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Humira® 40 mg/0.8 mL for Subcutaneous Injection

Study Protocol for Special Investigation (all-case survey) (ankylosing spondylitis)

AbbVie GK.

1. Purpose of the surveillance

This post-marketing surveillance will be conducted to confirm the following parameters of safety and efficacy in patients with ankylosing spondylitis (AS) receiving Humira® 40 mg/0.8 mL Syringe for Subcutaneous injection (generic name: adalimumab (recombinant)):

① Unknown adverse reactions (especially clinically significant adverse reactions)

② Incidence and conditions of occurrence of adverse reactions in the clinical setting

③ Factors that may affect the safety and efficacy 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

2. Target number of patients

Target sample size: 100 patients

All patients who receive Humira for the treatment of AS following approval of Humira for this disease will be registered. Following completion of the 24-week observation period for the first 100 patients, the case report forms will be retrieved, and the results of tabulation and analysis will be reported to the regulatory authority. Registration of patients will be continued after the submission of the report until the authority concludes the evaluation. However, the case report forms (CRFs) for the 101st patient and thereafter will in principle not be retrieved.

<Rationale>

The ADRs requiring careful monitoring during the use of Humira for the treatment of AS are serious infections. The incidence of serious infection was 4.9% (2/41 patients) in clinical studies of Humira in AS in Japan. Based on this incidence, the number of patients required to detect at least one case of serious infection at a probability of 95% is about 60 patients. However, the all-case survey is also being conducted to detect unknown ADRs. Considering the number of patients for whom registration is considered feasible, we will analyze the data for about 100 patients to detect ADRs with an incidence of 3% at a probability of 95%.

3. Patients to be investigated

All patients with AS who are not responding well to conventional therapy and receive adalimumab will be enrolled in the surveillance.

4. Number of participating institutions by department

Not yet determined

<Rationale>

Since this is an all-case survey to be conducted only in institutions that satisfy the criteria for institutions and physicians, it is impossible to accurately determine the number of applicable institutions. The number of participating institutions is thus not yet determined.

5. Participating institutions

The surveillance will be conducted in medical institutions and departments in which Humira is used for the treatment of AS. Treatment with Humira for patients with AS will be limited to those institutions that satisfy the following criteria for institutions and physicians and have concluded agreements with Abbvie GK for implementation of the all-case survey.

(1) Criteria for participating institutions

Institutions that meet all of the following criteria will be evaluated:

1) Institutions that can provide treatment of AS by specialists
2) Institutions that can make a diagnosis of tuberculosis in cooperation with in-house pneumologists or radiologists or with other institutions.
3) Institutions that can diagnose or treat severe infections in cooperation with in-house infectious disease specialists or with other institutions.

(2) Criteria for physicians

Physicians with at least one of the following criteria will participate in the surveillance after they receive a complete set of informational materials on safety measures and are informed about Humira by medical representatives to ensure full understanding of the characteristics of Humira and treatment of AS.

1) Physicians who have participated in clinical studies of adalimumab in patients with AS
2) Physicians who have expertise in the treatment of AS
3) Physicians who have used anti-TNFα drugs for patients with AS.

6. Methods of surveillance

(1) Methods of surveillance

This surveillance involves all-case surveillance for patient enrolled using a central registration method. All patients receiving Humira in institutions which meet the criteria for physicians and institutions and have concluded agreements with Abbvie GK for enrollment in the surveillance will be investigated.

(2) Procedures for requesting cooperation and concluding agreements

1) Medical representatives will provide investigators with documents containing information on measures to assure the safety of Humira treatment, and fully explain the characteristics of Humira and treatment of AS as well as the purpose, subjects, and methods of the surveillance.
2) Investigators and other healthcare professionals receiving the materials will confirm that they have received an explanation of Humira and the surveillance using the complete set of materials, that they will cooperate in the postmarketing surveillance of Humira for AS, and that they and their institutions meet the criteria for institutions and physicians in the surveillance, and then sign a "Confirmation of Distribution of Proper Use Information" form. Medical representatives will obtain the signed Form and confirm its contents, and then formally request that the institutions participate in the surveillance and conclude written agreements between these institutions and Abbvie GK regarding surveillance.

