1.0 Title Page

AbbVie GK
PMOS PROTOCOL (P13-684)

Assessment of clinical effectiveness and safety of adalimumab and high dose methotrexate in routine clinical practice

(Combo study; Adalimumab with high dose MTX)

Product Name:	Humira® 40mg for S.C. Injection (generic name: adalimumab)	
Type of Study:	Post-Marketing Observational Study (PMOS)	
Date:	08-11-2013	
CRO(s):	EPS Corporation	Phone: [redacted]
		Fax: [redacted]
Biometrics:	N.N.	Phone
		Fax
Sponsor:	AbbVie GK	Phone: +81-3-4577-1125
	3-5-27, Mita, Minato-ku, Tokyo 108-6302, Japan	Fax: [redacted]

This study will be conducted in compliance with this protocol.

Version 7.0

2.0 Synopsis

Sponsor;	AbbVie GK 3-5-27, Mita, Minato-ku, Tokyo 108-6302, Japan
Title;	**Assessment of clinical effectiveness and safety of adalimumab and high dose methotrexate in routine clinical practice (**Combo study; Adalimumab with high dose MTX)
Short title;	HAWK study
Type of study;	Post-Marketing Observational Study (PMOS)
Product, dose, and administration form;	Humira® 40mg for S.C. Injection (generic name: adalimumab) 40 mg subcutaneous (s.c.) every other week
Project code;	JPN 12-01
Indication;	Rheumatoid arthritis (RA)
Study objectives;	The primary objective of the study is to assess the clinical effectiveness of adalimumab in combination with high dose MTX (≥12 mg/week). The clinical effectiveness is measured by assessing the percentage of patients with the DAS28 score of <2.6 at week 52. <u>The secondary objective</u> of the study is to assess the clinical effectiveness of adalimumab in combination with high dose MTX (≥12 mg/week) by the following variables: ・Clinical Disease Activity Index (CDAI) ・Simplified Disease Activity Index (SDAI) ・The severity of functional impairment (HAQ)

	・The health-related quality of life (EQ-5D) ・The severity of hand and foot mTSS used for assessment of radiographic joint damage. <u>Target parameters for safety evaluation of adalimumab + MTX are:</u> ・The evaluation of safety and tolerability by the documentation and analysis of serious adverse events (SAEs) and adverse events (AEs).
Study population;	Adult patients (≥16 years) with early (≤2 years), MTX (≥12mg/week) for at least 3 months before starting on adalimumab and DAS28-CRP >3.2, Bio Naive RA patients
Study design;	Single-arm, multi-center format, prospective cohort study
Treatment duration;	104 weeks
Methodology;	Disease Activity Score 28 (DAS28), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), Health Assessment Questionnaire (HAQ), EuroQol-5 Dimensions (EQ-5D), Radiographic joint damage (mTSS)
Total number of patients;	350 Patients
Adverse Events;	As reported by patients and diagnosed at visits
Data analysis plan;	The general biometric approach consists of evaluation of changes by descriptive statistical methods, as well as of regression analysis of parameters influencing the clinical effectiveness and additional stratified group analysis. Correlation between baseline visit and treatment visits: ・DAS28, CDAI, SDAI, HAQ, EQ-5D

	(week 0, 12, 24, 52, 76, 104) ・Radiographic joint damage (mTSS) (week 0, 52, 104) Additionally, the strength of the relationship between the predictors and the parameters of clinical effectiveness will be determined. The impact of the variables determined by regression analysis on the therapeutic success will be illustrated by stratified group analysis. Two interim analyses are planned.
Planned recruitment phase;	September 2012 - December 2014
Planned study duration;	September 2012 - March 2017
Product manufacturer;	AbbVie GK

