


## Title Page

<b>Title</b>	A Prospective , Mono-Country, Multi-Center Study to observe the frequency of Extra-Axial symptoms in Korean Ankylosing Spondylitis patients on adalimumab therapy
<b>Protocol Version Identifier</b>	Version 2.0
<b>Date of Last Version of Protocol</b>	06 March, 2015
<b>Marketing Authorisation Holder(s)</b>	AbbVie Korea
<b>Research Question and Objectives</b>	<p>What is the frequency of EAMs in Korean AS patients and the effectiveness of adalimumab on EAMs?</p> <p><u>Primary Objective</u></p> <p>To investigate the frequency of EAMs in AS patients on adalimumab therapy in routine clinical practice</p> <p><u>Secondary Objectives</u></p> <ul style="list-style-type: none"><li>• To observe the effectiveness of adalimumab on AS spinal disease activity in routine clinical practice</li><li>• To investigate the effectiveness of adalimumab on EAMs in routine clinical practice</li></ul>
<b>Country(-ies) of Study</b>	South Korea
<b>Author</b>	

**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.**

**Marketing Authorisation Holder(s)**

<b>Marketing Authorisation Holder(s)</b>	AbbVie Korea <div></div>
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## 2.0 Abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
CRA	Clinical Research Associate
CRF	Case Report Form
EAM	Extra-Axial Manifestations
AS	Ankylosing Spondylitis
SAE	Serious Adverse Event
IBD	Inflammatory Bowel Disease
NSAID	Non-steroidal Anti-inflammatory drug
DMARDs	Disease Modifying Anti Rheumatic Drugs
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
TJC	Tender Joint Counts
SJC	Swollen Joint Counts
TNF	Tumor Necrosis Factor

## 3.0 Responsible Parties

SDP :

CRO(s):



## 4.0 Abstract

### Title:

A Prospective, Mono-Country, Multi-Center Study to observe the frequency of Extra-Axial symptoms in Korean Ankylosing Spondylitis patients on adalimumab therapy

### Rationale and Background:

In addition to chronic inflammation of the spine, extra-axial manifestations are common features in patients with ankylosing spondylitis (AS). Although AS is primarily a disease of the axial skeleton, peripheral joint involvement occurs in up to 70% of the patients<sup>(1)</sup>. An epidemiological study of 847 patients in Belgium who fulfilled the modified New York criteria for AS found that 42% had one or more extra-articular manifestations, including acute anterior uveitis (27%), IBD (10%) and psoriasis (11%)<sup>(2)</sup>. According to a cross-sectional study in Korea of 830 AS patients<sup>(3)</sup>, three hundred and ninety-one patients (47.1%) were found to have a history of peripheral arthritis and six hundred and four patients (73.9%) were found to have a history of hip joint involvement. In same study, three hundred and forty-four patients (42.7%) were found to have enthesitis, which was the most common extra-articular symptom and also two hundred and forty-six patients (29.7%) were found to have a history of uveitis.

In a large cohort of patients with active AS, adalimumab effectively reduced enthesitis and peripheral arthritis<sup>(11),(12)</sup>.

A single center, cross-sectional study<sup>(3)</sup> revealed that Korean patients with AS have a higher frequency of peripheral arthritis and hip joint involvement. Though the frequency of peripheral arthritis was higher than reported results in Western countries<sup>(14)</sup>, epidemiological data on extra-axial manifestations in Korean AS patients are poor. Adalimumab is approved for immune mediated inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease and psoriasis in Korea. There is currently no data on the effectiveness of adalimumab in extra-axial symptoms like peripheral arthritis, enthesitis or dactylitis in Korean AS patients.

This study will be the first prospective study of the frequency of EAMs in Korean AS patients being treated with adalimumab in routine clinical practice. .

### Research Question and Objectives:

What is the frequency of EAMs in Korean AS patients and the effectiveness of adalimumab on EAMs?

