Title Page

Title	Post-Marketing Surveillance of Humira® in Korean Pediatric CD Patients under the "New-Drug Re-examination"
Protocol Version Identifier	P15-619
Date of Last Version of Protocol	April 29, 2017
Marketing Authorization Holder(s)	AbbVie Korea Ltd.
Research Question and Objectives	To evaluate the safety profile of Humira® for Pediatric CD patients in normal medical practice
Country(-ies) of Study	South Korea
Author	[redacted]

This study will be conducted in compliance with this protocol.

Confidential Information

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	AbbVie Korea Ltd. [redacted]

1.0 Table of Contents

2.0 Abbreviations

AE	Adverse Event
5-ASA	5-Aminosalicylic Acid
CDAI	Crohn's Disease Activity Index
CRA	Clinical Research Associate
CRF	Case Report Form
CD	Crohn's Disease
SAE	Serious Adverse Event
MFDS	Ministry of Food and Drug Safety
PCDAI	Pediatric Crohn's Disease Activity Index
PMS	Post-Marketing Surveillance
PPD test	Purified Protein Derivative test
TB	Tuberculosis
TNF	Tumor Necrosis Factor

3.0 Responsible Parties

SDP : [redacted]

CRO(s): [redacted]

4.0 Abstract

Title: Post-Marketing Surveillance of Humira® in Korean Pediatric CD Patients under the "New-Drug Re-examination"
Rationale and Background: This non-interventional, observational study will be conducted in compliance with the New Drug Re-examination Guideline in Korea
Research Question and Objectives: To evaluate the safety profile of Humira® for Pediatric CD patients in normal medical practice: (1) Serious adverse event•adverse drug reaction (2) Unexpected adverse event•adverse drug reaction (3) Already known adverse drug reaction (4) Non-serious adverse drug reaction (5) Adverse events resulting from drug misuse, drug abuse or drug interaction (6) Other information related to the product's safety and effectiveness (including the influence to the laboratory value)
Study Design: Post-Marketing Surveillance
Population: Pediatric CD patients who have been prescribed Humira® by the treating physician
Variables: Demographics, Medical History, PPD Skin Test, Chest X-ray, Interferon Gamma Release Assay, Concomitant Medication, Safety, PCDAI score (CDAI score if it is evaluated)
Data Sources: paper Case Report Form
Study Size: 141 patients
Study Duration : 12 Sep 2013 ~ 11 Sep 2017
Data Analysis: (1) The safety analysis data set : all subjects who have received at least one dose of Humira® during the study and have been followed up for the safety information (2) The effectiveness analysis data set: • Effectiveness of Humira® induction therapy: all subjects who have been administered Humira® and received Humira ® for 4 weeks including induction period (±1 week) and for whom effectiveness evaluation parameters have been recorded. • Maintenance effectiveness of Humira®: all subjects who have been administered Humira® and received Humira® for 6 months (±4 weeks) and for whom effectiveness evaluation parameters have been recorded.
Milestones: (1) Start of Data collection : 1Q 2015 (2) End of Data collection : 3Q 2017 (3) Final Report of Study Results : 4Q 2017

5.0 Amendments and Updates

The purpose of the amendments and updates is below:

11.1.6 Pregnancy Reporting	To clarify a scope of expedited reporting requirements for pregnancy	Amendment 1
11.1.7 Malignancy Reporting	To add Humira specific expedited reporting requirements for Malignancies in Pediatric and Young Adult Patients according to global SOP	Amendment 1
11.2 Product Complaint	To add a definition of product complaints and reporting requirements	Amendment 1
9.5 Study Size/9.7 Data Analysis	To change the number of subjects to be collected for surveillance to meet the local regulatory requirements	Amendment 2

In addition, administrative changes were incorporated to clarify the person in charge and the references.

