

HUMIRA® for Subcutaneous Injection
Protocol for Special investigation on Long-Term administration
Ulcerative Colitis

AbbVie GK

1. Purpose of Surveillance

The following were investigated in the Special investigation on Long-Term administration of “HUMIRA® for Subcutaneous Injection (Nonproprietary name: Adalimumab (Genetical Recombination))” in patients with ulcerative colitis.

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

< Priority items of investigation >

Infection, tuberculosis, malignant tumor, injection site reaction, autoimmune disease, pancytopenia, demyelinating disorders, congestive cardiac failure, and interstitial pneumonia
For enteral infection, the cause (virus or bacteria) will be examined.

2. Sample Size

The number of patients to be included: 1500

They are patients with ulcerative colitis who use this drug after approval.

< Rationale for setting >

1. Since this survey will be conducted in actual clinical practice, the proportion of patients who have been treated with anti-TNF α products is anticipated to be high. First, considering that a dropout rate may be higher than that in Japanese clinical studies due to the enrollment of such patients, the planned sample size was calculated by assuming a dropout rate at Week 52 of 70%. Next, in the all-case survey in patients with Crohn's disease, the CDAI, an efficacy endpoint, was not recorded for approximately 30% of all the patients. Thus, by assuming the proportion of patients without assessment of Mayo score of 30%, a remission rate of 30% and the accuracy of 95% confidence interval estimation of $\pm 5\%$, the sample size was determined to be 1500 patients (Table 1).

Table 1 Sample size calculated based on the dropout rate and accuracy

Dropout rate 70%				
Sample size	Sample size at Week 52	No. of patients assessed for Mayo score	Remission rate 30% at Week 52 95%CI	Accuracy
500	150	105	21.2~38.8	$\pm 8.8\%$
1000	300	210	23.8~36.2	$\pm 6.2\%$
1500	450	315	24.9~35.1	$\pm 5.1\%$
2000	600	420	25.6~34.4	$\pm 4.4\%$

No. of patients assessed for Mayo score is calculated 70% of sample size at Week 52.

2. Next, for the presence or absence of history of use of anti-TNF α products, the accuracy of the remission rate used for setting the above sample size of 1500 patients was evaluated (Table 2). The following conditions were specified for the evaluation:

In data from the all-case survey of Humira in patients with Crohn's disease, 80% and 20% of the patients had used and had not used anti-TNF α products. Immediately after the drug was approved for Crohn's disease, because there were many patients waiting for the drug such as non-responders to anti-TNF α products in previous treatment, patients are likely to be enrolled in the present survey at the same ratio. Therefore, the rate for the use of anti-TNF α products in the survey was selected to be 80% and 20% for patients have used and have not used them.

The remission rate based on the Mayo score at Week 52 was set to 10% for patients who have used anti-TNF α products based on data from an overseas clinical study (M06-827) and 30% for patients who have not used them which was utilized for calculating the above sample size of 1500 patients.

Table2 Remission rate of history of anti-TNF α products use

	No. of patients assessed for Mayo score	Remission rate at Week 52	95%CI	Accuracy
History of anti-TNF α products use	252	10%	6.1~13.9	$\pm 3.8\%$
Without history of use of anti- TNF α products	63	30%	17.9~42.1	$\pm 12.1\%$

Based on these results, while the accuracy is poor because the number of patients in the group without history of use of anti-TNF α products is small, the data from the group with a history of use of anti-TNF α products is assumed to be an assessable numerical value (Table 2).

In a domestic clinical study of this drug in patients with ulcerative colitis (Study M10-447: 52 weeks), adverse events occurred in one patient where the incidence rate was 0.6% (1/177). On the basis of this incidence, when 1500 patients are accumulated, the 95% confidence interval for the incidence would be 0.3 to 1.1% and assessable. Even if the incidence of tuberculosis is 2%, which is higher than that in the clinical study, in this survey, by accumulating 1500 patients, the upper and lower limit of the confidence interval would be 2.84 and 1.35, respectively. Hence, because the incidence of tuberculosis (as an adverse event) shown in the Japanese clinical study in patients with rheumatoid arthritis is higher than 1.0%, it is evaluable.

In the above mentioned, we set sample size of 1500 patients in order to verify the result of

both safety and effectiveness in the clinical study.

3. Patients to Be Surveyed

Patients with moderate to severe active ulcerative colitis (only when ineffectively treated with the existing medications) who use this drug are surveyed.

< Precautions related to the indications >

This drug should be administered only to patients who present with the definite disease-related clinical symptoms even after preceding treatments with immunomodulatory agents (such as azathioprine and 6-mercaptopurine).

4. Number of Survey Centers by Clinical Practice

At least 250 centers which are department of digestive organs or likes.

< Rationale for setting >

This surveillance is carried out centering on departments specialized in digestive organs. Assuming 6 patients per center on average, more than 250 centers are required for the patients to participate in the surveillance in consideration of the feasibility.

5. Survey Centers Involved

Study centers or departments using this drug in this indication.