3.0 Abbreviated and Definition

ADR	Adverse Dug Reaction
AE	Adverse Event
CDAI	Clinical Disease Activity Index
CRF	Case Report Form
CRO	Clinical Research Organization
CRP	C-Reactive Protein
DAS28	Disease Activity Score 28
DMARD	Disease Modifying Anti-Rheumatic Drug
EQ-5D	EuroQol 5 Dimensions
ESR	Erythrocyte Sedimentation Rate
FAS	Full Analysis Set
HAQ	Health Assessment Questionnaire
IL-6	Interleukin-6
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor and Welfare
MR	Medical Representative
mTSS	modified Total Sharp Score
MTX	Methotrexate
PMDA	Pharmaceuticals and Medical Devices Agency
PMOS	Post-Marketing Observational Study
QOL	Quality Of Life
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
S.C.	Subcutaneus injection
SDAI	Simplified Disease Activity Index
SJ	Swollen Joint
SPC	Summary of Product Characteristics
TJ	Tender Joint
TNF-α	Tumor Necrosis Factor-α
VAS	Visual Analog Scale

4.0 Table of Contents

5.0 Introduction

Treatment of rheumatoid arthritis (RA) has advanced significantly after the introduction of biological agents and improved treatment recommendations. Current treatment guidelines for the management of RA advocate the use of an TNF-inhibitor in combination with MTX as first line biological therapy. Multiple studies have shown the synergistic effect of TNF-inhibitors and MTX. In February 2011, dosage regimens of methotrexate (MTX) were approved up to until ≤16 mg/week in Japan (2011 Japanese Guideline for MTX treatment with RA patient). Thus physicians may prescribe MTX in a maximum dose of ≤16 mg/week. Moreover MTX was also approved as first-line therapy in adult patients with RA.

MTX is a low-molecular-weight disease-modifying antirheumatic drug (DMARD) that has been demonstrated highly beneficial in inducing clinical remission, preventing the progression of bone destruction, improving quality of life (QOL), and ensuring durability and safety of treatment.[1-6] On the basis of its usefulness in combination with other low-molecular-weight DMARDs and biologics, MTX is positioned as an anchor drug in the treatment of RA, and is one of the most commonly used low-molecular-weight DMARD in RA.[7] The benefits of MTX in combination with biological agents have been assessed in retrospective analyses of the data of post-marketing surveillance of biologics conducted prior to the approval of high-dose MTX treatment at ≥10, ≤16 mg/week. Safety evaluation based on the incidence and patterns of adverse drug reactions (ADRs) by dose of MTX have revealed that the ADR profile does not differ significantly between lower and higher doses of MTX. Moreover, the efficacy of treatment appears better in patients receiving MTX at higher doses, which indicates a tendency toward dose-effect relationship. These results of retrospective analyses support the necessity of prospective studies to investigate the usefulness of treatment combining biological agents and high-dose MTX.

In the present prospective post-marketing observational study (PMOS), we will investigate the effectiveness and safety of treatment with adalimumab (Humira®) and high-dose MTX (≥12 mg/week).

6.0 Rationale

In Japan, Humira was approved on April 16, 2008 and launched in the market on June 18, 2008. As a condition of the approval, the Pharmaceuticals and Medical Devices Agency (PMDA) requested Abbott Japan to collect data on the safety and efficacy of adalimumab in all patients receiving the drug in order to take all necessary measures to ensure appropriate use of adalimumab. According to this requirement, Abbott Japan conducted an all-case survey of adalimumab in 7,740 Japanese patients with rheumatoid arthritis (RA) receiving the drug during the period between June 2008 and October 2010. The results of a recent retrospective data analysis of the all-case survey of Japanese patients with RA suggested that the effectiveness of adalimumab in bio-naïve patients with RA was more efficacious when they receive adalimumab in combination with MTX at a dose of ≥10 mg/week. We thus designed a prospective special investigation of ADA + MTX ≥12 mg/week assessment for DAS28, mTSS and HAQ in bio-naïve and early patients with RA and following within the current labeling in Japan.

