PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrREMICADE®

Infliximab for injection

Powder for Solution, Sterile, Lyophilized, 100 mg/vial, Intravenous Infusion

Biological Response Modifier

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RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

REMICADE® (infliximab) is indicated for:

- use in combination with methotrexate for the reduction in signs and symptoms, inhibition of the progression of structural damage and improvement in physical function in adult patients with moderately to severely active rheumatoid arthritis.

- the reduction of signs and symptoms and improvement in physical function in patients with active ankylosing spondylitis who have responded inadequately, or are intolerant to, conventional therapies.

- reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing and reduction of corticosteroid use in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to a corticosteroid and/or aminosalicylate. Remicade® can be used alone or in combination with conventional therapy.

- reduction of signs and symptoms and induction and maintenance of clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy (corticosteroid and/or aminosalicylate and/or an immunosuppressant). The safety and efficacy of Remicade® is not established in patients less than 9 years of age.

- treatment of fistulising Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment.

- reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction or elimination of corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant).

- reduction of signs and symptoms, induction and maintenance of clinical remission, and induction of mucosal healing in pediatric patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant). The safety and efficacy of Remicade® have not been established in patients less than 6 years of age.

- reduction of signs and symptoms, induction of major clinical response, and inhibition of the progression of structural damage of active arthritis, and improvement in physical function in patients with psoriatic arthritis.

- treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, Remicade® should be used after phototherapy has been shown to be ineffective or inappropriate. When assessing the severity of psoriasis, the health professional should

consider the extent of involvement, location of lesions, response to previous treatments, and impact of disease on the patient's quality of life.

Remicade® should be used by health professionals who have sufficient knowledge of rheumatoid arthritis and/or ankylosing spondylitis and/or Crohn's disease, ulcerative colitis and/or psoriatic arthritis and/or plaque psoriasis and who have fully familiarized themselves with the efficacy/safety profile of Remicade®.

1.1 Pediatrics

Pediatrics (6-17 years of age): Remicade® is indicated for reducing signs and symptoms and for inducing and maintaining clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Remicade® is also indicated for reducing signs and symptoms, inducing and maintaining clinical remission and inducing mucosal healing in pediatric patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant). In general, the adverse events in pediatric patients with Crohn's disease or ulcerative colitis who received Remicade® were similar to those seen in adult patients with Crohn's disease or ulcerative colitis respectively. It should be noted that in the Phase 3 trial (REACH) of pediatric patients with Crohn's disease, all patients were required to be on a stable dose of either 6-mercaptopurine (6-MP), azathioprine (AZA), or methotrexate (MTX). (See 1 INDICATIONS, 7.1.3 Pediatrics, 8.2.1 Clinical Trial Adverse Reactions - Pediatrics, 4 DOSAGE AND ADMINISTRATION and 14 CLINICAL TRIALS.)

The safety and efficacy of Remicade® has not been established in pediatric patients with Crohn's disease <9 years of age or with ulcerative colitis <6 years of age. The safety and efficacy of Remicade® in pediatric patients with plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, and in juvenile rheumatoid arthritis have not been established.

1.2 Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies suggests that the use in geriatric population is associated with no overall differences in safety and efficacy.

In rheumatoid arthritis clinical trials (ATTRACT) and plaque psoriasis trials, no overall differences were observed in the effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque psoriasis, aged 65 or older compared to younger patients although the incidence of serious adverse events in patients aged 65 or older was higher in both Remicade® and control groups compared to younger patients. In Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 64. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly (see 8.2 Clinical Trial Adverse Reactions, **Infections**).

2 CONTRAINDICATIONS

- Patients with severe infections such as sepsis, abscesses, tuberculosis and opportunistic infections (see 7 WARNINGS AND PRECAUTIONS, **Risk of Infections**).

- Patients with moderate or severe (NYHA Class III/IV) congestive heart failure (see 7 WARNINGS AND PRECAUTIONS, **Cardiovascular** and 8.2 Clinical Trial Adverse Reactions, **Congestive Heart Failure**).

- Patients with a history of hypersensitivity to infliximab, to other murine proteins, or to any of the excipients. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

RISK OF INFECTIONS

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving Remicade®. Some of these infections have been fatal.

Patients must be evaluated for the risk of tuberculosis, including latent tuberculosis, prior to initiation of Remicade®. This evaluation should include a detailed medical history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e. tuberculin skin test and chest x-ray (if indicated), should be performed in all patients. Prescribers are reminded of the risk of false negative tuberculin skin test results especially in patients who are severely ill or immunocompromised. Treatment of latent tuberculosis infection should be initiated prior to therapy with Remicade® (see 7 WARNINGS AND PRECAUTIONS, **Risk of Infections**).

Hepatosplenic T-cell Lymphoma

Postmarketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF-blockers including Remicade®. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with or immediately prior to a TNF-blocker. The vast majority of Remicade® cases have occurred in patients with Crohn's disease or ulcerative colitis and most were reported in adolescent or young adult males (see 7 WARNINGS AND PRECAUTIONS, **Carcinogenesis and Mutagenesis**).

Pediatric Malignancy

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF-blockers, including Remicade® (see 7 WARNINGS AND PRECAUTIONS, **Carcinogenesis and Mutagenesis**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The infusion solution must be administered over a period of not less than 2 hours, except as noted in 4.4 Administration.

All patients administered Remicade® should be observed for at least 1-2 hours post-infusion for side effects. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available (see 8.2 Clinical Trial Adverse Reactions, **Infusion-related Reactions**).

At the discretion of the treating healthcare professional, treatment with Remicade® may be delayed if the patient has a planned surgical procedure (see risk of post-procedural complication in 8.5 Post-Market Adverse Reactions), considering the long half-life of infliximab.

The BioAdvance® Network has been established to facilitate the administration of Remicade®. BioAdvance® Network clinics are staffed by qualified healthcare professionals specially trained in the administration of Remicade® infusions and are available across Canada. Information about the BioAdvance® Network and location of the nearest BioAdvance® Network clinic can be obtained by calling Janssen Inc. Medical Information at: 1-800-567-3331.

4.2 Recommended Dose and Dosage Adjustment

For recommended intravenous infusion duration for patients with each of the indications described below, see 4.4 Administration.

Rheumatoid Arthritis
The recommended dose of Remicade® is 3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. Remicade® should be given in combination with methotrexate. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg and/or treating as often as every 4 weeks. Duration of treatment needed to achieve a response after dose escalation is not known. However, higher doses of Remicade® were associated with a slightly higher proportion of patients experiencing adverse events (97% for the 3 mg/kg dose given every 8 weeks vs. 100% for the 10 mg/kg dose given every 4 weeks), including infections (84% for the 3 mg/kg dose given every 8 weeks vs. 91% for the 10 mg/kg dose given every 4 weeks).

Ankylosing Spondylitis
The recommended dose of Remicade® is 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks thereafter.

Ulcerative Colitis
The recommended dose of Remicade® is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by 5 mg/kg every 8 weeks thereafter, for the treatment of adults and pediatric patients (≥6 years of age) with moderately to severely active ulcerative colitis. In some adult patients, consideration may be given to adjusting the dose up to 10 mg/kg to sustain clinical response and remission. Some adult patients may not benefit from dose escalation. In addition to the health professional's clinical assessment, measurement of infliximab trough levels and titers of antibodies to infliximab should be taken into account before considering dose adjustment.

Crohn's Disease
Adults:
The recommended dose of Remicade® is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderate to severe, active Crohn's disease. For patients who have an incomplete

response, consideration may be given to adjusting the dose up to 10 mg/kg. Some adult patients may not benefit from dose escalation. In addition to the health professional's clinical assessment, measurement of infliximab trough levels and titers of antibodies to infliximab should be taken into account before considering dose adjustment.

The recommended dose of Remicade® is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of fistulising Crohn's disease. Patients who do not respond by Week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue Remicade® in these patients. For patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. In the ACCENT II clinical study, among patients who lost response at 5 mg/kg Remicade® and re-established response following dose escalation to 10 mg/kg Remicade®, most had done so after 1 dose and all had done so after 2 doses of 10 mg/kg.

Pediatric:
The recommended dose of Remicade® for pediatric patients (≥ 9 years of age) with moderately to severely active Crohn's disease is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. Patients who do not respond by week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue Remicade® in these patients.

Psoriatic Arthritis
The recommended dose of Remicade® is 5 mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. Remicade® can be used with or without methotrexate. If a patient shows no response at 24 weeks, no additional treatment with Remicade® should be given.

Plaque Psoriasis
The recommended dose of Remicade® is 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient does not show an adequate response at Week 14, after infusions at weeks 0, 2, and 6, no additional treatment with Remicade® should be given.

Special Populations

Renal Impairment

Remicade® has not been studied in patients with renal impairment. No dose recommendations can be made (see 10.3 Pharmacokinetics, **Special Populations and Conditions**).

Hepatic Impairment

Remicade® has not been studied in patients with hepatic impairment. No dose recommendations can be made (see 10.3 Pharmacokinetics, **Special Populations and Conditions**).

4.3 Reconstitution

Table 1: Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
100 mg as lyophilized powder	10 mL Sterile water for injection, USP	250 mL The total volume of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP	Between 0.4 mg/mL and 4 mg/mL

Since no preservative is present, it is recommended that the Remicade® infusion be started within 3 hours of reconstitution and dilution unless the Remicade® infusion is prepared under controlled and validated aseptic conditions (see 11 STORAGE, STABILITY AND DISPOSAL, **After Reconstitution and Dilution** and **Handling Under Controlled and Validated Aseptic Conditions**).

4.4 Administration

Use aseptic technique.

Remicade® vials do not contain antibacterial preservatives. Therefore, after reconstitution, the vials should be used immediately, not re-entered or stored. The diluent to be used for reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The infusion concentration should range between 0.4 mg/mL and 4 mg/mL. Since no preservative is present, it is recommended that the Remicade® infusion be started within 3 hours of reconstitution and dilution.

1. Calculate the dose and the number of Remicade® vials needed. Each Remicade® vial contains 100 mg of infliximab. Calculate the total volume of reconstituted Remicade® solution required.

2. Reconstitute each Remicade® vial with 10 mL of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the centre of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. The solution should be colourless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if opaque particles, discolouration, or other foreign particles are present.

3. Dilute the total volume of the reconstituted Remicade® solution dose to 250 mL with 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of reconstituted Remicade® from the 0.9% Sodium

Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted Remicade® solution to the 250 mL infusion bottle or bag. Gently mix. For volumes greater than 250 mL, either use a larger infusion bag (e.g. 500 mL, 1000mL) or use multiple 250 mL infusion bags to ensure that the concentration of the infusion solution does not exceed 4 mg/mL.

4. For patients with ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis, the infusion solution must be administered over a period of not less than 2 hours.

   For patients with rheumatoid arthritis, the recommended infusion duration is over a period of not less than 2 hours in patients not previously treated with Remicade®. At the discretion of the treating health professional, some patients with rheumatoid arthritis who have tolerated 3 initial 2-hour infusions of Remicade® may be considered for receiving subsequent infusions at the same dose over a period of not less than 1 hour (see 14.1 Clinical Trials by Indication, **Rheumatoid Arthritis** and 8.2 Clinical Trial Adverse Reactions, **Infusion-related Reactions**). The safety of shortened infusions at doses >6 mg/kg has not been studied.

   For pediatric and adult patients with Crohn's disease or ulcerative colitis, the recommended infusion duration is over a period of not less than 2 hours. At the discretion of the treating health professional, adult patients with Crohn's disease or ulcerative colitis who have tolerated at least 3 consecutive 2-hour infusions of Remicade® may be considered for receiving subsequent infusions of the 5 mg/kg dose over a period of not less than 1 hour (see 8.2 Clinical Trial Adverse Reactions, **Infusion-related Reactions**). For patients receiving the 10 mg/kg dose, administration should still occur over a period of not less than 2 hours.

   Use only an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less). Do not store any unused portion of the infusion solution for reuse.

5. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. If visibly opaque particles, discolouration or other foreign particulates are observed, the solution should not be used.

6. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of Remicade® with other agents. Remicade® should not be infused concomitantly in the same intravenous line with other agents.

4.5 Missed Dose

Patients who forget or miss an appointment to receive Remicade® should be advised to make another appointment as soon as possible.

5 OVERDOSAGE

Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous injection	Powder for Solution / 100 mg/vial	Dibasic sodium phosphate dihydrate, monobasic sodium phosphate monohydrate, polysorbate 80, sucrose

Remicade® (infliximab) is supplied as a sterile white lyophilized powder for intravenous infusion. Each vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate and 6.1 mg dibasic sodium phosphate, dihydrate. No preservatives are present.

Remicade® (infliximab) lyophilised concentrate for IV injection is supplied in individually-boxed single-use vials in the following strength: 100 mg infliximab.

Vial stopper is free of natural rubber latex.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General
Remicade® should be used by health professionals who have sufficient knowledge of rheumatoid arthritis and/or ankylosing spondylitis and/or Crohn's disease, ulcerative colitis and/or psoriatic arthritis and/or plaque psoriasis and who have fully familiarized themselves with the efficacy/safety profile of Remicade®.

In order to improve the traceability of biological medicinal products, the trademark and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Risk of Infections

Serious infections due to bacterial (including sepsis and pneumonia), invasive fungal, viral, and other opportunistic pathogens, have been reported in patients receiving TNF-blocking agents. Some of these infections have been fatal. Many of the serious infections in patients treated with Remicade® (infliximab) have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections.

Remicade® should not be given to patients with a clinically important, active infection, including tuberculosis. Caution should be exercised when considering the use of Remicade® in patients with a chronic infection or a history of recurrent infection. Patients should be monitored for signs and symptoms of infection while on or after treatment with Remicade®. New infections should be closely monitored. If a patient develops a serious infection, Remicade® therapy should be discontinued (see 8.2 Clinical Trial Adverse Reactions**, Infections).**

Cases of histoplasmosis, coccidioidomycosis, blastomycosis, listeriosis, pneumocystosis, and tuberculosis have been observed in patients receiving Remicade®. For patients who have resided in or travelled to regions where histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of Remicade® treatment should be carefully considered before initiation or continuation of Remicade® therapy.

