Protocol Synopsis

AbbVie Inc.	**Protocol Number:** P11-282
Name of Study Drug: HUMIRA®	**Phase of Development:** Post-Marketing Observational Study (PMOS)
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 10 December 2019
Protocol Title: A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of HUMIRA® (Adalimumab) in Patients with Moderately to Severely Active Ulcerative Colitis (UC)	
Objectives: The primary objective of the Registry is to evaluate the long-term safety of HUMIRA® in moderately to severely active UC adult patients (18 years of age or older) who are treated per routine clinical practice. The long-term safety of patients being prescribed and treated with IMM (6-MP or AZA) with no concurrent biologic will also be evaluated. The secondary objective is to evaluate long-term effectiveness of HUMIRA® in patients with moderately to severely active UC who have had an inadequate response to conventional therapy and who are treated as per routine clinical practice. The long-term effectiveness of patients being prescribed and treated with IMM (6-MP or AZA) with no concurrent biologic use will also be evaluated.	
Investigators: Multicenter global Registry (Physician information on file at AbbVie).	
Study Sites: Approximately 500 to 750 sites representing gastroenterologists who will prescribe HUMIRA® or IMM therapy for patients with moderately to severely active UC in countries where Market Authorization for HUMIRA® has been obtained.	
Study Population: An adult patient (18 years of age or older) with moderately to severely active UC as per the physician's assessment who has been prescribed HUMIRA® per routine clinical practice or IMM therapy per local clinical practice.	
Number of Subjects to be Enrolled: 5,450 patients (approximately 2,700 patients prescribed HUMIRA®, either without or with concurrent IMM therapy, and approximately 2,750 patients prescribed IMM with no concurrent biologic use). Enrollment in the IMM registry group was completed in 2018. The sample size for the HUMIRA® arm was re-calculated after discussion with regulatory agencies in November 2019.	
Methodology: This is a Post-Marketing Observational Study. All patients that agree to take part in the Registry will be followed for 10 years. With patient authorization for use/disclosure of data and having met all the inclusion criteria and none of the exclusion criteria, the physician may enroll the patient into the Registry either in HUMIRA® treatment group or IMM treatment group. The decision to prescribe drug to patients should be made separately from the decision to enroll them in the Registry. The physician will follow the patient during regular office visits at intervals as determined by routine clinical practice or as recommended by national guidelines. Physicians will be asked to collect and report safety data (SAEs and AEIs). Patients who discontinue the Registry prior to 10 years will be offered the option to participate in a direct to Healthcare Provider (HCP) process and have their physicians complete a simplified HCP questionnaire on an annual basis.	

Methodology (Continued):

All patients that are unreachable after three documented attempts to contact via phone, email, or certified letter will be considered lost to follow-up.

For patients who are lost to follow-up during the Registry prior to the completion of the10 year observational period, AbbVie will take reasonable actions to ascertain vital status at the end of the 10 year period. The National Death Index in the US, national/regional cancer registries and vital registries as applicable/available per local databases will be contacted for all lost to follow up patients. Information to evaluate the effectiveness of Registry drug therapy will be collected from patients and their physicians if part of routine clinical assessment.

Healthcare resource utilization (e.g., UC-related hospitalization, all-cause hospitalization, length of stay, colectomy), Partial Mayo Score (Full Mayo Score will be assessed if endoscopy data is available per routine care), CRP, Hemoglobin and Fecal Calprotectin values will be collected as effectiveness variables if deemed to be part of routine patient care. Patient reported outcomes questionnaires (Short Quality of Life in Inflammatory Bowel Disease Questionnaire, Work Productivity and Activity Impairment, Treatment Satisfaction Questionnaire for Medication and EQ-5D-5L) will be completed at the enrollment visit, every 6 months through Month 72, and thereafter every 12 months through Month 120 if part of routine clinical assessment.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

A patient will be eligible for participation in this registry if he/she meets inclusion criteria 1 and 3 or 2 and 3:

1. An adult patient (18 years of age or older) with moderately to severely active UC as per the physician's assessment who has been prescribed HUMIRA®, without or in combination with an IMM (6-MP or AZA), according to routine clinical practice and meets one of the following criteria:
   - Is currently taking HUMIRA® therapy, and has received at least 8 weeks of HUMIRA® therapy prior to registry entry and the physician can provide source documentation (if available and/or applicable) of SAEs, AEIs, and dosing information since initiation of therapy; OR
   - Is entering after participation in an Abbott or AbbVie sponsored UC study and;
     - Has received continuous (no more than 70 consecutive days off drug) HUMIRA® therapy since initiation of therapy.
2. An adult patient (18 years of age or older) with moderately to severely active UC as per the physician's assessment who has been prescribed IMM (6-MP or AZA) therapy is currently taking IMM (6-MP or AZA) therapy without a concurrent biologic, has received at least 12 consecutive weeks of IMM therapy prior to registry entry and the physician can provide source documentation (if available and/or applicable) of SAEs, AEIs, and dosing information since initiation of therapy.
3. Patients capable of and willing to grant authorization for use/disclosure of data being collected and provided to AbbVie and to comply with the requirements of the registry protocol.

