Title Page

AbbVie GK
PMOS PROTOCOL (P14-152)

Humira® 40mg Syringe 0.8mL for Subcutaneous Injection Special Investigation in patients with Intestinal Behcet's disease

Title	Humira® 40mg Syringe 0.8mL subcutaneous injection Special investigation in patients with intestinal Behcet's disease
Protocol Version Identifier	P14-152
Date of Last Version of Protocol	14 Jun 2013
EU PAS Register Number	Not applicable
Active Substance	Not applicable
Medicinal Product	Not applicable
Product Reference	Not applicable
Product Number	Not applicable
Marketing Authorization Holder(s)	
Joint PASS	Not applicable
Research Question and Objectives	A specified use-results survey of HUMIRA® is to be performed for the purpose of obtaining the safety and effectiveness data in the patients with Intestinal Behcet's disease.
Country of Study	Japan
Author	

This study will be conducted in compliance with this protocol.

Confidential Information

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

1.0 Table of Contents

2.0 Abbreviations

ADR	Adverse Dug Reaction
AE	Adverse Event
CRF	Case Report Form
CRO	Clinical Research Organization
CRP	C-Reactive Protein
DNA	Deoxyribonucleic acid
FAS	Full Analysis Set
HBc	Hepatitis B core
HBs	Hepatitis B surface
HBV	Hepatitis B virus
MR	Medical Represantatives
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor and Welfare
NIS	Non-Interventional Study
PMDA	Pharmaceuticals and Medical Devices Agency
QOL	Quality Of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
S.C.	Subcutaneous injection
SPC	Summary of Product Characteristics
PMS	Post marketing surveyllance
TNF-α	Tumor Necrosis Factor-α

WBC	White blood cell

3.0 Responsible Parties

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4.0 Abstract

Title : Humira® 40mg Syringe 0.8mL Subcutaneous Injection Special Investigation in patients with Intestinal Behcet's disease
Rationale and Background : See 7.1 and 7.2
Research Question and Objectives : A specified use-results survey of HUMIRA® 40 mg Syringe 0.8 mL for Subcutaneous Injection (Nonproprietary name: Adalimumab (recombinant)" is to be performed for the purpose of obtaining the following information in the Japanese patients with intestinal Behcet's disease.
Study Design : See 9.1
Population : Setting : <inclusion Criteria> Patients receiving Humira® for the treatment of Behcet's disease on proper use after the approval of the indication are to be all enrolled. The survey is to be performed in the patients with intestinal Behcet's disease (not sufficiently responsive to existing therapies, e.g. steroids, immunomodulator), who are treatable with Humira® (Also refer to "Precautions relating to the indications"). When using this drug, please pay adequate attention to the latest package insert. <Exclusion Criteria> Patients included in "Contraindication" in the package insert 1. Patients with serious infection (sepsis etc.) [Symptomatic worsening may occur.]

2. Patients with active tuberculosis [Symptomatic worsening may occur.] 3. Patients with a history of hypersensitivity to any of the ingredients of HUMIRA 4. Patients with a current or past history of demyelinating disorder (multiple sclerosis, etc.) [Symptomatic relapse or worsening may occur.] 5. Patients with congestive heart failure [Symptomatic worsening may occur.]
Variables : See 9.3
Data Sources : Not appplicable
Study Size : Number of sample size : No decided ＜Rationale for setting＞ It is impossible to determine the number of survey centers and the number of survey centers is not decided because the survey is to be performed in all treated subjects and the drug is used only in the institutions qualified for the facility-related and doctor-related requirements.
Data Analysis : All statistical analysis procedures will be described in detail in the Statistical Analysis Plan (SAP). This plan will be developed by the responsible protocol author in collaboration with CRO. The SAP shall be finalized and approved by the responsible protocol author and study-designed physician before the database is used for the final analysis.
Milestones : Start of Data Collection : 01 July 2013 End of Data Collection : 15 May 2017 Study Progress Report : Not Applicable Interim Report : Not Applicable Registration in the EU PAS register : Not Applicable Final Report of Study results : 15 Aug 2017 (Submit to PMDA)