(3) Methods of surveillance

1) A paper-based case report form (CRF) will be used to collect surveillance data.
2) Each patient will be observed for 24 weeks.

3) Physicians will fully explain the surveillance and obtain informed consent from each patient who is to receive Humira for the treatment of AS.
4) When physicians decide to prescribe Humira to an eligible patient who has provided informed consent, the physician will fill out a registration form and submit it to the registration center to register the patient.
5) Physicians will fill out the case report form for each patient following the 24-week observation period to indicate findings, and provide it to a medical representative. When treatment with Humira is discontinued during the 24-week observation period for any reason, physicians will continue to follow these patients for 24 weeks after the first administration and fill out case report forms for them at the end of the observation period.
6) The sponsor will confirm the contents of the registration and CRFs and perform reinvestigation whenever necessary.
7) Medical representatives will also visit investigators once every one or two weeks, in principle, to monitor for the occurrence of adverse events, provide proper use information, and confirm the progress of patient registration.
8) Following the 24-week observation period, findings for the sacroiliac joint and the vertebral bodies and presence/absence of development of malignant tumors will be collected annually using a separate questionnaire form for 2 years after the first administration. Detailed investigation will be conducted for patients in whom development of malignant tumor is reported through the questionnaires. Investigators will be requested to report cases of malignant tumors promptly to Abbvie GK regardless of the duration of the questionnaire survey.

7. Duration of surveillance

Duration of surveillance: 27 Oct 2010 to 31 May 2016
Duration of registration: 27 Oct 2010 to 28 May 2015

<Milestones>
Major study milestones and their planned dates are as follows:

Start of Data Collection:	27 Oct 2010
Registration in the EU PAS register:	Not Applicable
End of Study:	31 May 2016
Final Report of Study Result:	30 Nov 2016

8. Items of the surveillance

(1) Observation period

Each patient will be followed for 24 weeks. Even if patients discontinue Humira treatment within 24 weeks, physicians will continue observation of them for 24 weeks after the first administration of Humira.

(2) Registration form

Name of institution, date of completion of the registration form, department, name of physician, patient

ID number, informed consent, birth date or age, sex and pregnancy/lactation status (for females), reasons for use of Humira, day (or planned day) of initiation of Humira treatment, contraindications to use of Humira, conditions requiring special care in administration, presence/absence and efficacy of previous treatment of AS, history of biological treatment, presence/absence of tuberculosis or other infection (tuberculin skin test, Quantiferon test, chest X-ray, and chest CT), hepatitis B virus test (HBs antigen test), presence/absence of preventive anti-tuberculosis treatment, and baseline laboratory data (blood β-D-glucan level, peripheral blood WBC, and peripheral blood lymphocyte count, serum creatinine level, HLA-B27).

(3) Case Report Form

1) Patient information

Smoking history, in-/outpatient status, height, weight, duration of illness, complications (e.g., uveitis, inflammatory bowel disease, psoriasis), past illnesses, and history of allergy.

2) Treatment with Humira

Method of administration, dosage, frequency, duration of treatment, reasons for change in dose or dosing interval.

Self-injection: Presence/absence of written consent for transition to self-injection, and presence/absence of self-injection transition record.

Errors in self-injection: Presence/absence, date of onset, description, and reasons.

3) Previous drug treatment of AS (treatment during the 3-month period prior to the surveillance).

Presence/absence and contents of previous treatment of AS

4) Use of antituberculosis drugs

Names of drugs, dosages, durations

5) Status of concomitant Drugs

① Use of drugs for AS

Name of drug, route, dose, and duration

② Use of other drugs

Name of drug, route, dose, and duration

Drugs for adverse events: Names of drugs, reasons for use, routes, doses, durations

6) Usage of non-drug treatment for AS

Presence/absence and contents of non-drug treatment

7) Bath AS Disease Activity Index (BASDAI) rating

Evaluate at baseline and Weeks 12 and 24 of treatment or discontinuation of treatment

8) Overall improvement rating (by physicians)

Patients will be evaluated for improvement at weeks 12 and 24 of treatment or discontinuation of treatment or participation in the survey based on the clinical course from baseline using the following scale:

1. Markedly improved, 2. Improved, 3.Not improved, 5. Not assessable

9) Progress of the survey

Date of the final coming to a hospital and reasons for discontinuation

10) Discontinuation of treatment with Humira (When treatment is discontinued during the observation

period)

Reasons for discontinuation of Humira treatment.