#### Primary Objective

To investigate the frequency of EAMs in AS patients on adalimumab therapy in routine clinical practice

#### Secondary Objectives

- To observe the effectiveness of adalimumab on AS spinal disease activity in routine clinical practice
- To investigate the effectiveness of adalimumab on EAMs in routine clinical practice

**Study Design:**

This is a prospective, mono-country, multi-center study in AS patients treated with adalimumab. At least 200 subjects will be enrolled at approximately 10 sites.

The baseline assessment should be performed prior to the first dose of adalimumab (Visit1). Study visits will be conducted at 12, 28, 36 and 52 week after baseline. All subjects will have one Follow-up approximately 30days after the last dose of adalimumab.

The prescription of adalimumab is at the discretion of the physician in accordance with clinical practice and label, is made independently from this study and precedes the decision to offer the patient the opportunity to participate in this study.

Primary Endpoint:

The frequency of EAMs of interest at baseline: peripheral arthritis, enthesitis and dactylitis

Secondary Endpoints:

- The percentage of patients with 50% improvement of baseline BASDAI (BASDAI 50) at week 12, 28, 36, and 52
- The change of MASES (Maastricht Ankylosing Spondylitis Enthesitis Score) from baseline to week 12, 28, 36, and 52 in patients who had enthesitis at baseline
- The percentage of patients who have enthesitis of the plantar fascia from baseline to week 12, 28, 36 and 52.
- The change of dactylitis score from baseline to week 12, 28, 36 and 52 in patients who had dactylitis at baseline.
- The change of tender and swollen joint counts (TJC, 0-46; SJC, 0-44) from baseline to week 12, 28, 36 and 52 in patients who had peripheral arthritis ( $\geq 1$  swollen joint) at baseline.

**Population:**

Subject will be adults with AS who meet the eligibility criteria.

Inclusion Criteria

- Subject must be an adult  $\geq 19$  years
- Subject has been diagnosed with ankylosing spondylitis according to the 1984 modified New York criteria for at least 3months
- Subject has active disease defined by a BASDAI score  $\geq 4$  despite treatment with at least 2 NSAIDs based on Korea AS reimbursement guideline.
- Subject is eligible for adalimumab in daily rheumatologic practice
- Subject must provide written authorization form to use personal and/or health data prior to the entry into the study.

Exclusion Criteria

- Female subjects who are pregnant or breast feeding

<ul style="list-style-type: none"> <li>• Subject applies contraindication to any anti-TNF agent</li> <li>• Subject is participating in other clinical trials</li> </ul>
<p><b>Variables:</b></p> <ul style="list-style-type: none"> <li>• Demographics: Age, Gender, Family History of AS, Co-morbidity</li> <li>• Previous AS-related medication (medication, dosage)</li> <li>• Concomitant medication</li> <li>• BASDAI 50</li> <li>• Extra-axial symptoms: Enthesitis, Peripheral arthritis and Dactylitis (presence or absence)</li> <li>• Extra-axial symptoms assessment: MASES, enthesitis of the plantar fascia, TJC's and SJC's, Counts of dactylitic digits</li> <li>• Adalimumab administration</li> <li>• Extra-axial symptoms excluding Enthesitis, Peripheral arthritis and Dactylitis (If applicable, such as IBD, uveitis, etc.)</li> </ul>
<p><b>Data Sources:</b></p> <p>The investigator should maintain source documents for each subject in the study, consisting of medical records containing demographic data, and other information to be collected.</p>
<p><b>Study Size:</b></p> <p>The primary end point of this study is to investigate the frequency of extra-axial symptoms such as peripheral arthritis, enthesitis and dactylitis in eligible Korean AS patients.</p> <p>With reference to a study in Korean AS patients<sup>(1),(3)</sup>, peripheral arthritis, enthesitis and dactylitis were found in 70%, 53% and 1% in AS patients, respectively. We calculated sample size based on the expected frequency of peripheral arthritis and enthesitis.</p> <p>By assuming 95% confidence interval and 15% confidence interval width, the sample size is estimated at 144 and 171 for peripheral arthritis and enthesitis, respectively. Considering 20% of drop-out rate, about 200 patients will be recruited.</p>
<p><b>Data Analysis:</b></p> <p>The study population will be classified by ITT (Intention-To-Treat) set and PP (Per-Protocol) set.</p> <ul style="list-style-type: none"> <li>- ITT set: The ITT set will consist of those patients who have received at least one adalimumab treatment and have assessed EAMs at baseline.</li> <li>- PP set: The PP set will consist of those patients who meet inclusion/exclusion criteria and complete the study without any major protocol deviation of the patients included in the ITT set.</li> </ul> <p><u>General Considerations</u></p> <p>Continuous variables will be described with the number of patients, arithmetic mean, standard deviation, median, minimum, and maximum. For categorical variables, the frequency and proportion will be presented. The values such as arithmetic mean, standard deviation, and proportion will be rounded to</p>