6.0 Milestones

Major study milestones and their planned dates are as follows:

Start of Data Collection:	1Q 2015
End of Data Collection:	3Q 2017
Final Report of Study Results:	4Q 2017 (Date of submission to MFDS: 11 December 2017)

7.0 Rationale and Background

Rationale

This surveillance will be conducted in compliance with the New Drug Re-examination Guideline in Korea and this protocol is written in accordance with the guideline. Safety data of this study will be compared to product label claim for evaluation of the consistency of the safety profile in the real word setting.

Background

Approximately 25% of IBD patients are diagnosed as children, and the IBD characteristics of pediatric patients differ from those of adults as outlined below.[1-3] A recent single center study showed that the incidence of pediatric IBD has been rapidly increasing in Korea in recent years.[4] In this study, relevant family history was less prevalent and phenotypic expression differed from what was seen in Western countries.

Children with Crohn's disease can experience abdominal pain, intestinal obstruction and strictures, fistulas, abscesses, perianal disease, adverse events of treatment such as corticosteroids and surgery, and nutritional complications. A major difference between adult and pediatric CD is an impact of malnutrition. It can lead to delayed puberty and growth impairment which result in significant psychosocial complications.[5-8] At first, the goal of treatment of CD for children is to induce and maintain clinical remission. Restoration and/or preservation of normal growth and pubertal development are additional therapeutic goals in children with CD.[9]

The first line conventional therapy for mild patients includes 5-aminosalicylates and exclusive enteral nutrition (EEN). Corticosteroids are prescribed for moderate patients for induction. Immunomodulators such as azathioprine, 6-MP or MTX are used for maintenance for those.[10]

Therapeutic options for Crohn's disease are evolving, and recently, a new treatment approach has been suggested using biological agents to heal mucosa and alter natural history of disease.[11-12]

Until now, TNF blockade including adalimumab and infliximab has been prescribed for adult CD patients. In randomized controlled trials, adalimumab rapidly induced and

maintained clinical remission in adults.[13-17] The efficacy and safety of adalimumab for induction and maintenance of clinical remission in Western children with moderate to severe CD who had failed corticosteroids or immunosuppressants, including prior infliximab in > 40% of subjects, was demonstrated in the Imagine 1 trial.

This study will evaluate the safety and effectiveness of adalimumab for Korean pediatric patients with moderate to severe Crohn's disease (CD).

8.0 Research Question and Objectives

The objective of this surveillance is to evaluate the following items regarding the safety profile of Humira® for Pediatric CD patients in normal medical practice:

(1) Serious adverse event & adverse drug reaction

(2) Unexpected adverse event & adverse drug reaction

(3) Already known adverse drug reaction

(4) Non-serious adverse drug reaction

(5) Adverse events profile resulting from drug misuse, drug abuse or drug interaction

(6) Other information related to the product's safety and effectiveness (including the influence to the laboratory value)

The hypothesis of this study is that Humira® will present a safety profile consistent with that seen in the phase 3 clinical studies and will be efficacious in Korean Pediatric CD patients.

9.0 Research Methods

9.1 Study Design

This study is a non-interventional, observational study of Humira® in the treatment of pediatric CD as per the New Drug Re-examination Guideline in Korea.

This study will be conducted in institutions which provide a written agreement to AbbVie Korea, and where the use of Humira® for pediatric CD is following their normal medical practice setting. Pediatric patients who are prescribed Humira® as per physician's medical judgment in accordance with the approved SmPC will be enrolled in the study.

As this is a post marketing surveillance, AbbVie is NOT involved in the product supply since the drug is being used according to the approved marketing label and is to be prescribed by the physician under usual and customary practice of physician prescription.

9.2 Setting

Selection of Study Population

Pediatric CD patients who has been prescribed Humira® by the treating physician as per Korean label will be enrolled.

The patients who are receiving Humira® for pediatric CD during study period and meet the inclusion /exclusion criteria will be enrolled in the sites which signed a contract with AbbVie.

Once the study agreement is in place, the surveillance will be initiated at the site, and all patients who are prescribed Humira® for pediatric CD treatment during the surveillance period and who meet the inclusion /exclusion criteria will be enrolled in the study until the assigned number of subjects are registered at the site.

