# Humira® for Subcutaneous Injection

## Protocol for Special Investigation

## (Long-term treatment for Crohn's Disease patients)

**AbbVie GK**

Protocol No. P13-170

## 1. Purpose of the investigation

This special investigation of Humira for Subcutaneous Injection will be conducted to obtain information on the safety (especially profile of malignant tumors and serious infections) and effectiveness in patients with Crohn's disease who are receiving Humira for a long period of time.

## 2. Target number of patients

(1) Target sample size

A total of 500 patients.

(2) Rationale

The incidence of malignant tumors in clinical studies in CD patients conducted in- and outside Japan prior to the approval of Humira for CD were 1.1% (1/90 patients) and 1.1% (16/1459 patients). Based on these incidences, we plan to investigate 300 patients to detect at least one case of malignant tumor at a probability of 95%, and register 500 patients, since a substantial number of patients will discontinue or withdraw from the investigation.

## 3. Patients to be investigated

Patients who meet the following criteria at baseline will be evaluated in the investigation:

(1) Patients with Crohn's disease indicated for Humira treatment with the recommended dosage regimen.

(2) Patients with no past- or present malignant tumors.

(3) Patients who are not currently receiving Humira.

## 4. Number of participating institutions by department

The investigation will be conducted in about 100 eligible institutions.

## 5. Criteria of participating institutions and investigators

The investigation will be conducted by the institutions and physicians that satisfy the following criteria and have concluded agreements with AbbVie GK. for implementation of the investigation.

(1) Participating institutions

Institutions that satisfy the following criteria will participate in the investigation:

1) Institutions that have concluded or will conclude agreement with AbbVie GK. for implementing the all-case investigation of Humira in patients with Crohn's disease

2) Institutions where the effectiveness of Humira can be evaluated using Crohn's Disease Activity Index (CDAI) whenever possible.

(2) Participating investigators

Investigators that satisfy the following criteria will participate in the investigation:

1) Physicians who have participated in the all-case investigation of Humira in Crohn's disease[*1]

2) Physicians who have experienced anti-TNFα antibody treatment to patients with Crohn's disease [*2]

*1 This condition will be used during the all-case investigation of Humira in Crohn's disease

*2 This requirement will be used after the conditions for approval were completely removed.

## 6. Methods of the investigation

(1) Principles of the investigation

Patients who receive Humira in the applicable institutions (that satisfy the criteria for institutions and physicians and have concluded agreements with AbbVie GK.) will be registered using a central registration method.

(2) Procedures for requesting cooperation and concluding agreements

1) Medical representatives will provide investigators and other healthcare professionals with a complete set of informational materials on safety measures (for physicians expect the investigators participating in the all-case investigation), and will inform them about the characteristics of Humira, the purpose of the investigation, patients to be investigated, and methods of investigation.

(3) Procedures of the investigation

1) A paper-based case report form (CRF) will be used to collect investigation data.
2) Each patient will be observed during 3 years after the onset of Humira treatment.
3) When the treatment with Humira is selected for a patient who has expressed his/her consent for treatment, the investigator will fill out a registration form without delay* and submit it to the registration center to register the patient.

* Basically, we accept registration forms with a postmark date within 14 days after the date of first administration of Humira (the first treatment date is Day 0).

4) Investigators will fill out the CRF for each patient every 6 months for 3 years after the initiation of Humira treatment, and provide it to a medical representative (MR). Accordingly, a total of 6 copies of CRFs will be obtained for each patient. When a patient discontinues Humira treatment during the investigation period, the investigator will fill out the CRF for the patient without delay at the time of discontinuation of treatment, and provide it to a MR.
5) The sponsor (AbbVie GK.) will confirm the contents of the registration form and CRFs, and perform reinvestigation whenever necessary.

(4) 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 the investigation

Registration period: November 2011 ~ October 2013

Investigation period: November 2011 ~ March 2017

<Milestones>

Major study milestones and their planned dates are as follows:

| | |
|---|---|
| Start of Data Collection: | November 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: 30 Sep 2018

## 8. Items to be investigated

(1) Observation period

Patients will be observed for 3 years after the initiation of Humira treatment. (Patients who will continue Humira treatment for more than 3 years will also be evaluated at the end of third year to enable completion of the CRF). Patients who have been lost to follow-up during the observation period due to transfer to another hospital, discontinuation of treatment* or for other reasons will be handled as cases of discontinuation of the survey.

* A patient who has suspended Humira treatment for at least 2 months should be considered a case of discontinuation of Humira treatment that will be handled as a case of discontinuation of the survey.

(2) Registration form

Name of institution, date of completion of the registration form, name of department, name of investigator, patient ID, patient's birthdate (year/month) or age, sex, presence/absence of pregnancy/lactation (for female patients), reasons for use of Humira, date (or planned date) of initiation of Humira treatment, contraindications to use of Humira, conditions requiring special care in administration, presence/absence and effectiveness of previous treatment of Crohn's disease, history of biological therapy, 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).

(3) Data to be collected via CRF

1) Patient background

Smoking history, in/outpatient, past and current history of Crohn's disease, height, weight, duration of illness, complications, past illnesses, and history of allergy.

2) Previous anti-TNFα treatment of Crohn's disease

Presence/absence, history, and reasons for discontinuation of anti-TNFα treatment.

3) Previous drug treatment of Crohn's disease (treatment during the 3-month period prior to the investigation)

Presence/absence and contents of previous treatment of Crohn's disease

4) Treatment with Humira

At the time of first administration: method of administration, initial dose, and date of initial administration.

