Abstract

Title: A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of Humira® (Adalimumab) in Pediatric Patients with Moderately to Severely Active Crohn's Disease (CD) – *CAPE*

Rationale and Background: This protocol describes a non-interventional registry that will evaluate the long-term safety and effectiveness of Humira as used in routine clinical practice in pediatric patients (between the ages of 6 and 17 years inclusive at the time of enrollment) with moderately to severely active CD, who receive Humira therapy according to routine clinical practice. This registry is part of a post-marketing commitment from AbbVie to the European Medicines Agency (EMA).

Research Question and Objectives: The primary objective of this registry is to evaluate long-term safety of Humira in pediatric patients (between the ages of 6 and 17 years inclusive at the time of enrollment) with moderately to severely active CD who are prescribed and treated according to routine clinical practice. Patients being prescribed and treated with conventional immunosuppressant therapy with no concurrent biologic use will also be enrolled as a reference group.

The secondary objective of this registry is to evaluate the long-term effectiveness of Humira in pediatric patients (between the ages of 6 and 17 years inclusive at the time of enrollment) with moderately to severely active CD who are prescribed and treated in accordance with routine clinical practice. Patients being prescribed and treated with conventional immunosuppressant therapy with no concurrent biologic use will be considered a reference group. In addition, the impact of treatment interruptions on the safety and effectiveness of Humira will be evaluated.

Study Design: This is a global, multicenter, non-interventional registry of pediatric patients with moderately to severely active CD treated in a routine clinical setting with Humira or immunosuppressant non-biologic therapy. Patients meeting entry criteria will be enrolled. All patients who consent to take part in the registry will be followed for up to 10 years, providing long-term safety and effectiveness data on Humira or immunosuppressant non-biologic therapy. This registry will collect data on serious adverse events (SAEs), protocol defined Adverse Events of Special Interest (AESI), and pregnancies. SAEs, all AESI, and pregnancies, will be collected through Year 5. Starting at Year 6 of the patient's registry participation, SAEs, only AESI related to infections, malignancies, and AEs leading to permanent discontinuation of registry treatment, and pregnancies will be collected through Year 10 of the registry.

SAEs will be reported to AbbVie from the time the physician obtains the patient's parent/guardian signed Authorization for Use/Disclosure of Data (AUDD) form/Informed Consent (ICF) throughout the patient's participation in the registry.

Information to evaluate the effectiveness of Humira or immunosuppressant non-biologic therapy will be collected from patients and their physicians if part of routine clinical assessment. In the event that registry therapy is interrupted, effectiveness variables will be collected during the interruption. Evaluations of the effectiveness of registry therapy to be collected from patients and their physicians will include the Short Pediatric Crohn's Disease Activity Index (sh-PCDAI) and Physician's Global Assessment of Disease Activity (PGA), and these evaluations will be collected with clinical assessments beginning with the Enrollment visit, at regularly scheduled visits that are closest to Months 3 and 6, and every 6 months thereafter through Year 5, if part of routine clinical assessment.