two decimal places. If the observation value is missing value, it will be treated as a missing value in the analysis.

Baseline Characteristics including demographics

Descriptive statistics will be used to present variables regarding demographics and disease/medication related data. Continuous variables will be described with the number of patients, arithmetic mean, standard deviation, median, minimum and maximum. For categorical variables, the frequency and proportion will be presented. The values such as arithmetic mean, standard deviation, and proportion will be rounded to two decimal places.

If the observation value is missing value, it will be treated as a missing value in the analysis. Statistical analyses will be performed using SAS V9.2 or higher.

**Milestones:** Start of Data Collection: 4Q 2014

End of Data Collection: 1Q 2017

Final Report of Study Results: 4Q 2017

## **5.0 Amendments and Updates**

NA

## **6.0 Milestones**

Major study milestones and their planned dates are as follows:

Start of Data Collection:	4Q 2014
End of Data Collection:	1Q 2017
Final Report of Study Results:	4Q 2017

## **7.0 Rationale and Background**

### **7.1 Introduction**

In addition to chronic inflammation of the spine, extra-axial manifestations are common features in patients with ankylosing spondylitis (AS). Although AS is primarily a disease of the axial skeleton, peripheral joint involvement occurs in up to 70% of the patients<sup>(1)</sup>. An epidemiological study of 847 patients in Belgium who fulfilled the modified New York criteria for AS found that 42% had one or more extra-articular manifestations, including acute anterior uveitis (27%), IBD (10%) and psoriasis (11%)<sup>(2)</sup>. According to a cross-sectional study in Korea of 830 AS patients<sup>(3)</sup>, three hundred and ninety-one patients (47.1%) were found to have a history of peripheral arthritis and six hundred and four patients (73.9%) were found to have a history of hip joint involvement. In same study, three hundred and forty-four patients (42.7%) were found to have enthesitis, which was the most common extra-articular symptom and also two hundred and forty-six patients (29.7%) were found to have a history of uveitis.

Non-steroidal anti-inflammatory drugs (NSAIDs) remain first-line agents for the treatment of AS<sup>(4)</sup>. Disease-modifying anti-rheumatic drugs (DMARDs) do not have a satisfactory effect on axial disease. Sulfasalazine has some effect on extra-axial arthritis<sup>(5)</sup> but its benefit for treating enthesitis does not outweigh its risks<sup>(4)</sup>. Tumor necrosis factor

(TNF) antagonists, including the monoclonal antibodies adalimumab, infliximab and the TNF-receptor construct etanercept are highly effective agents for the treatment of patients who still have active AS despite the treatment with NSAID<sup>(5)-(10)</sup>. In a large cohort of patients with active AS, adalimumab effectively reduced enthesitis and peripheral arthritis<sup>(11),(12)</sup>. Most clinicians understand that the presence of comorbid conditions reduces the quality of life (QoL) of patients. Two patients with the same degree of back pain and radiographic findings will not have the same QoL if one of them also has psoriasis, for example. The presence of comorbidities is a significant determinant of the mental health-related impact of AS on QoL<sup>(13)</sup>; therefore, it is important to screen for extra-articular manifestations and comorbid conditions in patients diagnosed with AS.

