

## 1.0 Abstract

### Title

Special Investigation (All Cases Investigation in Patients with Ankylosing Spondylitis)

### Keywords

Humira, Ankylosing Spondylitis

### Rationale and Background

#### <Background>

Ankylosing spondylitis (AS) is an immune disease with increases in TNF $\alpha$  concentration within joints. TNF $\alpha$  has been observed in biopsy of sacroiliac joints in patients with active AS. Also, in surgical open biopsy of lesions at the insertions of elbow and groin tendons in patients with spondyloarthritis, activated macrophages were observed in the subchondral bone marrow in association with chronic inflammation. In Japan, for Humira, application for approval of partial change in approved items of indications and dosage/administration was made in October 2009, and the indication of AS was approved in October 2010.

#### <Rationale>

This surveillance was conducted as the condition for approval of AS under the direction of the authorities.

### Research Questions and Objectives

This postmarketing surveillance was conducted to investigate the following parameters of safety and efficacy in patients with AS receiving Humira:

1. ADRs unexpected from PRECAUTIONS (especially clinically significant adverse drug reactions)

2. Incidence and conditions of occurrence of adverse drug reactions in the clinical setting
3. Factors that may affect the safety and effectiveness of Humira

<Important items of investigation>

Development of infections, tuberculosis, malignant tumor, administration site reactions, autoimmune diseases, pancytopenia, demyelinating disease, congenital heart failure, and interstitial pneumonia

## **Research Methods**

### **Study Design**

This was a single-arm, multicenter, prospective cohort study (postmarketing observational study). The observation period was 24 weeks. Even if patients discontinue Humira treatment within 24 weeks, physicians continued observation of them for 24 weeks after the first administration of Humira.

### **Setting**

This study was conducted from 10 October 2010 to 31 May 2017. This registration period of subjects was from 10 October 2010 to 28 May 2015.

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

<Subjects>

Japanese patients with AS

<Study size>

Number of sample size: 100 patients

<Inclusion Criteria>

Patients receiving Humira for the treatment of AS after the approval of the indication are to be all enrolled.

#### <Exclusion Criteria>

Contraindications according to the Package Insert

- Patients who have serious infections
- Patients who have tuberculosis
- Patients with a history of hypersensitivity to any ingredient of Humira
- Patients who have demyelinating disease or with a history of demyelinating disease
- Patients who have congestive cardiac failure

#### **Variables and Data Sources**

##### <Variables>

Safety

Adverse events, adverse drug reactions

Effectiveness

Overall improvement rating (by physicians), BASDAI

##### <Data Sources>

Data sources in this study are from the institute's medical charts. Participant physicians in this study transcribed the data from medical charts to case report forms (CRF) which AbbVie prepared.

#### **Results**

This surveillance was conducted from October 2010 to May 2017.

403 subjects were registered, and the survey form was fixed for 400 subjects. From the subjects with survey form fixed, the subjects excluded from safety analysis were excluded, and consequently there were 396 subjects included in safety analysis. There were 4 subjects excluded from safety analysis: 3 transferred subjects (the 3 overlapped subjects in the surveillance were the same as the transferred subjects)

and 1 subject who started treatment outside the registration period (a subject who used this drug from before the approval).

From the subjects included in safety analysis, the subjects excluded from efficacy analysis were excluded, and consequently, there were 374 subjects included in efficacy analysis. There were 22 subjects excluded from efficacy analysis: 4 subjects with a disease other than the target disease for survey and 18 subjects not available for effectiveness evaluation.

#### <Safety>

In the 396 subjects included in safety analysis, there were 144 reports of adverse drug reactions in 101 subjects, and the incidence rate of adverse drug reactions was 25.51% (101/396).

In the 396 subjects included in safety analysis, there were 15 reports of serious adverse drug reactions in 15 subjects, and the incidence rate of serious adverse drug reactions was 3.79%. Events of which 2 or more reports were made were 2 reports of "Bronchitis" (outcome: resolved) in 2 subjects.

#### <Effectiveness>

In the 374 subjects included in efficacy analysis, the overall improvement rating "Markedly improved or improved" was seen in 89.5% (257/287) at 12 weeks after the start of treatment and 91.0% (292/321) at 24 weeks after the start of treatment.

### **Discussion**

This study's results supports the safety and effectiveness in the clinical setting of Humira used in AS

According to this study result, no new safety signals were observed. Safety data are consistent with those observed in previous Humira clinical trials and in post marketing surveillance.