abbvie Humira® 40 mg/0.8 ml for subcutaneous injection (generic name: adalimumab)
P15-084

Title Page

AbbVie GK

PMOS PROTOCOL (P15-084)

Special Investigation (Working Productivity and Activity Impairment / WPAI in Japanese patients with psoriatic arthritis / PsA.)

Title	Special Investigation (Working Productivity and Activity Impairment / WPAI in Japanese patients with psoriatic arthritis / PsA.)
Protocol Version Identifier	P15-084
Date of Last Version of Protocol	28 Aug 2015
EU PAS Register Number	Not applicable
Active Substance	Adalimumab
Medicinal Product	Humira®
Product Reference	Humira®
Product Number	D2E7
Marketing Authorization Holder(s)	AbbVie GK 3-5-27 Mita Minatoku Tokyo 108-6302 Japan [redacted]
Joint PASS	No
Research Question and Objectives	To assess the effectiveness of adalimumab on PsA-related Overall work impairment (OWI) after 24weeks.
Country of Study	Japan
Author	[redacted]

This study will be conducted in compliance with this protocol.

1.0 Table of Contents

2.0 Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
CASPAR	ClASsification criteria for Psoriatic ARthritis
CRF	Case Report Form
CRO	Clinical Research Organization
DAS28	Disease Activity Score 28
EDC	Electric Data Capture
eow	every other week
GPSP	Good Post-marketing Study Practice
GVP	Good Vigilance Practice
HAQ	Health Assessment Questionnaire
LOCF	Last Observation Carried Forward
MR	Medical Representatives
MedDRA	Medical Dictionary for Regulatory Activities
PASE	Psoriatic Arthritis Screening and Evaluation questionnaire
PASI	Psoriasis Area and Severity Index
PMDA	Pharmaceuticals and Medical Devices Agency
PMOS	Post Marketing Observational Study
PsA	Psoriatic Arthritis
PsV	Psoriatic vulgaris
RA	Rheumatoid Arthritis
SADR	Serious Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SJC	Swollen Joint Counts
TJC	Tender Joint Counts
TNF	Tumor Necrosis Factor
VAS	Visual Analog Scale
WPAI-PsA	Work productivity and Activity Impairment questionnaire:PsA

3.0 Responsible Parties

1) FUJITSU FIP CORPORATION
Zip Code : 105-8668
Address : Seavans N Bldg., 1-2-1, Shibaura, Minato-ku, Tokyo, Japan
Tel : [redacted]

4.0 Abstract

Title: Special Investigation (Working Productivity and Activity Impairment / WPAI in Japanese patients with psoriatic arthritis / PsA.)
Rationale and Background : <Background> In Japan, scientific evidence which shows improvement in WPAI-PsA with biologics is missing. <Rationale> Previous studies showed 1) significant work productivity and activity impairment in Japanese patients with psoriasis arthritis (PsA) compared to psoriasis without arthritis (M Hayashi et al. Journal of Dermatological Science 72 (2013), 2) improvements in work productivity and activity impairment after 16 weeks of adalimumab treatment for patients with psoriasis (including 25% PsA) (Alex Boer Kimball et al. J Am Acad Dermatol 2012), 3) improvements in PASI score and DAS28 (Humira® 40 mg for S.C. Injection - Study Protocol for Special Investigation in patients with Ps and PsA (All-Case study) P12-077). Accordingly, improvement of disease activity scores and WPAI-PsA scores is expected in this study of patients with PsA
Research Question and Objectives : To assess the effectiveness of adalimumab on PsA-related Overall work impairment (OWI) after 24weeks.
Study Design : Single-arm, multi-center, prospective cohort study
Population : Setting : <inclusion Criteria> Patients who have never been administered adalimumab. PsA patients meet diagnostic criteria for CASPAR criteria. They should be Paid worker (including part-time worker).

<Exclusion Criteria> Patients showing decreased basic activities of daily life such as hospitalization and bedridden. Patients with contraindications to adalimumab.
Variables : WPAI:PsA, PASE, PASI, DAS28, Tender Joint Counts(0-68), Swollen Joint Counts(0-66), HAQ, BASDAI, Spondylitis(Yes/No), Dactylitis(Yes/No), Enthesitis(Yes/No), Nail Psoriasis(Yes/No)
Data Sources : Data sources for collection of data in this investigation are from institute's medical charts and reports from subjects.
Study Size : Sample size : 130 patients
Data Analysis : All statistical analysis procedures will be described in detail in the 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-designated physician before the database is used for the final analysis.
Milestones : Start of Data Collection : 01 Dec 2014 End of Data Collection : 31 Aug 2017 Study Progress Report : Not Applicable Interim Report : Not Applicable Registration in the EU PAS Register : Not Applicable Final Report of Study Results : 1 May 2018