7.0 Study Objective (s)

In daily clinical setting, patients with RA who receive adalimumab (Humira®) and high-dose MTX (≥12 mg/week) will be observed prospectively and the effectiveness will be assessed by DAS28 and mTTS, In addition the safety of the combination of adalimumab and high dose MTX will be assessed in terms of the incidence and pattern of the occurrence of adverse events.

The primary objective of the study is to assess the clinical effectiveness of adalimumab in combination with high dose MTX (≥12 mg/week). This will be measured by assessing the percentage of patients with the DAS28 score of <2.6 at week 52.

The secondary objective of the study is to assess the clinical effectiveness of adalimumab in combination with high dose MTX (≥12 mg/week) by assessing the proportion of patients with a change in the following variables from baseline to week 104:

・Clinical Disease Activity Index (CDAI)

・Simplified Disease Activity Index (SDAI)

・The severity of functional impairment (HAQ)

・The health-related quality of life (EQ-5D)

・The inhibition of structural progression will be assessed by measuring the modified Van der Heijde Total Sharp Score (mTSS).

The safety profile will be assessed by measuring the following variables:

・All serious adverse events (SAEs) and adverse events (AEs)

7.1 Investigational Plan

7.2 Selection of Study Population

The study population will consist of adult patients (≥16 years) with early RA (disease duration of RA ≤2years) who have failed other anti-rheumatic drugs (with prior MTX). Patients who have been previously treated with biologics (including TNF inhibitors others) cannot be included in the PMOS. The inclusion and exclusion criteria adhere to the approved label as stated in the Japan Summary of Product Characteristics (SPC) "Interview-form" for adalimumab. Investigators will fully explain the PMOS and obtain informed consent from each patient who is to receive adalimumab for the treatment of RA. Patients to be included will be informed about the PMOS and the use of their anonymous data.

7.2.1 Inclusion Criteria

The subjects of this study are patients with a diagnosis of RA and to whom adalimumab is prescribed as part of their normal treatment of RA. All subjects should be satisfying the following conditions.

1) Disease duration of RA ≤2 years

2) MTX administration ≥3 months prior to starting adalimumab

3) Dose of MTX ≥12mg/week

4) DAS28-CRP >3.2

7.2.2 Exclusion Criteria

1) Patients who have been previously treated with biologics (including TNF inhibitors others)

7.3 Number of Patients to be Enrolled

The primary endpoint of this study is the proportion of subjects who achieve DAS28 (CRP) remission (DAS28 <2.6) after 52 weeks of adalimumab + high dose MTX. Based on data from another trial assessing the effectiveness of adalimumab in daily clinical practice, the following power calculation was done [9]. With a significance level of 0.05 (two-sided) and a power of 0.90 (1-β), 350 subjects are required to detect an expected remission rate, i.e., the percentage of patients with the DAS28 score of <2.6 at week 52.

7.4 Investigator Selection Criteria

The data for this PMOS will be collected from rheumatology outpatient departments and office based rheumatologists that routinely treat patients with RA in Japan.

Physicians from about 100 sites which are spread across all of Japan will participate in this PMOS.

Principal Investigator:

Name; Prof. Dr. Yoshiya TANAKA

Institution; University of Occupational and Environmental Health

Address; 1-1 Iseigaoka, Yawata Nishi-ku, Kita Kyushu, Fukuoka, Japan

7.5 Study Duration

1) The duration of the whole PMOS is estimated to be about 4 years.

・Study start: September 2012

・Recruiting phase: September 2012 - December 2014

・Data completion: January 2018

・End of study: The date on which statistical analysis dataset for Clinical Study Report becomes available

・Data analysis and final report: April 2018 – October 2018

2) For each individual patient, the PMOS starts with the enrollment at the beginning of the treatment with adalimumab.

・Observation period
- 104 weeks (or discontinuation of this study)

・Discontinuation of this study
- Patients within 52 weeks into this study: When adalimumab treatment is discontinued.
- Patients after 52 weeks into this study: When any biologics other than adalimumab is administered.

7.6 Study Conduct

7.6.1 Schedule of Observations

This PMOS will be a single-arm, multi-center, prospective cohort study.