Invasive Fungal Infections:

In patients treated with Remicade®, an invasive fungal infection such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if they develop a serious systemic illness. Invasive fungal infections may present as disseminated rather than localized disease, and antigen and antibody testing may be negative in some patients with active infection. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. The decision to administer empiric antifungal therapy should be made in consultation with a health professional with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

Tuberculosis:

Cases of active tuberculosis have occurred in patients treated with Remicade during and after treatment for latent tuberculosis. Patients receiving Remicade® should be monitored closely for signs and symptoms of active tuberculosis during and after treatment, including patients who tested negative for latent tuberculosis infection. The possibility of undetected latent tuberculosis should be considered, especially in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or had close contact with a person with active tuberculosis. All patients treated with Remicade® should have a thorough history taken prior to initiating therapy. Some patients who have previously received treatment for latent or active tuberculosis have developed active tuberculosis while being treated with Remicade®. Anti-tuberculosis therapy should be considered prior to initiation of Remicade® in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Anti-tuberculosis therapy prior to initiating Remicade® should also be considered in patients who have several or highly significant risk factors for tuberculosis infection and have a negative test for latent tuberculosis. The decision to initiate anti-tuberculosis therapy in these patients should only be made following consultation with a health professional with expertise in the treatment of tuberculosis and taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy.

Opportunistic Infections:

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis,

histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF-blockers, including Remicade®. Patients have frequently presented with disseminated rather than localized disease.

Concurrent Administration of TNF-alpha Inhibitor and Anakinra:

Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNFα-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNFα-blocking agents. Therefore, the combination of Remicade® and anakinra is not recommended.

Concurrent Administration of Remicade® with Abatacept:

In clinical studies, concurrent administration of TNF-blocking agents and abatacept has been associated with an increased risk of infections including serious infections compared with TNF-blocking agents alone, without increased clinical benefit. Because of the nature of the adverse events seen with the combination of TNF-blocking agents and abatacept therapy, the combination of Remicade® and abatacept is not recommended.

Concurrent Administration with other Biological Therapeutics:

There is insufficient information regarding the concomitant use of Remicade® with other biological therapeutics used to treat the same conditions as Remicade®. The concomitant use of Remicade® with these biologics is not recommended because of the possibility of an increased risk of infection.

Switching between Biological Therapeutics:

When switching from one biologic to another, patients should continue to be monitored, since overlapping biological activity may further increase the risk of infection.

Carcinogenesis and Mutagenesis

Pediatric malignancy

Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤18 years of age), including Remicade®. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF-blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous post-marketing reports.

Lymphoma

Lymphomas have been observed in patients treated with TNF-blocking agents, including

Remicade®. In clinical trials, patients treated with infliximab had a higher incidence of lymphoma than the expected rate in the general population. Patients with rheumatoid arthritis and Crohn's disease, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) for the development of lymphoma than the general population, even in the absence of TNF-blocking therapy. The role of TNF-blockers in the development of malignancy is not known.

Hepatosplenic T-cell lymphoma

Post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF-blockers including Remicade®. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with or immediately prior to a TNF-blocker. The vast majority of Remicade® cases have occurred in patients with Crohn's disease or ulcerative colitis and most were reported in adolescent or young adult males. Cases of hepatosplenic T-cell lymphoma have also occurred in Crohn's disease and ulcerative colitis patients receiving azathioprine or 6-mercaptopurine who were not treated with Remicade®. Before initiating or continuing Remicade® therapy in a patient who is receiving an immunosuppressant such as azathioprine or 6-mercaptopurine, carefully assess the need for continuing the immunosuppressant therapy in light of the potential risks of concomitant treatment. The causal relationship of hepatosplenic T-cell lymphoma to Remicade® therapy remains unclear.

Leukemia

Cases of acute and chronic leukemia have been reported with post-marketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Non-lymphoma malignancy

In the controlled portions of clinical trials of some TNF-blocking agents, including Remicade®, more malignancies (excluding lymphoma and non-melanoma skin cancer [NMSC]) have been observed in patients receiving those TNF-blockers compared with control patients (see 8.2 Clinical Trial Adverse Reactions, **Malignancies/Lymphoproliferative Disease**). The rate of non-lymphoma malignancies among Remicade®-treated patients was similar to that expected in the general population whereas the rate among control patients was lower than expected.

In an exploratory clinical trial evaluating the use of Remicade® in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies were reported in Remicade®-treated patients compared with control patients. All patients had a history of heavy smoking.

Cervical cancer

A population-based retrospective cohort study using data from Swedish national health registries found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age. A causal relationship between infliximab and cervical cancer cannot be excluded. Periodic screening should continue in women treated with Remicade®, including those over 60 years of age.

Skin cancers

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocker therapy, including Remicade® (see 8.5 Post-Market Adverse Reactions). Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Psoriasis patients should be monitored for nonmelanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for Remicade®, NMSCs were more common in patients with previous phototherapy (see 8.2 Clinical Trial Adverse Reactions, **Malignancies/Lymphoproliferative Disease**).

The potential role of TNF-blocking therapy in the development of malignancies is not known. Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy (see 8.2 Clinical Trial Adverse Reactions, **Malignancies/Lymphoproliferative Disease**).

Long-term studies in animals have not been performed to evaluate the carcinogenic potential. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella–Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. Tumourigenicity studies in mice deficient in TNFα demonstrated no increase in tumours when challenged with known tumour initiators and/or promoters.

Cardiovascular

Doses greater than 5 mg/kg should not be administered to patients with congestive heart failure (CHF). Remicade® should be used with caution in patients with mild heart failure (NYHA Class I/II). Patients should be closely monitored, and Remicade® must not be continued in patients who develop new or worsening symptoms of heart failure (see 2 CONTRAINDICATIONS and 8.2 Clinical Trial Adverse Reactions, **Congestive Heart Failure**). The results of a randomized study evaluating the use of Remicade® in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg Remicade®, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg.

Driving and Operating Machinery

Remicade® may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of Remicade®.

Hematologic

There have been reports of pancytopenia, leukopenia, neutropenia, and thrombocytopenia in patients receiving TNF-blockers, including Remicade®. Caution should be exercised in patients treated with Remicade® who have a current or past history of significant cytopenias. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of Remicade® therapy should be considered in patients with confirmed significant hematologic abnormalities.

Hepatic/Biliary/Pancreatic

Cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of Remicade®. Isolated cases of liver failure resulting in liver transplantation or death have occurred. A causal relationship between Remicade® and these events has not been established. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or ALT elevations ≥5 times the upper limit of normal develop, Remicade® should be discontinued immediately, and a thorough investigation of the abnormality should be undertaken. As also observed with the use of other immunosuppressive drugs, reactivation of hepatitis B has occurred very rarely in patients receiving Remicade® who are chronic carriers of this virus (i.e., surface antigen positive). Patients should be tested for hepatitis B virus (HBV) infection before initiating treatment with immunosuppressants, including Remicade®. For patients who test positive for hepatitis B surface antigen, consultation with a health professional with expertise in the treatment of hepatitis B is recommended. Chronic carriers of hepatitis B should be appropriately evaluated prior to the initiation of Remicade® therapy and monitored closely during treatment and for several months following discontinuation of therapy.

Immune

To minimize the incidence of hypersensitivity reactions, including infusion reactions and serum sickness-like reactions, Remicade® should be administered as regular maintenance therapy after an induction regimen at weeks 0, 2 and 6 (see 4 DOSAGE AND ADMINISTRATION).

Hypersensitivity Reactions

Remicade® has been associated with hypersensitivity reactions that vary in their time of onset. Hypersensitivity reactions, which include urticaria, dyspnea, and/or bronchospasm, laryngeal edema, pharyngeal edema and hypotension, have occurred during or within 2 hours of infliximab infusion. However, in some cases, serum sickness-like reactions have been observed in Crohn's disease and rheumatoid arthritis patients 3 to 12 days after Remicade® therapy was reinstituted following an extended period without Remicade® treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with marked increase in antibodies to infliximab, loss of detectable serum concentrations of Remicade®, and possible loss of drug efficacy. Remicade® should be discontinued for severe reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction (see 8.2 Clinical Trial Adverse Reactions, **Infusion-related Reactions**).

During clinical trials, Remicade® was sometimes readministered within 14 weeks following the last infusion. After a drug free interval of 15 weeks to 2 years, the risk of delayed hypersensitivity following readministration has not been accurately determined (see 8.2 Clinical Trial Adverse Reactions, **Infusion-related Reactions**, ***Delayed hypersensitivity/Reactions following readministration of Remicade®***).

Infusion reactions following readministration of Remicade®:

In a rheumatoid arthritis clinical trial where subjects were receiving low dose methotrexate and in a psoriasis clinical trial, a 3-dose induction of Remicade® after a period of no treatment

resulted in a higher incidence of serious and severe infusion reactions during the reinduction regimen than had been observed in rheumatoid arthritis, psoriasis and Crohn's disease trials in which a period of no drug treatment was followed by regular maintenance therapy without reinduction. Most of these reactions occurred during the second reinduction infusion at Week 2. The serious infusion reactions included anaphylaxis, urticaria, facial edema, chills and itching. Retreatment with a reinduction regimen after a period of no treatment is not recommended (see 8.2 Clinical Trial Adverse Reactions, **Infusion-related Reactions***, **Infusion Reactions following readministration of Remicade®***).

The BioAdvance® Network has been established to facilitate the administration of Remicade®. BioAdvance® Network clinics are staffed by qualified healthcare professionals specially trained in the administration of Remicade® infusions and are available across Canada. Information about the BioAdvance® Network and location of the nearest BioAdvance® Network clinic can be obtained by calling Janssen Inc. Medical Information at: 1-800-567-3331.

Autoimmunity

Treatment with Remicade® may result in the formation of autoantibodies and in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Remicade®, treatment should be discontinued (see 8.2 Clinical Trial Adverse Reactions, **Autoantibodies/Lupus-like Syndrome**).

Immunogenicity

Treatment with Remicade® can be associated with the development of antibodies to infliximab (see 7 WARNINGS AND PRECAUTIONS, **Immune**). Approximately 10% of patients were antibody positive. The majority of antibody positive patients had low titers.

In a Phase III study of Crohn's disease (SONIC) in patients who were immunomodulator-naïve, antibodies occurred at Week 30 in 14% of patients receiving Remicade® monotherapy and in 1% of patients receiving Remicade® in combination with azathioprine (AZA). Through Week 50, anti-infliximab antibodies occurred in 19% and 2.5% of patients, respectively. In the 20 patients on Remicade® monotherapy who were positive for anti-infliximab antibodies at some point during the study through Week 50, 10 patients had an infusion reaction, one of which was serious. None of the 3 patients on Remicade® in combination with AZA who were positive for anti-infliximab antibodies had an infusion reaction.

Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction (see 8.2 Clinical Trial Adverse Reactions, **Infusion-related Reactions**) than were patients who were antibody negative. Antibody development was lower among adult rheumatoid arthritis, Crohn's disease, and psoriatic arthritis patients receiving immunosuppressant therapies such as 6-mercaptopurine (6-MP), azathioprine (AZA), or methotrexate (MTX), although among patients with juvenile rheumatoid arthritis antibody development occurred in a high percentage of patients receiving 3 mg/kg Remicade® with concomitant MTX (see 8.2.1 Clinical Trial Adverse Reactions - Pediatrics, **Juvenile Rheumatoid Arthritis**).

With repeated dosing of Remicade®, serum concentrations of infliximab were higher in rheumatoid arthritis patients who received concomitant MTX. In the 2 Phase 3 studies of psoriasis (EXPRESS and EXPRESS II), Remicade® was administered as induction followed by maintenance and without concomitant immunosuppressive therapy. In these studies, antibodies

occurred in approximately 26.5% – 35.8% of patients who received 5 mg/kg every 8 week maintenance for 1 year and at higher rates (up to 1.4-fold) with other dose regimens (3 mg/kg q8 week, 3 mg/kg dosed as needed, and 5 mg/kg dosed as needed). Despite the increase in the rate of antibody formation, the infusion reaction rates in the 2 psoriasis Phase 3 studies (EXPRESS and EXPRESS II) in patients treated with 5 mg/kg induction followed by every 8 week maintenance for 1 year (14.1% and 23.0%, respectively) and serious infusion reaction rates (<1%) were similar to those observed in other study populations. In the Phase 3 study of psoriatic arthritis (IMPACT 2), where patients received 5 mg/kg with and without MTX, antibodies to infliximab occurred in 15.4% of patients.

Immunogenicity tests are generally product-specific. Comparison of antibody rates to those from other products, or comparison of the incidence of antibodies between different tests without cross-validation is not appropriate.

Vaccinations

It is recommended that all patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating Remicade® therapy.

Live Vaccines/Therapeutic Infectious Agents

In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines can result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with Remicade® is not recommended.

Infant exposure in utero

Fatal outcome due to disseminated Bacille Calmette-Guérin (BCG) infection has been reported in an infant who received BCG vaccine after *in utero* exposure to infliximab. A twelve month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab. Administration of the live vaccine prior to 12 months of age might be considered if infliximab exposure was limited to the first trimester of pregnancy, or if infant infliximab serum levels are undetectable, or if there is a clear clinical benefit for the individual infant (see 7.1.1 Pregnant Women).

Infant exposure via breast milk

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see 7.1.2 Breast-feeding).

Therapeutic Infectious Agents

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with Remicade®.

Non-Live Vaccines

In a subset of patients from the ASPIRE study, a similar proportion of patients in each treatment group mounted an effective two-fold increase in titers to a polyvalent pneumococcal vaccine indicating that Remicade® did not interfere with T-cell independent humoral immune responses.

Neurologic

Infliximab and other agents that inhibit TNF have been associated with seizure, and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of Remicade® in patients with these neurological disorders, and should consider discontinuation of Remicade® if these disorders develop.

Health professionals should alert patients to the presence of the Patient Package Insert, provide this information to them, and ensure full understanding of the content.

Peri-Operative Considerations

There is limited safety experience of Remicade® treatment in patients who have undergone surgical procedures, including arthroplasty. The long half-life of infliximab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Remicade® should be closely monitored for infections, and appropriate actions should be taken.

Reproductive Health: Female and Male Potential

- **Fertility**

Women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last Remicade® treatment.

It is not known whether Remicade® can affect reproductive potential.

