Humira® for Subcutaneous Injection

Special Investigation (All-case survey) in Patients with Juvenile idiopathic arthritis

Study Protocol

AbbVie GK

1. Purpose of the surveillance

This postmarketing surveillance of Humira® for Subcutaneous Injection (generic name: adalimumab (recombinant)) will be conducted to clarify the following with regard to the treatment of juvenile idiopathic arthritis (JIA) affecting multiple joints with this drug:

① Unknown adverse drug reactions (ADRs) (especially important ADRs)
② Incidence and conditions of occurrence of adverse reactions in the clinical setting
③ Factors that may affect the safety and efficacy of Humira

< Items of investigation of particular interest>

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

2. Target number of patients

Target sample size: 100 patients

Immediately after the approval of JIA as an indication for treatment with Humira, all patients who receive Humira for the treatment of JIA affecting multiple joints will be registered, and the data for the first 100 patients will be tabulated and analyzed, and the results reported to the regulatory authority. Registration of patients will be continued until the authority concludes its final evaluation.

<Rationale>

Considering the number of patients for whom registration is considered feasible, we will analyze data for 100 patients to detect ADRs with an incidence of 3% at a probability of 95%.

3. Patients to be investigated

All patients with JIA affecting multiple joints who have not responded well to conventional therapy and receive Humira will be enrolled in the survey.

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

(1) Institutions participating in the survey

Institutions that meet the following criteria will participate in the survey:

1) Institutions that can cooperate with and conclude a contract for the all-case survey
2) Institutions that can provide treatment of JIA by specialists.

(Such as hospitals certified by the Pediatric Rheumatology Association of Japan (PRAJ) as institutions providing specialist education in JIA, hospitals in which PRAJ-certified JIA specialists are working, hospitals in which biological therapy has been performed etc).

3) Institutions that can diagnose and treat tuberculosis in cooperation with in-house pneumologists or radiologists or in cooperation with other institutions.

4) Institutions that can diagnose and treat severe infections in cooperation with in-house infectious disease specialists or in cooperation with other institutions.

(2) Investigators participating in the survey

Investigators with at least one of the following qualifications will participate in the survey after they receive a complete set of informational materials on safety measures from medical representatives to ensure full understanding of the characteristics of Humira and its use in the treatment of JIA.

Physicians who have treated patients with JIA and satisfy any of the following criteria will be allowed to participate.

① Physicians who are board-certified specialists of the Japan Pediatric Society and board-specified specialists of the JCR

② Physicians who are members of the PRAJ and board-specified specialists of the JCA

③ Physicians who have participated in all-case survey(s) of biologic agents including Humira in patients with RA and JIA.

④ Physicians who have participated in clinical studies of Humira in patients with JIA.

⑤ Physicians who have been educated by physicians with expertise in the treatment of JIA by Humira.

⑥ Physicians who can prescribe Humira or treat patients with JIA under the instruction of physicians who satisfy any of the above criteria ①~④.

6. Methods of surveillance

(1) Methods of registration and agreement

This surveillance involves all-patient enrollment using a central registration method. All patients receiving Humira for the treatment JIA affecting multiple joints in institutions which meet the criteria for physicians and institutions and have concluded agreements with AbbVie GK Japan for enrollment in the all-case survey will be investigated.

(2) Procedures for requesting cooperation and obtaining agreement

1) Medical representatives will provide investigators and other healthcare professionals with a complete set of informational materials on safety measures, and will inform them about the characteristics of Humira, treatment of JIA, the purpose of the surveillance, patients to be investigated, and methods of investigation.

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 with the surveillance, and that they and their institutions meet the criteria for institutions and physicians in the survey, 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 Japan regarding surveillance.