5.0 Amendments and Updates

No.	Date	Section of study Protocol	Amendment or Update	Reason
1	26 Feb 2016	11.5 Serious Adverse Event Reporting 11.7 Management and Reporting of Complaints	Amendment	FDA requirement

6.0 Milestones

Start of Data Collection : 01 July 2013
End of Data Collection : 15 May 2017
Study Progress Report : Not Applicable
Interim Report : Not Applicable
Registration in the EU PAS register : Not Applicable
Final Report of Study results : 15 Aug 2017 (Submit to PMDA)

7.0 Rationale and Background

7.1 Background

Although there are not so many clinical reports of anti-TNF agents for intestinal Behcet's disease, infliximab is reported effective. Naganuma et al. performed a drip infusion of infliximab at the dosage of 5 mg/kg in Weeks 0, 2, 6, and at the interval of 8 weeks subsequently to six Japanese patients with intestinal Behcet's disease and assessed efficacy based on gastrointestinal symptoms and endoscopic findings. As a result, infliximab was assessed effective in four of the six patients and the effectiveness was maintained under continued therapy in the patients who were responsive to infliximab. Iwata et al. also performed a drip infusion of infliximab at the dosage of 3 mg/kg in Weeks 0, 2, 6, and at the interval of 8 weeks subsequently to ten Japanese patients with intestinal Behcet's disease. As a result, all the patients had alleviation of gastrointestinal symptoms and ulcer disappearance was confirmed in the endoscopy performed six month later in five patients and twelve months later in nine patients.Apart from these reports, some case reports suggest that infliximab is effective but they do not include any clinical study report. Meanwhile, it is also suggested based on a retrospective study performed in patients with intestinal Behcet's disease treated with infliximab in 38 Japanese institutions that infliximab was effective in 42 (61%) of the 69 patients. These findings suggest that TNFα plays important roles in the pathological condition of intestinal Behcet's disease. Meanwhile, adalimumab, as well as infliximab, is expected effective for the treatment of intestinal Behcet's disease judged from the report that patients maintained endoscopic and histological remission under adalimumab monotherapy even in 22 months after switch from concomitant therapy with infliximab and immuneregulator which alleviated intestinal Behcet's disease.

7.2 Rationale

This survey is to be performed as a total survey in Japanese patients with intestinal Behcet's disease for the purpose of verifying the safety and efficacy of the Product used for the patients in usual clinical practice.

The Japanese clinical study (Study M11-509) is to be performed in patients with intestinal Behcet's disease for the first time in the world for verifying the safety and efficacy of adalimumab in the patients with intestinal Behcet's disease (including "complete type of Behcet's disease", "incomplete type of Behcet's disease", and "suspected Behcet's disease") who are not adequately responsive to existing therapy (adrenocorticosteroid or immunoregulator also used for the treatment of Crohn's disease