6. Survey Methods

(1) Surveillance system

Patients are subjected to centralized enrollment, and administered this drug at the contracted centers or departments.

(2) Request and contract of post-marketing surveillance

- 1) MR provides a full set of materials of information on safety measures for HUMIRA® to physicians in charge of surveillance, and explains the character of this drug, the objective of surveillance, patients to be surveyed, and survey methods.
- 2) After the surveillance was accepted by the physician in charge, MR asks the center or department for implementation of post-marketing surveillance and contracts in writing.

(3) Survey methods

- 1) Paper-based CRF (case report form) is used to collect the survey data.
- 2) Patients are observed for a period of 52 weeks after administration of this drug was initiated.
- 3) A physician in charge of surveillance explains proper use information on this drug to participating patients, to obtain their written informed consent to participate in the surveillance.
- 4) A physician in charge completes the enrollment form as soon as this drug was decided to be administered to the patients who consented to participation, and sends it to the

enrollment center.

5) A physician in charge completes CRF with the observation results at week 52 after initiation of administration, and submits the CRF to MR. In cases of the observation period uncompleted, CRF is completed promptly when the surveillance was discontinued, and submitted to MR.

6) MR who asked the surveillance checks enrollment form and CRF, and rechecks them as needed.

(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.

(5) 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.

7. Surveillance Schedule

Surveillance period: July 2013 to March 2018

Enrollment period: July 2013 to July 2016

If the number of enrolled patients reached the planned sample size of the survey, the enrollment period and survey period will be reduced.

<Milestones>

Major study milestones and their planned dates are as follows:

Start of Data Collection: July 2013

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: 15 Aug 2018

8. Survey Items

(1) Observation period

Patients are observed for a period of 52 weeks after administration of this drug was started (even though the treatment is continued even after 52nd week, the CRF should be completed at the time point of week 52). When the patient is no longer followed up because of move to other hospital during the observation period, it is handled as a discontinued case.

(2) Enrollment form

Name of center, enrollment date, name of department, name of physician in charge, identification No. of patient, patient's consent, birth date or age, sex, pregnant or lactating status(in case of women), race, reason for use, initial (or scheduled) day of administration, administration status, examination category, contraindication items, careful administration, presence or absence of prior medications for ulcerative colitis and their effects, use history of biological products, tuberculosis and infection tests (tuberculin skin test, Quanti-Feron®

test, chest X-ray test, and CT test), HB virus tests (HBs antigen, HBs antibody, and HBc antibody), preventive administration of anti-tuberculosis agents, and clinical laboratory test values (β -D-glucan, peripheral WBC count, and peripheral lymphocyte count) before administration should be recorded.

(3) CRF

1) Patient information

height, body weight, smoking history, pathological condition of ulcerative colitis, disease duration, complication, past history, and allergy history

2) Ulcerative colitis-affected site

3) Treatment history of ulcerative colitis with anti-TNF α

Presence or absence of prior treatment with anti-TNF α , administration history, and reason for discontinuation

4) Prior medications or therapy for ulcerative colitis (within 3 months before administration of this drug)

History and type of prior medications or therapy

5) Administration status of this drug

Initial administration: Category of administration method, initial dose, and first administration day

2nd administration: Category of administration method, 2nd dose, and day of 2nd administration

3rd and subsequent administrations: Category of administration method, daily dose, administration frequency, administration period, and reasons for change to the dose and administration frequency

Self-injection: Presence or absence of consent to initiation of self-injection and record on initiation of self-injection

Malpractice of self-injection: Y/N, onset day, and type/reason

6) Discontinuation of survey

Reason for discontinuation

7) Administration status of anti-tuberculosis agents

Presence or absence of administration of anti-tuberculosis agents, product name, daily dose, and administration period

8) Administration status of concomitant drug(s)

Concomitant drug for ulcerative colitis: drug name, reason for use, administration route, dose, and administration period

9) Other concomitant drugs: drug name, reason for use, administration route, dose, and administration period

10) Drugs/combination therapies other than medication for ulcerative colitis

- Presence or absence of drugs/combination therapies other than medication for ulcerative colitis, name of therapy, and therapeutic duration
- 11) Presence or absence of onset of tuberculosis or serious respiratory disorders
Examination day, imaging diagnostic method, abnormal findings, and abnormality
- 12) Mayo Score
Examination day (at initiation of administration, week 4, 8, 16, 24, 32, and 52 of administration, and discontinuation of administration)
- 13) CRP
Examination day (at initiation of administration, week 4, 8, 16, 24, 32, and 52 of administration, and discontinuation of administration)
- 14) Endoscopic finding
Examination day (at initiation of administration, week 24, 52 of administration, and discontinuation of administration)
- 15) Overall improvement (judgment by attending physician)
Judgment day (at week 52 of administration or at discontinuation)
Overall improvement (Remarkably effective, Effective, Ineffective, and Unevaluable)
- 16) Adverse events (including abnormal change in laboratory values)
Occurrence of adverse events, name of adverse events, onset day, seriousness, causal relationship to this drug, suspected drug(s), symptom and clinical course, treatment (with this drug or symptomatic treatment), outcome, laboratory values (if abnormally changed), and judgment reason if no causality
- 17) Key survey items
Infection, tuberculosis, malignant tumor, administration site reaction, autoimmune disease, pancytopenia, demyelinating disorders, congestive cardiac failure, and interstitial pneumonia
- 18) Measurement of anti-adalimumab antibody
If measurement of anti-adalimumab antibody is judged to be necessary

