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

AbbVie GK

Marketing Authorization Holder(s)
3-5-27 Mita Minatoku Tokyo 108-6302 Japan

Joint PASS
No

Research Question and Objectives
To assess the effectiveness of adalimumab on PsA-related Overall work impairment (OWI) after 24 weeks.

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

1.0 Table of Contents.................................................................2
2.0 Abbreviations.........................................................................4
3.0 Responsible Parties...............................................................5
4.0 Abstract.....................................................................................5
5.0 Amendments and Updates......................................................7
6.0 Milestones.................................................................................8
7.0 Rationale and Background.......................................................8
  7.1 Background..............................................................................8
  7.2 Rationale................................................................................8
8.0 Research Question and Objectives..........................................9
9.0 Research Methods.................................................................9
  9.1 Study design...........................................................................9
  9.2 Setting....................................................................................9
  9.3 Variables.............................................................................15
  9.4 Data sources.........................................................................15
  9.5 Study Size............................................................................15
  9.6 Data Management...............................................................16
  9.7 Data Analysis.......................................................................16
  9.8 Quality Control.....................................................................17
  9.9 Limitation of the Research Methods.................................18
  9.10 Other aspects.......................................................................18
10.0 Protection of Human Subjects..............................................18
11.0 Management an Reporting of Adverse Events/Adverse Reactions/Complaints............................................18
  11.1 Adverse Event Definition and Serious Adverse Event Categories .......18
  11.2 Severity...............................................................................19
  11.3 Relationship to Pharmaceutical Product............................20
11.4 Serious Adverse Event Collection Period ........................................21
11.5 Serious Adverse Event Reporting ................................................21
11.6 Pregnancy Reporting ....................................................................21
11.7 Management and Reporting of Complaints ..................................21
11.7.1 Definition ..............................................................................22
11.7.2 Reporting ..............................................................................22
12.0 Final Report and Publications .....................................................22
13. Reference .....................................................................................23
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>BASDAI</td>
<td>Bath Ankylosing Spondylitis Disease Activity Index</td>
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<tr>
<td>CASPAR</td>
<td>CIASsification criteria for Psoriatic ARthritis</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRO</td>
<td>Clinical Research Organization</td>
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<tr>
<td>DAS28</td>
<td>Disease Activity Score 28</td>
</tr>
<tr>
<td>EDC</td>
<td>Electric Data Capture</td>
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<tr>
<td>eow</td>
<td>every other week</td>
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<tr>
<td>GPSP</td>
<td>Good Post-marketing Study Practice</td>
</tr>
<tr>
<td>GVP</td>
<td>Good Vigilance Practice</td>
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<tr>
<td>HAQ</td>
<td>Health Assessment Questionnaire</td>
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<tr>
<td>LOCF</td>
<td>Last Observation Carried Forward</td>
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<td>MR</td>
<td>Medical Representatives</td>
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<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
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<td>PASE</td>
<td>Psoriatic Arthritis Screening and Evaluation questionnaire</td>
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<td>PASI</td>
<td>Psoriasis Area and Severity Index</td>
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<td>PMDA</td>
<td>Pharmaceuticals and Medical Devices Agency</td>
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<tr>
<td>PMOS</td>
<td>Post Marketing Observational Study</td>
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<tr>
<td>PsA</td>
<td>Psoriatic Arthritis</td>
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<tr>
<td>PsV</td>
<td>Psoriatic vulgaris</td>
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<tr>
<td>RA</td>
<td>Rheumatoid Arthritis</td>
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<td>SADR</td>
<td>Serious Drug Reaction</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
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<tr>
<td>SJC</td>
<td>Swollen Joint Counts</td>
</tr>
<tr>
<td>TJC</td>
<td>Tender Joint Counts</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor Necrosis Factor</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analog Scale</td>
</tr>
<tr>
<td>WPAI-PsA</td>
<td>Work productivity and Activity Impairment questionnaire:PsA</td>
</tr>
</tbody>
</table>
Humira® 40 mg/0.8 ml for subcutaneous injection (generic name: adalimumab)
P15-084

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: __________________________

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 psoriatic 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) (A personal communication of 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 24 weeks.