or ulcerative colitis). Complete type of Behcet's disease and incomplete type of Behcet's disease based on the diagnostic criteria for Behcet's disease are certified as designated diseases and patients having typical ileocecal ulcer are diagnosed as having intestinal Behcet's disease. Meanwhile, there is no difference in the intestinal lesion (ileocecal ulcer, gastrointestinal symptoms) between "complete type or incomplete type" of Behcet's disease and "suspected" Behcet's disease and they are treated in the same way in usual clinical practice. The number of patients with "suspected" Behcet's disease is considered almost the same as the number of patients with "complete type" or "incomplete type" of Behcet's disease in combination. Since medical needs are considered high and adalimumab, anti-TNFα agent, is equivalently expected effective, trial subjects include those with "suspected" Behcet's disease. It is estimated that there are 2000 to 3000 patients with intestinal Behcet's disease ("complete type or incomplete type" of Behcet's disease) in Japan and when patients with "suspected" Behcet's disease are included, the number is about twice larger. Of the patients, 10 to 20% were not considered adequately responsive to existing therapies and the number of patients who would fulfill the inclusion/exclusion criteria for the clinical study and give consent was considered limited. Actually, 20 patients participated in the clinical study.
In the Japanese clinical study performed in the above described 20 patients with intestinal Behcet's disease (Study M11-509), the percentage of marked response was 45.0% (9/20) after 24 weeks of treatment and 60.0% (12/20) after 52 weeks.
During 52 weeks of treatment, adverse events were seen in 100% of the patients (20 patients, 102 cases), and adverse events were assessed "definitely" or "probably" causally related with the study drug in 25.0% (5 patients, 9 cases) of the patients, were assessed serious in 5.0% (1 patient, 1 case) of the patients, and needed study discontinuation in 10.0% (2 patients, 2 cases) of the patients. None of the adverse events was severe or resulted in death. None of the trial subjects died in the study. Infectious diseases were reported from 70.0% (14 patients, 30 cases) of the patients, non-dermal angitis and hepatic dysfunction were reported from 15.0% each of the patients (non-dermal angitis 3 patients, 3 cases, hepatic dysfunction 3 patients, 4 cases), injection site reaction and allergic reaction were reported from 10.0% each of the patients (2 patients, 2 cases), and tuberculosis-related adverse event, intestinal stenosis, and ALT increase were reported from 5.0% each of the patients (1 patient, 1 case). The patient with tuberculosis-related adverse event was tested positive for tubercle bacillus (QuantiFERON-TB2G) but was assessed less likely to have active tuberculosis.
The sponsor was instructed to perform a total survey for the purpose of verifying the safety and efficacy of adalimumab in the patients with intestinal Behcet's disease in actual clinical use since the clinical study substantiated the safety and efficacy but was performed in a limited number of patients.

8.0 Research Question and Objectives

A specified use-results survey of HUMIRA® 40 mg Syringe 0.8 mL for Subcutaneous Injection (Nonproprietary name: Adalimumab (recombinant)" is to be performed for the purpose of obtaining the following information in the Japanese patients with intestinal Behcet's disease.

(Primary Endpoints)

1. Unknown adverse reactions (in particular, clinically significant)
2. Incidence and conditions of occurrence of adverse reactions in clinical practice
3. Factors likely to affect the safety

< Key survey items in safety>

Infection, tuberculosis, malignant tumor, administration site reaction, autoimmune disease, pancytopenia, demyelinating disorders, congestive cardiac failure, and interstitial pneumonia

(Secondary Endpoints)

4. Efficacy measured by overall evaluation of gastrointestinal symptoms, evaluation of gastrointestinal symptoms of Behcet's disease, evaluation of main symptoms of Behcet's disease, evaluation of secondary symptoms of Behcet's disease, degree of improvement of endoscopic findings, and CRP
5. Factors likely to affect the efficacy

9.0 Research Methods

9.1 Study design

The observation period of the survey is 156 weeks at the longest and is segmented to 52 weeks, 104 weeks, and 156 weeks depending on the treatment stage. The observation period differs from patient to patient because of the need to recover CRFs from all patients registered during the re-examination period (4 years) and submit the report to PMDA.

Primary Endpoints

Safety

- List of adverse reactions and infections

Stratified analyses of safety

- Factors likely to affect the safety
  - Incidence of adverse reactions stratified by patient background (sex, age, morbidity period, smoking history, presence or absence of concomitant symptom, presence or absence of past medical history, presence or absence of past history of allergic disease, presence or absence of foregoing medication, presence or absence of concomitant medication)
  - Incidence of adverse reactions stratified by non-intestinal symptom of Behcet's disease
  - Incidence of adverse reactions stratified by the changes in the corticosteroid dose in the patients treated with corticosteroids
  - Adverse events which were developed during or after administration
  - List of serious adverse events
  - Onset of self-injection malpractice
  - Relation with the safety when anti-adalimumab antibody is measured

Secondary Endpoint

Efficacy

- Overall evaluation of gastrointestinal symptoms, evaluation of gastrointestinal symptoms of Behcet's disease , evaluation of main symptoms of Behcet's disease , evaluation of secondary symptoms of Behcet's disease, degree of improvement of endoscopic findings, and CRP

