1.0 Abstract

Title

A Long-Term, Multi-Center, Longitudinal, Postmarketing, Observational Registry to Assess Long-Term Safety and Effectiveness of HUMIRA® (Adalimumab) in Children with Moderately to Severely Active Polyarticular or Polyarticular-Course Juvenile Idiopathic Arthritis (JIA) STRIVE

Keywords

Humira; pediatric; polyarticular or polyarticular-course JIA; observational registry; long-term safety.

Rationale and Background

This registry, Registry P10-262, as well as the submission of this final report, is part of a postmarketing commitment from AbbVie to the US FDA (PMR 2630-1) and the EMA (MEA/ISR 046.9). This postmarketing observational registry was designed to assess the long-term safety and effectiveness of HUMIRA® (adalimumab) in patients diagnosed with moderately to severely active polyarticular or polyarticular-course JIA (defined as arthritis affecting ≥ 5 joints at the time of diagnosis) who are candidates for anti-tumor necrosis factor therapy and who are prescribed and treated in accordance with the approved local Humira product label under the conditions of a routine clinical setting. Enrollment for this registry is complete. Patients were followed for 10 years (within a registry group) providing long-term safety data for 10 years and long-term effectiveness data for 5 years, including patients who permanently discontinued Humira for any reason (including switching to an adalimumab biosimilar) before reaching 10 years of participation in the registry. Patients who switched from the MTX treatment group to the Humira treatment group were to be followed as patients in the Humira treatment group. These patients may have participated in the registry for longer than 10 years, as the 10-year follow-up

period started at the time of enrollment into the Humira treatment group. This final report provides cumulative long-term safety and effectiveness data from the registry through the data cutoff of 01 March 2024. The data collected in this registry are complementary to those from the pre-registration pediatric studies of Humira (Studies DE038, M10-444, and M10-240) in patients with moderately to severely active polyarticular or polyarticular-course JIA.

Research Question and Objectives

The primary and secondary objectives of this registry were to evaluate the long-term safety and effectiveness, respectively, of Humira in patients with moderately to severely active polyarticular or polyarticular-course JIA who were prescribed and treated in accordance with the approved local Humira product label under the conditions of a routine clinical setting. In addition, the impact of treatment interruptions on the safety and effectiveness of Humira was evaluated. Patients prescribed and treated with MTX per the local product label were considered as a reference group.

Setting

It was expected that approximately 120 physicians from the US, EU, and Australia would participate in this registry. Approximately 40 to 45 physicians were to be included based on participation in prior AbbVie-sponsored Humira clinical JIA studies.

The participating physicians, with regard to countries and sites, were intended to be representative of the pediatric rheumatologists who prescribe Humira to patients with moderately to severely active polyarticular or polyarticular-course JIA. The patients enrolled in this registry corresponded to the target population as described in the current approved Humira label for polyarticular JIA in the participating countries.

Patients and Study Size, Including Dropouts

Approximately 800 patients were to be enrolled in the US, EU, and Australia. Approximately 500 patients were to receive Humira (alone or in combination with MTX) and approximately 300 patients were to receive MTX without Humira. Enrollment is complete.

Variables and Data Sources

Safety

AEs were collected throughout the duration of the registry for all patients. For patients enrolled at age 4 to 17 years, SAEs, and AESIs were reported through Year 5. Beginning at Year 6, these patients were followed annually for SAEs, a subset of AESI that included CHF, malignancies, and AEs at least possibly related to and/or leading to discontinuation of registry treatment through Year 10.

For polyarticular or polyarticular-course JIA patients enrolled at age 2 to < 4 years in countries with available local approval and consent, SAEs and all AESI were collected for the full 10 years of the study.

Pregnancy was followed throughout the study.

Effectiveness

Effectiveness measures included: PGA of disease activity, Parent's global assessment of patient's disease activity, Parent's assessment of patient's pain, Physical Function of Disability Index of Childhood Health Assessment Questionnaire, tender joint count, swollen joint count, pain on passive motion, limitation of passive motion, active joint count, C-reactive protein, erythrocyte sedimentation rate, Child Health Questionnaire Parent Form 50, joints with inactive disease, JIA-associated uveitis, PedACR30/50/70/90; and Juvenile Arthritis Disease Activity Score.