7.1 Special Populations

7.1.1 Pregnant Women

Available observational studies in pregnant women exposed to Remicade® showed no increased risk of major malformations among live births as compared to those exposed to non-biologics. However, findings on other birth outcomes were not consistent across the studies. In one study conducted in a North America IBD pregnancy registry, Remicade® exposure was not associated with increased rates of miscarriage/stillbirth, low birth weight, small for gestational age, or infant infection in the first year of life as compared to exposure to non-biologics. In another study in Northern Europe among IBD and non-IBD patients, exposure to Remicade® in combination with immunosuppressants (mainly systemic corticosteroids and azathioprine), but not Remicade® as monotherapy, was associated with increased rates of preterm birth, small for gestational age, low birth weight, and infant hospitalization for infection compared with non-biologic systemic treatment. Both studies have potential for confounding (e.g., the concomitant use of other medications or treatments was not controlled and disease severity was not assessed).

Since infliximab does not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with Remicade®. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies.

As with other IgG antibodies, infliximab crosses the placenta. Infliximab has been detected in the serum of infants up to 12 months following birth. The clinical significance of low serum levels of infliximab on the immune status in infants is unknown. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including disseminated infection that can become fatal (see 7 WARNINGS AND PRECAUTIONS, **Immune**).

7.1.2 Breast-feeding

Remicade® has been detected at low levels in human milk and in infant serum via breast milk. While systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract, the administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. Limited data from published literature reported that infants exposed to infliximab through breast milk had no increase in rates of infections and developed normally. The consideration of Remicade® use during breast-feeding should take into account the importance of the drug to the mother and health benefits of breast-feeding for the infant.

7.1.3 Pediatrics

Pediatrics (6-17 years of age): Remicade® is indicated for reducing signs and symptoms and for inducing and maintaining clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Remicade® is also indicated for reducing signs and symptoms, inducing and maintaining clinical remission and inducing mucosal healing in pediatric patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant). In general, the adverse events in pediatric patients with Crohn's disease or ulcerative colitis who received Remicade® were similar to those seen in adult patients with Crohn's disease or ulcerative colitis respectively. It should be noted that in REACH, all patients were required to be on a stable dose of either 6-MP, AZA, or MTX. (See 1.1 Pediatrics; 8.2.1 Clinical Trial Adverse Reactions - Pediatrics, **Crohn's Disease** and **Ulcerative Colitis**; 4 DOSAGE AND ADMINISTRATION and 14 CLINICAL TRIALS. For additional pediatric information also see 7 WARNINGS AND PRECAUTIONS, **Immune** and 10.3 Pharmacokinetics).

The safety and efficacy of Remicade® has not been established in pediatric patients with Crohn's disease <9 years of age or with ulcerative colitis <6 years of age. The safety and efficacy of Remicade® in pediatric patients with plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, and juvenile rheumatoid arthritis have not been established.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): In rheumatoid arthritis clinical trials (ATTRACT) and in plaque psoriasis studies no overall differences were observed in the effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque psoriasis, aged 65 or older compared to younger patients although the incidence of serious adverse events in patients aged 65 or older was higher in both Remicade® and control groups compared to younger patients. Mean duration of Remicade® treatment in this population (154) was approximately 50 weeks. In Crohn's disease, ulcerative colitis, ankylosing spondylitis, and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and over to determine whether they responded differently from patients aged 18 to 64. There is a greater incidence of infections in the elderly population in general. The incidence of serious infections in Remicade®-treated patients 65 years and older was greater than in those under 65 years of age; therefore caution should be used in treating the elderly (see 8.2 Clinical Trial Adverse Reactions, **Infections**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse drug reactions reported from both clinical trials and post-marketing reports are infections, allergic reactions and infusion-related reactions. Less common adverse drug reactions from these sources which may be serious and clinically relevant include hepatobiliary events (see 7 WARNINGS AND PRECAUTIONS, **Hepatic/Biliary/Pancreatic**), demyelinating disorders (see 7 WARNINGS AND PRECAUTIONS**, Neurologic**), and lymphoma (see 7 WARNINGS AND PRECAUTIONS, **Carcinogenesis and Mutagenesis**). One of the most common reasons for discontinuation of treatment in clinical trials was infusion-related reactions (dyspnea, flushing, headache and rash) (see 7 WARNINGS AND PRECAUTIONS, **Immune**). Adverse events have been reported in a higher proportion of rheumatoid arthritis patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no differences were observed in the frequency of adverse events between the 5 mg/kg dose and the 10 mg/kg dose in patients with Crohn's disease or ulcerative colitis and between the 3 mg/kg and 5 mg/kg dose in patients with plaque psoriasis.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Description of Data Sources

The data described herein reflect the exposure to Remicade® in 5561 patients in adequate and well-controlled studies. Infliximab was studied in patients with rheumatoid arthritis (1304 patients exposed), juvenile rheumatoid arthritis (117 patients exposed), Crohn's disease (1566 patients exposed, including 1427 adult and 139 pediatric patients), ulcerative colitis (544 patients exposed, including 484 adults and 60 children), plaque psoriasis (1373 patients exposed), psoriatic arthritis (293 patients exposed), ankylosing spondylitis (347 patients exposed) and other conditions (17 patients exposed), primarily in double-blind, placebo-controlled trials. In general, integration of data in the following sections is based on clinical trials in rheumatoid

arthritis and adult Crohn's disease. See 14 CLINICAL TRIALS for a description of the individual studies conducted in each indication.

Relative Frequency of Adverse Drug Reactions

Adverse events occurring at a frequency of at least 5% in Remicade®-treated adult patients with rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, and ulcerative colitis are shown in Table 3. Adverse events occurring at a frequency of at least 5% in Remicade®-treated pediatric patients with Crohn's disease or ulcerative colitis are shown in Table 4. Adverse events occurring at a frequency of ≥1% to <5% in Remicade®-treated adult patients are shown in Table 5. Adverse events occurring at a frequency of ≥1% to <5% in Remicade®-treated pediatric patients with Crohn's disease or ulcerative colitis are shown in Table 6. Adverse events in a juvenile rheumatoid arthritis (JRA) trial are set forth in the section entitled 8.2.1 Clinical Trial Adverse Reactions - Pediatrics**,** Juvenile Rheumatoid Arthritis. In general, the adverse events in pediatric patients with Crohn's disease or ulcerative colitis who received Remicade® were similar in frequency and type to those seen in adult patients with Crohn's disease or ulcerative colitis respectively. Differences from adults and other special considerations are discussed in the section 8.2.1 Clinical Trial Adverse Reactions - Pediatrics, **Crohn's Disease** and **Ulcerative Colitis**.

Table 3: Number of patients with 1 or more adverse events (with frequency of ≥ 5%) by WHOART system-organ class and preferred term; treated patients ≥ 18 years of age

	RA Studies		CD studies		AS studies		UC studies		Pso Studies		PsA studies	
	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX
Treated patients ≥ 18 years of age[a,b]	427	1304	217	1427	76	275	248	493	334	1373	98	191
Avg duration of follow-up (weeks)	52.0	59.9	29.8	44.8	25.3	87.8	31.9	40.5	18.1	41.9	20.2	42.8
Patients with 1 or more adverse events	353 (82.7%)	1198 (91.9%)	179 (82.5%)	1297 (90.9%)	57 (75.0%)	268 (97.5%)	199 (80.2%)	425 (86.2%)	210 (62.9%)	1209 (88.1%)	66 (67.3%)	162 (84.8%)
System-organ class / preferred term												
Respiratory system disorders												
URTI	22%	29%	15%	23%	14%	49%	17%	18%	16%	25%	13%	24%
Pharyngitis	7%	12%	6%	13%	5%	20%	6%	10%	4%	9%	4%	10%
Sinusitis	7%	13%	6%	9%	1%	11%	5%	9%	3%	8%	4%	11%
Coughing	7%	12%	6%	7%	3%	13%	4%	6%	1%	5%	1%	7%
Rhinitis	4%	8%	5%	6%	5%	21%	2%	4%	1%	6%	2%	4%
Bronchitis	8%	9%	3%	5%	1%	8%	3%	4%	2%	4%	3%	6%
Gastro-intestinal system disorders												
Nausea	19%	19%	25%	21%	9%	11%	9%	11%	4%	8%	6%	5%
Abdominal pain	7%	12%	17%	24%	4%	16%	13%	12%	1%	4%	2%	5%
Diarrhea	11%	11%	7%	9%	5%	20%	5%	5%	2%	5%	3%	2%
Vomiting	6%	7%	13%	12%	4%	6%	7%	6%	1%	3%	2%	1%
Dyspepsia	6%	9%	2%	6%	4%	4%	2%	3%	1%	2%	2%	2%
Skin and appendages disorders												
Rash	5%	9%	6%	10%	7%	10%	8%	8%	1%	2%	0%	2%
Pruritus	2%	6%	3%	6%	7%	12%	4%	6%	4%	9%	3%	6%

	RA Studies		CD studies		AS studies		UC studies		Pso Studies		PsA studies	
	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX
Body as a whole - general disorders												
Pain	7%	7%	6%	13%	5%	29%	12%	11%	5%	10%	1%	4%
Fatigue	6%	8%	13%	14%	4%	15%	8%	10%	2%	7%	3%	4%
Musculo-skeletal system disorders												
Arthralgia	6%	7%	8%	15%	1%	8%	10%	15%	2%	10%	2%	4%
Back pain	4%	7%	6%	8%	3%	12%	8%	4%	3%	5%	6%	9%
Myalgia	3%	3%	4%	6%	3%	4%	5%	6%	1%	6%	0%	2%
Central & peripheral nervous system disorders												
Headache	12%	17%	15%	23%	11%	20%	18%	19%	8%	17%	5%	10%
Dizziness	6%	7%	6%	10%	4%	10%	5%	6%	2%	4%	4%	4%
Resistance mechanism disorders												
Fever	4%	7%	11%	11%	0%	8%	9%	10%	1%	4%	1%	2%

[a] Rheumatoid Arthritis Studies include C0168T07, C0168T09, C0168T14, C0168T15, C0168T18, C0168T22, and C0168T29. Crohn's Disease Studies include C0168T08, C0168T11, C0168T16, C0168T20, C0168T21, C0168T26, and C0168T67. Ankylosing Spondylitis Studies include C0168T51. Ulcerative Colitis Studies include C0168T12, C0168T37 (through Week 54), and C0168T46 (through Week 54 including 24-week study extension). Psoriasis Studies include C0168T31, C0168T38, and C0168T44. Psoriatic Arthritis Studies include C0168T50.

[b] The adverse events included in this table are determined by the frequency of events in the combined infliximab group over all indications in this table. Percentages are rounded to an integer value after the adverse event frequency is determined.

IFX – Infliximab; PBO – Placebo; URTI – Upper respiratory tract infection.

Table 4: Number of patients with 1 or more adverse events (with frequency of ≥ 5%) by WHOART system-organ class and preferred term; treated patients < 18 years of age in ulcerative colitis and Crohn's disease studies

	CD Studies[a]		UC Study[b]	
	Placebo	Infliximab 5 mg/kg	Placebo	Infliximab 5 mg/kg
Treated patients < 18 years of age in ulcerative colitis and Crohn's disease studies[c]	0	139	0	60
Avg duration of follow-up (weeks)	NA	44.1	NA	38.0
Patients with 1 or more	0 (NA)	125 (89.9%)	0 (NA)	57 (95.0%)

	CD Studies[a]		UC Study[b]	
	Placebo	Infliximab 5 mg/kg	Placebo	Infliximab 5 mg/kg
adverse events				
System-organ class/preferred term				
Gastro-intestinal system disorders				
Colitis ulcerative	NA	0%	NA	47%
Abdominal pain	NA	22%	NA	13%
Vomiting	NA	22%	NA	8%
Nausea	NA	19%	NA	5%
Blood in stool	NA	7%	NA	3%
Diarrhea	NA	13%	NA	3%
Crohn's disease	NA	27%	NA	0%
Respiratory system disorders				
Upper respiratory tract infection	NA	29%	NA	23%
Pharyngitis	NA	19%	NA	18%
Coughing	NA	11%	NA	10%
Sinusitis	NA	8%	NA	5%
Rhinitis	NA	8%	NA	2%
Resistance mechanism disorders				
Fever	NA	17%	NA	13%
Skin and appendages disorders				
Rash	NA	10%	NA	5%
Pruritus	NA	9%	NA	2%
Body as a whole - general disorders				
Pain	NA	9%	NA	8%
Central & peripheral nervous system disorders				
Headache	NA	31%	NA	13%
Musculo-skeletal system disorders				
Arthralgia	NA	9%	NA	2%
Red blood cell disorders				
Anemia	NA	9%	NA	10%
White cell and res disorders				
Neutropenia	NA	6%	NA	3%
Leukopenia	NA	8%	NA	2%
Vascular (extracardiac) disorders				
Flushing	NA	8%	NA	3%

[a] CD Studies include C0168T23, C0168T47 (through Week 54), and C0168T55.
[b] UC Study include C0168T72.
[c] The adverse events included in this table are determined by the frequency of events in the

	CD Studies[a]		UC Study[b]	
	Placebo	Infliximab 5 mg/kg	Placebo	Infliximab 5 mg/kg
combined infliximab group. Percentages are rounded to an integer value after the adverse event frequency is determined.				