Stratified analyses of efficacy

- Factors considered to have efficacy influence
  - Factors stratified by patient background (sex, age, morbidity period, smoking history, presence or absence of concomitant symptom, presence or absence of past medical history, presence or absence of past history of allergic disease, presence or absence of foregoing medication, presence or absence of concomitant medication)
  - Factors stratified by the diagnosis type of intestinal Behcet's disease
  - Factors stratified by the changes in the corticosteroid dose in the patients treated with corticosteroids
  - Relation with the efficacy when anti-adalimumab antibody is measured

9.2 Setting

Inclusion Criteria
Patients receiving Humira® for the treatment of Behcet's disease on proper use after the approval of the indication are to be all enrolled.
The survey is to be performed in the patients with intestinal Behcet's disease (not sufficiently responsive to existing therapies, e.g. steroids, immunomodulator), who are treatable with Humira® (Also refer to "Precautions relating to the indications").
When using this drug, please pay adequate attention to the latest package insert.

Exclusion Criteria
Patients included in "Contraindication" in the package insert

1. Patients with serious infection (sepsis etc.) [Symptomatic worsening may occur.]
2. Patients with active tuberculosis [Symptomatic worsening may occur.]
3. Patients with a history of hypersensitivity to any of the ingredients of HUMIRA
4. Patients with a current or past history of demyelinating disorder (multiple sclerosis, etc.) [Symptomatic relapse or worsening may occur.]
5. Patients with congestive heart failure [Symptomatic worsening may occur.]

Dosage and Administration
The product should be administered to the adults by subcutaneous injection at the adalimumab (recombinant) dose of 160 mg in the initial administration and 80 mg in 2 weeks after the initial administration. Subsequently after 4 weeks after the initial administration, the product should be administered once in two weeks by subcutaneous injection at the dosage of 40 mg.
When using this drug, please take sufficient cautions to the latest package insert.

Investigator site selection
The survey is to be performed in all institutions/departments where the drug is used for the indication. Use of the drug for the treatment of intestinal Behcet's disease is limited in the institutions and doctors that fulfill the following facility-related and doctor-related requirements and having concluded the agreement between medical centers and the company.

（1） Institutes criteria

The survey is to be performed in the institutions fulfilling all the following requirements.

1） Institution specializing in medical care for intestinal Behcet's disease
2） Institution capable of making a diagnosis of/providing treatment for tuberculosis in collaboration with internal or external specialists of respiratory diseases and radiology

3） Institution capable of making a diagnosis of/providing treatment for severe infections in collaboration with internal or external specialists of infections

（2） Doctor criteria

Doctors who are qualified as any of the following specialists and have received the set of materials of information on safety measures for HUMIRA® from Medical Representatives (MR) and have adequate knowledge about the properties of the drug

1） Specialist accredited by the Japanese Society of Gastroenterology
2） Specialist accredited by the Japan Gastroenterological Endoscopy Society
3） Specialist accredited by the Japan Society of Coloproctology
4） Specialist accredited by the Japanese Gastroenterological Association
5） Specialist accredited by the Japanese Society of Gastroenterological Surgery
6） Doctor who have participated in a clinical trial of adalimumab for intestinal Behcet's disease
7） Specialist accredited by the Japan College of Rheumatology or the doctor registered to the Japan Rheumatism Foundation Information Center
8） Doctor who have experienced joining to investigation of all cases PMOS for any biologics in Japan

Study Conduct

（1） Surveillance system

The survey is to be performed in all treated patients according to the central registration system in the institutions which fulfill facility-related and doctor-related requirements and have concluded the agreement.