Final Registry Results

The database for Registry P10-262 was open and dynamic until database lock; therefore, event details may have changed from those reported in the 10th Interim report if new information has been received.

As of the database lock, 849 patients enrolled in the registry and 828 were dosed and analyzed, 297 in the MTX treatment group and 531 in the Humira treatment group, including 40 patients who switched from the MTX treatment group to the Humira treatment group during the registry and were counted in both the MTX treatment group and Humira treatment group to reflect separate observations during exposure to these treatments. There are 21 patients who were not analyzed either due to the subjects never being dosed or the site's noncompliance.

Enrollment was completed and 131 patients completed the registry.

No deaths occurred in this registry.

The percentage of patients with at least 1 observational AE (events that occurred from the first day in the registry through the last contact irrespective of drug treatment duration), including AESI, was 53.9% and 50.5% for the MTX and the Humira treatment groups, respectively. The observation-time adjusted rate (E [events]/100 PYs) for observational AEs was 37.4 E/100 PYs and 38.5 E/100 PYs for the MTX and the Humira treatment groups, respectively.

A total of 33 MTX patients (11.1%) and 91 Humira patients (17.1%) reported at least 1 observational SAE. The observation-time adjusted observational SAE rate was 3.6 E/100 PYs in the MTX treatment group and 8.2 E/100 PYs in the Humira treatment group.

No patients reported any of the following observational AESI during the registry: Legionella infection, diverticulitis, oral candidiasis, active TB, reactivation of hepatitis B, PML, malignancy (including melanoma, leukemia, HSTCL, and other

malignancies), non-cutaneous vasculitis, sarcoidosis, autoimmune hepatitis, MI, CVA, CHF, pulmonary embolism, intestinal stricture, SJS, erythema multiforme, ALS, and Humira-administration medication error.

Observational AESI observed during the registry are summarized below:

- A total of 89 MTX patients (30.0%) and 159 Humira patients (29.9%) experienced at least 1 observational infection. The observation-time adjusted rate of observational infections was 13.7 E/100 PYs in the MTX treatment group and 13.1 E/100 PYs in the Humira treatment group.
  - The crude rate (N, %) and observation-time adjusted rate (E/100 PYs) for observational serious infections was similar between the MTX and Humira treatment groups. Sixteen MTX patients (5.4%) and 34 Humira patients (6.4%) reported a serious infection (1.3 E/100 PYs and 2.6 E/100 PYs, respectively).
  - One Humira patient (0.2%) reported an observational opportunistic infection of fungal esophagitis (< 0.1 E/100 PYs).
  - Two Humira patients (0.4%) experienced nonserious observational parasitic infections. The observation-time adjusted rate of observational parasitic infections was < 0.1 E/100 PYs in the Humira treatment group.
  - One MTX patient (0.3%) and 2 Humira patients (0.4%) reported observational latent TB (< 0.1 E/100 PYs each). Both Humira patients reported positive mycobacterium TB complex tests indicative of latent TB.
- Six MTX patients (2.0%) and 30 Humira patients (5.6%) reported an observational injection site reaction-related AE (0.6 E/100 PYs and 1.6 E/100 PYs, respectively).
- Two Humira patients (0.4%) reported observational lupus-like reaction (0.2 E/100 PYs).
- Five MTX patients (1.7%) and 12 Humira patients (2.3%) reported observational allergic reactions (0.3 E/100 PYs and 0.6 E/100 PYs, respectively).
- Two Humira patients (0.4%) reported observational cutaneous vasculitis (0.1 E/100 PYs).