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Table 5: Number of patients with 1 or more adverse events (with frequency of ≥ 1% to < 5%) by WHOART system-organ class and preferred term; treated patients ≥ 18 years of age

	RA Studies		CD Studies		AS Studies		UC Studies		Pso Studies		PsA Studies	
	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX
Treated patients ≥ 18 years of age[a,b]	427	1304	217	1427	76	275	248	493	334	1373	98	191
Avg duration of follow-up (weeks)	52.0	59.9	29.8	44.8	25.3	87.8	31.9	40.5	18.1	41.9	20.2	42.8
Patients with 1 or more adverse events	353 (82.7%)	1198 (91.9%)	179 (82.5%)	1297 (90.9%)	57 (75.0%)	268 (97.5%)	199 (80.2%)	425 (86.2%)	210 (62.9%)	1209 (88.1%)	66 (67.3%)	162 (84.8%)
System-organ class/preferred term												
Respiratory system disorders												
Dyspnea	2%	5%	1%	4%	3%	5%	2%	3%	1%	3%	1%	3%
Pneumonia	1%	4%	1%	1%	0%	1%	0%	2%	0%	1%	0%	3%
Respiratory tract allergic reaction	1%	2%	0%	1%	0%	1%	0%	1%	0%	2%	1%	2%
Epistaxis	1%	1%	0%	1%	0%	2%	0%	1%	0%	1%	0%	1%
Gastro-intestinal system disorders												
Gastroenteritis	3%	4%	6%	4%	4%	7%	2%	3%	1%	3%	3%	1%
Crohn's disease	0%	0%	12%	13%	0%	0%	0%	0%	0%	0%	0%	0%
Stomatitis ulcerative	5%	6%	1%	3%	1%	1%	1%	1%	0%	1%	1%	1%

	RA Studies		CD Studies		AS Studies		UC Studies		Pso Studies		PsA Studies	
	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX
Flatulence	1%	2%	3%	6%	0%	1%	2%	4%	0%	0%	0%	1%
Constipation	3%	2%	2%	4%	1%	3%	1%	2%	0%	1%	2%	0%
Gastroesophageal reflux	1%	2%	0%	2%	0%	3%	2%	1%	0%	1%	1%	2%
Colitis ulcerative	0%	0%	0%	0%	0%	0%	25%	16%	0%	0%	0%	0%
Tooth ache	0%	1%	1%	2%	0%	1%	0%	1%	1%	2%	0%	1%
Anorexia	1%	1%	2%	2%	0%	0%	1%	1%	0%	0%	0%	1%
Blood in stool	1%	1%	1%	2%	0%	1%	1%	1%	0%	0%	0%	0%
Intestinal obstruction	0%	0%	2%	4%	0%	0%	0%	0%	0%	0%	0%	0%
Skin and appendages disorders												
Urticaria	1%	4%	0%	2%	0%	2%	0%	1%	1%	4%	0%	4%
Sweating increased	0%	2%	3%	3%	5%	4%	3%	3%	0%	2%	0%	2%
Alopecia	2%	3%	2%	3%	0%	1%	1%	3%	1%	1%	2%	3%
Dermatitis	1%	2%	0%	2%	1%	7%	2%	1%	0%	2%	0%	1%
Dermatitis fungal	1%	3%	1%	1%	0%	5%	3%	1%	0%	2%	1%	2%
Psoriasis	0%	0%	1%	1%	1%	5%	1%	0%	7%	5%	2%	4%
Eczema	1%	2%	0%	3%	0%	3%	3%	1%	1%	1%	0%	1%
Acne	0%	1%	1%	3%	0%	3%	1%	2%	1%	1%	0%	0%
Skin dry	0%	1%	1%	2%	0%	7%	1%	3%	1%	1%	0%	0%
Skin wound	2%	2%	1%	1%	0%	2%	0%	1%	0%	2%	0%	1%
Erythema	0%	2%	1%	1%	0%	3%	1%	1%	0%	1%	1%	0%
Rash erythematous	1%	1%	0%	1%	1%	5%	0%	1%	0%	0%	0%	1%
Folliculitis	0%	1%	1%	1%	0%	1%	0%	1%	1%	1%	0%	0%
Body as a whole - general disorders												
Chest pain	3%	4%	4%	5%	1%	6%	2%	3%	0%	4%	2%	4%
Edema peripheral	4%	4%	2%	5%	1%	4%	4%	4%	2%	3%	0%	3%
Chills	2%	3%	1%	2%	3%	3%	2%	4%	1%	3%	0%	1%

	RA Studies		CD Studies		AS Studies		UC Studies		Pso Studies		PsA Studies	
	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX
Infusion syndrome	0%	2%	0%	2%	1%	3%	0%	2%	0%	3%	0%	2%
Wound	1%	1%	0%	1%	1%	3%	0%	1%	0%	3%	1%	3%
Hot flushes	0%	2%	1%	2%	1%	3%	2%	1%	0%	1%	0%	2%
Allergic reaction	0%	1%	1%	2%	0%	5%	0%	2%	1%	1%	1%	1%
Asthenia	1%	1%	0%	3%	0%	2%	0%	1%	0%	1%	1%	1%
Reaction unevaluable	0%	1%	2%	2%	0%	2%	1%	1%	1%	1%	0%	0%
Musculo-skeletal system disorders												
Arthritis	1%	1%	2%	4%	5%	14%	1%	1%	3%	7%	5%	5%
Bone fracture	3%	4%	0%	1%	0%	4%	0%	1%	1%	1%	0%	4%
Skeletal muscle strain	2%	2%	0%	1%	0%	1%	1%	0%	1%	3%	1%	2%
Tendinitis	2%	0%	0%	1%	1%	5%	1%	1%	0%	1%	2%	1%
Central & peripheral nervous system disorders												
Paresthesia	2%	3%	2%	3%	0%	7%	3%	3%	1%	3%	0%	0%
Muscle contractions involuntary	2%	4%	2%	2%	1%	3%	3%	2%	0%	2%	1%	1%
Hypesthesia	1%	2%	1%	2%	4%	3%	1%	1%	0%	2%	1%	1%
Migraine	1%	1%	1%	2%	0%	1%	0%	1%	0%	1%	0%	1%
Vertigo	2%	2%	0%	1%	3%	1%	1%	1%	0%	1%	1%	2%
Resistance mechanism disorders												
Abscess	3%	4%	4%	9%	3%	6%	3%	3%	1%	3%	2%	2%
Flu syndrome	3%	4%	1%	6%	1%	8%	2%	4%	1%	3%	0%	3%
Moniliasis	3%	5%	0%	5%	0%	5%	2%	3%	0%	1%	0%	1%
Influenza-like symptoms	0%	2%	2%	3%	1%	2%	2%	3%	1%	2%	0%	2%

	RA Studies		CD Studies		AS Studies		UC Studies		Pso Studies		PsA Studies	
	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX
Herpes simplex	1%	2%	2%	2%	0%	9%	2%	1%	1%	2%	1%	4%
Infection	2%	3%	0%	2%	3%	4%	1%	1%	1%	2%	0%	1%
Influenza	1%	2%	2%	3%	1%	1%	2%	2%	1%	2%	0%	1%
Cellulitis	1%	2%	0%	1%	0%	2%	0%	1%	1%	1%	1%	3%
Herpes zoster	1%	1%	0%	1%	0%	0%	0%	1%	1%	1%	0%	2%
Infection bacterial	1%	1%	2%	1%	0%	1%	0%	0%	0%	1%	0%	2%
Psychiatric disorders												
Insomnia	4%	4%	3%	6%	1%	4%	2%	4%	1%	2%	1%	0%
Depression	5%	5%	2%	4%	0%	4%	2%	3%	1%	3%	2%	3%
Anxiety	1%	3%	1%	3%	1%	2%	3%	2%	0%	2%	1%	0%
Liver and biliary system disorders												
Sgpt increased	4%	5%	1%	3%	5%	12%	1%	1%	1%	4%	1%	8%
Sgot increased	2%	3%	1%	2%	3%	9%	0%	1%	1%	3%	2%	5%
Hepatic enzymes increased	3%	4%	1%	1%	0%	2%	0%	1%	0%	4%	0%	2%
Hepatic function abnormal	1%	2%	2%	1%	0%	2%	0%	0%	0%	1%	1%	2%
Vascular (extracardiac) disorders												
Flushing	0%	3%	1%	2%	3%	4%	1%	2%	0%	5%	0%	3%
Ecchymosis	2%	4%	0%	2%	0%	2%	1%	1%	0%	2%	0%	1%
Hemorrhoids	1%	1%	0%	2%	1%	3%	3%	1%	0%	0%	0%	1%
Urinary system disorders												
Urinary tract infection	5%	7%	3%	4%	0%	2%	2%	2%	1%	2%	4%	3%
Metabolic and nutritional disorders												
Hypokalemia	0%	2%	1%	4%	0%	0%	0%	1%	0%	0%	0%	1%
Weight increase	2%	2%	0%	0%	1%	3%	0%	0%	0%	1%	0%	0%
Cardiovascular disorders, general												

	RA Studies		CD Studies		AS Studies		UC Studies		Pso Studies		PsA Studies	
	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX	PBO	IFX
Hypertension	5%	6%	2%	3%	5%	8%	2%	2%	3%	4%	2%	3%
Hypotension	1%	2%	0%	2%	1%	3%	0%	2%	0%	1%	0%	2%
Eye and vision disorders												
Conjunctivitis	2%	4%	2%	4%	1%	4%	3%	1%	0%	1%	1%	1%
Vision abnormal	1%	2%	1%	2%	0%	4%	2%	1%	0%	1%	0%	2%
Ear and hearing disorders												
Otitis	0%	2%	1%	1%	0%	2%	1%	1%	0%	1%	0%	0%
White cell and res disorders												
Leukopenia	1%	2%	3%	2%	0%	2%	0%	2%	0%	1%	0%	1%
Lymphadenopathy	0%	1%	1%	2%	0%	2%	1%	1%	0%	1%	0%	1%
Neutropenia	0%	1%	0%	1%	0%	3%	0%	0%	0%	1%	0%	3%
Red blood cell disorders												
Anemia	4%	4%	4%	4%	1%	4%	10%	5%	0%	1%	0%	0%
Heart rate and rhythm disorders												
Tachycardia	2%	2%	0%	1%	1%	1%	2%	1%	1%	1%	1%	1%
Palpitation	1%	2%	0%	1%	0%	3%	1%	1%	0%	1%	0%	1%
Administration / application site disorders												
Injection site infiltration	3%	2%	0%	1%	0%	0%	1%	0%	0%	2%	0%	0%
Collagen disorders												
Arthritis rheumatoid	6%	7%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

[a] Rheumatoid Arthritis Studies include C0168T07, C0168T09, C0168T14, C0168T15, C0168T18, C0168T22, and C0168T29. Crohn's Disease Studies include C0168T08, C0168T11, C0168T16, C0168T20, C0168T21, C0168T26, and C0168T67. Ankylosing Spondylitis Studies include C0168T51. Ulcerative Colitis Studies include C0168T12, C0168T37 (through Week 54), and C0168T46 (through Week 54 including 24-week study extension). Psoriasis Studies include C0168T31, C0168T38, and C0168T44. Psoriatic Arthritis Studies include C0168T50.

[b] The adverse events included in this table are determined by the frequency of events in the combined infliximab group over all indications in this table. Percentages are rounded to an integer value after the adverse event frequency is determined.

IFX – Infliximab; PBO – Placebo.

Table 6: Number of patients with 1 or more adverse events (with frequency of ≥ 1% to < 5%) by WHOART system-organ class and preferred term; treated patients < 18 years of age in ulcerative colitis and Crohn's disease studies

	CD Studies[a]		UC Study[b]	
	Placebo	Infliximab 5 mg/kg	Placebo	Infliximab 5 mg/kg
Treated patients < 18 years of age in ulcerative colitis and Crohn's disease studies[c]	0	139	0	60
Avg duration of follow-up (weeks)	NA	44.1	NA	38.0
Patients with 1 or more adverse events	0 (NA)	125 (89.9%)	0 (NA)	57 (95.0%)
System-organ class/preferred term				
Gastro-intestinal system disorders				
Stomatitis ulcerative	NA	2%	NA	5%
Diarrhea bloody	NA	1%	NA	2%
Pancreatitis	NA	2%	NA	2%
Anal fistula	NA	3%	NA	0%
Anorexia	NA	3%	NA	0%
Constipation	NA	6%	NA	0%
Dyspepsia	NA	6%	NA	0%
Dysphagia	NA	1%	NA	0%
Enterocolitis	NA	3%	NA	0%
Flatulence	NA	4%	NA	0%
Gastroenteritis	NA	5%	NA	0%
Hemorrhage rectum	NA	1%	NA	0%
Intestinal obstruction	NA	1%	NA	0%
Intestinal stenosis	NA	2%	NA	0%
Oral pain	NA	1%	NA	0%
Proctalgia	NA	2%	NA	0%
Tooth ache	NA	2%	NA	0%
Respiratory system disorders				
Dyspnea	NA	4%	NA	5%
Bronchitis	NA	5%	NA	3%
Asthma	NA	1%	NA	2%
Respiratory tract allergic reaction	NA	4%	NA	2%
Bronchospasm	NA	1%	NA	0%

	CD Studies[a]		UC Study[b]	
	Placebo	Infliximab 5 mg/kg	Placebo	Infliximab 5 mg/kg
Epistaxis	NA	3%	NA	0%
Pneumonia	NA	2%	NA	0%
Resistance mechanism disorders				
Influenza	NA	3%	NA	5%
Cellulitis	NA	1%	NA	3%
Infection	NA	3%	NA	3%
Influenza-like symptoms	NA	1%	NA	3%
Moniliasis	NA	4%	NA	3%
Herpes simplex	NA	1%	NA	2%
Herpes zoster	NA	1%	NA	2%
Infection bacterial	NA	5%	NA	2%
Infection viral	NA	6%	NA	2%
Abscess	NA	4%	NA	0%
Flu syndrome	NA	5%	NA	0%
Infectious mononucleosis	NA	1%	NA	0%
Skin and appendages disorders				
Alopecia	NA	1%	NA	3%
Eczema	NA	4%	NA	3%
Acne	NA	2%	NA	2%
Dermatitis	NA	1%	NA	2%
Onychocryptosis	NA	1%	NA	2%
Skin lesion	NA	3%	NA	2%
Sweating increased	NA	1%	NA	2%
Urticaria	NA	1%	NA	2%
Verruca	NA	2%	NA	2%
Cracking of skin	NA	4%	NA	0%
Dermatitis contact	NA	2%	NA	0%
Dermatitis fungal	NA	2%	NA	0%
Rash erythematous	NA	2%	NA	0%
Skin dry	NA	2%	NA	0%
Skin hypertrophy	NA	1%	NA	0%
Body as a whole - general disorders				
Chest pain	NA	3%	NA	3%
Fatigue	NA	5%	NA	3%
Chills	NA	1%	NA	2%
Cyst (type unknown)	NA	1%	NA	2%
Edema	NA	1%	NA	2%