5.0 Amendments and Updates

No.	Date	Section of study Protocol	Amendment or Update	Reason
1	18 Aug 2015	4.0 Abstract 6.0 Milestone -End of Data collection -Final Report of Study Results	Amendment	As of 18 Aug 2015, the enrollments are 25 cases and the mean enrollments of 3 months are 7-8 cases in a month. It is necessary to extend the registration period for nine months to enroll 130 cases.
2	18 Aug 2015	9.1 Study Design The registration period	Amendment	As of 18 Aug 2015, the enrollments are 25 cases and the mean enrollments of 3 months are 7-8 cases in a month. It is necessary to extend the registration period for nine months to enroll 130 cases.
3	18 Aug 2015	11.5 Serious Adverse Event Reporting	Amendment	FDA requirement for Humira
4	23 Feb 2016	11.7 Management and Reporting of Complaints	Amendment	FDA requirement

6.0 Milestones

Start of Data Collection :	Dec 2014
End of Data Collection :	31 Aug 2017
Study Progress Report :	Not Applicable
Interim Report :	Not Applicable
Registration in the EU PAS register :	Not Applicable
Final Report of Study results :	1 May 2018

7.0 Rationale and Background

7.1 Background

Psoriatic arthritis (PsA) is a multifaceted disease associated with psoriasis in skin, nail, chronic peripheral and/or axial arthritis, dactylitis, and enthsritis. Patients with PsA may experience significant physical, psychological, social, functional impairment and reduced quality of life. An important cytokine that activates and intensifies inflammation in PsA is tumor necrosis factor α (TNF-α). TNF-α inhibitors have been a major advance in PsA treatment, and showed significant effect on skin disease and arthritis. In Japanese guidance for use of biologics for psoriasis
(the 2013 version), TNF-a inhibitors shown to prevent the progression of joint destruction regardless of the pretreatment, should be positioned as the first-line treatment.[1]
Adalimumab which is a human monoclonal antibody inhibits the interaction of TNF-α with its receptors and suppresses the biological effect of this pro-inflammatory cytokine. In Japan, Humira® was approved for RA in 2008 and PsV (is this psoriasis?)and PsA in 2010. Humira® is administered as a subcutaneous (sc) injection at a recommended dose of 40 mg every other week after initial dosage of 80mg.
Previous studies have shown that adalimumab reduced the clinical symptoms (skin disease and arthritis) of PsA and improved health-related-quality life.
This is the first study that assesses work productivity of Japanese PsA patients being treated with adalimumab. This study is a PMOS according to GPSP/GVP, and will be conducted in compliance with the recommendations of the PMDA.

7.2 Rationale

Hayashi M, et al. reported significant WPAI in Japanese patients with PsA compared to psoriasis without arthritis [2]. Kimball A B, et al. reported improvements in work productivity and activity impairment after 16 weeks of adalimumab treatment for patients with psoriasis (including 25% PsA) [3]. Special Investigation (All cases investigation in patients with psoriasis vulgaris and psoriatic arthritis) (P12-077) showed improvements

in PASI score and DAS28. Accordingly, improvement of disease activity scores and WPAI-PsA scores is expected in patients with PsA.

8.0 Research Question and Objectives

Primary objective:
To assess the effectiveness in dairy clinical practice of adalimumab on PsA-related Overall work impairment (OWI) after 24weeks.

Secondly objectives:
To assess the effectiveness (PASE score, DAS28, PASI, TJC, SJC, HAQ and BASDAI) in daily clinical practice of adalimumab in PsA patients.

9.0 Research Methods

9.1 Study design

This study is a prospective, multicenter, post-marketing observational study (PMOS). For each individual patient, the PMOS starts with the enrollment at the beginning of the treatment with adalimumab.
・Observation period
-24 weeks (or discontinuation in this study)
・Discontinuation in this study
-When adalimumab treatment is discontinued.
The study shall be terminated for the patient on the day of discontinuation of adalimumab, if the adalimumab treatment is completed prior to Week 24.
The registration period will be 2014 December to 2016 September.

9.2 Setting

Inclusion Criteria
- PsA patients meeting CASPAR criteria. The CASPAR criteria are shown in Table1 [4].
- Patients who have never been administered adalimumab.
- Patientshould be paid worker (including part-time worker).