Main Exclusion:

1. Patients should not be enrolled if they are:
   - on IMM (6-MP or AZA) therapy without a concurrent biologic if they cannot continue to be treated with IMM therapy or
   - being treated with any investigational agents and/or approved biologics other than HUMIRA®.

Duration of Treatment:

Patients being treated with IMM (AZA or 6-MP) without a concurrent biologic at enrollment may add HUMIRA® or switch to HUMIRA® without concurrent IMM therapy or initiate therapy with another biologic or investigational drug during the registry. For these patients the 10 year follow-up period will start at the time of enrollment into the registry.

Criteria for Evaluation:

The Registry Population consists of all patients who received at least one dose of registry drug (HUMIRA® or IMM [6-MP or AZA]) referred to as HUMIRA® Registry Group, or IMM (6-MP or AZA) Registry Group. This will be the population for safety and effectiveness analyses in the Registry.

The HUMIRA® Episodic Dosing' population will consist of patients who enrolled into the HUMIRA® Registry Group and:

- Interrupted HUMIRA® at least once for at least 12 weeks during the Registry and received at least one dose of HUMIRA® after the treatment interruption,
- Did not receive any other biologics during the treatment interruption period(s) and
- Provided data before and after HUMIRA® treatment interruption periods(s).

Efficacy:

The following measures will be used to collect certain variables:

- Safety reporting forms will be used to estimate health care resource utilization (e.g., UC-related hospitalization, all-cause hospitalization, length of hospital stay, colectomy);
- Partial Mayo Score (Full Mayo Score will be assessed if endoscopy data is available per routine care); and
- CRP, hemoglobin and fecal calprotectin values.

The effectiveness of therapy evaluation provided by the patient will also be collected with Patient Reported Outcomes (PROs). They include:

- Short Quality of Life in Inflammatory Bowel Disease Questionnaire (SIBDQ);
- Work Productivity and Activity Impairment (WPAI);
- Treatment Satisfaction Questionnaire for Medication (TSQM); and
- EQ-5D-5L.

For effectiveness analyses of the HUMIRA® Episodic Dosing population, only patients providing evaluations of effectiveness at two time points will be considered:

- Data prior to the episodic HUMIRA® treatment interruption
- Data at/after the resumption of HUMIRA®

Criteria for Evaluation (Continued):

Safety:

Four main safety analyses will be reported from this Registry: Two analyses will summarize data excluding the direct to HCP process and two analyses will summarize data through the end-of-registry including the direct to HCP Process.

- Registry Treatment-emergent AEs excluding the Direct to HCP process: SAEs and AEIs occurring from the first day in the registry through up to 70 days (for HUMIRA®) or 30 days (for IMM) after the last dose of registry drug or up to the last registry drug dose date before the direct to HCP process, whichever period is shorter.
- All Humira Treatment-emergent AEs excluding the direct to HCP process: SAEs and AEIs occurring from the first recorded dose of HUMIRA® including those events which occurred in previous Abbott or AbbVie sponsored UC studies for patients who previously participated in such a study, through up to 70 days (for HUMIRA®) after the last dose of HUMIRA® if patients do not participate in the direct to HCP process, or up to the last dose of HUMIRA® before the direct to HCP process. For patients who previously participated in an Abbott or AbbVie sponsored UC study, the analysis will include data occurring from the first recorded dose of HUMIRA® in the previous study. For patients previously treated with commercial HUMIRA®, who are not Rollover Patients, analysis will begin from the first day in the registry.
- All Registry Treatment-emergent AEs including the direct to HCP Process: SAEs and AEIs occurring from the first day in the registry through up to 70 days (for HUMIRA®) or 30 days (for IMM) after the last dose of registry drug.
- Registry Observational AEs including the direct to HCP Process: All AEs occurring from the first day in the registry through the date of the last patient's visit in the registry or the direct to HCP process. Registry Observational AEs include all AEs reported during the registry, also nonserious events which are not AEIs, and irrespective of registry drug exposure.

Statistical Methods:

Descriptive statistics are to be provided for demographic, effectiveness, and safety parameters. Continuous variables will be summarized by the number of observations, mean, standard deviation, first quartile, median, third quartile, minimum, and maximum; whereas discrete variables will be summarized by counts and percentages. All analyses will be performed on the Registry Population that includes all patients who receive at least one dose of HUMIRA® or IMM in the registry unless otherwise specified.

Analyses will be completed periodically and at the end of the registry on all cumulative data at specific time points. The timing and content of the interim analyses will be based on commitments made globally to regulatory agencies and the Publication Plan.

In order to better characterize the long-term safety profile of HUMIRA® in moderately to severely active UC and to provide improved precision of the estimated risks for lymphoma, opportunistic infections, and malignancy, meta-analyses of available AbbVie sponsored clinical trials in adult UC and adult IBD (UC and CD) patients will be performed using a random effects Poisson regression model. The model will include the variable study as a random effect. This information will supplement the conclusions of this study. Details of these meta-analyses will be included in the statistical analysis plan.