(2) Request and contract of post-marketing surveillance

1） Medical representatives (MR) provides a full set of materials of information on safety measures for HUMIRA® to doctors in charge of survey, and explains the character of this drug, the objective of surveillance, patients to be surveyed, and survey methods.
2） The doctor in charge of the survey will check that he/she has received explanations about the set of materials of information on safety measures for HUMIRA® and that the doctor and the institution fulfill facility-related and doctor-related requirements and sign "Statement of Acceptance of Proper Use Information". MR will obtain and review "Statement of Acceptance of Proper Use Information" signed by the doctor in charge of the survey, commission the post-marketing survey to the institution, and conclude the written agreement.

（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, 104, or 156 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 weeks 52, 104, and 156 after commencement of administration, and submits the CRF to MR. In cases of the observation period uncompleted, CRF is completed promptly when the surveillance is discontinued, and submitted to Medical representatives (MR).
6） The sponsor will review the enrollment form and the CRF and recheck them where necessary.

Case Report Form
All data specified in Section 8.5 “Study Conduct” will be collected on paper forms (CRF). For each visit, the CRF includes forms to be completed by the physician as well as forms to be completed by the patient. Each center receives a folder with all documents and forms necessary for the baseline and follow-up documentation of contract number of cases.

Any observation of an adverse event in the time period up to 52, 104, and 156 weeks, beginning with the initiation of adalimumab therapy, is to be documented on the CRF. If the event fulfills the serious criterion (Serious Adverse Event), the "Serious Adverse Event Report” form is to be completed additionally.

The following table provides an overview of the required visits and corresponding activities for the study.

Table 1. Study Schedule

	Assessment time		
	At week 0	⇨	At Week 156 or discontinuation
Baseline patient characteristics	○		
Condition of administration of the product	○	→	
History of administration of biological preparations for intestinal Behcet's disease	○	→	
Foregoing medication/treatment for intestinal Behcet's disease	○		
Condition of use of antitubercular agent	○	→	
Condition of use of Concomitant Drugs	○	→	
Presence or absence of treatment other than drug therapy for intestinal Behcet's disease/concomitant therapy for intestinal Behcet's disease	○	→	
Presence or absence of onset of tuberculosis and serious respiratory diseases	Before start of administration	→	
Total evaluation of digestive symptoms (determined by the attending physician) Evaluation of digestive symptoms of Behcet's disease	○	Week 4, 8, 12, 24, 52, 76, 104 and 128	○
Evaluation of predominant symptoms of Behcet's disease Evaluation of accessory symptoms of Behcet's disease	○	Week 24, 52, 104 and 156	○
Improvement in endoscopic findings	○	1） Endoscopic findings implemented to Week 24 2） Endoscopic findings implemented from Week 24 to 52 3） Endoscopic findings implemented from Week 52 to 76 4） Endoscopic findings implemented from Week 76 to 104 5） Endoscopic findings implemented from Week 104 to 128 6） Endoscopic findings implemented from Week 128 to 156	
CRP value	○	Week 24, 52, 76,104 and 128	○
Global improvement rate			○
Therapeutic drugs after discontinuation of administration of this drug			○ (After discontinuation)
Adverse Event	→		

9.3 Variables

The following data are to be obtained using the Registration Sheet and CRF.

(1) Information to provide in the Registration Sheet

Institution name
Date of preparation of the Registration Sheet
Treatment department
Name of the attending investigator
Patient identification number
Patient consent
Birth date or age
Sex and pregnancy/breast feeding (for female patients)
Ethnicity
Reasons for use (intestinal Behcet's disease, complete, abortive, suspected)
Date (or) anticipated date of commencement of the product
Contraindications
Careful administration
Tuberculosis test and infection test (tuberculosis reaction test, QuantiFERON test, T-spot, chest X-ray, CT)
HBV test (HBs antigen, HBs antibody, HBc antibody, HBV-DNA quantitative assay)
Pre-treatment laboratory tests (D-glucan in blood, peripheral leukocyte count, peripheral lymphocyte count)