(3) Methods of investigation

1) A paper-based case report form (CRF) will be used to collect survey data.
2) All patients who use Humira during the period between approval of JIA as an indication for Humira and the conclusion of evaluation of the results of the all-case survey by the regulatory authority will be registered.
3) Each patient will be observed for 24 weeks.
4) Investigators will fully explain the proper use information on Humira and obtain informed consent for the treatment with Humira from each patient and his/her legal guardian (if the patient is less than 20 years of age).
5) When treatment with Humira is selected for a patient who has provided informed consent, the investigator will fill out a registration form and submit it to the registration center to register the patient.
6) Investigators will fill out the case report form for each patient following the 24-week observation period without delay, and provide it to a medical representative. When a patient discontinues treatment during the observation period, the investigator will follow up the patient until the end of the 24-week observation period, fill out the case report form for him/her at the end of the observation period, and provide it to a medical representative.
7) The sponsor will confirm the contents of the registration and case report forms, and perform reinvestigation whenever necessary.
8) Medical representatives will also visit investigators once every week or every other week, in principle, to monitor for the occurrence of adverse events, provide proper use information, and determine the progress of patient registration.
9) Following the 24-week observation period, the investigator will evaluate each patient for malignancy annually for 2 years after the initiation of Humira treatment using a separate follow-up investigation form. When the occurrence of malignancy is found in a patient, the investigator will perform detailed investigation of him/her. Investigators will be instructed to report the occurrence of malignancy to the sponsor without delay when they are found, regardless of the timing of follow-up investigation.
10) Adverse Event Reporting
In the event of a serious adverse event, and additionally, any non-serious events of malignancy in patients 30 years of age and younger, whether related to adalimumab or not, if applicable - the physician will notify the AbbVie contact person (Medical Representative in Japan) within 24 hours of the physician becoming aware of the event.

7. Duration of surveillance

Duration of surveillance: 1st JUL2011~26thFEB2018
Duration of registration: 1st JUL2011~26thFEB2016

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

Start of Data Collection:	1 JUL 2011
Registration in the EU PAS register:	Not Applicable
End of Study:	The date on which statistical analysis dataset for

Clinical Study Report becomes available

Final Report of Study Result: 2 Oct 2018

8. Items to be investigated

(1) Duration of observation

Each patient will be observed for 24 weeks.

(2) Registration form

Date of completion of the registration form, name of institution, department, name of investigator, obtaining of informed consent of the patient or his/her legal guardian, history of Humira treatment, sex, age, patient ID, reasons for use of Humira and type of JIA, 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 JIA, presence/absence of tuberculosis or other infection (tuberculin skin test, Quantiferon test, chest X-ray, and chest CT), preventive anti-tuberculosis treatment, hepatitis B virus test, and baseline laboratory data (blood β-D glucan level, peripheral blood WBC, peripheral blood lymphocyte count, serum creatinine).

(3) Case Report Form

1) Patient background

History of Humira treatment, in/out-patient status, duration of illness, Steinbrocker classification, Steinbrocker functional classification, complications, past illness, history of allergy, history of vaccines

2) Treatment with Humira

In/outpatient treatment, dosage, interval of administration, duration of administration, reasons for change in dose or interval of administration

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

Errors in administration during self-injection: presence/absence, date of onset, description, and reasons for.

3) History of biological treatment of JIA

Presence/absence of history of biological therapy, name of drug, dose, duration (start date and end date), and reason for discontinuation.

4) Previous treatment of JIA affecting multiple lesions (treatment during the 3-month period preceding Humira treatment)

Presence/absence of previous treatment of JIA, names of drugs [methotrexate and other DMARDs, NSAIDs, corticosteroids].

* For patients who have received methotrexate and/or corticosteroids, the routes, doses and durations, as well as the use of NSAIDs and other DMARDs will be investigated.

5) Status of administration of concomitant drugs

① Use of drugs for JIA

Presence/absence of concomitant drug use for JIA, names of drugs, routes, doses, and durations

② Use of other drugs

Presence/absence of concomitant drug use for conditions other than JIA, names of drugs, routes, doses, and durations

If an adverse event occurs: Names of drugs, reasons for use, routes, doses, and durations

6) Non-drug concomitant therapy

Non-drug concomitant therapy for JIA

7) Presence/absence of tuberculosis or serious respiratory diseases

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

8) Clinical evaluation

Patients will be evaluated for the following at the time points described below:

① DAS28 (number of tender joints and number of swollen joints), global assessment by patient (VAS), global health by physician (VAS), erythrocyte sedimentation rate (ESR, 1 hr value), and CRP. (Baseline, and Weeks 4, 8, 16, and 24 weeks of treatment)

② Serum MMP-3 level. (Baseline, and Weeks 4, 8, 16, and 24 weeks of treatment)

③ Anti-CCP antibody (Baseline and 24 weeks of treatment)

④ Height and body weight. (Baseline, and Weeks 4, 8, 16, and 24 weeks of treatment)

9) Discontinuation of Humira treatment

Reasons for discontinuation of Humira treatment

Treatment after discontinuation of Humira treatment

10) Adverse events (including abnormal laboratory findings)

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

11) Items of investigation of particular interest

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

(4) Preparation of written consent form for transition to self-injection and self-injection transition record

It will be confirmed whether written consent for transition to self-injection has been obtained and a self-injection transition record has been prepared.