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

<table>
<thead>
<tr>
<th>No.</th>
<th>Date</th>
<th>Section of study Protocol</th>
<th>Amendment or Update</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18 Aug 2015</td>
<td>4.0 Abstract 6.0 Milestone - End of Data collection - Final Report of Study Results</td>
<td>Amendment</td>
<td>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.</td>
</tr>
<tr>
<td>2</td>
<td>18 Aug 2015</td>
<td>9.1 Study Design The registration period</td>
<td>Amendment</td>
<td>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.</td>
</tr>
<tr>
<td>3</td>
<td>18 Aug 2015</td>
<td>11.5 Serious Adverse Event Reporting</td>
<td>Amendment</td>
<td>FDA requirement for Humira</td>
</tr>
<tr>
<td>4</td>
<td>23 Feb 2016</td>
<td>11.7 Management and Reporting of Complaints</td>
<td>Amendment</td>
<td>FDA requirement</td>
</tr>
</tbody>
</table>
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 enthesitis. 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-α 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 daily clinical practice of adalimumab on PsA-related Overall work impairment (OWI) after 24 weeks.

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.
- Patients should 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 entheséal) 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-x 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, enthesitis, 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

<table>
<thead>
<tr>
<th>Activity</th>
<th>Visit (Week)</th>
<th>0</th>
<th>4</th>
<th>12</th>
<th>16</th>
<th>24 Discontinue</th>
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<tbody>
<tr>
<td>Patient characteristics</td>
<td></td>
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<td>Previous drug treatment for PsA</td>
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<tr>
<td>Previous non-drug treatment</td>
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<tr>
<td>adalimumab treatment</td>
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<td>concomitant drug</td>
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<tr>
<td>Current concomitant non-drug treatment</td>
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<tr>
<td>Clinical evaluation</td>
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<td>2) PASE</td>
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<td>3) PASI</td>
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<td>4) DAS28</td>
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<tr>
<td>5) TJC (0-68), SJC (0-66)</td>
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<td>6) VAS assessment by physician</td>
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<td>7) VAS assessment by patients</td>
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<td>o</td>
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<td>o</td>
<td>o</td>
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<td>8) HAQ</td>
<td></td>
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<td>-</td>
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<td>o</td>
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<tr>
<td>9) BASDAI</td>
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<tr>
<td>10) Presence/absence of spondylitis, enthesitis, dactylitis, nail psoriasis</td>
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<td>o</td>
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<tr>
<td>Adverse events</td>
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</tbody>
</table>
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 24 weeks 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. 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: 130 patients

<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 24 weeks 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)
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 24 weeks in actual clinical use. Unlike clinical studies, obtainable data are limited and there is a possibility of missing data.

Other aspects

None

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.

Management and Reporting of Adverse Events/Adverse Reactions/Complaints

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

<table>
<thead>
<tr>
<th>Serious</th>
<th>Not serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Cases of deaths suspected to be due to adverse events</td>
</tr>
<tr>
<td>Life-threatening condition</td>
<td>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.</td>
</tr>
<tr>
<td>Hospitalization or prolonged hospitalization</td>
<td>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.</td>
</tr>
<tr>
<td>Persistent or significant disability</td>
<td>Occurrence of persistent or significant disability/incapacity that affects the activities of daily living.</td>
</tr>
<tr>
<td>Congenital diseases or anomalies in the next generation</td>
<td>Anomalies in offspring suspected to be due to exposure to drugs before or during pregnancy</td>
</tr>
<tr>
<td>Other medically important condition</td>
<td>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.</td>
</tr>
</tbody>
</table>

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 discontiffion 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

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)
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.

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.

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


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:

Study-Designated Physician:

Statistics:

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

Group TA Lead
AbbVie GK.

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

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