Non-interventional studies are one of several methodical instruments to collect information on drugs available on the market. Their defining characteristic is the lack of influence on the relationship between individual physicians and patients in respect to determining indication as well as choice and conduct of the treatment, while at the same time allowing for the structured and systematic collection of treatment data (see also Section 6 “Rationale”). Adalimumab must not be prescribed for the purpose of including a patient in this PMOS.

Patients will be informed about the type of therapy, alternate therapies, and risks, and they have to provide informed consent before the start of adalimumab therapy. Before enrollment in the PMOS, the patients will be made anonymous. AbbVie GK will only receive access to anonymous data. AbbVie GK can only identify the patients via their patient number.

The documentation consists of patient self-assessments as well as assessments by the physician. The following table provides an overview of the study visits with corresponding study activities (Table 1 "Study Schedule").

Table 1. Study Schedule

Activity	Visit (Week)					
	0	**12**	**24**	**52**	**76**	**104***
Patient Background	✓					
Inclusion / Exclusion criteria	✓					
Previous RA therapies	✓					
Concomitant diseases and therapies	✓	✓	✓	✓	✓	✓
Current adalimumab therapy	✓	✓	✓	✓	✓	✓
Current RA therapies	✓	✓	✓	✓	✓	✓
Effectiveness						
· DAS28	✓	✓	✓	✓	✓	✓
· CDAI	✓	✓	✓	✓	✓	✓
· SDAI	✓	✓	✓	✓	✓	✓
· HAQ	✓	✓	✓	✓	✓	✓
· EQ-5D	✓	✓	✓	✓	✓	✓
· mTSS (X-rays of Hands and Feet)	✓			✓		✓
Adverse Events		✓	✓	✓	✓	✓

* Week 104 or last visit

7.6.2 Description of Activities

The following data will be documented (if assessed in routine care):

Physician:

Baseline Visit (Week 0)

1) Informed consent

2) Patient Background

・Patient ID code

・Demographic Data; Birth date or age, Sex (pregnant/lactation), Race, Weight

・Patient status (out-patient, in-patient)

・Duration of illness

・Indication for the current adalimumab therapy

・Complications

・Past illness

・History; Smoking history, History of allergy

・Progression of RA; Severity of RA (Stage), Functional class of RA (Class)

3) Previous treatment of RA; Biologics, DMARDs, Corticosteroids

4) Inclusion / Exclusion criteria

・Inclusion criteria; Age ≥16 years old, Duration of RA ≤2 years, MTX dose ≥12mg/week, MTX administration ≥3 months, DAS28-CRP >3.2

・Exclusion criteria; Patients who have been previously treated with biologics

5) Current treatment with adalimumab

6) Current concomitant drug treatment

・MTX (From 6 months before adalimumab treatment to current)

・DMARDs except MTX

・Corticosteroids

・Other concomitant drugs

7) Current non-drug treatment for RA

8) Current status

・Disease activity (Visual Analog Scale by the physician / VAS evaluation)

・Joint status (28 joints; tender, swollen)

・Laboratory values (CRP, ESR)

・X-rays of Hands and Feet

Follow-up Visits (Week 12, 24, 52, 76, 104, last visit)

1) Current treatment with adalimumab

2) Current concomitant drug treatment

・MTX

・DMARDs except MTX

・Corticosteroids

・Other concomitant drugs

3) Current non-drug treatment for RA

4) Current status

・Disease activity (Visual Analog Scale by the physician / VAS evaluation)

・Joint status (28 joints; tender, swollen)

・Laboratory values (CRP, ESR)

・X-rays of Hands and Feet (Week 52, 104)

・(S) AE

・Discontinuation of adalimumab treatment (Reason for discontinuation)

Patient:

Baseline Visit (week 0)

1) Informed consent

2) Disease activity (Visual Analog Scale by the patient / VAS evaluation)

