Four patients (3.51%) experienced serious adverse events: extranodal marginal zone B-cell lymphoma (MALT type), Meniere's disease, Behçet's syndrome, and myalgia, one patient each [0.88% each].

The highest proportion of ARs occurred within < 1 week after initiating treatment, accounting for 28.95% of the patients (33/114 patients) in the safety analysis set. The main ARs observed within < 1 week (≥ 5% cut off) were diarrhoea [13.16% (15/114 patients)], nausea [10.53% (12/114 patients)], and headache [7.02% (8/114 patients)]. The proportion of patients with ARs tended to decrease over time, and no specific trends were observed in the types of ARs occurring at different time points.

ARs related to gastrointestinal disorders, a key safety consideration of this study, were reported in 45.61% of patients (52/114 patients) in the safety analysis set; none of the reported events were serious. To investigate risk factors for gastrointestinal disorders, univariate and multivariate logistic regression analyses were performed. The results showed statistically significant differences in sex, disease duration, and eye symptoms. Females had a higher incidence of gastrointestinal disorders than males. Patients with a disease duration of 1 year or longer (1 to <2 years, 2 to <5 years, and 5 years or longer) had a higher incidence of gastrointestinal disorders than those with a disease duration of less than 1 year. Patients with eye symptoms had a lower incidence of gastrointestinal

disorders than those without eye symptoms. There were no statistically significant differences in the incidence of gastrointestinal ARs related to the presence or absence of gastrointestinal lesions represented by ileocecal ulcers or disease subtype classification, which are factors related to major organ involvement (e.g., gastrointestinal symptoms).

- **Discussions**

The incidence of ARs in this study was comparable to that observed in the pivotal phase III clinical trial in adult patients with Behçet's disease (Study CC-10004-BCT-002) that supported approval of the Behçet's disease indication in Japan. The most commonly reported ARs in this study (diarrhea, nausea, and headache) exhibited similar trends to those seen in Study CC-10004-BCT-002 and are in line with the adverse reactions identified in the apremilast package insert in Japan. In this study, 2 patients experienced serious ARs and 4 patients experienced serious adverse events. ARs and AEs types and incidence in this study were consistent with those reported in Study CC-10004-BCT-002.

Concerning the timing of AR onset, the highest proportion occurred within < 1 week. The most commonly reported ARs observed within < 1 week in this study showed similar trends to the results from the pivotal phase 3 clinical trial (CC-10004-BCT-002).

The incidence of ARs classified as gastrointestinal disorders in this study was not significantly different from that observed in Study CC-10004-BCT-002. Univariate and multivariate logistic regression analyses were performed to investigate risk factors for gastrointestinal ARs. Significant factors were sex, disease duration, and eye symptoms. No significant differences in the incidence of gastrointestinal ARs were observed in "presence or absence of gastrointestinal lesions represented by ileocecal ulcers" or "disease subtype classification," which are factors related to major organ involvement (e.g., gastrointestinal symptoms). No tendency for gastrointestinal disorders to become more serious or refractory was observed in patients with gastrointestinal lesions represented by ileocecal ulcers or in patients with the intestinal subtype classification. Therefore, no specific safety concerns about the safety of apremilast in patients with Behçet's disease-related major organ lesions (gastrointestinal lesions, etc.) were identified.

Overall, no new safety concerns for apremilast were identified in this study, and therefore no additional safety measures are warranted.

- **Marketing Authorization Holder(s)**

Amgen K.K.

- **Names and Affiliations of Principal Investigators**

There is no principal investigator for this study.