## **7.2 Rationale**

A single center, cross-sectional study<sup>(3)</sup> revealed that Korean patients with AS have a higher frequency of peripheral arthritis and hip joint involvement. Though the frequency of peripheral arthritis was higher than reported results in Western countries<sup>(14)</sup>, epidemiological data on extra-axial manifestations in Korean AS patients are poor. Adalimumab is approved for immune mediated inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease and psoriasis in Korea. There is currently no data on the effectiveness of adalimumab in extra-axial symptoms like peripheral arthritis, enthesitis or dactylitis in Korean AS patients.

This study will be the first prospective study of the frequency of EAMs in Korean AS patients being treated with adalimumab in routine clinical practice.

## **8.0 Research Quesiton and Objectives**

What is the frequency of EAMs in Korean AS patients and the effectiveness of adalimumab on EAMs?

**Primary Objective:**

To investigate the frequency of EAMs in AS patients on adalimumab therapy in routine clinical practice

**Secondary Objectives:**

- To observe the effectiveness of adalimumab on AS spinal disease activity in routine clinical practice
- To investigate the effectiveness of adalimumab on EAMs in routine clinical practice

## **9.0 Research Methods**

### **9.1 Study Design**

This is a prospective, mono-country, multi-center study in AS patients treated with adalimumab.

At least 200 subjects will be enrolled at approximately 10 sites.

Physicians will be asked to document on a separate log the number of patients who are possible to participate in this study. Presence or absence of EAMs and decision to participate will be collected.

The baseline assessment should be performed prior to the first dose of adalimumab (Visit1). Study visits will be conducted at 12, 28, 36 and 52 week after baseline. All subjects will have one Follow-up approximately 30days after the last dose of adalimumab.

**Primary Endpoint:**

- The frequency of EAMs of interest at baseline: peripheral arthritis, enthesitis and dactylitis

### **Secondary Endpoints:**

- The percentage of patients with 50% improvement of baseline BASDAI (BASDAI 50) at week 12, 28, 36, and 52
- The change of MASES (Maastricht Ankylosing Spondylitis Enthesitis Score) from baseline to week 12, 28, 36, and 52 in patients who had enthesitis at baseline
- The percentage of patients who have enthesitis of the plantar fascia from baseline to week 12, 28, 36 and 52.
- The change of dactylitis score from baseline to week 12, 28, 36 and 52 in patients who had dactylitis at baseline.
- The change of tender and swollen joint counts (TJC, 0-46; SJC, 0-44) from baseline to week 12, 28, 36 and 52 in patients who had peripheral arthritis ( $\geq 1$  swollen joint) at baseline.

The prescription of adalimumab is at the discretion of the physician in accordance with clinical practice and label, is made independently from this study and precedes the decision to offer the patient the opportunity to participate in this study.

## **9.2 Setting**

### **9.2.1 Selection of Study Population**

Subject will be adults with AS who meet the eligibility criteria.

#### **Inclusion Criteria**

- Subject must be an adult  $\geq 19$  years

- Subject has been diagnosed with ankylosing spondylitis according to the 1984 modified New York criteria for at least 3months
- Subject has active disease defined by a BASDAI score  $\geq 4$  despite treatment with at least 2 NSAIDs based on Korea AS reimbursement guideline
- Subject is eligible for adalimumab in daily rheumatologic practice
- Subject must provide written authorization form to use personal and/or health data prior to the entry into the study

#### **Exclusion Criteria**

- Female subjects who are pregnant or breast feeding
- Subject applies contraindication to any anti-TNF agent
- Subject is participating in other clinical trials

### **9.2.2 Drop-Out Subjects**

Once a subject is dropped out from the study, no further information for that subject will be collected. However, the reason for drop-out will be reported and serious adverse events will be reported to AbbVie until 30 days following the intake of the last dose of adalimumab.

Subjects will be dropped out from the study:

- 1) If the subjects choose to withdraw from the study
- 2) Where ethical or practical conflicts hinder the procedure of the study, and such cases will be determined based on the investigator's judgment
- 3) In case of Adalimumab discontinuation at any point during study period

### **9.2.3 Investigator Selection Criteria**

The rheumatologist will be selected based on the following criteria:

- Those who work in hospitals that have sufficient numbers of eligible patients.
- Those who agree to devote adequate time to conduct the study in accordance with the protocol.
- Those who will report any serious adverse events in patients using an AbbVie product to AbbVie in accordance with the protocol.