3) HAQ

4) EQ-5D

Follow-up Visits (Week 12, 24, 52, 76, 104, last visit)

1) Disease activity (Visual Analog Scale by the patient / VAS evaluation)

2) HAQ

3) EQ-5D

7.6.3 Scales and Scores

The following scores will be derived from the documented data:

1) Disease Activity Score (DAS28):

The DAS28 indicates the severity of the RA. The score varies between 0 and 10, with 10 indicating the highest degree of severity. The DAS28 is calculated from the following

data documented on the physician form:

A) Joint status: Number of tender joints (each with a maximum of 28)

B) Joint status: Number of swollen joints (each with a maximum of 28)

C) ESR (mm/1. h) or CRP (mg/dL)

D) Patient's assessment of current disease activity (from 0 = inactive to 100 = highly active)

The DAS28 is calculated by means of a validated algorithm.

2) Clinical disease activity index (CDAI):

The CDAI indicates the severity of the RA. The CDAI is calculated from the following data documented on the physician form:

A) Joint status: Number of tender joints (each with a maximum of 28)

B) Joint status: Number of swollen joints (each with a maximum of 28)

C) Patient's assessment of current disease activity (from 0 = inactive to 10 = highly active)

D) Physician's assessment of current disease activity (from 0 = inactive to 10 = highly active)

The CDAI is calculated by following formula.

CDAI = A) + B) + C) + D)

3) Simplified disease activity index (SDAI):

The SDAI indicates the severity of the RA. The SDAI is calculated from the following data documented on the physician form:

A) Joint status: Number of tender joints (each with a maximum of 28)

B) Joint status: Number of swollen joints (each with a maximum of 28)

C) Patient's assessment of current disease activity (from 0 = inactive to 10 = highly active)

D) Physician's assessment of current disease activity (from 0 = inactive to 10 = highly active)

E) CRP (mg/dL)

The SDAI is calculated by following formula.

SDAI = A) + B) + C) + D) + E)

4) Health Assessment Questionnaire (HAQ):

The HAQ is the internationally most-used instrument for assessing RA-related functional impairment. The patient has to answer 20 questions concerning impairment in daily activities within the following 8 areas:

・Dressing & Grooming

・Arising

・Eating

・Walking

・Hygiene

・Reach

・Grip

・Activities

Patients assess their functionality over the past week by means of a 4-level scale ranging from 0 (without any difficulty) to 3 (unable to do). The highest (worst) values will be

calculated into a mean value which indicates the degree of functional impairment (HAQ Disability Index: 0-3).

5) EuroQol 5 Dimensions (EQ-5D):

The EQ-5D is a generic (not disease specific) instrument for measuring health-related quality of life. The patient questionnaire includes statements for the following five areas (dimensions):

・Agility & Mobility

・Self-care

・Usual activities

・Pain & Bodily discomfort

・Anxiety & Depression

For each dimension the patient is asked for a three-level assessment of his health on the current day: “no problems” (1), “some problems” (2), “extreme problems” (3). From the possible combinations of the five three-level areas result 241 different health-statuses.

6) X-ray findings of joint damage:

According to the guidelines for X-ray examination, investigators will obtain X-ray images of the both hands and both feet of each patient at baseline and week 52 of treatment. Members of the TSS Academy will score the X-ray images systemically and objectively in terms of bone erosion and joint space narrowing using the mTTS method.

Criteria for evaluation of joint lesions using the mTTS method:

The van der Heijde-modified total Sharp score (mTSS) will be used to score the severity of bone erosion and join space narrowing shown on the X-ray pictures of the hands and feet. Table 2 shows the scoring criteria[8)].