	CD Studies[a]		UC Study[b]	
	Placebo	Infliximab 5 mg/kg	Placebo	Infliximab 5 mg/kg
Edema peripheral	NA	1%	NA	2%
Reaction unevaluable	NA	1%	NA	2%
Allergic reaction	NA	4%	NA	0%
Asthenia	NA	1%	NA	0%
Central & peripheral nervous system disorders				
Hyperkinesia	NA	0%	NA	3%
Dizziness	NA	6%	NA	2%
Muscle contractions involuntary	NA	1%	NA	2%
Migraine	NA	1%	NA	0%
Paresthesia	NA	2%	NA	0%
Musculo-skeletal system disorders				
Back pain	NA	2%	NA	3%
Bone development abnormal	NA	1%	NA	2%
Joint swelling	NA	1%	NA	2%
Sprain	NA	1%	NA	2%
Bone fracture	NA	6%	NA	0%
Myalgia	NA	4%	NA	0%
Red blood cell disorders				
Anemia iron deficiency	NA	1%	NA	2%
Psychiatric disorders				
Anxiety	NA	2%	NA	2%
Depression	NA	2%	NA	2%
Insomnia	NA	4%	NA	2%
Thinking abnormal	NA	1%	NA	2%
Irritability	NA	1%	NA	0%
Somnolence	NA	3%	NA	0%
Suicide attempt	NA	1%	NA	0%
Urinary system disorders				
Urinary tract infection	NA	1%	NA	8%
Dysuria	NA	1%	NA	0%
Liver and biliary system disorders				
Hepatic enzymes increased	NA	2%	NA	3%
Hepatic function abnormal	NA	2%	NA	2%
Sgot increased	NA	1%	NA	2%
Sgpt increased	NA	1%	NA	2%

	CD Studies[a]		UC Study[b]	
	Placebo	Infliximab 5 mg/kg	Placebo	Infliximab 5 mg/kg
White cell and res disorders				
Neutrophilia	NA	1%	NA	2%
Eosinophilia	NA	3%	NA	0%
Lymphadenopathy	NA	1%	NA	0%
Monocytosis	NA	1%	NA	0%
Eye and vision disorders				
Conjunctivitis	NA	4%	NA	3%
Eye pain	NA	3%	NA	0%
Metabolic and nutritional disorders				
Dehydration	NA	2%	NA	0%
Weight decrease	NA	3%	NA	0%
Vascular (extracardiac) disorders				
Ecchymosis	NA	4%	NA	0%
Cardiovascular disorders, general				
Hypotension	NA	1%	NA	0%
Syncope	NA	2%	NA	0%
Collagen disorders				
Antinuclear factor test positive	NA	3%	NA	2%
Ear and hearing disorders				
Otitis	NA	1%	NA	2%
Otitis media	NA	2%	NA	2%
Earache	NA	2%	NA	0%
Platelet, bleeding & clotting disorders				
Thrombocythemia	NA	1%	NA	3%
Thrombocytopenia	NA	1%	NA	0%
Heart rate and rhythm disorders				
Palpitation	NA	1%	NA	2%
Administration/application site disorders				
Injection site infiltration	NA	4%	NA	0%
Reproductive disorders				
Dysmenorrhea	NA	2%	NA	0%
Ovarian cyst	NA	1%	NA	0%

	CD Studies[a]		UC Study[b]	
	Placebo	Infliximab 5 mg/kg	Placebo	Infliximab 5 mg/kg

[a] CD Studies include C0168T23, C0168T47 (through Week 54), and C0168T55.
[b] UC Study include C0168T72.
[c] The adverse events included in this table are determined by the frequency of events in the combined infliximab group. Percentages are rounded to an integer value after the adverse event frequency is determined.

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Infusion-related Reactions

Acute infusion reactions

An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 hour after an infusion. In Phase 3 clinical studies, 18% of Remicade®-treated patients experienced an infusion reaction compared with 5% of placebo-treated patients. Of infliximab-treated patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period. Approximately 3% of patients discontinued Remicade® because of infusion reactions, and all patients recovered with treatment and/or discontinuation of infusion.

In clinical trials, approximately 3% of Remicade® infusions were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in less than 1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension.

Remicade® infusions beyond the initial infusion were not associated with a higher incidence of reactions. In psoriatic arthritis (IMPACT 2), infusion reactions were reported in 12% of Remicade®-treated patients compared with 7% of placebo-treated patients. Among the 1376 Remicade® infusions, 2% of these led to an infusion reaction. In plaque psoriasis, infusion reactions were reported in 22% of Remicade®-treated patients compared with 5% of placebo-treated patients. Among the 8366 Remicade® infusions, 5% of these led to an infusion reaction. In the ankylosing spondylitis study ASSERT, infusion reactions were reported in 19% of Remicade®-treated patients compared with 9% of placebo-treated patients. Among the 4257 Remicade® infusions, 2% of these led to an infusion reaction.

In a clinical study of patients with early rheumatoid arthritis (ASPIRE), 66% of all treated patients (686 out of 1040) received at least one shortened infusion of 90 minutes or less and 44% of the patients (454 out of 1040) received at least one shortened infusion of 60 minutes or less. Of the Remicade®-treated patients who received at least one shortened infusion **of 90 minutes or less** at the dose of 3 mg/kg, infusion-related reactions occurred in 19% (48/248) of patients and serious infusion reactions occurred in 0.4% (1/248) of patients. Of the Remicade®-treated patients who received at least one shortened infusion **of 90 minutes or less** at the dose of 6 mg/kg, infusion-related reactions occurred in 11% (26/246) of patients and serious infusion

reactions occurred in 0.4% (1/246) of patients. Shortened infusions at doses >6 mg/kg have not been studied (see 14.1 Clinical Trials by Indication, **Rheumatoid Arthritis**).

In the UC studies ACT 1 and ACT 2 through Week 30, the proportion of subjects with infusion reactions was comparable in the placebo and combined infliximab treatment groups. Through Week 54, the proportion of subjects with infusion reactions rose and was greater in the combined infliximab treatment group than in the placebo treatment group (13.4% versus 9.4%, respectively). A greater proportion of subjects in the 10 mg/kg than in the 5 mg/kg infliximab treatment group (16.1% versus 10.7%) experienced an infusion reaction.

In a clinical study of patients with Crohn's disease (SONIC), infusion-related reactions occurred in 17% of patients receiving Remicade® monotherapy, 5% of patients receiving Remicade® in combination with azathioprine (AZA) and 6% of patients receiving AZA monotherapy. One patient experienced a serious infusion reaction with Remicade® monotherapy.

Patients who became positive for antibodies to infliximab were more likely to develop infusion reactions than were those who were negative (approximately 3-fold). Use of concomitant immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and infusion reactions (see 7 WARNINGS AND PRECAUTIONS, **Immune** and 9 DRUG INTERACTIONS).

In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal edema, severe bronchospasm, and seizure have been associated with Remicade® administration (see 7 WARNINGS AND PRECAUTIONS, **Neurologic**). Cases of transient visual loss occurring during or within 2 hours of Remicade® infusion have been reported. Cerebrovascular accidents, myocardial ischemia/infarction (some fatal), and arrhythmia occurring within 24 hours of initiation of infusion have also been reported.

Infusion reactions following readministration of Remicade®

In rheumatoid arthritis, Crohn's disease and psoriasis clinical trials, readministration of Remicade® after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment.

In a clinical trial of patients with moderate to severe psoriasis designed to assess the efficacy of long-term maintenance therapy versus re-treatment with an induction cycle of Remicade®, 4% (8/219) of patients in the intermittent therapy arm experienced serious infusion reactions versus <1% (1/222) in the maintenance therapy arm. Patients enrolled in this trial did not receive any concomitant immunosuppressant therapy. Intermittent therapy in this trial was defined as the re-administration of an induction cycle (maximum of four infusions at 0, 2, 6, and 14 weeks) of Remicade® upon disease flare after a period of no treatment. In this study, the majority of serious infusion reactions occurred during the second infusion at Week 2. Symptoms included, but were not limited to, dyspnea, urticaria, facial edema, and hypotension. In all cases, Remicade® treatment was discontinued and/or other treatment instituted with complete resolution of signs and symptoms (see 7 WARNINGS AND PRECAUTIONS, **Immune**).

Delayed hypersensitivity/Reactions following readministration of Remicade®

In a clinical study where 37 of 41 patients with Crohn's disease were retreated with infliximab following a 2 to 4 year period without infliximab treatment, 10 patients experienced adverse events manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs

and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache. Patients experiencing these adverse events had not experienced infusion-related adverse events associated with their initial infliximab therapy. Of these patients, adverse events occurred in 9 of 23 (39%) who had received liquid formulation which is no longer in use and 1 of 14 (7%) who received lyophilized formulation. The clinical data are not adequate to determine if occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms improved substantially or resolved with treatment in all cases. There are insufficient data on the incidence of these events after drug-free intervals of 1 to 2 years. These events have been observed only infrequently in clinical studies and post-marketing surveillance with retreatment intervals up to 1 year.

In 3 other psoriasis studies, 1% (15/1373) of patients experienced a possible delayed hypersensitivity reaction with symptoms of arthralgia, myalgia, fever, and rash, often early in the treatment course following infliximab infusions. There were no possible delayed hypersensitivity reactions identified in the psoriatic arthritis study (IMPACT 2) (see 7 WARNINGS AND PRECAUTIONS, **Immune**).

Infections

In Remicade® clinical studies, primarily of RA and CD, treated infections were reported in 36% of Remicade®-treated patients (average of 53 weeks of follow-up) and in 28% of placebo-treated patients (average of 47 weeks of follow-up). In the ATTRACT[1] study, 60% of Remicade®-treated RA patients (average of 97 weeks of follow-up) had treated infections reported vs. 43% of placebo-treated patients (average of 75 weeks of follow-up); treated infections were more common with higher doses of Remicade®. In the ASPIRE[2] study, 37% of Remicade®-treated RA patients (average of 54 weeks of follow-up) had treated infections reported vs. 30% of placebo-treated patients (average of 52 weeks of follow-up). The infections most frequently reported in the RA studies were respiratory tract infections (including URI, sinusitis, pharyngitis, and bronchitis) and urinary tract infections. No increased risk of serious infections or sepsis was observed with Remicade® compared with placebo in the ATTRACT or ACCENT I[3] and II[4] studies. However, in the ATTRACT study, the incidence of serious events of pneumonia and lobar pneumonia combined was higher in patients receiving infliximab plus MTX vs. MTX alone (2.6% vs. 1.2%, respectively). In the ASPIRE study, the incidence of serious pneumonia was also higher in patients receiving infliximab plus MTX vs. MTX alone (2.5% vs. 0%, respectively). In other RA trials, the incidence of serious infections including pneumonia was higher in infliximab plus MTX treated patients compared with methotrexate alone, especially at higher than recommended induction regimen of Remicade® 6 mg/kg or greater. Among Remicade®-treated patients, serious infections included pneumonia, cellulitis, abscess and sepsis. In ATTRACT, one patient died with miliary tuberculosis, one died with disseminated coccidioidomycosis and one died due to sepsis. In the ASPIRE study, four patients were diagnosed with tuberculosis. In the ACCENT I study, one patient was diagnosed with tuberculosis. In EXPRESS II[5], two patients with psoriasis were diagnosed with tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-

[1] ATTRACT (the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy)
[2] ASPIRE (the Active-controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset
[3] ACCENT I (the Anti-TNF Trial in Long-term Treatment of Moderately to Severely Active Crohn's Disease)
[4] ACCENT II (the Anti-TNF Trial in Long-term Treatment of Fistulising Crohn's Disease)
[5] EXPRESS II Evaluation of Infliximab for Psoriasis in a Remicade® Efficacy and Safety Study

marketing. Most of the cases of tuberculosis occurred within the first two months after initiation of therapy with infliximab and may reflect recrudescence of latent disease (see 7 WARNINGS AND PRECAUTIONS, **Risk of Infections**). In the ACCENT II study, serious infections of nocardiosis (one patient) and cytomegalovirus (one patient) were reported. Twelve percent of patients with fistulising Crohn's disease developed a new abscess 8 to 16 weeks after the last infusion of Remicade® in the T20 study. In the ACCENT II study, there was no difference between the Remicade® and placebo maintenance arms for proportions of patients with newly diagnosed fistula-related abscesses. (see 14.1 Clinical Trials by Indication, **Fistulising Crohn's Disease**). In the psoriasis studies, 1.5% of patients (average of 41.9 weeks of follow up) receiving Remicade® and 0.6% of patients (average of 18.1 weeks of follow up) receiving placebo developed serious infections. In EXPRESS[6], one patient died due to sepsis. In the IMPACT 2[7] study of psoriatic arthritis, 1.6% of patients (average 42.8 weeks of follow-up) receiving Remicade® and 2.0% of patients (average 20.2 weeks of follow-up) receiving placebo developed serious infections.

In the Remicade® clinical studies in patients with ulcerative colitis (ACT 1 and ACT 2[8]), the most frequently reported infections were upper respiratory infection (URI), sinusitis, pharyngitis, bronchitis and moniliasis. In the UC studies, infections were reported in 30.6% and 40.1% of Remicade®-treated patients at Week 30 (average 26.9 weeks of follow-up) and at Week 54 (average 41.1 weeks of follow-up) and in 29.5% and 32.8% of placebo-treated patients at Week 30 (average 22.2 weeks of follow up) and at Week 54 (average 32.2 weeks of follow-up). The types of infections, including serious infections, reported in patients with ulcerative colitis were similar to those reported in other clinical studies, and included one case of tuberculosis and a fatal case of histoplasmosis.

In post-marketing experience, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving Remicade® alone or in combination with immunosuppressive agents.

Autoantibodies/Lupus-like Syndrome

Approximately 55% of 1598 infliximab-treated patients in clinical trials (primarily RA and CD) who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately 20% of 265 placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately 19% of 2116 infliximab-treated patients compared with 0% of 422 placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

In the ATTRACT rheumatoid arthritis study through Week 102, 62% of Remicade®-treated patients developed antinuclear antibodies (ANA) between screening and last evaluation, compared with 27% of placebo-treated patients. In the ASPIRE study through Week 58, 66% of Remicade®-treated patients developed antinuclear antibodies (ANA) between screening and last evaluation, compared with 21% of placebo-treated patients. In both RA studies, anti-dsDNA antibodies developed in approximately 15% of Remicade®-treated patients, compared to none of the placebo-treated patients. No association was seen between Remicade® dose/schedule and development of ANA or anti-dsDNA antibodies.

[6] EXPRESS European infliximab for Psoriasis (Remicade®) Efficacy and Safety Study
[7] IMPACT 2 Induction and Maintenance Psoriatic Arthritis Clinical Trial
[8] ACT 1 and ACT 2 (the Anti-TNF Trials in moderately to severely active ulcerative colitis)

Of Crohn's disease patients treated with Remicade® who were evaluated for antinuclear antibodies (ANA), 40% developed ANA between screening and last evaluation. Anti-dsDNA antibodies developed in approximately 20% of Crohn's disease patients treated with Remicade®. The development of anti-dsDNA antibodies was not related to either the dose or duration of Remicade® treatment. However, baseline therapy with an immunosuppressant in Crohn's disease patients was associated with reduced development of anti-dsDNA antibodies (3% compared to 21% in patients not receiving any immunosuppressant). Crohn's disease patients were approximately 2 times more likely to develop anti-dsDNA antibodies if they were ANA-positive at study entry.