(2) Information to provide in CRF

Survey items	
1) Patient Information (Items other than those covered in the Registration Sheet)	[1] History of smoking (presence or absence, years) [2] Treatment category [3] Body height [4] Body weight [5] Disease duration [6] Concomitant symptoms (presence or absence, disease name) [7]Past history (presence or absence, disease name) [8] Allergic history (presence or absence, cause)
2) Previous medication/therapy for intestinal Behcet's disease	[1] Previous medication/therapy [2] Previous medication (other than biological products) [3] Previous medication (biological products) [4] History of administration (period of administration, dosage) [5] Reason for discontinuation [6] Previous therapy
3) Status of Administration of This Drug	Initial administration [1] Classification of administration method [2] Starting dose [3] Date of initial administration Second administration [1] Classification of administration method [2] 2nd dose [3] Date of 2nd dose 3rd and subsequent administration: [1] Classification of administration method [2] One-time dose [3] Number of administration [4] Treatment period (Date of commencement, date of completion) [5] Reason for change Other [1] Obtainment of consent on shift to self-administration [2] Preparation of record on shift to self-administration [3] Presence or absence of error associated with self-injection, description/reason
4) Discontinuation of the Survey	Reason for discontinuation (onset of adverse event, inadequate efficacy, patient request, no show, other) Provide the information when the administration of the product is discontinued or the patient is not followable during the survey (not earlier than 156 weeks after the commencement of administration).
5) Status of Administration of Antituberculous Drugs	Presence or absence of use of the antitubercular agent, name of the drug, dose, period of administration
6) Status of Administration of Concomitant Drugs	[Concomitant drugs for intestinal Behcet's disease and other concomitant drugs] [1] Name of drug [2] Reason for use [3] Route of administration [4] Dose [5] Duration of administration
7) Presence or absence of treatment other than drug therapy for intestinal Behcet's	[1] Presence or absence of treatment other than drug therapy for intestinal Behcet's disease/concomitant therapy for intestinal Behcet's disease [2] Name of treatment/therapy other than drugs

disease/concomitant therapy for intestinal Behcet's disease	[3] Treatment period
8) Presence/Absence of Occurrence of Tuberculosis and Serious Respiratory Diseases	[1] Date of test/exam [2] Diagnostic imaging [3] Abnormal finding [4] Name of abnormal finding
9) Total evaluation of digestive symptoms (determined by the attending physician)	At commencement of administration, 4, 8, 12, 24, 52, 76, 104, 128 and 156 weeks after commencement of administration, discontinuation of administration
10) Evaluation of digestive symptoms of Behcet's disease	At commencement of administration, 4, 8, 12, 24, 52, 76, 104, 128 and 156 weeks after commencement of administration, discontinuation of administration
11) Evaluation of predominant symptoms of Behcet's disease	At commencement of administration, 24, 52, 104 and 156 weeks after commencement of administration, discontinuation of administration
12) Evaluation of accessory symptoms of Behcet's disease	At commencement of administration, 24, 52, 104 and 156 weeks after commencement of administration, discontinuation of administration
13) Improvement in endoscopic findings	[1] Endscopic findings to Week 0 (before administration of Humira) [2] Endoscopic findings implemented to Week 24 [3] Endoscopic findings implemented from Week 24 to 52 [4] Endoscopic findings implemented from Week 52 to 76 [5] Endoscopic findings implemented from Week 76 to 104 [6] Endoscopic findings implemented from Week 104 to 128 [7] Endoscopic findings implemented from Week 128 to 156
14) CRP value	At commencement of administration, 24, 52, 76, 104, 128 and 156 weeks after commencement of administration, discontinuation of administration
15) Therapeutic drugs after discontinuation of administration	Therapeutic drugs used after discontinuation of administration of this drug
16) Global improvement rate (determined by the attending physician)	[1] Date of assessment of efficacy (at commencement of administration, 52, 104, 156weeks after commencement, discontinuation) [2] Overall improvement (markedly effective, effective, not effective, unassessable)

*1) For endoscopic findings, determine overall improvement by diameter of the maximum ulcer at implementation of the test.

9.4 Data sources

Not applicable

9.5 Study Size

Number of sample size : No decided

＜Rationale for setting＞
It is impossible to determine the number of survey centers and the number of survey centers is not decided because the survey is to be performed in all treated subjects and the drug is used only in the institutions qualified for the facility-related and doctor-related requirements.

