SYNOPSIS

Issue Date: 24 Sep 2010

Name of Sponsor/Company	**Centocor Research & Development, Inc.**
Name of Finished Product	REMICADE®
Name of Active Ingredient(s)	Infliximab

Protocol No.: C0168T72

Title of Study: A Phase 3, Randomized, Open-label, Parallel-group, Multicenter Trial to Evaluate the Safety and Efficacy of Infliximab (REMICADE®) in Pediatric Subjects with Moderately to Severely Active Ulcerative Colitis

EudraCT Number: 2006-000410-20

Coordinating Investigator: Jeffrey S. Hyams, MD, Connecticut Children's Medical Center, Hartford, CT, USA

Publication (Reference): None

Study Period: 25 Aug 2006—24 Jun 2010; database lock16 Jul 2010

Phase of Development: Phase 3

Objectives: Primary: To evaluate the efficacy of a 3-dose induction regimen of infliximab in inducing clinical response, as measured by the Mayo score, in pediatric subjects with moderately to severely active ulcerative colitis (UC), and to evaluate the safety profile of infliximab during induction and maintenance treatment. Secondary: To evaluate the efficacy of 2 infliximab maintenance dosing regimens (every 8 or every 12 weeks) in maintaining remission, as measured by the Pediatric Ulcerative Colitis Activity Index (PUCAI) score; to evaluate the efficacy of a 3-dose induction regimen of infliximab in inducing clinical remission, as measured by the Mayo score and the PUCAI score; and to evaluate the efficacy of a 3-dose induction regimen of infliximab in inducing mucosal healing.

Methods: This was a Phase 3 open-label study of infliximab in pediatric subjects with moderately to severely active UC. All subjects received a 3-dose infliximab induction regimen at Weeks 0, 2, and 6; at Week 8, subjects who met criteria for response were randomly assigned in a 1:1 ratio to receive infliximab 5 mg/kg in a maintenance treatment regimen, either every 8 weeks (q8w) through Week 46 or every 12 weeks (q12w) through Week 42. Subjects who were not in response at Week 8 returned for safety evaluations and received no further infusions. Randomized subjects who lost response could have their dose or dose frequency increased (step-up). Subjects had to be receiving or have failed to respond to 5-ASA compounds, immunomodulators, or oral or IV corticosteroids at screening. Efficacy and safety evaluations were performed through Week 54 for subjects in both groups; the presence of antibodies to infliximab was evaluated in blood samples collected at an additional visit at Week 62.

Number of Subjects (planned and analyzed): Planned enrollment was 60 subjects; 60 subjects were enrolled and included in the primary efficacy endpoint analysis and the safety analyses; all endpoints evaluated at or before the Week 8 visit were also based on all 60 treated subjects. At Week 8, 45 subjects were randomized to 1 of 2 maintenance treatment regimens.

Diagnosis and Main Criteria for Inclusion: Male or female subjects, aged 6 to 16 or 17 years (depending on the study site), with moderately to severely active UC (defined as a baseline Mayo score of 6 to 12) diagnosed at least 2 weeks before screening and confirmed by biopsy and a screening Mayo endoscopy subscore ≥ 2. Subjects also had to be receiving adequate treatment with, have failed to respond to an adequate dose of, or had medical complications or AEs from treatment with 5-ASA compounds, immunomodulators, or oral or IV corticosteroids.

Test Product, Dose and Mode of Administration, Batch No.: Infliximab was supplied as a sterile, white, lyophilized powder in single-use, 20 mL glass vials (lot numbers 05C153 and 7JM18011; also commercial REMICADE). Infliximab was administered by infusion over a period of not less than 2 hours, using an infusion pump, via a separate line using an administration set with a (supplied) 1.2 micron (or smaller) filter.

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

Duration of Treatment: Infliximab 5 mg/kg was administered by IV infusion as an induction regimen at Weeks 0, 2, and 6. Subjects in clinical response at Week 8, as measured by the Mayo score, were to be randomized in a 1:1 ratio to receive 1 of 2 maintenance treatment regimens: 5 mg/kg infliximab administered q8w through Week 46 or q12w through Week 42. Subjects who were not in clinical response at Week 8 returned for safety evaluations and received no further infusions.