In the EXPRESS plaque psoriasis study through Week 50, 59% of Remicade®-treated patients developed antinuclear antibodies following Remicade® treatment compared to 2% of placebo-treated patients. Anti-dsDNA antibodies developed in 16% of Remicade®-treated patients, compared to none of the placebo-treated patients. In the EXPRESS II plaque psoriasis study through Week 50, 65% of Remicade®-treated patients developed antinuclear antibodies following Remicade® treatment compared to 8% of placebo-treated patients. Anti-dsDNA antibodies developed in 27% of Remicade®-treated patients, compared to none of the placebo-treated patients. No association was seen between Remicade® dose/schedule and development of ANA or anti-dsDNA antibodies.

In the IMPACT 2 psoriatic arthritis study through Week 66, 59% of Remicade®-treated patients developed antinuclear antibodies following Remicade® treatment compared to 11% of placebo-treated patients. Anti-dsDNA antibodies developed in 12% of Remicade®-treated patients, compared to none of the placebo-treated patients.

In the ASSERT ankylosing spondylitis study through week 102, 35% of Remicade®-treated patients developed antinuclear antibodies following Remicade® treatment compared to 1% of placebo-treated patients. Anti-dsDNA antibodies developed in 30% of Remicade®-treated patients, compared to none of the placebo-treated patients.

In clinical studies, 22 patients were diagnosed with a possible lupus-like syndrome, four with Crohn's disease, eight patients with plaque psoriasis [seven (0.5%) patients treated with infliximab and one (0.3%) patient treated with placebo], 8 patients with ankylosing spondylitis, and two with rheumatoid arthritis. Twenty-one patients improved following discontinuation of therapy and/or appropriate medical treatment. One psoriasis patient on concomitant hydralazine had central nervous system involvement. No patients had renal involvement. No cases of lupus-like syndromes were reported in the psoriatic arthritis studies. The lupus-like syndrome in one patient with rheumatoid arthritis and one patient with ankylosing spondylitis remained ongoing at the end of the study. One case of a lupus-like reaction has been observed in a Crohn's disease patient in up to three years of long-term follow-up (see 7 WARNINGS AND PRECAUTIONS, **Immune**).

Hepatobiliary Events

In post-marketing surveillance, cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving Remicade® (see 7 WARNINGS AND PRECAUTIONS, **Hepatic/Biliary/Pancreatic**).

In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving Remicade® without progression to severe hepatic injury. Elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of

patients receiving Remicade® than in controls, both when Remicade® was given as monotherapy and when it was used in combination with other immunosuppressive agents. Most aminotransferase abnormalities were transient; however, a small number of patients experienced more prolonged elevations. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of Remicade®, or modification of concomitant medications.

Malignancies/Lymphoproliferative Disease

The potential role of TNF-blocking therapy in the development of malignancies is not known. Rates in clinical trials for Remicade® cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering Remicade® treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving Remicade®.

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF-blocker compared with control patients. In the controlled and open-label portions of Remicade® clinical trials, 5 patients developed lymphomas among 5780 patients treated with Remicade® (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately 3-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, psoriasis, ankylosing spondylitis, and ulcerative colitis, 5 lymphomas were observed for a rate of 0.09 cases per 100 patient-years of follow-up, which is approximately 4-fold higher than expected in the general population. Patients with Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies**,** may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy.

In the controlled portions of clinical trials of some TNF-blocking agents including Remicade®, more cases of non-lymphoma malignancies have been observed in patients receiving those TNF-blockers compared with control patients. During the controlled portions of Remicade® trials in patients with moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, psoriasis, ankylosing spondylitis, and ulcerative colitis, 14 patients were diagnosed with non-lymphoma malignancies among 4019 Remicade®-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among Remicade®-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for Remicade®-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of non-lymphoma malignancies among Remicade®-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected.

Among the 345 patients who received Remicade® in ankylosing spondylitis trials, 3 patients developed malignancies (1 patient had a squamous cell and a basal cell carcinoma, 1 patient had a pulmonary carcinoma, and 1 patient had breast cancer). Additionally, 1 patient in ASSERT developed a nonseminoma testicular carcinoma after leaving the trial, approximately 1 year after his last dose of Remicade®.

In the IMPACT 2 study of psoriatic arthritis, 2 malignancies were reported through Week 54 (Stage I Hodgkin's lymphoma in a Remicade®-treated patient and basal cell carcinoma in a

placebo-treated patient). No malignancies were reported through Week 50 of IMPACT. An adenocarcinoma of the pancreas was reported 2 months after completing the year 2 extension of IMPACT.

During the Remicade® plaque psoriasis trials, no patients developed lymphoma. In the placebo-controlled portions of the psoriasis studies, 7 of 1123 patients who received Remicade® at any dose (443 patient-years) were diagnosed with a nonmelanoma skin cancer (NMSC) compared to 0 of 334 patients who received placebo (113 patient-years). Among the 1373 patients with psoriasis who received Remicade® at any dose in the controlled and uncontrolled portions of the psoriasis studies (1101 patient-years), a total of 17 were diagnosed with NMSC (12 basal cell cancers, 5 squamous cell cancers). The size of the placebo group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions. Patients on Remicade® should be monitored for the development of NMSC. Two noncutaneous malignancies (breast cancer and adenocarcinoma) were reported during the psoriasis clinical trials.

A population-based retrospective cohort study found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age.

Congestive Heart Failure

In a phase II study evaluating Remicade® in NYHA Class III/IV CHF patients (left ventricular ejection fraction ≤35%), higher incidences of mortality and hospitalization due to worsening heart failure were seen in Remicade®-treated patients, especially those treated with 10 mg/kg. One hundred and fifty patients were treated with 3 infusions of Remicade® 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 28 weeks, 4 of 101 patients treated with Remicade® (1 at 5 mg/kg and 3 at 10 mg/kg) died compared with no deaths among the 49 placebo-treated patients. In follow-up, at 38 weeks, 9 patients treated with Remicade® (2 at 5 mg/kg and 7 at 10 mg/kg) died compared with one death among the placebo-treated patients. At 28 weeks, 14 of 101 patients treated with Remicade® (3 at 5 mg/kg and 11 at 10 mg/kg) were hospitalized for worsening CHF compared with 5 of the 49 placebo-treated patients (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, **Cardiovascular**).

There have also been post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age.

8.2.1 Clinical Trial Adverse Reactions - Pediatrics

Crohn's Disease

Adverse events occurring at a frequency of ≥5% or from ≥1% to <5% in Remicade®-treated pediatric patients with Crohn's disease are shown in Tables 4 and 6, respectively. In general, the adverse events in pediatric patients who received Remicade® were similar in frequency and type to those seen in adult patients with Crohn's disease. Differences from adults and other special considerations are discussed in the following paragraphs.

The following adverse events were reported more commonly in the 103 randomised pediatric patients with Crohn's disease (Phase 3 Trial, REACH) who received 5 mg/kg Remicade® through 54 weeks than in the 385 adult patients with Crohn's disease (ACCENT I) where

193/385 patients received 5 mg/kg and 192/385 received 10 mg/kg Remicade® through 54 weeks: anemia (10.7%), blood in stool (9.7%), leukopenia (8.7%), flushing (8.7%), viral infection (7.8%), neutropenia (6.8%), bone fracture (6.8%), bacterial infection (5.8%), and respiratory tract allergic reaction (5.8%). The Phase 3 study (REACH) enrolled 112 pediatric patients 6 to 17 years old (median age 13.0 years) with moderately to severely active Crohn's disease and an inadequate response to conventional therapies.

Infections were reported in 56.3% of randomised pediatric patients in the REACH trial, and in 50.3% of patients in the ACCENT I Study. In the pediatric Phase 3 trial, infections were reported more frequently for subjects who received q8 week as opposed to q12 week infusions (73.6% and 38.0%, respectively), while serious infections were reported for 3 patients in the q8 week and 4 patients in the q12 week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported for 3 patients, 2 in the q8 week and 1 in the q12 week maintenance treatment groups. Herpes zoster was reported for 2 patients in the q8 week maintenance treatment group.

In REACH, 17.5% of randomised patients experienced 1 or more infusion reactions, with no notable difference between treatment groups (17.0% and 18.0% of patients in the q8 week and q12 week maintenance treatment groups, respectively). There were no serious infusion reactions, and 2 patients had non-serious anaphylactic reactions.

Antibodies to Remicade® developed in 3 (2.9%) pediatric patients in the REACH trial and in none of the patients in the Phase 2 trial (T23).

Juvenile Rheumatoid Arthritis

The efficacy of Remicade® in the treatment of children with juvenile rheumatoid arthritis, JRA, has not been established. In a clinical trial where children were treated with either 3 mg/kg or 6 mg/kg of Remicade®, the proportion of children with infusion reactions, most commonly vomiting, fever, headache and hypotension, was 35% at a dosage of 3 mg/kg. Four of these reactions were serious, and three were considered to be possible anaphylactic reactions. Two of the 4 patients who experienced serious infusion reactions at a dose of 3 mg/kg received infliximab by rapid infusion (duration time less than 2 hours). Antibodies to infliximab developed in 37.7% of children receiving that dosage, but only in 12.2% receiving a higher dosage (6 mg/kg).

Ulcerative Colitis

Overall, the adverse reactions reported in the pediatric ulcerative colitis (Study Peds UC) and adult ulcerative colitis (ACT 1 and ACT 2) studies were generally consistent. In Study Peds UC, the most common adverse reactions were upper respiratory tract infection, pharyngitis, abdominal pain, fever, and headache. In Study Peds UC, there were a total of 20 serious adverse events: 10 were serious adverse events of ulcerative colitis, 7 were infections (which included cellulitis, urinary tract infection, pneumonia, pharyngitis, ulcerative colitis, viral infection, and infection not otherwise specified) and one event each of anemia, neutropenia and pancreatitis. An additional 12 adverse events were considered to be severe (4 events of ulcerative colitis, 3 of abdominal pain and 1 event each of pharyngitis, sinusitis, malnutrition, inflammation and headache). None of these serious or severe adverse events were opportunistic infections.

Infections were reported in 31 (51.7%) of 60 treated patients in Study Peds UC and 22 (36.7%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in Study Peds UC was similar to that in the pediatric Crohn's disease study (REACH) but higher than the proportion in the adults ulcerative colitis studies (ACT 1 and ACT 2). Unlike REACH, in which infections were reported more frequently for patients who received q8 week as opposed to q12 week infusions; in Study Peds UC, the overall incidence of infections was similar in the q8 week (13/22 [59.1%]) and q12 week (14/23 [60.9%]) maintenance treatment groups. In Study Peds UC, serious infections were reported for 3 of 22 (13.6%) patients in the q8 week and 3 of 23 (13.0%) patients in the q12 week maintenance treatment group. Upper respiratory tract infection (7/60 [11.7%]) and pharyngitis (5/60 [8.3%]) were the most frequently reported respiratory system infections among all treated patients. The infections occurring in more than one patient in a treatment group that required antimicrobial treatment were pharyngitis (4/60 [6.7%]), urinary tract infection (4/60 [6.7%]), and bronchitis (2/60 [3.3%]).

Overall, 8 (13.3%) of 60 treated patients experienced one or more infusion reactions, with 4 of 22 (18.2%) in the q8 week and 3 of 23 (13.0%) in the q12 week treatment maintenance group. No serious infusion reactions were reported. All infusion reactions were mild or moderate in intensity.

Antibodies to Remicade® were detected in 4 of 52 (7.7%) patients through week 54.

In Study Peds UC, there were more patients in the 12 to 17 year age group than in the 6 to 11 year age group (45/60 [75.0%]) vs.15/60 [25.0%]). While the numbers of patients in each subgroup are too small to make any definitive conclusions about the effect of age on safety events, there were higher proportions of patients with serious adverse events and discontinuation due to adverse events in the younger age group than in the older age group. While the proportion of patients with infections was also higher in the younger age group, the proportions of patients with serious infections were similar in the two age groups. Overall proportions of adverse events and infusion reactions were similar between the 6 to 11 and 12 to 17 year age groups.

8.3 Less Common Clinical Trial Adverse Reactions

Other medically relevant adverse events occurring at a frequency <1% were as follows, presented by body system:

Administration / application site: injection site inflammation, injection site ecchymosis, injection site swelling, injection site infection
Autonomic Nervous System: fecal incontinence
Body as a whole: anaphylactoid reaction, diaphragmatic hernia, generalized edema, surgical/procedural sequela, substernal chest pain, rigors
Blood: pancytopenia, splenomegaly
Cardiovascular: circulatory failure, hypotension postural, pallor
Collagen: LE syndrome, anti-DNA antibodies, positive antinuclear factor test, anticardiolipin antibodies
Ear and Hearing: otitis externa
Endocrine: adrenal insufficiency, hypothyroidism
Eye and Vision: lacrimation abnormal, iritis, scleritis, eye pain, glaucoma
Gastrointestinal: ileus, intestinal stenosis, pancreatitis, peritonitis, rectal hemorrhage, appetite increased, anal fistula, diarrhea bloody, gastritis, intestinal obstruction, intestinal perforation

Central & Peripheral Nervous: meningitis, neuritis, optic neuritis, peripheral neuropathy, neuralgia, ataxia, dysesthesia, tremor, hyperkinesia
Heart Rate and Rhythm: arrhythmia, bradycardia, cardiac arrest, palpitations
Liver and Biliary: cholelithiasis, hepatitis, bilirubinemia, cholecystitis, hepatocellular damage, elevated GGT, fatty liver, hepatomegaly
Metabolic and Nutritional: hypercholesterolemia
Musculoskeletal: intervertebral disk herniation, tendon disorder, joint stiffness
Myo-, Endo-, Pericardial and Coronary Valve: myocardial infarction, mitral insufficiency, heart murmur, cardiac failure
Platelet, Bleeding and Clotting: thrombocytopenia
Neoplasms: adenocarcinoma, basal cell carcinoma, breast cancer, lymphoma, malignant melanoma, squamous cell carcinoma, bladder carcinoma, rectal carcinoma, uterine cancer, pulmonary carcinoma
Psychiatric: confusion, suicide attempt, irritability, nervousness, amnesia
Red Blood Cell: iron deficiency anemia, hemolytic anemia
Reproductive: menstrual irregularity, dysmenorrhea, menorrhagia, breast fibroadenosis, amenorrhea, female breast pain
Resistance Mechanism: sepsis, serum sickness, tuberculosis, fungal infection, viral infection, sarcoid-like reaction
Respiratory: Adult respiratory distress syndrome, respiratory tract infection, pleural effusion, lobar pneumonia, pulmonary edema, respiratory insufficiency, bronchospasm, asthma, hemoptysis, epistaxis, laryngitis
Skin and Appendages: erythema nodosum, rash maculopapular, rash pustular, photosensitivity reaction, edema periorbital, fasciitis
Special Senses, Other: taste perversion, taste loss
Urinary: renal failure, dysuria, renal calculus, pyelonephritis
Vascular (Extracardiac): brain infarction, thrombophlebitis, vasculitis, brain ischemia, pulmonary embolism
White Cell and Reticuloendothelial: neutropenia, neutrophilia, lymphocytosis
Investigations: Weight Increased*

* At month 12 of the controlled period for adult clinical trials across all indications, the median weight increase was 3.50 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects. The median weight increase for inflammatory bowel disease indications was 4.14 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects, and the median weight increase for rheumatology indications was 3.40 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Serious, medically relevant hematologic adverse events ≥0.2%, or clinically relevant hematologic adverse reactions observed in clinical trials include: pancytopenia, thrombocytopenia, anemia, hemolytic anemia, neutropenia and leukopenia.