Study Design (Continued): Evaluations of the effectiveness of therapy to be provided by the parent/guardian or patient (if 18 years of age and older)will include, the Work Productivity and Activity Impairment Questionnaire (WPAI-caregiver through age 17 years inclusive and WPAI at age 18 years and older), IMPACT III (10 through 17 years old - to be completed by the patient), and Short Quality of Life in Inflammatory Bowel Disease Questionnaire (SIBDQ for patients age 18 years or older), and these evaluations will also be collected beginning with the Enrollment visit, and at regularly scheduled visits through Year 5, if part of routine clinical assessment.
Population: Male and female pediatric patients (between the ages of 6 and 17 years inclusive at the time of enrollment) who have been diagnosed with moderately to severely active CD and have been prescribed and treated (see Section 9.2.4) in accordance with routine clinical practice or who have been prescribed and treated with immunosuppressant therapy [azathioprine, 6-mercaptopurine or methotrexate].
Variables: Data collected from all patients who receive at least one dose of Humira or at least one dose of conventional immunosuppressant therapy in the registry will be used for analysis of safety and effectiveness in each group. **Safety:** Data on SAEs, protocol defined AESI, and pregnancies will be collected throughout the registry. Data on SAEs, all AESI, and pregnancies, will be collected from the time of AUDD/ICF signature and patient assent/authorization or appropriate form(s) per local regulations are signed through Year 5 of the registry. Starting at Year 6 of the patient's registry participation, SAEs, only AESI related to infections, malignancies, and AEs leading to permanent discontinuation of registry treatment, and pregnancies, will be collected through Year 10 of the registry. **Effectiveness:** When applicable, information about the effectiveness of registry therapy will be provided by the patients and their physician. Information to evaluate the effectiveness of registry therapy will be collected through assessment of the following indicators of disease activity: sh-PCDAI and PGA. Outcome measurements including the WPAI-caregivers through age 17 years old, IMPACT III (10 through 17 years old), and SIBDQ for patients age 18 years old and older will be completed at every visit through year 5, if part of routine care.
Data Sources: Patient source data will include patient medical records, health care provider completed questionnaires, and patient reported questionnaires. Vital status will be obtained for patients lost to follow-up at the end of the 10-year follow-up from National Death Indices and cancer registries, physician, family, or patient reports where available and allowed per local regulations.
Study Size: Approximately 1300 pediatric patients with moderately to severely active CD will be enrolled in the European countries and additional countries after Marketing Authorization is obtained in these regions (e.g., Australia and USA).
Data Analysis: <u>Statistical Methods:</u> Safety is the primary objective for this registry. Safety analyses will be performed for all patients who receive at least one dose of Humira or at least one dose of conventional immunosuppressant therapy in this registry to be used for analysis of safety in each group. The total number and percentage of subjects with treatment-emergent SAEs and AESI will be summarized. The event rate per 100 patient years (PYs) of treatment-emergent SAEs and AESI will also be presented. In addition, observational SAEs and AESI occurring from the first dose of Humira in the registry through the last patient contact will be tabulated.

Data Analysis (Continued):

Statistical Methods (Continued):

The secondary objective of this registry is to evaluate the long-term effectiveness of registry therapy in patients with moderately to severely active CD. Effectiveness measures (sh-PCDAI and PGA) and outcomes measures (WPAI-caregivers, IMPACT III, and SIBDQ) will be summarized descriptively at each registry visit.

Prior and concomitant CD medications, duration of exposure, and Baseline characteristics (i.e., race/ethnicity, duration of CD, body mass index [BMI], and prior therapies for CD) will be summarized descriptively.

Sample Size Consideration:

The sample size for this registry is approximately 1,300 patients with a 10-year follow-up period with 800 patients in the Humira group and 500 patients in the immunosuppressant without biologics group. Due to the low incidence and prevalence of pediatric CD, the size of the registry is based on the expected availability of eligible patients to be enrolled in a 5- to 6-year time frame. The attrition rates were estimated using the data from the ongoing juvenile idiopathic arthritis (JIA) registry (Study P10-262) resulting in a Kaplan-Meier estimated median time to dropout of 3.5 years (1,280 days). Using the exponential attrition rate function of $R(t) = 1 - e^{-\lambda * t}$, this corresponds to an estimated $\lambda = 0.198$. With 1,300 patients, the total cumulative PYs over the 10 year follow-up period will be approximately 5,659 patient years (3,482 for patients on Humira and 2,177 for patients on immunosuppressants without biologics).

The rate of malignancy among young adult CD patients (age ≤ 30 years old) treated with Humira from AbbVie's pediatric CD studies, adult CD studies, and ongoing adult CD registry was 0.35 events per 100 PYs (17 events and 4,813 PYs) with a 95% confidence interval (CI) of 0.22 – 0.57 events per 100 PYs.

For the Humira group, using the lower bound of the 95% CI above of 0.2235 as a conservative estimate for the malignancy event rate and taking the attrition rate of the JIA registry into account, 800 patients for a total of 3,482 PYs will provide a greater than 99% chance of observing at least two cases of malignancy, a 98% chance of observing three or more cases of malignancy, a 95% chance of observing at least four cases of malignancy, and an 88% chance of observing at least five cases of malignancy.

For the immunosuppressant therapy group, the rate of malignancy was assumed to be 0.38 events per 100 PYs based on historical data from the literature. Taking the same attrition rate as for the Humira group into account resulted in a total of 2,050 PYs with 471 patients which will provide a greater than 99% chance of observing at least two cases of malignancy, a 98% chance of observing three or more cases of malignancy, a 95% chance of observing at least four cases of malignancy, and an 89% chance of observing at least five cases of malignancy.

Milestones:

Start of Data Collection: April 2014

End of Data Collection: April 2030

Study Progress Report: August 2014

Interim Report: Every August from 2015 throughout the registry

Registration in the EU PAS Register: TBC

Final Report of Study Results: October 2030