Inclusion Criteria

1. Pediatric patients with Crohn's Disease who are prescribed Humira in accordance with the Korean label for Humira authorization (labeling)

2. Patients who have given written authorization or patients whose legal representatives have given it to use their personal health data for the purposes of this study.

Physician will refer to the product market authorization (label) for inclusion criteria.

Exclusion Criteria

Patient with any of the following should not be registered in this surveillance:

1. Any contraindications to Humira as listed on the approved product market authorization (labeling)

2. Patients who is participating on other clinical trials.

Patients will be observed for 6 months following first dose of Humira®.

It is planned to include all patients who are treated with Humira® until the planned number of cases are collected to obtain meaningful safety data including TB incidence in the early stage of the study conduct. Once this study has been initiated in an institution, physicians are recommended to include/recruit all eligible patients who are prescribed Humira®.

An evaluable patient is a patient who has been administered Humira® at least once and has safety information at subsequent visits. (or telephone contact, correspondence)

Drop-out patients also will be considered for safety evaluation, if the safety information is obtained by follow-up contact. If there is loss of follow-up, the reason will be recorded.

Investigator Selection Criteria

The surveillance will be conducted in medical institutions in Korea. The institutions include clinics and hospitals. The physician must meet the following criteria:

1. A physician who is working in a hospital or clinic and has a patient pool eligible for this surveillance.

2. A physician who can conduct the study in accordance with the protocol.

3. A physician who agrees to devote adequate time to conduct of the study including enrollment activities, following up the patients and filling out the case report forms.

4. A physician who will report to the sponsor any safety and effectiveness data in accordance with the protocol.

9.3 Variables

Demographics

Basic demographics including patient initials, age (year and month of birth), sex, weight, height, name of institution, department and physician will be taken and recorded.

Diagnosis and Medical History

Diagnosis and medical history including previous TB history or vaccination, will be taken and recorded and will include the following items to get patient's medical status:

- CD related history ; date of pediatric CD diagnosis, involved intestinal area, presence of draining fistula, previous CD related therapy including antibiotics, steroids, 5-ASA, Immunosuppressants, biologics and nutritional therapy
- Previous TB history ; presence of TB, TB treatment regimen received, completeness and appropriateness of the therapy regimen, vaccination
- Other medical history ; history of previous disease(s), concurrent disease(s), history of allergy, pregnancy etc.

PPD Skin Test

PPD skin test will be performed and recorded. It will include: Date of PPD test, induration at PPD test site (in mm). (Refer to MFDS Guideline for Latent TB Management in TNF-Antagonist Use and TB screening Aide provided by AbbVie.)

Chest X-ray

Chest X-ray interpretation result will be taken and recorded and will include: Date of Chest-X-Ray, presence of latent or active TB lesion. (Refer to MFDS Guideline for Latent TB Management in TNF-Antagonist Use and TB screening Aide provided by AbbVie.)

Interferon gamma release assay

Interferon gamma release assay will be performed, recorded and will include: date of interferon gamma release assay and result. (Refer to MFDS Guideline for Latent TB Management in TNF-Antagonist Use and TB screening Aide provided by AbbVie.)

Treatment with Humira®

Patients will be administered Humira® as per the package label. Unit dose, frequency, length of treatment (start date, end date) will be recorded on the appropriate case report form.

Concomitant Medication

Concomitant medications, including TB prophylaxis regimen, corticosteroids, immunosuppressants, will be recorded and will include: generic name (brand name in case of combination drug), total daily dose, length of administration (start date and end date), indication(s).

Safety (Adverse Event)

Regardless of results of causality assessment, presence of adverse event(s), type of adverse event(s), onset, end date, severity, causality assessment by physician on the adverse event(s), action taken, outcome will be captured, during the study, from the first administration to the surveillance period (from informed consent to up to 70 days following the last administration of Humira®) (Section 11.0 Management and Reporting of Complaints).