Table 7: Proportion of patients with elevated ALT in clinical trials

	Proportion of patients with elevated ALT					
	>1 to <3 X ULN		≥3 X ULN		≥5 X ULN	
	Placebo	infliximab	placebo	infliximab	placebo	infliximab
Rheumatoid arthritis[1]	24.0%	34.4%	3.2%	3.9%	0.8%	0.9%
Crohn's disease[2]	24.1%	34.9%	2.2%	4.9%	0.0%	1.5%
Ulcerative colitis[3]	12.4%	17.4%	1.2%	2.5%	0.4%	0.6%
Psoriatic arthritis[4]	16.3%	49.5%	0.0%	6.8%	0.0%	2.1%
Plaque psoriasis[5]	23.8%	49.4%	0.4%	7.7%	0.0%	3.4%
Pediatric Crohn's Disease[6]	n/a	18.2%	n/a	4.4%	n/a	1.5%
Ankylosing Spondylitis[7]	14.5%	51.1%	0.0%	9.5%	0.0%	3.6%
Pediatric Ulcerative Colitis[8]	n/a	16.7%	n/a	6.7%	n/a	1.7%

[1] Note that placebo patients received methotrexate while infliximab patients received both infliximab and methotrexate. Median follow-up was 58 weeks for placebo patients and infliximab-treated patients. RA trials include ATTRACT (T22) and ASPIRE (T29).
[2] Note that placebo patients in 2 of the 3 Phase III trials in Crohn's disease, ACCENT I and ACCENT II, received an initial dose of 5 mg/kg infliximab at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in this table. Median follow-up time was 54 weeks. In SONIC, placebo patients received AZA 2.5 mg/kg/day.
[3] Ulcerative colitis trials include ACT I (C0168T37) through Week 54 and ACT II (C0168T46) through Week 30; median duration of follow up was 30.8 weeks for the infliximab group and 30.1 weeks for placebo group.
[4] IMPACT 2 median duration of follow up was 39.1 weeks for the infliximab group and 18.1 weeks for placebo group.
[5] EXPRESS and EXPRESS II median duration of follow up was 16.1 weeks for placebo and 50.1 weeks for infliximab groups.
[6] Patients from pediatric Crohn's disease trials T23, T55 and T47 (REACH). Median follow-up was 53.0 weeks.
[7] Patients from the ASSERT trial (T51); median duration of follow-up was 24.1 weeks for placebo and 101.9 weeks for the infliximab group.
[8] Data from the pediatric ulcerative colitis study T72.

The difference in rates of ALT elevations ≥3 X ULN between infliximab and placebo treatment groups tended to be greater in ankylosing spondylitis, psoriasis and psoriatic arthritis clinical trials than in rheumatoid arthritis, Crohn's disease and ulcerative colitis clinical trials. See 8.2 Clinical Trial Adverse Reactions, **Hepatobiliary Events**.

8.5 Post-Market Adverse Reactions

Additional adverse events, some with fatal outcome, reported from worldwide post-marketing experience with Remicade® are included in Table 8 (see 8.2 Clinical Trial Adverse Reactions, **Infections** and **Infusion-related Reactions**). Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Remicade® exposure.

The most common serious adverse events reported in the post-marketing experience in children were infections (some fatal) including opportunistic infections and tuberculosis, infusion

reactions, and hypersensitivity reactions. Spontaneous serious adverse events in the post-marketing experience with Remicade® in the pediatric population have also included malignancies, transient hepatic enzyme abnormalities, lupus-like syndromes, and the development of autoantibodies.

Post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with Remicade® with the vast majority of cases occurring in Crohn's disease and ulcerative colitis, most of whom were adolescent or young adult males (see 7 WARNINGS AND PRECAUTIONS, **Carcinogenesis and Mutagenesis**). Hemophagocytic lymphohistiocytosis (HLH) has been very rarely reported in patients treated with Remicade®.

Table 8: Post-marketing Reports

Blood and Lymphatic System Disorders	Agranulocytosis (including infants exposed *in utero* to infliximab), idiopathic thrombocytopenic purpura, hemolytic anemia, pancytopenia, thrombotic thrombocytopenic purpura
General Disorders and Administration Site Conditions	Anaphylactic reactions, anaphylactic shock, infusion-related reactions, serum sickness
Cardiac Disorders	Pericardial effusion, myocardial ischemia/myocardial infarction (within 24 hours of initiation of infusion), arrhythmia (within 24 hours of initiation of infusion)
Eye Disorders	Transient visual loss occurring during or within 2 hours of infusion
Immune System Disorders	Vasculitis, sarcoidosis, paradoxical drug-induced immune disorders (e.g., new onset psoriasis)
Neoplasm Benign and Malignant	Hepatosplenic T-cell lymphoma (the vast majority in Crohn's disease and ulcerative colitis: primarily adolescents and young adults), pediatric malignancy, leukemia, melanoma, Merkel cell carcinoma, cervical cancer
Hepatobiliary System Disorders	Hepatocellular damage, hepatitis, jaundice, autoimmune hepatitis, liver failure
Nervous System Disorders	Central nervous system demyelinating disorders (such as multiple sclerosis and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), neuropathies, numbness, seizure, tingling, transverse myelitis, cerebrovascular accidents occurring within approximately 24 hours of initiation of infusion, orbital apex syndrome

Infections and Infestations	Opportunistic infections (such as aspergillosis, atypical mycobacteria, coccidioidomycosis, cryptococcosis, candidiasis, histoplasmosis, legionellosis, listeriosis, pneumocystosis), salmonellosis, sepsis, tuberculosis, protozoal infections, hepatitis B reactivation and vaccine breakthrough infection (after *in utero* exposure to infliximab)*
Respiratory, Thoracic and Mediastinal Disorders	Interstitial lung disease, including pulmonary fibrosis/interstitial pneumonitis, and rapidly progressive disease
Skin and Subcutaneous Tissue Disorders	Vasculitis (primarily cutaneous), psoriasis including new onset and pustular (primarily palmar/plantar), erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, linear IgA bullous dermatosis (LABD), acute generalized exanthematous pustulosis (AGEP), lichenoid reactions
Injury, poisoning, and procedural complications	Post-procedural complication (including infectious and non-infectious complications)

* including bovine tuberculosis (disseminated BCG infection), see 7 WARNINGS AND PRECAUTIONS, Live Vaccines/Therapeutic Infectious Agents.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Specific drug interaction studies have not been conducted. The majority of patients in rheumatoid arthritis, Crohn's disease or ulcerative colitis clinical trials received one or more concomitant medications. In rheumatoid arthritis, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-mercaptopurine/azathioprine (6-MP/AZA), methotrexate (MTX), and aminosalicylates Patients with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients using no immunosuppressants (see 7 WARNINGS AND PRECAUTIONS, **Immune**, and 8 ADVERSE REACTIONS, **Infusion-related Reactions**).

9.3 Drug-Behavioural Interactions

Not applicable

9.4 Drug-Drug Interactions

Concurrent Use of Remicade® with other Biological Therapeutics

The combination of Remicade® with other biological therapeutics used to treat the same conditions as Remicade®, including anakinra or abatacept, is not recommended (see 7 WARNINGS AND PRECAUTIONS, **Risk of Infections**).

Live Vaccines/Therapeutic Infectious Agents

It is recommended that live vaccines not be given concurrently with Remicade®. It is also recommended that live vaccines not be given to infants after *in utero* exposure to infliximab for at least 12 months following birth. Administration of the live vaccine prior to 12 months of age might be considered if infliximab exposure was limited to the first trimester of pregnancy, or if infant infliximab serum levels are undetectable, or if there is a clear clinical benefit for the individual infant (see 7 WARNINGS AND PRECAUTIONS, **Immune** and 7.1.1 Pregnant Women).

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see 7 WARNINGS AND PRECAUTIONS, **Immune** and 7.1.2 Breast-feeding).

It is recommended that therapeutic infectious agents not be given concurrently with Remicade® (see 7 WARNINGS AND PRECAUTIONS).

Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-1, IL-6, IL-10, IFN) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as infliximab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of Remicade® in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Infliximab is a chimeric IgG1κ monoclonal antibody with an approximate molecular weight of 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab binds specifically to human tumour necrosis factor alpha (TNFα) with an association constant of 10^{10} M^{-1}. Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

Infliximab neutralises the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors. Infliximab does not neutralise TNFβ (lymphotoxin α), a related cytokine that utilises the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, and induction of acute phase reactants and other liver proteins. Cells expressing transmembrane TNFα bound by infliximab can be lysed *in vitro* by complement or effector cells. Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilising human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes, and epithelial cells. Anti-TNFα antibodies reduce disease activity in a cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and, when administered after disease onset, facilitates eroded joints to heal.

10.2 Pharmacodynamics

Preclinical

Infliximab binds to the soluble and transmembrane forms of TNFα with high affinity and blocks the interaction of TNFα with its receptors, thereby neutralising the biological activity of TNFα. Cells expressing transmembrane TNFα can be lysed *in vitro* by complement or effector cell-mediated mechanisms after infliximab binds. Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilising human fibroblasts, endothelial cells, neutrophils B and T lymphocytes, and epithelial cells.

Infliximab specifically neutralises TNFα-induced cell cytotoxicity but not lymphotoxin α. Lymphotoxin α is a cytokine that shares 30% homology with TNFα and utilises the same receptors as TNFα. Species cross-reactivity of infliximab is limited to human and chimpanzee TNFα. *In vivo*, infliximab rapidly forms stable complexes with human TNFα, a process that parallels the loss of TNFα bioactivity.

In a transgenic mouse (Tg197) that constitutively expresses human TNFα, infliximab administered twice weekly at 5 mg/kg or once weekly at 10 mg/kg prevents the development of polyarthritis by Week 10, demonstrating that infliximab neutralises TNFα *in vivo*.

Clinical

Elevated concentrations of TNFα have been found in the joints of rheumatoid arthritis patients, in the joints of psoriatic arthritis patients, in the skin lesions of plaque psoriasis patients, and in the stools of Crohn's disease and ulcerative colitis patients. This correlates with elevated disease activity. In rheumatoid arthritis, treatment with Remicade® reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], chemoattraction [IL-8 and monocyte chemotactic protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3]. In Crohn's disease, treatment reduces infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduces the proportion of mononuclear cells in the *lamina propria* able to express TNFα and interferon γ *ex vivo*. After treatment with Remicade®, patients with rheumatoid

arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein compared to baseline. Peripheral blood lymphocytes from Remicade®-treated patients showed no decrease in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients. In psoriatic arthritis, treatment with Remicade® resulted in a reduction in the number of T cells and blood vessels in the synovium and psoriatic skin lesions as well as a reduction of macrophages in the synovium. Infliximab treatment alters the histopathological features of plaque psoriasis as demonstrated in lesional skin biopsies collected at baseline, day 3 and Week 10 following initiation of treatment. Infliximab treatment reduced epidermal thickness and infiltration of inflammatory cells, downregulated the percentage of activated and cutaneous lymphocyte antigen (CLA)-positive inflammatory cells, including CD3-, CD4-, and CD8-positive lymphocytes, and upregulated the percentage of CD1a-positive epidermal Langerhans cells. In ulcerative colitis, treatment with Remicade® showed changes consistent with histological healing and decreased expression of pharmacodynamic markers of tissue injury and inflammation in colonic biopsies. Treatment with Remicade® also decreased serum levels of the proinflammatory molecules with statistically significant and consistent decreases observed for IL-2R, and ICAM-1. In patients with ankylosing spondylitis, infliximab was more effective at decreasing levels of serum markers of inflammation (IL-6 and VEGF) at both weeks 2 and 24 than placebo. In addition, serum levels of markers of bone formation (bone alkaline phosphatase and osteocalcin) were increased at both weeks 2 and 24 in patients with ankylosing spondylitis treated with infliximab compared with patients receiving placebo.

10.3 Pharmacokinetics

Single intravenous infusions of 1 to 20 mg/kg showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Median pharmacokinetic results for the doses of 3 mg/kg to 10 mg/kg in rheumatoid arthritis, 5 mg/kg in Crohn's disease and 3 mg/kg to 5 mg/kg in plaque psoriasis indicate that the terminal half life of infliximab is approximately 7.7 to 10 days. The terminal half-life in ulcerative colitis trials was 12.3 to 14.7 days.

Table 9: Summary of Remicade® Pharmacokinetic Parameters in Rheumatoid Arthritis and Crohn's Disease

	Rheumatoid Arthritis		Crohn's Disease	
Study	T09	T09	T11	T11
	(n=14)	(n= 29)	(n=5)	(n=5)
Dose	3 mg/kg	10 mg/kg	5 mg/kg	10 mg/kg
Cmax (µg/mL)	77.3	277	74.9	181.0
AUC (µg • day/mL)	461	2282	788	2038
CL (mL/day/kg)	6.4	4.4	6.3	4.9
Vss (mL/kg)	67.5	57.2	80	65
t1/2(day)	8	9.1	7.8	10

Absorption: Remicade® is administered intravascularly and thus has no absorption profile.