### **9.3 Variables**

Participating subjects will be followed up at week 12, 28, 36, and 52 for 12 months after baseline. At baseline, demographics, disease and medication related data, the presence of extra-axial symptoms such as peripheral arthritis, enthesitis and dactylitis will be collected.

On every follow-up visit, BASDAI 50 will be measured to observe the effectiveness of AS. Also, the change of MASES, TJC (0 to 46), SJC (0 to 44), Dactylitis score and the presence of plantar fascia will be evaluated to investigate the effectiveness of adalimumab on EAMs.

After baseline visit, if subjects have extra-axial symptoms other than Enthesitis, Peripheral arthritis and Dactylitis, relevant data will be collected.

Enthesitis is defined as at least 1 inflamed enthesis in the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES, 0 to 13) or of the plantar fascia of the foot. Peripheral arthritis is defined as at least 1 of swollen joint counts (SJC, 0 to 44, excluding hip joints). Dactylitis will be measured by a simple count of dactylitic digits.

Patients will be administered adalimumab 40 mg every other week in addition to their preexisting anti-rheumatic treatment for a study period of 1 year as per Korean AS reimbursement guideline.

In the event of Adalimumab discontinuation, the reason for discontinuation will be collected. If the reason for treatment discontinuation is due to an adverse event, the event will be collected.

The following variables will be collected at baseline, and every follow-up visit thereafter during the study period.

### **Baseline**

- 1) Demographics: Age, Gender, Family History of AS, Co-morbidity
- 2) Previous AS-related medication (medication, dosage)
- 3) Concomitant medication
- 4) BASDAI 50
- 5) Extra-axial symptoms: Enthesitis, Peripheral arthritis and Dactylitis (presence or absence)
- 6) Extra-axial symptoms assessment: MASES, enthesitis of the plantar fascia, TJC and SJC, Counts of dactylitic digits
- 7) Adalimumab administration

### **Week 12, 28, 36 and 52 after baseline**

\*Window period for each follow up visit will be  $\pm 4$  weeks.

- 1) BASDAI 50



- 2) Extra-axial symptom assessment: MASES, enthesitis of the plantar fascia, TJC's and SJC's, Counts of dactylitic digits
- 3) The change of AS-related medication (If applicable)
- 4) Extra-axial symptoms excluding Enthesitis, Peripheral arthritis and Dactylitis (If applicable, such as IBD, uveitis, etc.)

#### **9.4 Data Sources**

The investigator should maintain source documents for each subject in the study, consisting of medical records containing demographic data, and other information to be collected.

Case Report Forms will be supplied by AbbVie, and used to transmit the collected information during this study to AbbVie.

Case report forms will include patient demographic information, e.g., gender, age, unique patient study number, family history of AS, co-morbidity and the information to be evaluated according to the study protocol. Case report forms will maintain patient confidentiality, e.g., patient names must not be collected and full date of birth must not be collected (age is acceptable). The investigator or staff under his/her supervision must complete the case report forms, and neither AbbVie nor any agents acting on behalf of AbbVie may complete the case report forms.

#### **9.5 Study Size**

The primary endpoint of this study is to investigate the frequency of extra-axial symptoms such as peripheral arthritis, enthesitis and dactylitis in eligible Korean AS patients.

With reference to a study in Korean AS patients<sup>(1),(3)</sup>, peripheral arthritis, enthesitis and dactylitis were found in 70%, 53% and 1% in AS patients, respectively. We calculated sample size based on the expected frequency of peripheral arthritis and enthesitis.

By assuming 95% confidence interval and 15% confidence interval width, the sample size is estimated at 144 and 171 for peripheral arthritis and enthesitis, respectively. Considering 20% of drop-out rate, about 200 patients will be recruited.