Table 1: The CASPAR criteria

To meet the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with 3 points from the following 5 categories:
1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis. Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.†
A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.
A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.
2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.
3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.
4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.
5. Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

† Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

Exclusion Criteria
- Patients showing decreased basic activities of daily life such as hospitalization and bedridden.
- Patients with contraindications to adalimumab.

Dosage and Administration
Humira® 40mg for S.C. Injection (generic name: adalimumab)
The dose of HUMIRA for psoriasis patients is an initial dose of 80 mg followed by 40 mg given eow, starting 2 week after the initial dose as subcutaneous injection.
The dose may be increased to 80 mg eow when the effect of treatment with 40 mg eow is insufficient.

Investigator site selection
The medical representative (MR) will fully explain the purpose and methods of the study to participating physicians in medical institutions where Humira® is used or adopted

using the implementation guidance for special investigation. Written agreement will be signed between AbbVie and each participating institution.

Study Conduct

(1) Request and contract of PMOS

The data for this PMOS will be collected from rheumatologists and dermatologists. MR will fully explain the purpose and methods of the study to participating physicians in medical institutions where Humira® is used or adopted using the implementation guidance for special investigation. Written agreement will be finalized between AbbVie and each participating institution.

(2) Study methods

1) An Internet-based Electric Data Capture (EDC) (including some paper-based CRF) will be used to collect the study data.
2) Investigators will describe information about eligible patients who are receiving or will receive Humira® during the period from the date of agreement to the end of the registration period in patient registration form.
3) Investigators will send the patient registration form via EDC by 14 days from the day of the first Humira injection.
4) The sponsor will register patients according to the information described in the sent registration form.
5) In the study, the enrolled patients will be observed for 24 weeks from the day of the first HUMIRA® injection. During the observational period, investigators will observe the following points:
   ① Patients should be observed carefully for clinical course and incidence of adverse events.
   ② Incidence of adverse events must be reported to MR without delay.
6) After the end of the observation period, investigators will describe information about each participant in the CRF, and send the CRF via EDC. Investigators will be requested to describe information of patients who experienced adverse events on their case report forms during the observation period and provide them to MR.
   The sponsor will confirm the descriptions of the consecutive patient registration form and the CRF, and conduct reinvestigation whenever necessary.

Registration form

Investigator site, name, patient's agreement to treat, date of the first Humira injection, date of birth or age, Patient's identification number, sex, outpatient/inpatient, history of Humira injection, CASPAR criteria (Yes/No), working situation, Humira contraindications, Testing for tuberculosis (presence/absence of the implementation of Tuberculin skin test or Interferon-γ release assay or Plain chest X-ray or Chest CT), Hepatitis B virus marker test (presence/absence)

Case Report Form

1) Patient characteristics

Patient's identification number , sex, presence/absence of pregnancy/breast-feeding and gestation (in the case of women), body weight, body height, reason for use, outpatient/inpatient, type of psoriasis (plaque / erythroderma / pustular / guttate), working situation, disease duration (Ps / PsA), comorbidity (presence/absence, disease name), medical history (presence/absence, disease name), allergic history (presence/absence, detail), drinking history (presence/absence), smoking history (presence/absence, years of smoking), Rheumatoid Factor (positive / negative)

2) adalimumab treatment

Physician/self -injection, dosage, date of the first and the last injection

3) Reason of discontinuation of injection

4) Previous drug treatment for PsA

Presence/absence of previous drug treatment for PsA,
Biologics (every biologics that was used before),

- Reason of discontinuation, date of discontinuation

Other drugs (3 month ago from start of Humira injection)

4) Previous non-drug treatment for skin disease and arthritis of PsA

5) Current concomitant drug

Presence/absence of current concomitant, product name, route of administration, reason of use, dosage, date of first and last administration

6) Current concomitant non-drug treatment for skin disease and arthritis of PsA

7) Testing for tuberculosis or serious respiratory disease
- Tuberculin skin test
- Interferon-γ release assay
- Plain chest X-ray
- Chest CT

8) Clinical evaluation

Physician:
- PASI
- DAS28
- TJC (0-68), SJC(0-66)
- Presence/absence of spondylitis, enthelitis, dactylitis, nail psoriasis

Patient:
- WPAI:PsA
- PASE
- HAQ
- BASDAI

9) Adverse events

Presence / absence of adverse events, If present, collect nature of adverse events, date of onset, seriousness, outcome (if death, collect date and cause of death, causal relationship to Humira, autopsy), causal relationship with Humira, alternative etiology, course and treatment of adverse events, comments on causality, and laboratory findings.