Table 2. Scoring for Sharp-van der Heijde method

Sharp / van der Heijde method

Erosions:
1 = erosions exist discretely
2 = large erosion
3 = large erosion, extends over the imaginary middle of the bone
5 = collapse completely
Erosion score per joint: sum of erosions with a maximum of 5 per joint for the hands (0-5) and 10 per joint for feet (0-10: max 5 at each site of the joint)

Joint space narrowing:
0 = normal
1 = focal or doubtful
2 = generalized, >50% of the original joint space left
3 = generalized, <50% of the original joint space left or subluxation
4 = bony ankylosis or complete luxation

7.6.4 Study Medication

This is a non-interventional observational study with adalimumab. Adalimumab is used according to the approved label for rheumatoid arthritis and is prescribed by the attending physician. AbbVie GK 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 RA is 40 mg sc every other week.

8.0 Amendments and Updates

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	31JUL2012		Create New	
2	25APR2013	2.0 Synopsis 7.0 Study objectives	Amendment	1) PMDA requirement 2) Increase the number of patients
3	27NOV2013	2.0 Synopsis 7.0 Study objectives	Amendment	Unachieved registration
4	23FEB2016	9.0 Adverse events 10.0Product complaint	Amendment updated	FDA requirement
5	28MAR2017	7.5 Study Duration	Amendment	Add the day of data analysis and the end of study date due to became clear
6	23AUG2017	7.5 Study Duration	Amendment	Add the day of data analysis and the end of study date due to correct
7	11DEC2017	7.5 Study Duration	Amendment	Change the day of data completion and data analysis

9.0 Adverse Events

9.1.1 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.

9.2 Relationship to Pharmaceutical Product

If an adverse event is occurred in the observation period, the physician will assess the causality of adalimumab with reference to the latest package inserts of adalimumab and concomitant drugs (e.g., methotrexate, corticosteroids). When the causality of an adverse event to the use of a concomitant drug other than adalimumab is suspected, the physician will describe the suspected drug.

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.**

9.3 Serious Adverse Event Collection Period

Serious adverse events will be reported to AbbVie GK 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 PMOS (week 104 or discontinuation of this study).

9.4 Serious Adverse Event Reporting

In the event of a serious adverse event, and additionally, any non-serious events of malignancy in patient 30 years of age and younger, whether related to adalimumab or not, if applicable - the physician will notify the AbbVie GK contact person (Medical Representative in Japan) within 24 hours of the physician becoming aware of the event.

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]

9.5 Pregnancy Reporting

In the event of a pregnancy, the physician will notify the AbbVie MR within 24 hours of the physician becoming aware of the pregnancy.

AbbVie MR will send the AbbVie Pharmacovigilance department identified in Section 9.4.

10.0 Product Complaint

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).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 10.2.) For product complaints, please refer to Section 10.2.

10.1 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.

10.2 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.

11.0 Ethics and Quality

In accordance to the code of conduct of MHLW/PMDA, the AbbVie GK will forward the PMOS protocol to the PMDA for approval. The PMOS result will also be reported to the PMDA.

All patient data entered in the patient's CRF will be forwarded to AbbVie GK for evaluation - without naming the patient. Each CRF bears a pre-printed patient identification number, which replaces the patient's initials. Accordingly, the patient's identity will not be disclosed to AbbVie GK.

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

12.0 Case Report Forms

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 104 weeks (or discontinuation of this study), 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.

13.0 Data Analysis Plan

All statistical analysis procedures will be described in detail in a Statistical Analysis Plan (SAP). This plan will be developed by the responsible biometrician in collaboration with the sponsor. The SAP will be finalized and approved by the responsible biometrician, the sponsor, and the principle investigator before the database will be opened for the first interim analysis.

13.1 Sample Size Calculation

The primary endpoint of this study is the proportion of subjects who achieve DAS28 (CRP) remission (DAS28 <2.6) after 52 weeks of adalimumab + high dose MTX. We calculated the target sample number for this survey on the basis of an expected remission

rate, i.e., the percentage of patients with a DAS28 score of <2.6, at week 52 during the treatment with adalimumab 40 mg and MTX at ≥12 mg/week.

Table 3 lists the percentages of patients with a DAS28 score of <2.6 at week 52 in a study conducted by Takeuchi et al.[9)] in patients receiving adalimumab and MTX.