9.6 Data Management

CRO will prepare the database of information obtained using the Registration Sheet and CRF and perform the tabulation and statistical analysis in the survey. SAS is used for the tabulation and statistical analysis
In the survey, data will be collected using the paper form of CRF, and EDC will not be used. MRs will collect the CRFs. Data clarification for missing data will be performed through the requested doctors by mediation of MRs and MRs will recover the CRFs for data clarification.

9.7 Data Analysis

All statistical analysis procedures will be described in detail in the Statistical Analysis Plan (SAP). This plan will be developed by the responsible protocol author in collaboration with CRO. The SAP shall be finalized and approved by the responsible protocol author and study-designed physician before the database is used for the final analysis.

1) Sample size calculation
Number of patients to be included: All patients
Patients receiving the drug for the treatment of Behcet's disease after the approval of the indication are to be all enrolled.

＜Rationale for setting＞
The survey is to be performed in all treated patients since Japan is the first country, in the world, where the drug is to be used for the treatment of intestinal Behcet's disease and data from only 20 patients were obtained in the clinical study performed as an open study. Since each subject is to be followed for at least 52 weeks for the purpose of the post-re-examination report, enrollments are to be performed for 3 years after the date of approval of the additional indication. In the subsequent years after 3 years, subjects continuously using the drug will remain enrolled.

2) Analysis population
Data from all the document patients will be used in the statistical analysis.

3) Missing observations will be documented as missing values. Instructions for the minimum documentation required for a patient to be evaluable will be established in the SAP.

All data will be analyzed on the basis of "observed cases". For the statistical analysis of data concerning the course of disease (if related to changes from baseline values), an additional approach will be followed considering only patients with complete data at all visits.

4) Level of Significance
Inferential statistics will be performed at a nominal significance level of 0.05 (two-sided)

9.8 Quality Control

Doctors will be requested to complete the Registration Sheet promptly after administration of the Product to the patient and complete the CRF promptly after

completion of the observation period. MRs will recover all the Registration Sheet and CRF.
The inspection of the Registration Sheet and CRF will be performed for missing or erroneous entries and theoretical contradictions using DM Checklist.
The sponsor will inspect the Registration Sheet and CRF after data recovery for missing or erroneous entries and CRO will also inspect the Registration Sheet and CRF for missing or erroneous entries during data entry. Data clarification for missing data will be performed for doctors by mediation of MRs and doctors will be requested to provide missing essential information.
In-house monitoring of incoming CRF pages with respect to completeness and plausibility will be done by the CRO responsible for data management and statistics. Queries to the study centers will be handled by the sponsor.

This NIS will be sponsored by AbbVie GK. (Mita 3-5-27, Minato-ku, Tokyo, Japan)

9.9 Limitation of the research Methods

The survey is to be performed as a non-interventional survey for assessing the safety and efficacy of the Product in patients with intestinal Behcet's disease in actual clinical use. Unlike clinical studies, obtainable data are limited and there is a possibility of missing data.,

9.10 Other aspects

Study Medication

This is a non-interventional observational study with adalimumab. Adalimumab is used according to the approved label for intestinal Behcet's disease and is prescribed by the attending physician. AbbVie does not provide any study medication. HUMIRA®-injection is available as ready-to-use syringes (injector, pre-filled) and includes 40 mg adalimumab. The recommended dose of adalimumab for adult patients with intestinal Behcet's disease is 160mg of first dose, 80mg at Week 2 after first dose and 40 mg every other week after 80mg..

10.0 Protection of Human Subjects

In accordance with the code of conduct of the Ministry of Health, Labour and Welfare (MHLW)/PMDA, AbbVie will forward the study protocol to the PMDA for approval. The study results will be reported to the PMDA.

Doctors will obtain consent from patients for use of the Product for the treatment of intestinal Behcet's disease before use of the Product. Doctors will explain appropriately that patients will incur no disbenefit even if they choose other therapies. .