Table 2: Study schedule

Activity	Visit (Week)				
	0	4	12	16	24 or Discontinue
Patient characteristics	○	—	—	—	○
Previous drug treatment for PsA	○	—	—	—	—
Previous non-drug treatment	○	—	—	—	—
adalimumab treatment	—	◄	———	———	►
concomitant drug	—	◄	———	———	►
Current concomitant non-drug treatment	—	◄	———	———	►
Clinical evaluation 1) WPAI:PsA	○	○	○	○	○
2) PASE	○	○	○	○	○
3) PASI	○	○	○	○	○
4) DAS28	○	○	○	○	○
5) TJC (0-68), SJC(0-66)	○	○	○	○	○
6) VAS assessment by physician	○	○	○	○	○
7) VAS assessment by patients	○	○	○	○	○
8)HAQ	○	-	○	-	○
9)BASDAI	○	-	○	-	○
10) Presence/absence of spondylitis, enthelitis, dactylitis, nail psoriasis	○	—	—	—	○
Adverse events	—	◄	———	———	►

9.3 Variables

As special investigation (PMOS/non-mandatory) of HUMIRA® subcutaneous injection 40 mg syringe 0.8 mL (generic name: Adalimumab) will be performed to examine the following (1) and (2) (planned visit time; before the start of treatment, and at 4, 12, 16, and 24 weeks, 4 data collection points) in Japanese PsA patients who are engaged in paid work.

(1) Primary Endpoints

・To assess adalimumab therapeutic efficacy with Japanese PsA patients, measured by improvement in OWI score after 24weeks from baseline.

(2) Secondary Endpoint

・To assess adalimumab therapeutic efficacy and safety with Japanese PsA patients, measured by following variables;

・OWI scores (baseline, 4, 12 and 16 weeks)

・Absenteeism, Presenteeism, Activity impairment (AI) scores (baseline,4,12,16 and 24 weeks)

・PASE score (baseline,4,12,16 and 24 weeks)

・PASI (baseline,4,12,16 and 24 weeks)

・DAS28 (baseline,4,12,16 and 24 weeks)

・TJC (0-68) , SJC (0-66) (baseline,4,12,16 and 24 weeks)

・BASDAI (baseline, 12 and 24 weeks)

・HAQ (baseline, 12 and 24 weeks)

・Spondylitis, Dactylitis, Enthesitis, Nail psoriasis (Yes/No) (baseline and 24 weeks)

・Adverse events

9.4 Data sources

Data sources for collection of data in this investigation are from institute's medical charts medical charts. As this investigation is for PsA patients for proper use of Humira®, base of data sources is from carte. Participant physicians in this investigation transcribe from carte to CRF which AbbVie prepares.

9.5 Study Size

Sample size: 130patients

＜Rationale for setting＞

In the report by Kimball A B et al. [3], in which the effect on work productivity was examined in 557 North American patients with psoriasis (including 137 PsA patients), the change of overall work impairment (OWI) during the 16 weeks of treatment with

adalimumab was 13.4±23.8 (mean ± SD). In this Study, the number of subjects necessary to detect the same change of OWI score was calculated to be 87 subjects at the 0.05 significance level (two-sided) and a power of 0.80. The dropout rate up to 24weeks from the start of adalimumab treatment of the PsA patients was about 20% during all-case study for HUMIRA® in Japanese PsV and PsA patients. And the evaluable rate of OWI was about 85% during special investigation for HUMIRA® in Japanese RA patients (P12-772). Therefore, the number of patients to be enrolled is 130 cases.

9.6 Data Management

CRO will prepare the database of information obtained using the Registration form and CRF and perform the tabulation and statistical analysis in the study. SAS is used for the tabulation and statistical analysis. In the study, data will be collected using the EDC.

9.7 Data Analysis

Descriptive analyses will be provided. All statistical analysis procedures will be described in detail in the 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) Analysis population
The data of all documented patients will be used in the statistical analysis of efficacy and safety of HUMIRA®. The data of patients with PsA that had been treated with HUMIRA® previously will be excluded from the analysis of efficacy.

(i) Patients parameters
- Number of subjects whose registration forms are collected
- Number of subjects whose case report forms are collected
- Number of subjects for safety evaluation
- Number of subjects for efficacy evaluation

(ii) Safety parameters
- Listing of the situation of the occurrence of adverse drug reactions/infections
- Factors considered to affect the safety
  Incidence of adverse drug reactions by factor of patient characteristics, etc.
- Adverse events that occur during or after administration
  Listing of the situation of the occurrence of serious adverse events, etc.