## **9.6 Data Management**

Investigator should complete, sign and date the CRFs accurately. All CRFs must be legible and completed in indelible ballpoint ink. Corrections to the CRFs should be made with a single line, be initialed and dated, with the reason for changes given. Data are not to be obliterated by blacking out, correction fluid, or by erasing the original entry.

At the completion of the study, the completed signed and dated case report forms of all enrolled patients should be provided to AbbVie by the investigator. ONLY data specified in the protocol should be collected and submitted to AbbVie.

CRAs or their designees will be responsible to review the collected case report forms for completeness and conclusiveness.

## **9.7 Data Analysis**

The study population will be classified by ITT (Intention-To-Treat) set and PP (Per-Protocol) set.

- ITT set: The ITT set will consist of those patients who have received at least one adalimumab treatment and have assessed EAMs at baseline.

- PP set: The PP set will consist of those patients who meet inclusion/exclusion criteria and complete the study without any major protocol deviation of the patients included in the ITT set.

### **General Considerations**

Continuous variables will be described with the number of patients, arithmetic mean, standard deviation, median, minimum, and maximum. For categorical variables, the frequency and proportion will be presented. The values such as arithmetic mean, standard deviation, and proportion will be rounded to two decimal places. If the observation value is missing value, it will be treated as a missing value in the analysis.

### **Baseline Characteristics including demographics**

Descriptive statistics will be used to present variables regarding demographics and disease/medication related data. Continuous variables will be described with the number of patients, arithmetic mean, standard deviation, median, minimum and maximum. For categorical variables, the frequency and proportion will be presented. The values such as arithmetic mean, standard deviation, and proportion will be rounded to two decimal places.

If the observation value is missing value, it will be treated as a missing value in the analysis. Statistical analyses will be performed using SAS V9.2 or higher.

### **Primary Endpoint:**

**The frequency of EAMs of interest at baseline: peripheral arthritis, enthesitis and dactylitis**

-The frequency and the proportion of patients who are having peripheral arthritis, enthesitis or dactylitis in Korean AS patients at baseline will be presented, and 95% confidence intervals will be calculated.

### **Secondary Endpoints:**

- The percentage of patients with 50% improvement of baseline BASDAI (BASDAI 50) at week 12, 28, 36, and 52  
  
-The frequency and the proportion of patients with 50% improvement of baseline BASDAI at week 12, 28, 36, 52 will be presented.
- The change of MASES (Maastricht Ankylosing Spondylitis Enthesitis Score) from baseline to week 12, 28, 36, and 52 in patients who had enthesitis at baseline  
  
-The descriptive statistics (the number of patients, mean, standard deviation, median, min, max) for MASES according to study visit and the change from baseline at week 12, 28, 36, 52 will be presented.
- The percentage of patients who have enthesitis of the plantar fascia from baseline to week 12, 28, 36 and 52.  
  
-The frequency and the proportion of patients who have enthesitis of the plantar fascia at week 12, 28, 36, 52 will be presented.
- The change of dactylitis score from baseline to week 12, 28, 36 and 52 in patients who had dactylitis at baseline.  
  
-The descriptive statistics (the number of patients, mean, standard deviation, median, min, max) for dactylitis score according to study visit and the change from baseline at week 12, 28, 36, 52 will be presented.
- The change of tender and swollen joint counts (TJC, 0-46; SJC, 0-44) from baseline to week 12, 28, 36 and 52 in patients who had peripheral arthritis ( $\geq 1$  swollen joint) at baseline.  
  
-The descriptive statistics (the number of patients, mean, standard deviation, median, min, max) for tender and swollen joint counts (TJC, 0-46; SJC, 0-44) according to study visit and the change from baseline at week 12, 28, 36, 52 will be presented.

### **9.7.1 Safety Analysis**

The serious adverse event will be coded by MedDRA (Medical Dictionary for Regulatory Activities).

The cumulative total number and percentage of patients reporting serious adverse event and adverse drug reaction will be tabulated. The reason for treatment discontinuation will also be summarized.

### **9.8 Quality Control**

Prior to the initiation of the study, an investigator's meeting or initiation visit will be held with AbbVie personnel or his/her designee, the investigators and their study coordinators. This meeting will include a review of the protocol and CRF completion.