- One MTX patient (0.3%) and 1 Humira patient (0.2%) reported an observational interstitial lung disease-related AE (< 0.1 E/100 PYs in both groups).
- One MTX patient (0.3%) reported observational pancreatitis (< 0.1 E/100 PYs). Observational pancreatitis was not observed in the Humira treatment group.
- Two Humira patients (0.4%) reported observational intestinal perforation (< 0.1 E/100 PYs).
- Six MTX patients (2.0%) and 9 Humira patients (1.7%) reported observational hematologic events (including pancytopenia, anemia, leukopenia, neutropenia, platelet disorder, and thrombocytopenia) (0.5 E/100 PYs and 0.4 E/100 PYs, respectively).
- Four Humira patients (0.8%) reported observational liver events (hepatic cytolysis, hepatic steatosis, and hepatic disorder) (0.2 E/100 PYs).
- Twenty (6.7%) MTX patients and 5 (0.9%) Humira patients reported increased or abnormal liver function tests. The observation-time adjusted rate of observational increased or abnormal liver function tests was 2.3 E/100 PYs for the MTX treatment group and 0.4 E/100 PYs for the Humira treatment group.
- One MTX patient (0.3%) and 9 Humira patients (1.7%) reported observational new onset PsO or worsening of PsO (<0.1 E/100 PYs and 0.4 E/100 PYs, respectively). One Humira patient (0.2%) experienced a serious worsening of PsO.
- One MTX patient (0.3%) and 4 Humira patients (0.8%) reported an observational seizure disorder (including epilepsy, convulsion, febrile convulsion, and seizure) (< 0.1 E/100 PYs and 0.2 E/100 PYs, respectively).
- Two Humira patients (0.4%) reported severe observational creatine phosphokinase elevation (defined as Common Toxicity Grade 3 and above) (0.2 E/100 PYs).
- Twenty-seven MTX patients (9.1%) and 45 Humira patients (8.5%) reported observational AEs leading to discontinuation of registry drug (2.6 E/100 PYs and 2.8 E/100 PYs, respectively).

- One MTX patient (0.3%) and 6 Humira patients (1.1%) reported observational AEs leading to discontinuation from the registry (<0.1 E/100 PYs and 0.5 E/100 PYs, respectively).
- Eighty-six MTX patients (29.0%) and 129 Humira patients (24.3%) reported at least 1 observational AE considered by the physician as at least possibly related to registry drug (14.3 E/100 PYs and 11.4 E/100 PYs, respectively).

Rates of registry treatment-emergent AEs were similar to those reported for observational AEs.

Review of reported pregnancy outcomes from Registry P10-262 following maternal exposure to adalimumab indicated no new safety concerns. There were no product complaints during the registry that impacted patient safety.

Discussion

Humira continues to be well-tolerated in patients with moderately to severely active polyarticular or polyarticular-course JIA. No new safety signals were observed in the registry as of database lock. Based on this analysis, the known benefit-risk profile of Humira remains unchanged.

Effectiveness measures evaluated for this report generally showed improvement compared to baseline.

Marketing Authorisation Holder(s)

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Germany

Names and Affiliations of Principal Investigators

The list below includes only physicians who enrolled patients.

Principal Physician[a,b]	Site Name	Country	Central or Local IRB/EC
[redacted]	Women's and Children's Hospital	Australia	Local
	Kepler Universitätsklinikum GmbH	Austria	Central
	Univ. Kinderklinik Wien	Austria	Central
	LKH Bregenz	Austria	Central
	Kepler Universitätsklinikum	Austria	Central
	Univ. KinderKlinik Graz	Austria	Central
	Fakultni nemocnice v Motole	Czech Republic	N/A does not require EC submission
	Revmatologicky ustav Praha	Czech Republic	Local
	II. Detska klinika Fakultni nemocnice Brno	Czech Republic	Local
	Klinika detskeho a dorostoveho lekarstvi VFN	Czech Republic	Local
	Fakultni nemocnice v Motole	Czech Republic	N/A does not require EC submission
	Arhus University Hospital	Denmark	N/A does not require EC submission
	Rigshospitalet	Denmark	N/A does not require EC submission
	CHU Rennes Hôpital Sud	France	N/A does not require EC submission; however, regulatory approval for the study was obtained.

Principal Physician[a,b]	Site Name	Country	Central or Local IRB/EC
[redacted]	CHU Strasbourg Hôpital de Hautepierre	France	N/A does not require EC submission; however, regulatory approval for the study was obtained.
	CHU Tours, Hopital Bretonneau	France	N/A does not require EC submission; however, regulatory approval for the study was obtained.
	Hopital Cochin	France	N/A does not require EC submission; however, regulatory approval for the study was obtained.
	CHU Bicêtre Secteur Alagille	France	N/A does not require EC submission; however, regulatory approval for the study was obtained.
	CHU Rennes Hôpital Sud	France	N/A does not require EC submission; however, regulatory approval for the study was obtained.
	CHU Nancy Hôpital Brabois Enfants	France	N/A does not require EC submission; however, regulatory approval for the study was obtained.
	CHRU Lille Hôpital Jeanne De Flandre	France	N/A does not require EC submission; however, regulatory approval for the study was obtained.