At the second administration: method of administration, dosage, and date of second administration

At the third administration and thereafter: method of administration, dosage, interval of administration, duration of administration, and 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.

5) Treatment with antituberculosis agents

Presence/absence of antituberculosis agents, names of drugs, daily dose, and duration

6) Status of administration of concomitant drugs

Presence/absence of concomitant drug use for Crohn's disease, name of drug, route, dose, and duration.

7) Usage of non-drug treatment for Crohn's disease

Presence/absence and type of non-drug treatment, and duration.

8) Presence/absence of development of tuberculosis or serious infections

Day of examination, imaging technique, presence/absence of abnormal laboratory findings, and description of abnormal findings.

9) Crohn's Disease Activity Index (CDAI)

Evaluate at baseline and week 4, month 3, month 6, year 1, year 1.5, year 2, year 2.5 and year 3 of Humira treatment, and at the time of discontinuation of the treatment

10) Work Productivity and Activity Impairment Questionnaire: Crohn's disease (WPAI: CD )

Evaluate at baseline and week 4, month 3, month 6, year 1, year 1.5, year 2, year 2.5 and year 3 of Humira treatment, and at the time of discontinuation of the treatment.

11) C-reactive protein (CRP)

Evaluate at baseline and week 4, month 3, month 6, year 1, year 1.5, year 2, year 2.5 and year 3 of Humira treatment, and at the time of discontinuation of the treatment

12) Endoscopic examination

Date (baseline, during treatment and year 3 or after discontinuation) and endoscopic findings

13) Discontinuation of the investigation

Reasons for discontinuation of the investigation [occurrence of adverse event (AEs), insufficient response to Humira, patient's request, no visits, others].

14) AEs (including abnormal laboratory findings)

Presence/absence and nature of AEs, date of onset, seriousness, causal relationship with Humira treatment, suspected drugs, clinical course of AEs, measures taken (measures related to Humira treatment and symptomatic treatment), outcome, laboratory findings (indicate laboratory values when abnormal laboratory findings are observed), and reasons for the rating of causal relationships when the investigator concludes that there is no causal relationship.

15) 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.

16) Items of investigation of particular interest

Occurrence of malignant tumor and serious infections.

(4) Measurement of anti-adalimumab antibody (AAA)

Patients who receive Humira and meet the following conditions during the observation period (from the first administration of Humira to the end of week 24 of treatment) may undergo AAA assay.

1) The attending physician considers determination of AAA necessary for investigation of the reasons for ADRs or loss of efficacy, among other conditions.

2) The patient gives consent to undergo determination of AAA.

## 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 CRFs have been retrieved

③ Number of patients who are evaluable for safety

④ Number of patients who are evaluable for effectiveness

2) Information on the safety of Humira

① Table of adverse drug reactions (ADRs)/infections

② Factors which may affect the safety of Humira

- Incidence of ADRs by patient background factor

③ Occurrence of AEs

- e.g., list of occurrences of serious AEs

④ Errors in administration during self-injection

3) Information on the effectiveness of Humira

CDAI, WPAI:CD, endoscopy, and CRP

4) Others

Stratified analysis of incidence of malignant tumor, tuberculosis, serious infections and other events are planned.

(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 investigation, follow-up investigation will be performed whenever necessary to examine its effects on labor and/or neonates.

## 11. Organizations conducting the investigation

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

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

(1) Contractor #1

1) Address: 4-6-10 Koishikawa, Bunkyo-ku, Tokyo 112-8088, Japan
Name: Eisai Co., Ltd.
GPSP Controller [redacted]

2) Duties

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

(1) Contractor #2

1) Address: [redacted] Sumitomo Fudosan Korakuen Bldg., 1-4-1, Koishikawa, Bunkyo-ku,

Tokyo

Name:,A2 Healthcare

President: Tadashi Katori President and CEO

2) Duties

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

## 13. Other requirements

(1) Amendment of the protocol

The protocol for the investigation will be amended as appropriate according to the results of evaluation of the need for such amendment, considering the findings obtained during the investigation. 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 effectiveness 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 investigation 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 investigation.

## 14. Amendments and Updates

| Number | Date | Section of study Protocol | Amendment or Update | Reason |
|---|---|---|---|---|
| 1 | 23July2012 | 7. Duration of the investigation | Amendment | Change the surveillance schedule |
| 2 | 23 Feb 2016 | 6.4 Adverse Event Reporting<br>8.3.15 Product Quality Complaints<br>12. Names and addresses of parties | Amendment | FDA requirement<br><br>FDA requirement<br><br>Change the GPSP controller and the company name of CRO |
| 3 | 6 Apr 2018 | Dosage form<br><br>7. Duration of surveillance | Amendment<br><br>Amendment | Delete dosage name<br><br>Add the end of study date and final report of study result due to this date became clear. |

**Attachments**

a. Contract document

b. Guidance of implementation of the special investigation

c. Registration form and case report form for the special investigation

d. Written consent for transition to self-injection

e. Self-injection transition record

# AbbVie GK

# PMOS PROTOCOL (P13-170)

## Special Investigation on Long-term treatment for Crohn's Disease patients

**Approved by**

[redacted] 06-Apr-2018

Protocol Author - [redacted] Date

[redacted] Apr. 6. '18

Study-Designed Physician - [redacted] Date

[redacted] Apr. 6, 2018

Statistics Representative - [redacted] Date

[redacted] April 6th/2018

Project Director- [redacted] Date

[redacted] April 18 2018

Project D[redacted] Date

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[redacted] Apr. 6, 2018
Statistics Representative - [redacted] Date

[redacted] April 6th/2018
Project Director- [redacted] Date

Project Director- [redacted] Date