Table 3. Patients with a DAS 28 score of <2.6 at week 52 during the treatment with adalimumab and MTX

adalimumab + MTX dose (mg/week)	Percentage of patients with DAS28 <2.6 (Week 52)
8.5 ± 2.9	42.7% (61/143 patients)
≥12	61.7% (29/47 patients)

As Table 3 shows, 42.7% of patients receiving MTX at 8.5 ± 2.9 mg/week at the initiation of adalimumab treatment achieved a DAS 28 of <2.6 at week 52, and the corresponding percentage of patients receiving DAS at ≥12 mg/week at baseline was 61.7%. When 55% of patients receiving MTX at ≥12 mg/week at the initiation of adalimumab treatment are assumed to achieve a DAS 28 of <2.6 at week 52 (subtracting the standard error (7.10%) from the above mentioned percentage; 61.7 – 7.1 = 54.6%), the number of patients required to achieve a power (1-β) of 0.90 at an α level of 0.05 (two-tailed) would be 171 (one-sample test).

Since 32% of patients enrolled in the all-case survey of adalimumab in patients with rheumatoid arthritis dropped out during the 24-week survey period, we assumed that 50% of the participants in the survey would drop out during the 52-week survey period, and calculated that 342 patients should enroll in the survey. We thus set the target sample size at 350.

13.2 Analysis Population(s)

The data of all documented patients will be used in the statistical analysis of tolerability and safety.

13.3 Missing Values

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.

13.4 Level of Significance

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

13.5 Times of Statistical Analyses

Interim analyses are planned after 24 and 36 month after the inclusion of the first patients. The general analysis will be performed after closure of the follow-up of the last patient (4 years after starting the study).

14.0 Final Report and Publications

After the end of the study, an Integrated Final Report is generated in cooperation with the Principal Investigator. The report includes a description of the objectives of the study, 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 study may be published by AbbVie GK or any of the participating investigators after approval by AbbVie GK.

15.0 References

(1) Aletaha D and Smolen Js: Effectiveness profiles and dose dependent retention of traditional disease modifying anti-rheumatic drugs for rheumatoid arthritis; an observational study. J Rheumatol, 29: 1631-38, 2002

(2) Jones G, Halbert J, Crotty M, et al.: The effect of treatment on radiological progression in rheumatoid arthritis; a systematic review of randomized placebo-controlled trials. Rheumatology, 42(1): 6-13, 2003

(3) Weinblatt ME, Kaplan H, Germain BF, et al.: Methotrexate in rheumatoid arthritis; a five-year prospective multicenter study. Arthritis Rheuma, 37: 1492-98, 1994

(4) Emery P, Breedveld FC, Lemmel EM, et al.: A comparison of the efficacy and safety of Leflunomide and Methotrexate for the treatment of rheumatoid arthritis, Rheumatology, 39: 655-665, 2000

(5) Choi HK, Hernan MA, Seeger JD, et al.: Methotrexate and mortality in patients with rheumatoid arthritis; a prospective study. Lancet, 359(9313): 1173-77, 2002

(6) Krishanan E, Lingala VB, Singh G: Declines in mortality from acute myocardial infraction in successive incidence and birth cohorts of patients with rheumatoid arthritis. Circulation, 110: 1774-79, 2004

(7) Pincus T, Yazici Y, Sokka T, et al.: Methotrexate as the “anchor drug” for the treatment of early rheumatoid arthritis. Clin Exp Rheumatol, 21 (Suppl 31): S179-85, 2003

(8) D van der Heijde: How to Read Radiographs According to the Sharp / van der Heijde Method. J Rheumatol, 27: 261-3, 2000

(9) Takeuchi T, Tanaka Y, et al.: Effectiveness and safety of adalimumab in Japanese patients with rheumatoid arthritis: retrospective analysis of data collected during the first year of Adalimumab treatment in routine clinical practice (HARMONY study). Mod Rheumatol, 2011