1. ABSTRACT

- **Title**

Otezla® Tablets Drug Use-Results Survey

- **Keywords**

Otezla tablets, apremilast, drug use-results survey, psoriasis vulgaris, psoriasis arthropathica

- **Rationale and Background**

Owing to PMDA's opinion that the safety of Otezla® Tablet 10 mg, 20 mg, 30 mg (hereinafter referred to as Otezla; generic name, apremilast) in clinical practice needs to be further investigated when approving Otezla in Japan, this survey was planned to understand the safety and efficacy of Otezla in clinical practice.

- **Research Question and Objectives**

This survey was conducted on patients with psoriasis vulgaris and patients with psoriasis arthropathica who received Otezla to understand the safety and efficacy of Otezla in clinical practice.

- **Study Design**

This was a non-interventional (observational) study in which Otezla was administered in a Japanese post-marketing clinical setting without a control group.

- **Setting**

The planned enrollment period for this survey was two years from 6 months after the launch of Otezla. A total of 1086 patients who were enrolled from 1 September 2017, 6 months after the launch of Otezla in Japan, to 31 August 2019, a two-year period, were included in the data-collection.

The planned survey period for this survey was four years from 6 months after the launch of Otezla. After completion of data collection on 31 October 2021, additional data were received; therefore, data collection was finally completed on 24 May 2022, and data for this survey were fixed on 15 August 2022.

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

Those who were diagnosed with the following indications and received Otezla for the first time were included in this survey:

・ Psoriasis vulgaris that is with inadequate response to topical therapies
・ Psoriasis arthropathica

The planned number of patients surveyed was 1000. In practice, 1086 patients were enrolled, exceeding the planned number of patients surveyed.

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

The source documents for the data collected in this survey were the patient's medical records. Referring to the source documents, the investigator of the survey entered the data into the Case Report Form (CRF) on the Electronic Data Capture (EDC) provided by Amgen K.K., and transmitted it.

- **Results**

Patients

The CRF of 1080 patients was collected among 1086 registered patients. The safety analysis set consisted of 1063 patients excluding 17 patients. Among them, 954 patients were included in the efficacy analysis for psoriasis vulgaris (992 patients), excluding 38 patients, and 115 patients were included in the efficacy analysis for psoriasis arthropathica (127 patients), excluding 12 patients.

Patient characteristics

In the overall safety analysis (1063 patients), “males” were 70.1% (745 patients) and “female” were 29.9% (318 patients). Age was “<15 years” in 0.1% (1 patient), “≥15 years and <65 years” in 59.2% (629 patients), and “≥65 years” in 40.6% (432 patients). Disease duration was “less than 1 year” in 16.3% (173 patients), “at least 1 year and less than 2 years” in 6.7% (71 patients), “at least 2 years and less than 5 years” in 13.6% (145 patients), and “at least 5 years” in 48.1% (511 patients).

Safety

Among adverse events reported by physicians, adverse events assessed as other than "no" (including unknown or not specified) in the causality assessment by physicians were tabulated as adverse reactions, and events assessed as “serious” in the seriousness assessment by physicians were tabulated as serious events.
Adverse reactions were observed in 312 (29.35%) of 1063 patients included in the safety analysis. The most common adverse reactions were “diarrhea” 11.67% (124 patients), “nausea” 5.93% (63 patients), “loose stools” 3.01% (32 patients), “headache” 2.26% (24 patients), “decreased appetite” 1.60% (17 patients), “abdominal discomfort” and “psoriasis” 1.32% (14 patients each), and “malaise” 0.94% (10 patients). Serious adverse reactions were observed in 7 patients (0.66%), including “colon cancer”/”colon cancer with distant metastasis”, “hepatocellular carcinoma”, “cerebral infarction”, “myocardial infarction”, “hypertension”, “vomiting” and “abnormal liver function” (1 patient

each) (“colon cancer”/”colon cancer with distant metastasis” developed in the same patient). Serious adverse events were observed in 25 patients (2.35%), and those reported by at least 2 patients were colon cancer and cerebral infarction (2 patients each).

The incidence of adverse reactions by time period from the start of Otezla administration was most frequently less than 1 month in 20.04% (213 patients), and the most common adverse reactions observed in less than 1 month were “diarrhea” in 9.13% (97 patients), “nausea” in 4.14% (44 patients), “loose stool” in 2.45% (26 patients), “headache” in 1.98% (21 patients), and “abdominal discomfort” in 1.03% (11 patients). Afterwards, the adverse reaction manifestation tended to decrease, and there was no bias for delayed adverse reaction and specific adverse reaction.

The key survey items defined in this study were: “serious infections”, “gastrointestinal disorders”, “serious hypersensitivity”, “weight decreased”, “vasculitis”, “malignancies” and “depression and suicidal events”. The incidences of the key survey items were “gastrointestinal disorders” in 226 patients (21.26%), “weight decreased” in 3 patients (0.28%), “malignancies” in 2 patients (0.19%), and “depression and suicidal events” in 3 patients (0.28%), and “serious infection”, “serious hypersensitivity” and “vasculitis” were not observed. Univariate and multivariate logistic regression analyses were performed for the presence of adverse reactions of gastrointestinal disorders to investigate the risk factors related to the occurrence of adverse reactions, and the odds ratio and its 95% confidence interval were calculated. The explanatory variables were sex, age, diagnosis, disease duration, complications (gastrointestinal disorders), complications (liver diseases), complications (renal diseases), and complications (diabetes mellitus). The resulting, univariate and multivariate analyses were not significant.

Efficacy

Evaluation of efficacy in patients with psoriasis vulgaris.