Investigator must assure that the study is conducted in accordance with the protocol and all relevant regulations and CRF is completed accurately.

In general, monitoring for any site is not required, but, for quality assurance, internal consistency check for completeness and consistency of data will be done to ensure the integrity of the information reported.

CRF will be reviewed by CRAs at AbbVie or their designees for completeness and conclusiveness and when necessary, query will be generated and will be resolved by the site staffs.

All data hand-entered in the database will be verified by a double-key entry procedure. Any discrepancies will be reviewed against the hard copy CRF and corrected. After completion of the entry process, computer logic checks will be run. Any necessary corrections will be made to the database and documented.

### **9.9 Limitations of the Research Methods**

NA

## **9.10 Other Aspects**

NA

## **10.0 Protection of Human Subjects**

The study should receive approval from the Institutional Review Board (IRB) of the each institution, and then a written study agreement should be made with institutions before the initiation of the study in each institution.

Patient written authorization form to use and/or disclose personal and/or health data from patients must be obtained prior to enrolling the patient and the physician is required to document this authorization.

Patient confidentiality must be maintained at all times; therefore demographics that could identify the patients will not be collected.

## **11.0 Management and Reporting of Adverse Events/Adverse Reactions**

### **11.1 Adverse Event Definition and Serious Adverse Event Categories**

An adverse event (AE) is defined as any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with their treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event.

If an adverse event meets any of the following criteria, it is considered a serious adverse event (SAE):

<b>Death of Patient:</b>	An event that results in the death of a patient.
<b>Life-Threatening:</b>	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.
<b>Hospitalization:</b>	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
<b>Prolongation of Hospitalization:</b>	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
<b>Congenital Anomaly:</b>	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
<b>Persistent or Significant Disability/Incapacity:</b>	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. 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).
<b>Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:</b>	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 patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. 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 or drug abuse.

## 11.2 Severity

The following definitions will be used to rate the severity for any adverse event being collected as an endpoint/data point in the study and for all serious adverse events.

- |                  |   |
|------------------|---|
| <b>Mild:</b>     | The adverse event is transient and easily tolerated by the patient.   |
| <b>Moderate:</b> | The adverse event causes the patient discomfort and interrupts the patient's usual activities.  |
| <b>Severe:</b>   | The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life threatening. |

## 11.3 Relationship to Pharmaceutical Product

The following definitions will be used to assess the relationship of the adverse event to the use of product:

- |                                  |   |
|----------------------------------|---|
| <b>Reasonable Possibility</b>    | An adverse event where there is evidence to suggest a causal relationship between the product and the adverse event.    |
| <b>No Reasonable Possibility</b> | An adverse event where there is no evidence to suggest a causal relationship between the product and the adverse event. |

If no reasonable possibility of being related to product is given, an alternate etiology must be provided for the adverse event.



#### **11.4 Serious Adverse Event Collection Period**

Serious adverse events will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent) until 30 days following the intake of the last dose of physician-prescribed treatment.

#### **11.5 Serious Adverse Event Reporting**

In the event of a serious adverse event, the physician will:

- For events from patients using and AbbVie product - notify the AbbVie contact person identified below within 24 hours of the physician becoming aware of the event.



#### **11.6 Pregnancy Reporting**

In the event of a maternal/paternal pregnancy occurrence in the patient, the physician will notify AbbVie contact person identified in Section 11.5 within 24 hours of the physician becoming aware of the pregnancy and will be requested additional information on the progress and results of the pregnancy including fetus/infant information.

#### **12.0 Plans for Disseminating and Communicating Study Results**

At the end of the study, a study report will be written by AbbVie in collaboration with the principal investigator. This report will contain a description of the objectives of the study, the methodology of the study and its results and conclusions. The completed case report forms and the study report must be treated as the confidential property of AbbVie and

may not be released to unauthorized people in any form (publications or presentations) without express written approval from AbbVie. The results of this study may be published by AbbVie or by any one of the participating investigators after agreement with AbbVie.