(5) Presence/absence of malignant tumor during the long-term follow-up period.

Patients will be evaluated for the occurrence of malignancy during the first and second years of treatment.

(6) Product Quality Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this trial contains both:

-Biologic compound(s) and

-Device component(s) (pre-filled syringe, pen).

・Definition

A Product Complaint is any Complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the

labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

・ Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via local Product Complaint reporting practices. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product complaints involving a non-Sponsor investigational product and/or device should be reported to the identified contact or manufacturer, as necessary per local regulations.

Product Complaints may require return of the product with the alleged complaint condition (syringe, pen, etc.). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

9. Items to be analyzed and methods of analysis

(1) Items to be analyzed

1) Information on characteristics 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) Information on the safety of Humira

① List of adverse drug reactions (ADRs)/infections
② Factors which may affect the safety of Humira
- Incidence of ADRs by patient background factor
- Incidence of ADRs before and after increase in Humira dose

③ Adverse events occurring during or after the treatment period
- List of occurrences of serious adverse events

④ Errors in administration during self-injection

3) Information on the efficacy of Humira

① Clinical course
- DAS28 (number of tender joints and number of swollen joints), global assessment by

patient (VAS), global health by physician (VAS), erythrocyte sedimentation rate (ESR, 1 hr value), and CRP. (Baseline, and Weeks 4, 8, 16, and 24 weeks of treatment)

- Serum MMP-3 level (Baseline, and Weeks 4, 8, 16, and 24 weeks of treatment)
- Anti-CCP antibody (Baseline and 24 weeks of treatment)
- Height and body weight (Baseline, and Weeks 4, 8, 16, and 24 weeks of treatment)

② Factors that may affect the efficacy of Humira

- Summarized efficacy data by patient background factor

4) Matters related to special populations

List of occurrences of ADRs/infections in special populations such as 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

1) Address: 4-6-10, Koishi-gawa, Bunkyo-ku, Tokyo.
Name: Eisai Co., Ltd.
GPSP Controller: [redacted]

2) Duties

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

(2) Contractor #2

1) Address: 20th Floor (Reception), Sumitomo Fudosan Korakuen Bldg., 1-4-1, Koishikawa, Bunkyo-ku, Tokyo
Name:,A2 Healthcare Corporation
[redacted]

2) Duties

Implementation of the special surveillance (e.g., patient registration, report on progress of surveillance, data management, and data analysis)

13. Other requirements

(1) Amendment of the protocol

The protocol for the surveillance will be amended as appropriate according to the results of evaluation of the need for such amendment, considering the findings obtained during the surveillance. For example, when applications for partial modification of dosage & administration or indications are approved during the period of reexamination (this will not apply to cases in which the period of reexamination is newly designated), the sponsor will consider whether the protocol should be amended or not, and will revise the protocol whenever necessary.

(2) Responses to problems/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	28 JAN 2011		Create New	
2	26 ARP 2011	8. Items to be investigated 9. Items to be analyzed and methods of analysis	Amendment	Advice of KOL
3	8 JUL 2011	6. Methods of surveillance 8. Items to be investigated	Amendment	insufficient description
4	4 ARP 2013	Front cover	Amendment	Change to Avvibe
5	23 Feb 2016	6. Methods of surveillance 8. Items to be investigated	Amendment	FDA requirement
6	05 APR 2016	7. Duration of surveillance	Amendment	Released of all-case surveillance
7	20 DEC 2016	Dosage form	Amendment	Delete dosage name
8	20 DEC 2016	12. Names and addresses of parties entrusted activities related to the surveillance and the ranges of their activities	Amendment	Change due to merger of CRO
9	6 APR 2018	7. Duration of surveillance 12. Names and addresses of parties entrusted activities related to the surveillance and the ranges of their activities	Amendment	Add the end of study date due to this date became clear and change address of the CRO

Attachments

a. Contract document (draft)
b. Guidance of implementation of the special surveillance (draft)
c. Registration form and case report form for the special surveillance (draft)
d. Written confirmation of successful transmission of proper use information (draft)
e. Explanatory materials for informed consent and informed consent form (draft)

e. Written consent for transition to self-injection (draft)

g. Self-injection transition record (draft)