Global improvement: Among the 954 patients included in the efficacy analysis, the efficacy rate was 93.8% (486 patients) in 518 patients evaluated for global improvement of “1 year after the start of Otezla treatment”, and the efficacy rate at the best time point, including “at the time of discontinuation of Otezla”, was 84.6% (794 patients).

PGA: PGA scores after the start of Otezla treatment decreased compared with that of “at the start of Otezla treatment”. Among the 954 patients included in the efficacy analysis, the change in PGA score “1 year after the start of Otezla treatment” was 1.6 ± 1.01 in

458 patients evaluated for PGA of “at the start of Otezla treatment” and “1 year after the start of Otezla treatment”.

DLQI: DLQI total scores after the start of Otezla treatment decreased compared with that of “at the start of Otezla treatment. Among the 954 patients included in the efficacy analysis, the change in DLQI total score “1 year after the start of Otezla treatment” was 5.7 ± 6.81 in 137 patients evaluated for DLQI of “at the start of Otezla treatment” and “1 year after the start of Otezla treatment”.

Evaluation of efficacy in patients with psoriasis arthropathica

Global improvement: Among the 115 patients included in the efficacy analysis,The efficacy rate was 91.5% (54 patients) in 59 patients evaluated for the global improvement of “1 year after the start of Otezla treatment”, and the efficacy rate at the best time point, including “at the time of Otezla discontinuation”, was 75.4% (86 patients).

VAS: VAS scores after the start of Otezla treatment decreased compared with that of “at the initiation of Otezla treatment”. Among the 115 patients included in the efficacy analysis, the change in VAS score “1 year after the start of Otezla treatment” was 35.47 ± 26.246 in 15 patients evaluated for VAS of “at the start of Otezla administration” and “1 year after the start of Otezla treatment”.

DAS28: DAS28 scores after the start of Otezla treatment decreased compared with that of “at the initiation of Otezla treatment”. Among the 115 patients included in the efficacy analysis, the change in DAS28 score “1 year after the start of Otezla treatment” was 2.08 ± 0.741 in 9 patients evaluated for DAS28 assessment of “at the start of Otezla treatment” and “1 year after the start of Otezla treatment””.

DLQI: DLQI total scores after the start of Otezla treatment decreased compared with that of “at the start of Otezla treatment”. Among the 115 patients included in the efficacy analysis, the change in DLQI total score “1 year after the start of Otezla treatment” was 4.8 ± 4.49 in 16 patients evaluated for DLQI of “at the start of Otezla treatment” and “1 year after the start of Otezla treatment”.

- **Discussion**

Safety

The incidence of adverse reactions in this survey was 29.35% (312 of 1063 patients), which was lower or similar to that in the clinical study at the time of approval. The major adverse reactions showed a similar trend as those in the clinical study at the time of

approval. The number of patients with serious adverse reactions in this survey was 1 patient each, and there were no events that showed an increasing trend compared with the serious adverse reactions in the clinical studies at the time of approval. The incidence of serious adverse events in this survey was lower than the incidence of serious adverse events in the clinical studies at the time of approval, and no events showed an increasing trend.

In terms of the incidence of adverse reactions by time period from the start of Otezla administration, the major adverse reactions observed in less than 1 month tended to be similar to the major adverse events observed in the clinical studies at the time of approval, although there is a difference between the definitions of adverse reactions and adverse events.

The incidences of adverse reactions related to the key survey items were low for “weight decreased”, “malignancies”, and “depression and suicidal events”, and none of the events showed an increasing trend. The incidences of “gastrointestinal disorders” were not considered to be significantly different from those in the clinical studies at the time of approval. Univariate and multivariate logistic regression analyses were carried out on the existence of the adverse reactions of “gastrointestinal disorders” in order to examine the risk factor which is related to the adverse reaction of “gastrointestinal disorders”. The resulting, univariate and multivariate analyses were not significant.

Based on the abovementioned data/observation, the safety profile of Otezla in this survey is in line with the known safety profile of Otezla.

Efficacy

Evaluation of efficacy in patients with psoriasis vulgaris.

The global improvement efficacy rate of “1 year after the start Otezla treatment” was 93.8% (486 patients), indicating that the efficacy of Otezla in patients with psoriasis vulgaris was good. The change in PGA score of “1 year after the start of Otezla treatment” was 1.6 ± 1.01 (458 patients), and PGA score significantly decreased compared with that of “the start of Otezla treatment”. The change in DLQI total score of “1 year after the start of Otezla treatment” was 5.7 ± 6.81 (137 patients), and DLQI total score significantly decreased compared with that of “at the start of Otezla treatment.

Evaluation of efficacy in patients with psoriasis arthropathica

The global improvement efficacy rate of “1 year after the start of Otezla treatment” was 91.5% (54 patients), indicating that the efficacy of Otezla in patients with psoriasis

arthropathica was good. The change in VAS score of “1 year after the start of Otezla treatment” was 35.47 ± 26.246 (15 patients), and VAS score significantly decreased compared with that of “at the start of Otezla treatment”. The change in DAS28 score of “1 year after the start of Otezla treatment” was 2.08 ± 0.741 (9 patients), which was significantly decreased compared with that of “at the initiation of Otezla treatment”. The change in DLQI total score of “1 year after the start of Otezla treatment” was 4.8 ± 4.49 (16 patients), which was significantly decreased compared with that of “at the start of Otezla treatment”.

Based on the abovementioned data/observation, no new findings were found regarding the efficacy of Otezla at present.

As mentioned above, there are no new safety and efficacy findings, and the benefit risk balance of Otezla remains positive.

- **Marketing Authorization Holder(s)**

Amgen K.K.

- **Names and Affiliations of Principal Investigators**

There was no principal investigator for this survey.