9. Analysis and Methods

(1) Analytical items

1) Patient population

1. No. of enrolled patients
2. No. of CRFs recovered
3. Safety evaluation set
4. Efficacy evaluation set

2) Safety

1. List of adverse reactions and infections
2. Factors likely to affect the safety

- Incidence of adverse reactions by patient background
 - Presence or absence of the use experience with anti-TNF α preparation and the relationship of safety.
 - Safety in Long-Term administration
 - Relationship of safety when anti-adalimumab antibody was determined
 - Safety in patients conducting self-administration
3. Adverse events which developed during or after administration
 - List of serious adverse events
 - Status of onset of intestinal infections including cytomegalovirus colitis, etc.
 4. Main adverse events (infections including tuberculosis, malignant tumor, injection site reaction, allergic reaction, demyelinating disease, lupus-like syndrome, blood disorder) for which attention is called in the sections of warning, careful administration and important basic precautions in the package insert of the study drug
 5. Onset of self-injection malpractice
 6. Safety in pediatric UC patients
- 3) Efficacy
- Change in efficacy (Mayo score, Partial Mayo score etc.) by Week 52 of administration
 - Presence or absence of the use experience with anti-TNF α preparation and the relationship of efficacy.
 - Efficacy by the history of previous treatment
 - Efficacy (including the incidence of secondary ineffectiveness) in long-term administration
 - Relationship between efficacy and safety when anti-adalimumab antibody was determined
 - Efficacy in pediatric UC patients
- 4) Patients with special background
- List of adverse reactions and infections in patients with special background such as children, elderly, pregnancy, renal dysfunction, and hepatic dysfunction

(2) Analytical methods

Appropriate methods such as χ^2 test will be used, depending on the scale and property of the analytical data.

10. Action to be taken when use in pregnant woman was found

The effects on parturition and newborn are followed up as much as possible, if use in pregnant women was found.

11. Organization of Surveillance

This follows the master plan for post-marketing surveillance. The trustee appears in “12. Name

and Address of Person Who Was Entrusted with This Duty and Scope of the Duty” below.

12. Name and Address of Person Who Was Entrusted with This Duty and Scope of the Duty

(1) Trustee 1



2) Scope of duty

Implementation of “Specified Long-Term Use-Results Surveillance” (Asking the center or department for implementation of surveillance, contract, recovery of enrollment form and reinvestigation, recovery of CRF and reinvestigation, progress report of duty, and collection of information on adverse events (including abnormal change in laboratory values))

(2) Trustee 2



2) Scope of duty

The implementation of special use-results survey (patient enrollment activities, reporting the progress of activities, data management activities, statistical analysis activities, etc.)

13. Others

(1) Revision of protocol

The protocol is revised as needed after considering whether the revision of protocol is necessary or not, based on the new findings obtained as the surveillance advances. Similarly, the protocol is revised as needed after considering whether the revision of protocol is necessary or not, if a partial change application for dosage and administration or indications was approved during the reexamination period (excluding if a new reexamination period is designated).

(2) Measures to be taken for any problems or questions

When an unknown serious adverse event was suggested to develop, the incidence of adverse reactions extensively increased, some questions about the efficacy and safety were raised in comparison with clinical studies, or an alien adverse reaction was suggested to develop, “Specified Use-Results Surveillance” or “Post-marketing Clinical Study” is considered to be implemented to detect or validate their factors or to confirm the estimation results.

14. Amendments and Updates

Number	Date	Section of study Protocol	Amendment or Update	Reason
--------	------	---------------------------	---------------------	--------

1	23 Feb 2016	6.4 Adverse Event Reporting 6.5 Management and Reporting of Complaints 7 Surveillance Schedule	Amendment	FDA requirement Postpone the Surveillance Schedule
2	6 Apr 2018	Dosage form 7. Surveillance Schedule	Amendment Amendment	Delete dosage name Add the end of study date and final Report of study result due to this date became clear.

[Attachments]

- A) Written contract
- B) Guideline for “Specified Use-Results Surveillance”
- C) Enrollment form/CRF of “Specified Use-Results Surveillance”
- D) Communication form of proper use information
- E) Informed consent form/Consent form
- F) Consent form on change to self-injection
- G) Records on change to self-injection

AbbVie GK
PMOS PROTOCOL (P14-190)

**Special Investigation on Long-Term administration in patients with
Ulcerative Colitis / UC.**

Approved by



06-Apr-2018
Date

Apr. 6. '18
Date

Apr. 6, 2018
Date

April 6th/2018
Date

April 18 2018
Date