Principal Physician[a,b]	Site Name	Country	Central or Local IRB/EC
[redacted]	CHU Toulouse, Hôpital des Enfants	France	N/A does not require EC submission; however, regulatory approval for the study was obtained.
	CHU Bordeaux Hôpital des Enfants Pellegrin	France	N/A does not require EC submission; however, regulatory approval for the study was obtained.
	Hopital Necker Enfants malades	France	N/A does not require EC submission; however, regulatory approval for the study was obtained.
	Hopital Cochin	France	N/A does not require EC submission; however, regulatory approval for the study was obtained.
	Klinikum Dortmund gGmbH	Germany	Central
	Klinikum "St. Georg" Leipzig	Germany	Central
	Kinder und Jugendrheumatologische Praxis am Allgemeinen Krankenhaus Eilbek	Germany	Central
	Deutsches Zentrum fur Kinder und Jugendmedizin	Germany	Central
	Asklepios Klinik Sankt Augustin GmbH	Germany	Central
	Klinikum Bremen Mitte gGmbH	Germany	Central
	Universitatsklinikum Tubingen	Germany	Central
	Ambulanzstandort: Orthopädie Zentrum Altona	Germany	Central
	Kinderklinik der Charite, Otto Heubner Centrum	Germany	Central

Principal Physician[a,b]	Site Name	Country	Central or Local IRB/EC
[redacted]	Helios Klinikum Berlin Buch	Germany	Central
	Klinikum Bremen Mitte gGmbH	Germany	Central
	General Hospital of Thessaloniki "Ippokratio"	Greece	Local
	General Children's Hospital of Athens "Aglaia Kyriakou"	Greece	Local
	Semmelweis Egyetem, II. sz. Gyermekgyogyas zati Klinika, Reumatologiai Osztaly	Hungary	Central
	ORFI Orszagos Reumatologiai es Fizioterapias Intezet	Hungary	Central
	Universita di Napoli Federico II	Italy	Local
	Azienda Ospedaliero Universitaria Policlinico Vittorio Emanulele Presido G. Rodolicoo	Italy	Local
	Ospedale Pediatrico Bambino Gesù	Italy	Local
	University of Chieti	Italy	Local
	A.Meyer Children's Hospital, University of Firenze	Italy	Local
	Istituti clinici di perfezionamento Centro di Reumatologia	Italy	Local
	Ospedale Pediatrico Bambino Gesù	Italy	Local
	Azienda Ospedaliero Universitaria Policlinico Vittorio Emanulele Presido G. Rodolicoo	Italy	Local
	IRCCS Policlinico S. Matteo	Italy	Local
	Istituto Giannina Gaslini	Italy	Local
	Clinica Pediatrica Ospedali Riuniti di Brescia	Italy	Local
	IRCCS Policlinico S. Matteo	Italy	Local

Principal Physician[a,b]	Site Name	Country	Central or Local IRB/EC
[redacted]	Ospedale Pediatrico Bambino Gesù	Italy	Local
	Seconda Universita' degli Studi di Napoli	Italy	Local
	Istituto Giannina Gaslini	Italy	Local
	A.Meyer Children's Hospital, University of Firenze	Italy	Local
	University of Padua	Italy	Local
	Wilhelmina Children's Hospital	Netherlands	Local
	Rikshospitalet	Norway	Central
	Rikshospitalet	Norway	Central
	Centro Hospitalar do Porto, EPE Hospital de Santo Antonio	Portugal	Local
	Centro Hospitalar Lisboa Norte Hospital Santa Maria	Portugal	Local
	Hospital Garcia de Orta, EPE	Portugal	Local
	Centro de Reumatologia Pediatrico	Puerto Rico	Central
	Liza B. Vazquez Cobian, M.D.	Puerto Rico	Central
	Narodny ustav reumatickych chorob	Slovakia	Central
	Narodny ustav reumatickych chorob	Slovakia	Central
	Narodny ustav reumatickych chorob	Slovakia	Central
	Hospital Sant Joan de Deu	Spain	Local
	Hospital Vall d'Hebron	Spain	Central
	Hospital Ramon Y Cajal	Spain	Central
	Hospital La Fe de Valencia	Spain	Local
	Hospital Severo Ochoa	Spain	Central
	Hospital Ramon Y Cajal	Spain	Central