Criteria for Evaluation:

- Pharmacokinetics: Infliximab concentrations and antibodies to infliximab.
- Pharmacodynamics: Serum samples for inflammatory biomarkers; biopsy samples for expression of HLA-DR and tenascin; serum and first morning void urine samples for markers associated with bone formation and resorption.
- Efficacy: Efficacy evaluations included the Mayo score; PUCAI score; sigmoidoscopy; CRP; subject, parent/guardian, and physician global assessments; IMPACT III; autoantibody response by treatment group. Efficacy criteria included clinical response based on the Mayo score (decrease from baseline in the Mayo score by $\geq 30\%$ and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore ≥ 1 or a rectal bleeding subscore of 0 or 1), clinical remission based on the Mayo score (a Mayo score ≤ 2 points, with no individual subscore > 1), remission based on the PUCAI score (PUCAI < 10), and mucosal healing (an endoscopy subscore of 0 or 1).
- Safety: Assessment of AEs and laboratory test results, including antinuclear antibodies (ANA), and anti-dsDNA antibodies.

Statistical Methods: Categorical data were summarized using counts and percentages. Comparisons between the 2 maintenance treatment groups that involve categorical data were analyzed using the chi-square test. Continuous variables were summarized using descriptive statistics (ie, mean, median, standard deviation, interquartile range, range). Analysis populations included all treated subjects for analyses of efficacy endpoints at or before Week 8, and all randomized subjects for analyses of efficacy endpoints after Week 8. All subjects who received the Week 0 administration of study agent were included in the PK and safety analyses; analyses were based on the actual treatment received. No interim analysis was planned or performed. All statistical testing was performed at the $\alpha = 0.05$ (2-sided) level using SAS version 9.1.

RESULTS:

Subject and Treatment Information:

- A total of 60 subjects were enrolled at 23 sites in the United States, Canada, the Netherlands, and Belgium; at Week 8, 45 were randomized as responders (22 and 23 in the q8w and q12w maintenance treatment groups, respectively) and the remaining 15 discontinued study agent.
- Of the 45 randomized subjects, 23 stepped up (ie, increased their dose or dosing frequency); more subjects stepped up in the q12w group than in the q8w group (60.9% vs. 40.9%).
- Demographics, baseline disease characteristics, and the percentage of subjects receiving concomitant UC medications were generally similar in the groups that were and were not randomized at Week 8 and between the maintenance treatment groups.

- Overall, 30 subjects (50.0%) permanently discontinued infliximab treatment: 15 subjects each in the groups that were and were not randomized to maintenance treatment at Week 8. A higher proportion of subjects discontinued study agent in the q12w group (47.8%) than in the q8w group (18.2%). Of the 23 subjects who stepped up, 11 (47.8%) discontinued study agent.

Pharmacokinetic and Pharmacodynamic Results:

- Median serum infliximab concentrations were maintained above detectable levels after 5 mg/kg infliximab q8w or q12w maintenance treatment doses.
- Median preinfusion serum infliximab concentrations during maintenance treatment in subjects who received 5 mg/kg infliximab q8w were generally higher than those in subjects receiving 5 mg/kg infliximab q12w.
- An increase in infliximab dose or dose frequency resulted in higher serum infliximab concentration levels in subjects who stepped up their dose regimen.
- Among 52 infliximab-treated subjects with appropriate samples for the assessment of antibodies to infliximab, 4 (7.7%) subjects were positive for antibodies to infliximab through Week 62, all with low antibody titers (1:10 to 1:40).
- The development of antibodies to infliximab did not appear to be the major determinant of either clinical response during induction treatment or loss of clinical response during maintenance therapy, although the number of subjects who were antibody-positive was small.
- Infliximab treatment decreased proinflammatory marker IL-8 and increased IL-12.
- Subjects who responded to infliximab had increased bone formation and decreased bone resorption.
- Serum infliximab concentrations did not appear to be impacted by concomitant immunomodulator use at Week 8.

Efficacy Results:

- Infliximab induced clinical response at Week 8 in 73.3% (44/60) of pediatric subjects with UC. The criterion for a positive study was met because the lower limit of the 95% CI for the proportion of subjects in clinical response at Week 8 in this study was 62.1% (ie, > 40%).
- The proportion of subjects achieving a clinical response at Week 8 was generally consistent across subgroups, particularly between subjects on infliximab monotherapy (75.0%) and concomitant immunomodulator therapy (71.9%).
- At Week 54, a greater proportion of subjects were in remission (as measured by the PUCAI score) in the 5 mg/kg q8w maintenance treatment group (38.1% [8/21]) than in the 5 mg/kg q12w maintenance treatment group (18.2% [4/22]).
- Infliximab induced clinical remission (as measured by the Mayo score) in 40.0% (24/60) of subjects at Week 8. Infliximab induced remission (as measured by the PUCAI score) in 33.3% (17/51) of subjects at Week 8.
- At Week 8, 68.3% (41/60) of subjects achieved mucosal healing and 33.3% had normal or inactive disease (as measured by endoscopy).
- Reductions in the PUCAI score and partial Mayo score were evident as early as Week 2 in the randomized subject groups. During the maintenance phase, the substantial reductions in the PUCAI score and the partial Mayo score observed at Week 8 were maintained in the q8w group but not in the q12w group.
- A substantial reduction in median corticosteroid use had occurred by Week 8 in both maintenance treatment groups; this reduction in corticosteroid use was maintained through Week 54 in the q8w group but not in the q12w group. More subjects who were on corticosteroids at baseline were in

remission at Week 54 and off corticosteroids at Week 54 and from Week 30 through Week 54 in the q8w group (5 of 13 subjects) than in the q12w group (0 of 13 subjects).

