## SYNOPSIS

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| Name of Sponsor/Company | Janssen Research & Development, LLC* |
| Name of Investigational Product | C0168, REMICADE® (infliximab) |

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**Status:** Approved

**Date:** 20 July 2016

**Prepared by:** Janssen Research & Development, LLC

**Protocol No.:** C0168T62

**Title of Study:** Multicenter International Study of the Long-term Safety of Infliximab (REMICADE®) in Ulcerative Colitis

**Study Name:** RESULTS UC: REMICADE Safety Under Long-term Study in Ulcerative Colitis

**Clinical Registry No.:** CR004801

**NCT No.:** NCT00207688

**Principal Investigator(s):** Not applicable

**Study Centers:** One hundred and eight sites participated in RESULTS UC and all enrolled at least 1 subject at 56 sites in North America and 52 sites outside of North America (including 34 in Austria, Belgium, Denmark, France, Germany, Italy, The Netherlands, Switzerland, and the UK).

**Publication (Reference):** Not applicable

**Study Period:** 24 September 2003 through 09 September 2015

**Phase of Development:** 4

**Objectives:** To evaluate long-term safety information of infliximab in subjects who participated in clinical studies of infliximab for ulcerative colitis (UC).

**Methodology:** Multicenter, international, long-term safety follow-up study.

**Number of Subjects Analyzed:** (For safety only): 505

**Diagnosis and Main Criteria for Inclusion:** To be eligible for participation in RESULTS UC, subjects had to have been enrolled in ACT 1 (C0168T37) or ACT 2 (C0168T46) or their extensions, or C0168T72 (these were the primary studies). Subjects no longer enrolled in ACT 1 or ACT 2 (or their extensions), or C0168T72 were allowed to enroll in this study. Moreover, subjects had to have received at least 1 dose of study agent (placebo or infliximab) in the primary study. During follow-up, subjects could receive concomitant medications, including commercial REMICADE, according to their physician's judgment.

**Test Product, Dose and Mode of Administration, Batch No.:** Not applicable.

**Reference Therapy, Dose and Mode of Administration, Batch No.:** Not applicable.

**Duration of Treatment:** Not applicable. All subjects were to begin active participation in RESULTS UC at the time of their last safety visit in ACT 1 (C0168T37) or ACT 2 (C0168T46) or their extensions, or C0168T72, and followed for up to 5 years.

**Criteria for Evaluation:** No efficacy or clinical pharmacology data was collected. Safety analyses were performed on all subjects in the studies in adults, and the C0168T72 study in pediatric subjects (ie, subjects who received at least 1 dose of study agent [partial or complete]) who entered RESULTS UC and had follow-up data according to the actual treatment received in the primary study (placebo or infliximab). Safety was assessed by summarizing the number of subjects with each of the following long-term safety events: deaths, serious infections within 1 year of the last visit in the primary study, new malignancies (including colorectal cancer), new autoimmune diseases, probable delayed hypersensitivity (serum-like sickness) reactions, dysplasia of the colon in subjects identified at high risk for colon cancer, surgical procedures (including colectomy) and hospitalizations for the treatment of UC.

**Statistical Methods:** No hypothesis testing was performed. Data summaries were provided for each treatment group (placebo or infliximab). For categorical variables, counts and percentages were used to describe the data. Tabular displays and listings were used to summarize the data.

**RESULTS:** There were 505 total subjects enrolled in RESULTS UC, 358 who had received infliximab in the primary study and 147 who had received placebo. Forty-six of the 358 infliximab-treated subjects entered RESULTS UC from a pediatric study. The majority of subjects (83%) completed the planned 5 years of follow-up. The total subject-years of follow-up were 1,662 for the infliximab group and 695 for the placebo group.

Demographic characteristics were similar for subjects in the placebo and infliximab groups. Of the 505 subjects who participated in RESULTS UC, 284 were men and 221 were women. The majority of subjects were Caucasian. The median age of subjects upon entry in the primary study was 37 years in both the infliximab and the placebo groups.

SAFETY RESULTS:

The safety events that were reported in this long-term safety-follow-up (deaths, serious infections within 1 year of the last visit in the primary study, new malignancies [including colorectal cancer], new autoimmune diseases, probable delayed hypersensitivity [serum-like sickness] reactions, dysplasia of the colon in subjects identified at high risk for colon cancer, surgical procedures [including colectomy] and hospitalizations for the treatment of UC) are summarized in the table below, by the treatment received in the primary study. Note that 165 (46.1%) subjects in the infliximab group and 59 (40.1%) subjects in the placebo group also received commercial REMICADE during follow-up. A summary of the safety results are below, for all subjects in the infliximab group (including the pediatric subjects from C0168T72) and subjects in the placebo group, as assigned in the primary studies.

- A similar proportion of subjects in each group died during long-term follow-up: 8 subjects (2.2%) in the total infliximab group and 3 (2.0%) in the placebo group. One additional death in each group was reported beyond the 5-year follow-up period. There were no deaths among pediatric subjects. In the infliximab group, among the 8 subjects who died during the follow-up period, deaths were due to suicide, prostate cancer, pneumonia, an unknown reason, listeria encephalitis, colorectal cancer, glioblastoma, and a motor vehicle accident. The fatal listeria encephalitis case was reported 36 months after the last infliximab study infusion, and outside of the window for reporting serious infections. The 3 subjects in the placebo group who died during follow-up died of septic complications due to HIV (1 death), and unknown reasons (2 deaths).