Principal Physician[a,b]	Site Name	Country	Central or Local IRB/EC
[redacted]	Hospital Infantil Universitario Nino Jesus	Spain	Local
	Hospital Vall d'Hebron	Spain	Central
	Queen Silvia Children's Hospital	Sweden	Central
	The University of Vermont Children's Specialty Center	US	Local
	University of Utah Department of Pediatrics	US	Local
	Indiana University School of Medicine, Department of Pediatrics, Riley Hospital for Children	US	Local
	Akron Children's Hospital	US	Local
	Cincinnati Children's Hospital Medical Center Division of Rheumatology	US	Local
	Cooperman Barnabas Medical Center, Pediatric Specialty Center	US	Local
	Akron Children's Hospital	US	Local
	Methodist Medical Group Rheumatology, Unity Point Clinic	US	Central
	Arkansas Children's Hospital	US	Local
	Floating Hospital for Children at Tufts Medical Center	US	Local
	Arthritis Care Specialists of Maryland	US	Central
	Delray Research Associates	US	Central
	Cohen Children's Medical Center of NY, Pediatric Rheumatology	US	Local
	Ramesh C. Gupta, MD	US	Central

Principal Physician[a,b]	Site Name	Country	Central or Local IRB/EC
[redacted]	Methodist Medical Group Rheumatology, Unity Point Clinic	US	Central
	Nationwide Children's Hospital	US	Local
	The University of Vermont Children's Specialty Center	US	Local
	New York Medical College	US	Local
	Arthritis Associates, PLLC	US	Central
	Children's National Medical Center	US	Central
	Creighton University Medical Center	US	Local
	Legacy Emanuel Randall Children's Hospital	US	Local
	Children's Memorial Hospital/Northwestern University	US	Local
	Floating Hospital for Children at Tufts Medical Center	US	Local
	St. Christopher's Hospital for Children	US	Local
	Children's Hospital of Los Angeles	US	Local
	Baylor Scott & White Healthcare Round Rock	US	Local
	Floating Hospital for Children at Tufts Medical Center	US	Local
	Seattle Children's Hospital	US	Local
	Floating Hospital for Children at Tufts Medical Center	US	Local
	Children's Hospital of Wisconsin/MCW	US	Local
	Children's Hospital of Wisconsin/MCW	US	Local
	Medcenter One, Inc / Q&R Clinic	US	Local
	Catalina Pointe Clinical Research	US	Central

Principal Physician[a,b]	Site Name	Country	Central or Local IRB/EC
[redacted]	Centro de Reumatologia Pediatrico	US	Central
	Duke University Medical Center	US	Local
	Children's National Medical Center	US	Central
	University Pediatric Rheumatology of Kentucky LLC	US	Local
	Arizona Arthritis & Rheumatology Research, PLLC	US	Central
	University of Rochester Medical Center	US	Local
	Indiana University School of Medicine, Department of Pediatrics, Riley Hospital for Children	US	Local
	Centro de Reumatologia Pediatrico	US	Central
	The University of Chicago Hospital	US	Local
	Seattle Children's Hospital	US	Local

IRB internal review board; EC ethics committee; GCP Good Clinical Practice; N/A not applicable

a. There may be discrepancies in the spelling of physician's names within this list versus that found in the statistical tables.

b. Two principal physicians were permanently removed from the list since the 4 year interim report [redacted] was removed because full IRB/EC approval was not obtained. [redacted] received IRB/EC approval, but the physician withdrew consent to participate. In addition, the site for [redacted] was excluded from all analyses from the 2016 interim report onwards due to non compliance with GCP requirements (i.e., proper execution of informed consents/assents could not be confirmed). The site for [redacted] was also excluded from all analyses because the site became unresponsive, queries were not resolved and closed without resolution and the casebooks were not signed by the investigator.