Effectiveness

From the patients treated with Humira®, the effectiveness data (i.e. PCDAI score) at previous times before Humira® treatment, at 4 weeks (visit window: ±1 week) and at 6 months (visit window: ±4 weeks) post-treatment will be collected. (CDAI score will be collected as well, if possible.)

9.4 Data Sources

Case Report Forms will be supplied by AbbVie Korea. These forms will be used to transmit information collected during this study to AbbVie Korea. Case report form must maintain pertinent patient background information, e.g., gender, age, medical history, and the information to be evaluated. The case report form must maintain patient confidentiality, e.g. patient names must not be collected (patient initials are acceptable) and date of birth must not be collected (age or month and year of birth are acceptable).The physician 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

Number of Patients to be enrolled

At least 600 subjects were to be collected for surveillance to meet the local regulatory requirements, but the number of subjects was adjusted to 141 subjects based on the followings:

1) <u>Significantly low incidence and prevalence of Pediatric CD</u>

Based on the data obtained from 1996 to 2002 in North America, 93.6 per 100,000 people suffered from Crohn's disease and the incidence rate of Crohn's disease in children aged less than 18 years was 3.0 per 100,000 people.[18] Additionally, it is reported that when considering the ethnic differences, Crohn's disease is more prevalent in developed countries and relatively less common in Asia;[19] for example, a retrospective study conducted in China revealed than the prevalence of Crohn's disease was estimated to be 1.4 per 100,000 people,[20] which was much less than that reported in North America.

According to the data reported to Korea Health Insurance Review & Assessment Service in 2015, the number of patients aged 19 years or younger who are with 'K50: Crohn's disease [regional enteritis]' was only 3,051. Considering that ages eligible for enrollment in this Post-Marketing Surveillance are between 6 years and 17 years according to the its approved label in Korea, it is expected that the number of patients eligible for this Post-Marketing Surveillance would be much less than the number aforementioned, but there is no specific domestic data to prove it in Korea.

2) <u>Humira is not a primary therapeutic agent for Pediatric CD</u>

Humira® is indicated only to patients with severely active Crohn's disease with inadequate response, intolerance, or contraindication to primary trophotherapy, corticosteroids and/or immunomodulators according to the approved label, which is reflected in the very limited number of patients with Crohn's disease of all ages who received treatment with biologics, based on the data reported to Korea Health Insurance Review & Assessment Service [Table 1].

[Table 1] The estimated number of patients diagnosed with Crohn's disease and proportion of those patients with anti-TNF agents prescription

	The number of patients diagnosed*	Patients prescribed with anti-TNF agents	
		The mean number of patients†	% ‡
All ages	17,651	1,684	9.5%

* The number of patients diagnosed: The number of patients diagnosed in 2015 according to the disease code (K50: Crohn's disease [regional enteritis]); source: Health Insurance Review & Assessment Service; unit: people

† The mean number of patients: The number of patients prescribed with anti-TNF agents for relevant disease codes (K500, K501, K508 or K509); source: Health Insurance Review & Assessment Service; unit: people

‡ Percent: calculated by dividing the mean number of patients by the number of patients diagnosed

3) Difficulties in getting patients' consents

Pediatric CD is indicated for pediatric patients, it is difficult to get pediatric patients' consents from their parents.

However, we will make every effort to enroll maximum number of subjects. We expect maximum 141 patients will be recruited [Table 2].

[Table 2] The number of subjects expected to be enrolled in this study

Classification	No. of subjects
Enrolled subjects as of October, 2016	**100**
- subject who start Humira treatment after enroll in the study	71
- subject who starts Humira treatment before enroll in the study	29
Estimated No. of subjects to be enrolled	**Approx. 41**
- subject who will start Humira treatment after enroll in the study	31*
- subject who starts Humira treatment before enroll in the study	10
Total	**Approx. 141**

* Calculated as follows: 5.07 (mean number of newly diagnosed patients per month) x 6 months (remaining enrollment period) = 30.42

About 15 investigators across the country will be participating in this surveillance and the number of subjects to be collected by each investigator will vary.