- In the 8 subjects who had a 1-year delay in bone age, an increase in height was observed, as measured by age- and gender-specific z-scores.
- Subjects who achieved higher serum infliximab concentrations at Week 8 appear to have had generally greater efficacy as measured by the Mayo score and the PUCAI score.

Safety Results:

- Infliximab was generally well tolerated by pediatric subjects with moderately to severely active UC. The safety profile appears to be consistent with that reported in other studies of infliximab.
- No deaths, malignancies, serious neurologic events, opportunistic infections, tuberculosis, or congestive heart failure were reported. No subjects had a possible delayed hypersensitivity reaction or anaphylactic reaction.
- Through Week 54, the proportions of subjects experiencing SAEs were similar across the maintenance treatment groups. No individual SAEs were reported in more than 1 subject in any treatment group except for worsening of UC.
- All subjects in the q8w and q12w maintenance treatment groups reported 1 or more AEs through Week 54; the system-organ class with highest incidence of AEs was gastrointestinal system disorders.
- Worsening of UC occurred in a greater proportion of subjects in the q12w maintenance treatment group than in the q8w maintenance treatment group.
- Through Week 54, more subjects in the q12w group discontinued study infusions because of an AE compared with the q8w group. In the q12w group, all subjects who discontinued infusions did so due to worsening UC.
- Five of the 60 treated subjects underwent a colectomy through 54 weeks after their first study administration (2 in the group not randomized at Week 8, 2 in the q12w group, and 1 in the q8w group).
- Through Week 54, similar numbers of subjects in the q8w and q12w groups had infections. Most infections required oral or parenteral antimicrobial treatment.
- AEs were classified as serious infections in 1 subject in the group that was not randomized at Week 8 (pneumonia), 3 subjects in the q8w group (infection of unknown origin, viral infection, and facial cellulitis) and 3 subjects in the q12w group (pharyngitis, worsening UC, and urinary tract infection).
- Few subjects developed markedly abnormal hematologic or chemistry laboratory values. The majority of the abnormal values occurred only transiently.
- The proportions of subjects experiencing infusion reactions were similar across the maintenance treatment groups and were not impacted by concomitant immunomodulator therapy. The proportion of infusions resulting in an infusion reaction was slightly higher in the q8w group (7.9%) compared with the q12w group (2.2%). Within the q8w group, fewer infusions associated with infusion reactions were reported in subjects on concomitant immunotherapy than in subjects on monotherapy.
- Antibodies to infliximab developed in 4 subjects; 1 of the 4 antibody-positive subjects experienced an infusion reaction through Week 54.

STUDY LIMITATIONS: No notable study limitations were identified by the sponsor.

CONCLUSIONS: Study C0168T72 provided clinically important evidence that infliximab was efficacious in pediatric subjects with UC, with efficacy consistent with that seen in adults. Specifically, in this 54-week study of infliximab administered at 5 mg/kg at Weeks 0, 2, and 6 and then every 8 or 12 weeks in pediatric subjects with moderate to severe UC, infliximab:

- Reduced the signs and symptoms of disease activity at Week 8. At Week 8, the proportions of pediatric subjects with UC in clinical response and remission were consistent with those seen in adult subjects with UC (ACT 1 and ACT 2 studies).
- Demonstrated that the q8w maintenance treatment regimen was more effective than the q12w maintenance treatment regimen in maintaining remission at Week 54.
- Demonstrated mucosal healing in the majority of subjects at Week 8.
- Allowed for a substantial reduction in median corticosteroid use by Week 8 that was maintained through Week 54 in the q8w maintenance treatment group, with 38.5% of subjects in remission and off steroids at Week 54.
- Demonstrated an overall incidence of 7.7% (4/52) of subjects positive for antibodies to infliximab through Week 62.
- Was not notably affected, in terms of reducing the signs and symptoms of UC, by the concomitant use of immunomodulators, nor were the pharmacokinetics of infliximab or the formation of antibodies to infliximab particularly affected by concomitant immunomodulator use.
- Was generally well tolerated in this population, with a safety profile consistent with that reported in other studies. There were no reports of deaths, malignancies, opportunistic infections, serious neurologic events, or TB and the safety profiles observed in the q8w and q12w maintenance treatment groups were similar.

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