## 13.0 References

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## Annex 1.

### 1) Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)

#### MAASTRICHT ANKYLOSING SPONDYLITIS ENTHESITIS SCORE

JE

The MASES and Additional Enthesitis score should only be completed for patients with Enthesitis at the screening visit. Please grade each entheses below 0(absent), 1(present)

	Patient Right	Patient Left
1st Costochondral joint	<input type="checkbox"/> 0 <input type="checkbox"/> 1	<input type="checkbox"/> 0 <input type="checkbox"/> 1
7th Costochondral joint	<input type="checkbox"/> 0 <input type="checkbox"/> 1	<input type="checkbox"/> 0 <input type="checkbox"/> 1
Posterior Superior Iliac Spine	<input type="checkbox"/> 0 <input type="checkbox"/> 1	<input type="checkbox"/> 0 <input type="checkbox"/> 1
Anterior Superior Iliac Spine	<input type="checkbox"/> 0 <input type="checkbox"/> 1	<input type="checkbox"/> 0 <input type="checkbox"/> 1
Iliac Crest	<input type="checkbox"/> 0 <input type="checkbox"/> 1	<input type="checkbox"/> 0 <input type="checkbox"/> 1
Proximal Insertion of Achilles tendon	<input type="checkbox"/> 0 <input type="checkbox"/> 1	<input type="checkbox"/> 0 <input type="checkbox"/> 1
Patient Midline		
5th Lumbar Spinous process	<input type="checkbox"/> 0	<input type="checkbox"/> 1
<b>Total</b>		

#### ADDITIONAL ENTHESITIS SCORE

JE

	Patient Right	Patient Left
Fascia plantaris	<input type="checkbox"/> 0 <input type="checkbox"/> 1	<input type="checkbox"/> 0 <input type="checkbox"/> 1

## 2) Joint Evaluation

JOINT EVALUATION					JE			
Joint evaluation should only be completed for patients with peripheral arthritis at the screening visit.								
	0=Absent      1=Present							
Joint <i>(circle the correct answer)</i>	Pain/Tenderness				Swollen			
	R		L		R		L	
1. Sternoclavicular	0	1	0	1	0	1	0	1
2. Acromio-clavicular	0	1	0	1	0	1	0	1
3. Shoulder	0	1	0	1	0	1	0	1
4. Elbow	0	1	0	1	0	1	0	1
5. Wrist	0	1	0	1	0	1	0	1
6. Metacarpophalangeal I	0	1	0	1	0	1	0	1
7. Metacarpophalangeal II	0	1	0	1	0	1	0	1
8. Metacarpophalangeal III	0	1	0	1	0	1	0	1
9. Metacarpophalangeal IV	0	1	0	1	0	1	0	1
10. Metacarpophalangeal V	0	1	0	1	0	1	0	1
11. Thumb Interphalangeal	0	1	0	1	0	1	0	1
12. Proximal Interphalangeal II	0	1	0	1	0	1	0	1
13. Proximal Interphalangeal III	0	1	0	1	0	1	0	1
14. Proximal Interphalangeal IV	0	1	0	1	0	1	0	1
15. Proximal Interphalangeal V	0	1	0	1	0	1	0	1
16. Hip	0	1	0	1	N/A		N/A	
17. Knee	0	1	0	1	0	1	0	1
18. Ankle	0	1	0	1	0	1	0	1
19. Metatarsophalangeal I	0	1	0	1	0	1	0	1
20. Metatarsophalangeal II	0	1	0	1	0	1	0	1
21. Metatarsophalangeal III	0	1	0	1	0	1	0	1
22. Metatarsophalangeal IV	0	1	0	1	0	1	0	1



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23. Metatarsophalangeal V	0	1	0	1	0	1	0	1
<b>Total</b>								

**AbbVie Inc. (AbbVie)**  
**Post Marketing Observational Study**  
**Protocol (P15-238)**

**A Prospective , Mono-Country, Multi-Center Study to  
observe the frequency of Extra-Axial symptoms in  
Korean Ankylosing Spondylitis patients on  
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