Study Duration

The study duration designated by MFDS is from 12 September 2013 to 11 September 2017. The study will start after the launch of the product as a new drug for pediatric CD and the final report will be submitted to MFDS by 11 Dec 2017. Interim study reports will be submitted to MFDS every 6 months for the first 2 years, then annually thereafter during PMS period.

9.6 Data Management

Physician should complete the CRFs, 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 conclusion of the study, the completed signed and dated case report forms for the enrolled patients should be provided to the AbbVie Korea by the physician for every patient enrolled in the study. As distinct case report form should be created for each unique instance when data is to be collected ONLY data specified in the protocol should be collected and submitted to AbbVie Korea.

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

The data entered by the physician will be reviewed by CRAs or their designees and when necessary, query will be generated to correct the data by the physician. After completion of the data review, data will be locked to prevent further editing.

9.7 Data Analysis

Justification for the planned sample size

Information on at least 600 subjects will be collected in this surveillance study in accordance with the Korean regulations on New Drug Re-examination (i.e. New Drug Re-examination Standards: Ministry of Food and Safety (MFDS).

The sample size of 600 has been selected in order to give at least 95% probability of detecting at least one uncommon SAE that occurs in the Korean patient population at a rate of at least 0.5%. This estimate is based on the assumption that the occurrence of AEs has a Poisson distribution and that if the population rate of occurrence of an AE is 0.5% then the expected number of AEs in the proposed sample size of 600 would be 3. The probability of observing 1 or more events with a Poisson parameter of 3 is 0.95 or 95%.

If we have an AE with a population probability of 0.5% then the expected number of events in a sample size of 600 will be 3. Using the Poisson Distribution with a parameter of 3 the probability of getting zero AEs in our sample size of 600 is given by the formula:

$$\Pr\{X = 0\} = \frac{3^0 \times e^{-3}}{0!} = 1 \times 0.0498 = 0.0498$$

The probability, therefore, of having 1 or more AEs in that sample size is 1 - 0.0498 = 0.9502.

At least 600 subjects were to be collected for surveillance to meet the local regulatory requirements, but number of subjects to be enrolled was adjusted to 141 subjects. (Refer to section 9.5)

Analysis Population

Number of collected and analyzed patient will be presented as following items: Contracted cases, collected number of CRFs, safety-evaluable cases, effectiveness-evaluable cases, number of drop-out cases, Reasons for drop-out

The safety analysis data set will include all subjects who have received at least one administration of Humira® following the initiation of surveillance and have completed follow up for the safety information.

For induction effectiveness of Humira®, the effectiveness analysis data set will include all subjects who have been administered Humira® and prescribed Humira® for 4 weeks including induction period (±1 week) and for whom effectiveness evaluation parameters have been recorded. And for maintenance effectiveness of Humira®, effectiveness analysis data set will include all subjects who have been administered Humira® and prescribed Humira® for 6 months (±4 weeks) and for whom effectiveness evaluation parameters have been recorded. The subjects whose effectiveness evaluation was not properly conducted because their data from evaluation parameters were missing or they discontinued administration prior to the effectiveness evaluation will be excluded from the evaluation.

Safety Analysis

The adverse events will be coded by MedDRA dictionary. The number and percentage of subjects reporting any serious adverse events/adverse drug reactions will be tabulated overall and by MedDRA 17.0 or more recent version, in preferred term. The number and percentage of subjects reporting unexpected (unlabeled) adverse drug reactions will be tabulated in a similar fashion.

To investigate the factors affecting the safety, the number and percentage of subjects reporting adverse events will also be classified by various background factors (e.g., demographic factors, treatment factors such as medical history, dosing and administration, concomitant medications, beginning of administration before/after the registration date, etc.) and tabulated. If the incidence of adverse events in the subjects who began the administration before/after the registration date has statistical significance, it will be presented as a separate item. In addition, if there are patients who have already been

administered Humira® when participating in the surveillance, their adverse events from the first administration of Humira® to the inclusion will be presented in a separate table. If data from special patient groups are collected, they will be extracted and tabulated separately for adverse events/adverse drug reactions.