11) Presence/absence of tuberculosis or serious respiratory diseases

Date of examination, method of diagnostic imaging, and presence/absence and type of abnormal findings

12) Specific complications (uveitis, inflammatory bowel disease, psoriasis)

Compare clinical findings after treatment with baseline findings to rate the change using the following scale.

1. Improved, 2. Unchanged, 3. Worsened, 5. Not assessable (reasons for this)

13) Laboratory data

14) Adverse events

Presence/absence of adverse events, type of adverse events, date of onset, seriousness, causal relationship between adverse events and Humira treatment, suspected drugs, clinical course of adverse events, measures taken (measures related to Humira treatment and symptomatic treatment), outcome, and laboratory findings (indicate laboratory values when abnormal laboratory findings are observed).

15) Items of investigation of particular interest

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

9. Items to be analyzed and methods of analysis

(1) Items to be analyzed

1) Information on number of evaluable patients

① Number of registered patients

② Number of patients for whom case report forms have been retrieved

③ Number of patients who are evaluable for safety

④ Number of patients who are evaluable for efficacy

2) Items regarding safety

① List of adverse drug reactions (ADRs)/infections

② Factors which may affect the safety of Humira

- Incidence of ADRs by patient background factor
- Profile of ADRs before and after increase in Humira dose

③ Adverse events occurring during or after the treatment period

- List of cases of serious adverse events

④ Errors in administration during self-injection

3) Items regarding efficacy

① Clinical course

② Factors which may affect the efficacy of Humira

- Analysis of efficacy by patient characteristics
- Improvement of clinical symptoms after increase in Humira dose

③ Overall improvement rating

4) Evaluation of special populations

E.g., list of occurrences of ADRs/infections in special populations such as children, elderly patients, pregnant/lactating women, patients with renal function disorder, and patients with hepatic function disorder.

(2) Methods of analysis

Appropriate methods of analysis such as the chi-square test will be used according to the scale and nature of the data analyzed.

10. Measures to be taken when the use of Humira in pregnant women is observed

When the use of Humira in pregnant women is noted during the surveillance, follow-up investigation will be performed whenever necessary to examine its effects on labor and/or neonates.

11. Organizations conducting the surveillance

The organizations conducting the surveillance are described in the basic plan of the postmarketing surveillance. Parties who will be entrusted activities related to the surveillance are described in Section 12 "Names and addresses of parties entrusted activities related to the surveillance and the ranges of their activities".

12. Names and addresses of parties entrusted activities related to the surveillance and the ranges of their activities

(1) Contractor #1

[redacted]

2) Duties

Implementation of the special surveillance (e.g., requests, contracts, retrieval and reinvestigation of registration forms, retrieval and reinvestigation of CRFs, and collection of information on adverse events including abnormal laboratory findings)

(2) Contractor #2

[redacted]

2) Duties

Implementation of the special surveillance (e.g., case registration, monitoring of performance of duties, data management, and statistical analysis)

13. Other requirements

(1) Revision of the protocol

The sponsor will determine whether the protocol requires revision and, if necessary, revise it on the basis of new knowledge and findings obtained during the follow-up survey and/or when approval for partial changes to the approved dosage and administration or indication(s) of the product concerned is

obtained (not including cases for which the reevaluation period is newly specified).

2) Actions to be taken with regard to problems and questions.

(2) Actions to be taken with regard to problems and questions

When a serious unknown ADR appears to have occurred, when the incidence of an ADR is significantly increased, when any problems related to the efficacy or safety of Humira are found, or when the occurrence of ADRs that differ significantly from those observed during premarketing clinical studies is reported, among other conditions, the sponsor will consider whether special surveillance or postmarketing clinical studies should be conducted to detect or confirm the causes of such conditions, or to verify conclusions reached on the basis of the results of the present surveillance.

14. Amendments and Updates

Number	Date	Section of study Protocol	Amendment or Update	Reason
1	23 Feb 2016	7. Duration of surveillance <Milestones> Start of Date Collection Registration in the EU PAS register End of Study Final Report of Study Results	Update	Add the end of study date due to this date became clear.