- The overall malignancy rate including NMSC was generally comparable in the infliximab group than in the placebo group during the long-term follow-up period: 18 (5.0%) subjects in the infliximab group compared with 4 (2.7%) in the placebo group. There were no reported malignancies among pediatric subjects. There were no cases of lymphoma, Merkel cell carcinoma, HSTCL, or leukemia in the infliximab group. Among the 14 infliximab subjects with a malignancy other than NMSC (3.9%), 6 had colon cancer, 2 had prostate cancer, 2 had melanoma, and there was 1 reported case each of "carcinoid of appendix", DALM, glioblastoma, and intraepidermal carcinoma. Six of the 14 subjects received commercial REMICADE during follow-up. In the placebo group, among the 3 subjects with a malignancy other than NMSC (2.0%) during long-term follow-up, 1 case each of bladder cancer, prostate cancer, and lymphoma were reported; these subjects did not receive commercial REMICADE. None of the 59 subjects initially treated with placebo and who subsequently received commercial REMICADE reported a malignancy.
- The rate of colonic dysplasia identified on biopsy in adult subjects at high risk for dysplasia was higher in the infliximab group (15.9%) compared to placebo (5.3%).
- Comparable proportions of subjects in the total infliximab group reported a serious infection (1.4%) compared with subjects in the placebo group (3.4%) during the long-term follow-up period (through 1 year after the last visit in the primary study), which was 5 subjects in each group. In the infliximab group, 4 subjects had a non-specified bacterial or viral infection and 1 subject had both cholecystitis and pancreatitis. In the placebo group, 1 subject each was reported with sepsis, abscess, viral infection, cellulitis, and wound infection as well as intestinal perforation (these last 2 subjects [cellulitis and wound infection] received commercial REMICADE). There were no reports of opportunistic infections or tuberculosis during the reporting period for serious infections.
- Similar proportions of subjects in each group reported an autoimmune disorder during the long-term follow-up period: 13 (3.6%) in the total infliximab group and 5 (3.4%) in the placebo group. In the infliximab group, the autoimmune disorders reported were: 2 cases of Crohn's disease, 2 cases of psoriasis, and 1 case each of RA, lupus-like syndrome ("Le syndrome"), sicca syndrome, polyneuropathy, hepatitis, thrombocytopenic purpura, sarcoidosis, renal failure, and thrombopenic thrombotic purpura. Three of the 13 subjects received commercial REMICADE. The 5 subjects in the placebo group reported RA (2 subjects), and biliary tract inflammation, hearing decreased, and fibromyalgia, each reported in 1 subject. All but 1 subject with RA received commercial REMICADE.
- Generally comparable proportions of subjects receiving commercial REMICADE during long-term follow-up who were reported to have a probable delayed hypersensitivity reaction ranging from 3.0% to 6.8%: 5 (3.0%) subjects in the total infliximab group and 4 (6.8%) in the placebo group.
- A total of 96 subjects (26.8%) in the total infliximab group (81 adults and 15 pediatric subjects) and 45 subjects (30.6%) in the placebo group underwent UC-related surgery. All but 1 subject (in the placebo group) were hospitalized for the UC-related surgery. Furthermore, 48 (13.4%) subjects in the total infliximab group and 18 (12.2%) subjects in the placebo group were hospitalized for nonsurgical UC treatment.
- Data for 46 pediatric subjects who entered RESULTS UC from C0168T72 are included in the data for the infliximab group cited above; when evaluated separately, there were no deaths or malignancies reported in the long-term follow-up. There was 1 report of serious infection, and 3 reports of autoimmune disease (Crohn's disease and psoriasis). Among 29 of the pediatric subjects who received commercial REMICADE, 1 had a probable delayed hypersensitivity reaction.

Number (%) of Subjects with Safety Events During Long-Term Safety Follow-up

| Event | Placebo | Infliximab |
|---|---|---|
| Subjects enrolled/with long-term follow-up | 147 | 358 |
| Deaths | 3 (2.0) | 8 (2.2) |
| Malignancies[a] | 4 (2.7) | 18 (5.0) |
| Non-melanoma skin cancer | 1 (0.7) | 6 (1.7) |
| Lymphoma | 1 (0.7) | 0 |
| Other | 2 (1.4) | 14 (3.9) |
| Serious infections | 5 (3.4) | 5 (1.4) |
| Autoimmune disorders | 5 (3.4) | 13 (3.6) |
| Probable delayed hypersensitivity reactions[b] | 4/59 (6.8) | 5/165 (3.0) |
| UC-related surgeries | 45 (30.6) | 96 (26.8) |
| Hospitalization for surgeries | 44 (29.9) | 96 (26.8) |
| Dysplasia[c] | 2 (5.3) | 17 (15.9) |

UC = ulcerative colitis

a: Two subjects in the infliximab group had more than 1 event.

b: Denominator is total subjects who received commercial REMICADE.

c: Denominator is total subjects considered to be at high risk of colon cancer.

STUDY LIMITATIONS: By design, this follow-up safety study has limitations including: lack of information on timing, duration, and dose of commercial REMICADE, and lack of data on concomitant medications received during follow-up in both the infliximab and placebo groups. Some subjects, including the subjects originally treated with placebo in the primary studies and counted in the "placebo" group in the data presentations, may have received commercial REMICADE as well as other treatments.

CONCLUSIONS: The observations of serious infections (including opportunistic infections), malignancies (including lymphoma, leukemia, HSTCL, and melanoma), autoimmune disorders, intestinal dysplasia, and probable delayed hypersensitivity reactions from this long-term follow-up for infliximab are consistent with data from other clinical studies and other known safety information for REMICADE. Overall, the results of this study did not reveal any new safety concerns associated with REMICADE treatment in adult or pediatric subjects with UC.

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