Effectiveness Analysis

The effectiveness assessment of Humira® induction therapy and maintenance therapy will be presented by the number and percentage of the subjects with clinical response. Clinical response is defined as decrease in PCDAI score from baseline by ≥15 points and if CDAI score is collected, Clinical response is defined as decrease in CDAI score from baseline by ≥70 points.

To investigate the factors affecting the effectiveness, the number and percentage of subjects with clinical response will also be classified by background factors (e.g., demographic factors, treatment factors such as medical history, dosing and administration, concomitant medications, beginning of administration before/after the registration date, etc.) and tabulated. If the effectiveness evaluation of above factors has statistical significance, it will be presented as a separate item.

Statistical Methods

The descriptive statistics for safety and effectiveness parameter in each year will be presented in annual reports.

In final report (Re-examination report), safety and effectiveness outcome by background factor will be summarized and analyzed. The analysis for categorical variables will be performed using chi-square test or fisher's exact test and continuous variables will be performed using Wilcoxon rank sum test or t-test. Also, incidence rate of adverse event collected in overall PMS period will be analyzed and 95% CI will be presented.

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.

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

Open-label data from non-randomized patients; reporting bias with historical safety data.

9.10 Other Aspects

NA

10.0 Protection of Human Subjects

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

However, informed consent will not be required because as local pharmaceutical law does not require informed consent for regulatory-required post-marketing surveillance.

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

Monitoring for any sites is not required. However internal consistency check for completeness and consistency of data will be done to ensure integrity of the information reported.

11.0 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).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 11.2.2). For adverse events, please refer to Sections 11.1.1 through 11.1.6. For product complaints, please refer to Section 11.2.

11.1 Medical Complaints

11.1.1 Adverse Event Definition and Serious Adverse Event Categories

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

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

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

Death of Patient:	An event that results in the death of a patient.
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.
Hospitalization:	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.
Prolongation of Hospitalization:	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity:	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).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	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.

11.1.2 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.

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

11.1.3 Relationship to Pharmaceutical Product

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

Probable	An adverse event has a strong temporal relationship to 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.
Probably Not	An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology

	exists.
Not Related	An adverse event is due to underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator's opinion of possibly, probably not, or not related to pharmaceutical product is given, an alternate etiology must be provided by the investigator for the serious adverse event.

11.1.4 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 70 days or 5 half-lives following the intake of the last dose of physician-prescribed treatment.

11.1.5 Serious Adverse Event Reporting

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

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

11.1.6 Pregnancy Reporting

In the event of a pregnancy occurrence in the patient, the physician will notify AbbVie contact person identified in Section 11.1.5 within 24 hours of the physician becoming aware of the pregnancy. Pregnancies will be collected from the date of the first dose through 150 days following the last dose of study drug. The physician will be requested additional information on the progress and results of the pregnancy including fetus/infant informat

11.1.7 Malignancy Reporting

For any events of malignancy/premalignancy in subjects 30 years of age and younger using adalimumab, whether related to the product or not – the physician will notify AbbVie contact person identified in Section 11.1.5 within 24 hours of the physician becoming aware of the event.

11.2 Product Complaint

11.2.1 Definition

A Product Complaint is any Complaint (see Section 11.0 for the definition) related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

11.2.2 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 Plans for Disseminating and Communicating Study Results

Within 3 months of the completion of the study, a final study report will be generated by AbbVie and submitted to MFDS by December 11, 2017. This report will contain a description of the objectives of this Surveillance, the methodology of the study and its

results and conclusions. The CRFs and the study reports must be treated as the confidential property of AbbVie. It 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 upon the provisions of the executed study agreement with AbbVie.

13.0 References

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