SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	REMICADE
Name of Active Ingredient(s)	REMICADE (infliximab)

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved

Date: 6 March 2013

Prepared by: Janssen Research & Development, LLC

Protocol No.: C0168T45

Title of Study: A Multicenter International Observational Study of the Long-term Safety of Infliximab (REMICADE®)

Study Name: RESULTS: REMICADE Safety Under Long term Study

NCT No.: NCT00261976

Clinical Registry No.: CR004780

Study Center(s): In this long-term study, 324 sites participated. Sites were located in 20 countries: Argentina (10 sites) Austria (5 sites), Belgium (12 sites), Canada (47 sites), Denmark (6 sites) Finland (4 sites), France (13 sites), Germany (17 sites), Hungary (2 sites), Iceland (1 site), Israel (2 sites), Italy (6 sites), the Netherlands (5 sites), Norway (1 site), Poland (6 sites), Spain (2 sites), Sweden (1 site), Switzerland (2 sites), United Kingdom (15 sites) and the United States (167 sites).

Publication (Reference): None

Study Period: 03 Jan 2002 to 09 Mar 2012

Phase of Development: Phase 4

Objectives: To evaluate targeted long-term safety information on subjects who participated in the infliximab clinical studies that require long-term safety follow-up. Information was collected on death, serious infections, new malignancies, and new autoimmune diseases. In addition, information on delayed hypersensitivity (serum sickness-like) reactions following readministration of infliximab was collected.

Methodology: RESULTS is a long-term, multicenter, international, observational safety study. Information was collected on death, serious infections, new malignancies, and new autoimmune diseases. In addition, information on delayed hypersensitivity (serum sickness-like) reactions following readministration of infliximab was collected. The RESULTS report contains only long-term safety data and not integrated outcomes data from the primary study. This report can serve as a supplement to the primary study data to facilitate a comprehensive review of the overall infliximab safety profile.

Number of Subjects (planned and analyzed): RESULTS is an observational study; no study agent was administered. All subjects enrolled in selected Janssen-sponsored infliximab clinical studies that required long-term safety follow-up (ie, primary studies) were eligible to enroll in RESULTS.

Diagnosis and Main Criteria for Inclusion: All subjects enrolled in selected Janssen-sponsored infliximab clinical studies that required long-term safety follow-up (ie, primary studies). Primary studies are defined as Janssen-sponsored studies that evaluate infliximab on an investigational basis and that have been identified, a priori, by Janssen or health authorities as requiring long-term safety follow-up. Subjects must have received at least 1 dose of study agent to be eligible for participation in RESULTS.

Test Product, Dose and Mode of Administration, Batch No.: No study agent was administered.

Reference Therapy, Dose and Mode of Administration, Batch No.: No study agent was administered.

Duration of Treatment: All subjects were enrolled in RESULTS at the time of their last safety visit in the primary study and followed for up to 5 years.

Criteria for Evaluation: The primary endpoint was the number of subjects with each of the following long-term safety events: serious infections, new malignancies, new autoimmune diseases, death, or delayed hypersensitivity (serum sickness-like) reactions. Secondary endpoints were the number of subjects with malignancies by malignancy type (ie, lymphoma, nonmelanoma skin cancers, other malignancies), and the number of patients with serious infections by type of infection.

Statistical Methods: Data were summarized using descriptive statistics (eg, counts and percentages) and reported to regulatory authorities annually from 2003 through 2010. All subjects participating in this study and that provided long-term safety information were to be included in the tabulation. No hypothesis testing was performed.

RESULTS:

Of the 3811 subjects who were treated with placebo and/or infliximab in the primary studies, 1269 subjects currently had only "on-study" follow-up safety data. Subjects who were identified as having the on study follow-up status included subjects who 1) had completed or prematurely discontinued study treatment in the primary studies and had chosen not to participate in the long-term follow up program, or 2) had been lost to follow-up during primary studies. Thus, 2542 subjects enrolled in this study and had 8372 subject-years of follow-up.

Regardless of whether subjects received placebo or infliximab during the primary study, approximately one-third went on to receive commercial REMICADE. One notable exception was the subjects who participated in the pediatric Crohn's disease study; 86.8% of these subjects indicated that they received commercial REMICADE following the end of their primary study.

EFFICACY RESULTS: No efficacy data were collected during this study.

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS: No pharmacokinetic or pharmacodynamic data were collected during this study.

SAFETY RESULTS: The majority of deaths during long-term safety follow-up were cardiovascular in etiology or secondary to a malignancy, and occurred in similar frequency across the rheumatoid arthritis (RA) and psoriasis indications. There were no deaths in long term safety follow up for pediatric studies in juvenile rheumatoid arthritis (JRA) and Crohn's disease (CD). In general, data on therapy prior to the onset of the event is limited for subjects with death related to malignancy and, therefore, no conclusions can be drawn.

The majority of malignancies reported during the required long-term follow-up period were "other malignancies" (ie, malignancies excluding lymphomas and nonmelanoma skin cancers). Five subjects had non-Hodgkin's lymphoma during the long-term follow-up period. Three of the 5 lymphomas occurred in RA subjects for whom there is an increased risk of lymphoma. Most of the nonmelanoma skin cancers occurred in the psoriasis population, which is often treated with UV phototherapy.

The types of serious infections reported during long-term safety follow-up are consistent with those observed during the clinical trials of infliximab. The most common serious infections were pneumonia and abscesses. One case of mycobacterium abscess was reported in a subject who was receiving immunosuppressants and corticosteroids prior to the event. There were no apparent opportunistic infections reported.

Reported autoimmune events were also consistent with those reported during clinical trials of infliximab. The most common event reported was lupus erythematosus (LE) syndrome (11 subjects). There were also 3 reports of demyelinating events.

Consistent with data from clinical trials and the REMICADE prescribing information, delayed hypersensitivity reactions were observed during the long-term safety follow-up period. Most delayed hypersensitivity reactions occurred between 0 and 6 months after the previous REMICADE administration.

STUDY LIMITATIONS: A confounding factor that hinders the interpretation of data reported during long-term follow-up is the variety of treatments the subjects could receive after completion of the primary study. It should be noted that approximately one-third of subjects in the group that received placebo during the primary study received commercial REMICADE during long-term follow up, with the dose and duration of treatment unknown. Limited information was obtained on therapy received prior to the onset of the safety event reported in long-term follow-up (ie, immunosuppressives, chemotherapeutic agents, immunomodulators, phototherapy, corticosteroids, and anti-TNFα agents other than REMICADE). In addition, the complete medication history was not collected, and the number of subjects who received other commercially available anti-TNFα agents or experimental therapies is unknown. All these therapies could have influenced the incidence or severity of events reported in this long-term safety follow-up summary. Any interpretation of differences between the placebo and infliximab groups must take these disparities into account.

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