(iii) Efficacy parameters;

- Changes in WPAI-PsA scores over 4, 12, 16 and 24 weeks
- Changes in PASE score, DAS-28、HAQ, PASI score and BASDAI over 4, 12, 16 and 24 weeks
- Rate of PASI75,90 at 12, 24 weeks
- Correlation between WPAI:PsA scores and some parameters (PASE score, DAS-28, TJC, SJC, PASI score, HAQ, BASDAI)
- Factors considered to affect the WPAI:PsA scores (listing of efficacy by patient characteristics, etc.)
- Correlation between PASE score and disease/QOL parameters (DAS-28, Tender joint counts, Swollen joint counts, PASI, HAQ, BASDAI)

2) 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 and LOCF. 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.

3) Level of Significance
If applicable, inferential statistics will be performed at a nominal significance level of 0.05 (two-sided). Details will be described in the SAP.

9.8 Quality Control

Physicians will be requested to complete the Registration Form promptly after administration of the product to the patient and complete the CRF promptly after completion of the observation period.
The inspection of the Registration Form and CRF will be performed for missing or erroneous entries and theoretical contradictions using DM Checklist.
The sponsor will inspect the Registration Form and CRF after data recovery for missing or erroneous entries and CRO will also inspect the Registration Form and CRF for missing or erroneous entries during data entry. Data clarification for missing data will be performed for physicians via EDC and physicians 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 study will be sponsored by AbbVie GK. (Mita 3-5-27, Minato-ku, Tokyo, Japan)

9.9 Limitation of the Research Methods

The study is to be performed as a non-interventional study for assessing the effectiveness of adalimumab on PsA-related OWI after 24weeks in actual clinical use. Unlike clinical studies, obtainable data are limited and there is a possibility of missing data.

9.10 Other aspects

None

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.

Physicians will obtain consent from patients for use of the Product for the prevention of PsA before use of the Product. Physicians will explain appropriately that patients will incur no disbenefit even if they choose other therapies.

11.0 Management an 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 **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.

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

An adverse event is defined as any untoward or unintended medical occurrence (including abnormal laboratory findings and infections) in a patient administered a pharmaceutical product, which need not have a causal relationship with treatment with the product of concern. When an adverse event develops, the patient will be followed until the adverse event resolves whenever possible. Definition of severity in Japan is as following.

Criteria for seriousness of adverse events

Serious	Death	Cases of deaths suspected to be due to adverse events
	Life-threatening condition	The patient's life was threatened by the event. This does not mean that the event might have resulted in death had it been more severe than that actually observed.
	Hospitalization or prolonged hospitalization	Cases which require admission to or prolongation of the period of admission in a hospital or clinic for the treatment of adverse events. Cases of admission or prolongation of the period of admission for testing of adverse events are not included.
	Persistent or significant disability	Occurrence of persistent or significant disability/incapacity that affects the activities of daily living.
	Congenital diseases or anomalies in the next generation	Anomalies in offspring suspected to be due to exposure to drugs before or during pregnancy
	Other medically important condition	Important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent the outcomes listed above.
Not serious		Adverse events not applicable to the above criteria

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
disclose inuainformation (or the patient's informed consent) until the end of the PMOS (week 28 or disconttion of this study).

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 (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]

11.6 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

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.

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

After the end of the study, an Integrated Final Report is generated. 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.

13. Reference

[1] Ohtsuki M, Terui T, Ozawa A, Morita A, Sano S, Takahashi H, *et al.* Japanese guidance for use of biologics for psoriasis (the 2013 version). Journal of Dermatology 2013; 40: 683–695

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AbbVie GK
PMOS PROTOCOL (P15-084)

Special Investigation (Working Productivity and Activity Impairment / WPAI in Japanese patients with psoriatic arthritis / PsA.)

Approved by

Protocol Author/ [redacted]

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PMOS PROTOCOL (P15-084)

Special Investigation (Working Productivity and Activity Impairment / WPAI in Japanese patients with psoriatic arthritis / PsA.)

ANNEX1

23FEB2016

Section 11.0 Management and Reporting of Adverse Events/Adverse Reactions/Complaints
Previously read:

11.0 Management and Reporting of Adverse Events/Adverse Reactions

Has been changed to read:

11.0 Management and Reporting of Adverse Events/Adverse Reactions/ Complaints

Section 11.0 Management and Reporting of Adverse Events/Adverse Reactions/Complaints
Previously read:

NA

Has been changed to read:

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.

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.