All patients data entered in the patient's CRFs will be forwarded to AbbVie for evaluation, without naming the patients. Each CRF shall bear a pre-print patients identification number in place of the patient's initials. Accordingly, the patients's identify will not be disclosed to AbbVie.

11.0 Management Reporting of Adverse Events/Adverse Reactions/Complaints

11.1 Adverse Event Definition and Serious Adverse Event Categories

An adverse event (AE) is defined as any untoward medical occurrence in a patient which does not necessarily have a causal relationship with their treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product. Such an event can result from use of the drug as stipulated in the labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. If an adverse event meets any of the following criteria, it is considered a **serious adverse even (SAE)**:

Hospitalization or prolongation of hospitalization: An event that results in the admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility. Or An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay.

Disability: An event that results in a condition that substantially interferes with the

activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Life-Threatening: An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form

Death: An event that results in the death of a subject.

Congenital anomaly in the fetus/offspring: An anomaly detected at or after birth that results in fetal loss.

Other medically important conditions: An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency of drug abuse.

11.2 Severity

In Japan, 3 kinds of definitions, “Mild”, “Moderate”, and “Severe”, aren’t used to rate the severity for any adverse event being collected as an endpoint/data point in the study and for all SAEs.

11.3 Relationship to Pharmaceutical Product

The physician will use the following definitions for any adverse event being collected as an endpoint/data point the study and for all serious adverse events, to assess the relationship of the adverse event to the use of the pharmaceutical product:

Probable: An adverse event has a strong temporal relationship to the study drug or recurs on re-challenge, and another etiology is unlikely or significantly less likely.

Possible: An adverse event has a strong temporal relationship to the study drug, and an alternative etiology is equally or less likely compared to the potential relationship to study drug.

Not related: An adverse event is due to an underlying or concurrent illness or effect of

another drug is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

Impossible to judge:

If an investigator's opinion of "not related" to pharmaceutical product is given, **an alternate etiology must be provided by the investigator.**

11.4 Serious Adverse Event Collection Period

Serious adverse events will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent) until the end of the NIS (week 52, 104, and 156 or discontinuation of adalimumab therapy).

11.5 Serious 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 (MR:Medical Representative in Japan) within 24 hours of the physician becoming aware of the event. Serious adverse events will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent) until 70 days following the intake of the last dose of adalimumab taken during the study.

AbbVie MR will send the AbbVie Pharmacovigilance department identified below.

AbbVie GK 3-5-27, Mita, Minato-ku, Tokyo 108-6302, Japan Pharmacovigilance Department	[redacted]

11.6 Pregnancy Reporting

Pregnancies in patients and their partners will be collected from the date of the first dose through 150 days following the last dose of adalimumab taken during the study. In the event of a pregnancy occurrence in the patient, the physician will notify AbbVie contact person (MR in Japan) within 24 hours of the physician becoming aware of the pregnancy.

11.7 Management and Reporting of 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).

11.7.1 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.

11.7.2 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.

12.0 Final Report and Publications

The report of the survey will be submitted to PMDA within 3 months after completion of the re-examination period (4 years).

After the end of the NIS, an Integrated Final Report is generated in cooperation with the Principal Investigator. The report includes a description of the objectives of the NIS, the employed methods, the results, as well as the conclusions. As the property of AbbVie GK, the completed CRFs and the report are to be treated as confidential and may not be made accessible to unauthorized persons in any form (publication or presentation) without the explicit approval of AbbVie GK. The results of this NIS may be published by AbbVie GK or any of the participating investigators after approval by AbbVie GK.

AbbVie GK
PMOS PROTOCOL (P14-152)

Humira® 40mg Syringe 0.8mL for Subcutaneous Injection
Special Investigation in patients
with Intestinal Behcet's disease

Approved by:

Protocol Author/ [redacted]	Date
Study-Designated Physician/ [redacted]	Date
Statistics Representative/ [redacted]	Date
Project Director/ [redacted]	Date
GMA Therapeutic Area Lead / [redacted]	Date