Distribution: Remicade® is primarily distributed into the blood, its apparent median steady state volume of distribution of 57.2 to 80 mL/kg estimated to 4.0 to 5.60 litres in a 70 kg individual corresponds to the total blood volume.

Metabolism: It is believed that Remicade® is metabolized in a similar manner to other proteins in the body. It is probably hydrolysed into its component amino acids and recycled or catabolized.

Elimination: Remicade® as a whole molecule was not detected in the urine after its intravenous infusion.

Following an initial dose of Remicade®, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-week intervals in rheumatoid arthritis patients or patients with moderate or severe Crohn's disease retreated with 4 infusions of 10 mg/kg Remicade® at 8-week intervals. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 5 mg/kg at 8-week intervals in patients with psoriatic arthritis or plaque psoriasis. The proportion of patients with rheumatoid arthritis who had undetectable infliximab concentrations at 8 weeks following an infusion was approximately 25% for those receiving 3 mg/kg every 8 weeks, 15% for patients administered 3 mg/kg every 4 weeks, and 0% for patients receiving 10 mg/kg every 4 or 8 weeks. At steady state, the proportion of patients with plaque psoriasis who had undetectable infliximab concentrations at 8 weeks following an infusion ranged from 71.4% to 73.1% for patients receiving 3 mg/kg every 8 weeks (EXPRESS II), and from 25.9% to 46.4% for those administered 5 mg/kg every 8 weeks (EXPRESS and EXPRESS II). The proportion of patients with psoriatic arthritis who had undetectable infliximab concentrations was 15.8% at Week 38 when administered 5 mg/kg every 8 weeks (IMPACT 2). In IMPACT 2, approximately half of the patients received concomitant MTX.

Special Populations and Conditions

No major differences in clearance or volume of distribution were observed in patient subgroups defined by age. It is not known if gender differences, genetic polymorphism, renal insufficiency or hepatic insufficiency have effects on clearance or volume of distribution of Remicade®.

Pediatrics

Infliximab pharmacokinetic characteristics (including peak and trough concentrations) were generally similar in pediatric patients (aged 6 to 17 years) with Crohn's disease or ulcerative colitis following the administration of 5 mg/kg infliximab. Similar terminal half-life values were also observed in pediatric patients with Crohn's disease, and adult patients with Crohn's disease or ulcerative colitis. However, for pediatric patients with ulcerative colitis, median serum peak and steady-state trough infliximab concentrations were about 13% and 25% lower than those in adult patients with ulcerative colitis, respectively; the clinical significance of the relatively lower serum infliximab concentrations in pediatric patients is unknown (see 1.1 Pediatrics and 7.1.3 Pediatrics).

11 STORAGE, STABILITY AND DISPOSAL

Remicade® is stored in the original carton under refrigeration at 2°C to 8°C (36°F to 46°F). Do not use beyond the refrigerated expiration date (MM YYYY) printed on the carton.

Only at the location of reconstitution, Remicade® may also be stored in the original carton at temperatures up to a maximum of 30°C for a single period of up to 6 months; but not exceeding

the refrigerated expiration date printed on the carton. Once removed from refrigerated storage, the non-refrigerated expiration date (month/year) should be written on the carton and Remicade® cannot be returned to refrigerated storage.

After Reconstitution and Dilution

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at room temperature (25°C). Diluted Remicade® infusion solution is stable for 24 hours when stored between 2°C and 30°C (36°F to 86°F). This product contains no preservative. Since no preservative is present, it is recommended that the administration of the infusion solution should begin within 3 hours of reconstitution and dilution.

Handling Under Controlled and Validated Aseptic Conditions

Chemical and physical in use stability of the diluted solution in the infusion bag has been demonstrated for up to 28 days at 2 to 8°C and for an additional 24 hours at 25°C after removal from refrigeration when Remicade® reconstitution and dilution has taken place in controlled and validated aseptic conditions. If stored refrigerated after reconstitution and dilution, the infusion solution must be allowed to equilibrate at room temperature to 25°C for 3 hours prior to administration.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Infliximab

Chemical name: Infliximab

Molecular formula and molecular mass: 149,100 daltons

The infliximab molecule contains 1328 amino acids and consists of 2 identical H chains and 2 identical L chains which associate by non-covalent H-H and H-L interactions and covalent H-H and H-L disulfide bonds. Infliximab is a glycoprotein consisting of 5 major glycoforms, each containing 2 (1 on each H chain) asparagine-linked (N-linked) asialo-, core-fucosylated, biantennary oligosaccharide chains with terminal galactose microheterogeneity. The oligosaccharide is bound exclusively to Asn-300 in the C_H2 region of both H chains.

Physicochemical properties: Remicade® is a sterile, white, lyophilized powder for intravenous infusion.

Product Characteristics

Infliximab drug substance is a purified, recombinant DNA-derived, chimeric human-mouse IgG monoclonal antibody (MAb) which binds to and neutralises human tumour necrosis factor α (TNFα) with high affinity (Ka=1 X 10^{10} M^{-1}). Infliximab contains murine heavy (H) and light (L) chain variable regions (V_H and V_L, respectively) derived from the murine anti-TNFα MAb, A2, and genomic DNA-derived human H and L chain constant regions (C_H and C_L, respectively).

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Rheumatoid Arthritis

Table 10: Summary of patient demographics for clinical trials in rheumatoid arthritis

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Gender and Race n (%)
T22 (ATTRACT)	Randomised, multicentre. double-blind, placebo-controlled, 5-arm parallel study in patients with active RA despite treatment with MTX	Infliximab 3 mg/kg, 10/mg/kg, or placebo administered intravenously at Weeks 0, 2 and 6, followed by additional infusions every 4 or 8 weeks thereafter through Week 54	428	52 (19 to 80)	96 (22%) male 332 (78%) female 389 (91%) Caucasian 22 (5%) Black 3 (1%) Asian 14 (3%) Other
T29 (ASPIRE)	Randomised, multicentre, double-blind, active-controlled, 3-arm parallel study in MTX-naïve subjects with early RA	Infliximab 3 mg/kg, 6mg/kg, or placebo administered intravenously at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 46 MTX 7.5 mg/wk po at Week 0; gradually increased to 20 mg/wk by Week 8 and maintained through Week 46	1004	50 (18 to 76)	290 (29%) male 714 (71%) female 870 (86.7%) Caucasian 50 (5%) Black 15 (1.5%) Asian 69 (6.8%) Other

The safety and efficacy of Remicade® were assessed in two multicentre, randomised double-blind, well controlled trials: ATTRACT and ASPIRE. Concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or nonsteroidal anti-inflammatory drugs was also permitted. The primary endpoints were the reduction of signs and symptoms as assessed by the American College of Rheumatology criteria, the prevention of structural joint damage, and the improvement in physical function. A summary of the design and subject demographics of the two studies is presented in Table 10.

ATTRACT (T22) Study Results

The safety and efficacy of Remicade® when given in conjunction with methotrexate (MTX) were assessed in a multicenter, randomized, double-blind, placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with MTX (the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy or ATTRACT). Patients enrolled had a median age of

54 years, median disease duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively, and were on a median dose of 15 mg/week of MTX. Patients received either placebo + MTX or one of 4 doses/schedules of Remicade® + MTX: 3 mg/kg or 10 mg/kg of Remicade® by IV infusion at Weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks thereafter.

Clinical response

All doses/schedules of Remicade® + MTX resulted in improvement in signs and symptoms as measured by the American College of Rheumatology response criteria (ACR 20) with a higher percentage of patients achieving an ACR 20, 50 and 70 compared to placebo + MTX (Table 11). Statistically significant improvement was observed at as early as Week 2 and maintained through Week 102. Greater effects on each component of the ACR 20 were observed in all patients treated with Remicade® + MTX compared with placebo + MTX (Table 12). Approximately 10% of patients treated with Remicade® achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period compared to 0% of placebo-treated patients (p=0.018).

Table 11: Percentage of patients who achieved an ACR response at Weeks 30 and 54 [ATTRACT]

		Remicade® + MTX			
	Placebo + MTX	3 mg/kg[a]		10 mg/kg[a]	
Response		q8 wks	q4 wks	q8 wks	q4 wks
	n=88	n=86	n=86	n=87	n=81
ACR 20					
Week 30	20%	50%	50%	52%	58%
Week 54	17%	42%	48%	59%	59%
ACR 50					
Week 30	5%	27%	29%	31%	26%
Week 54	9%	21%	34%	40%	38%
ACR 70					
Week 30	0%	8%	11%	18%	11%
Week 54	2%	11%	18%	26%	19%

[a] $p<0.05$ for each outcome compared to placebo

Table 12: Components of ACR 20 at baseline and 54 weeks [ATTRACT]

	Placebo + MTX		Remicade® + MTX[a]	
	(n=88)		(n=340)	
Parameter (medians)	Baseline	Week 54	Baseline	Week 54
No. of Tender Joints	24	16	32	8
No. of Swollen Joints	19	13	20	7
Pain[b]	6.7	6.1	6.8	3.3
Physician's Global Assessment[b]	6.5	5.2	6.2	2.1
Patient's Global Assessment[b]	6.2	6.2	6.3	3.2
Disability Index (HAQ)[c]	1.8	1.5	1.8	1.3
CRP (mg/dL)	3	2.3	2.4	0.6

[a] All doses/schedules of Remicade® + MTX
[b] Visual Analog Scale (0=best, 10=worst)
[c] Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)

Radiographic response

Structural damage in both hands and feet was assessed radiographically at Week 54 by the change from baseline in the van der Heijde-modified Sharp score, a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet. Approximately 80% of patients had paired x-ray data at 54 weeks and approximately 70% at 102 weeks. The inhibition of progression of structural damage was observed at 54 weeks (Table 13) and maintained through 102 weeks.

Table 13: Radiographic change from baseline to Week 54

		Remicade® + MTX [ATTRACT]				
Median (10, 90 percentiles)	Placebo + MTX	3mg/kg		10mg/kg		
		q8 wks	q4 wks	q8 wks	q4 wks	p value[a]
Patients Evaluated	(n=64)	(n=71)	(n=71)	(n=77)	(n=66)	
Randomized	(n=88)	(n=86)	(n=86)	(n=87)	(n=81)	
Completed 54wks	(n=44)	(n=63)	(n=66)	(n=75)	(n=65)	
Total Score						
Baseline	55 (14, 188)	57 (15, 187)	45 (8, 162)	56 (6, 143)	43 (7, 178)	
Change from baseline	4.0 (-1.0, 19.0)	0.5 (-3.0, 5.5)	0.1 (-5.2, 9.0)	0.5 (-4.8, 5.0)	-0.5 (-5.7, 4.0)	p<0.001
Erosion Score						
Baseline	25 (8, 110)	29 (9, 100)	22 (3, 91)	22 (3, 80)	26 (4, 104)	
Change from baseline	2.0 (-1.0, 9.7)	0.0 (-3.0, 4.3)	-0.3 (-3.1, 2.5)	0.5 (-3.0, 2.5)	-0.5 (-2.7, 2.5)	p<0.001
JSN Score						
Baseline	26 (3, 88)	29 (4, 80)	20 (3, 83)	24 (1, 79)	25 (3, 77)	
Change from baseline	1.5 (-0.8, 8.0)	0.0 (-2.5, 4.5)	0.0 (-3.4, 5.0)	0.0 (-3.0, 2.5)	0.0 (-3.0, 3.5)	p<0.001
[a] For comparisons of each dose against placebo						

Physical function response

Physical function and disability were assessed using the Health Assessment Questionnaire (HAQ) and the general health-related quality of life questionnaire SF-36. All doses/schedules of Remicade® + MTX showed significantly greater improvement from baseline in HAQ and SF-36 physical component summary score averaged over time through Week 54 compared to placebo + MTX, and no worsening in the SF-36 mental component summary score.

The median (interquartile range) improvement from baseline to Week 54 in HAQ was 0.1 (-0.1, 0.5) for the placebo + MTX group and 0.4 (0.1, 0.9) for Remicade® + MTX (p<0.001). Both HAQ and SF-36 effects were maintained through Week 102. Approximately 80% of patients in all doses/schedules of Remicade® + MTX remained in the trial through 102 weeks.

ASPIRE (T29) Study Results

The ASPIRE trial (T29) evaluated efficacy at 54 weeks in 1004 MTX-naïve patients with early active RA (≤3 years' duration). All patients received MTX (optimized to 20 mg/wk by Week 8) and either placebo, 3 mg/kg, or 6 mg/kg Remicade® at Weeks 0, 2, and 6 and every 8 weeks thereafter. In this trial, infusions were to be administered over 2 hours for the first 3 infusions. The duration of subsequent infusions could be shortened to not less than 40 minutes in patients who did not experience serious infusion reactions. The primary endpoints were improvement of signs and symptoms (change from baseline ACR score) at Week 54, prevention of structural damage (change from baseline in the van der Heijde-modified-Sharp score) at Week 54, and prevention of physical disability (change from baseline HAQ) from Week 30 to Week 54. The results for the 3 co-primary endpoints and key secondary endpoints are summarized in Table 14.

Table 14: Efficacy results of study T29 (ASPIRE) in early RA

		Remicade® + MTX	
	Placebo + MTX	**3 mg/kg q8 wks**	**6 mg/kg q8 wks**
Patients randomized	n=282	n=359	n=363
Parameter			
Primary Endpoints			
Percentage ACR improvement from baseline at Week 54 Mean Median	24.8% 26.4%	37.3% 38.9% p<0.001	42.0% 46.7% p<0.001
Change from baseline total vdH-S score at Week 54 Mean Median	3.70 0.43	0.42 0.00 p<0.001	0.51 0.00 p<0.001
Improvement from baseline HAQ from Week 30 to Week 54 (averaged over time) Mean Median	0.68 0.75	0.80 0.78 p=0.030	0.88 0.79 p<0.001
Secondary Endpoints			
Proportion of subjects with clinical response at Week 54	n=274	n=351	n=355
ACR 20	54%	62% p=0.028	66% p=0.001
ACR 50	32%	46% p<0.001	50% p<0.001
ACR 70	21%	33% p=0.002	37% p<0.001
Radiographic change from baseline at Week 54	n=226	n=306	n=306

		Remicade® + MTX	
	Placebo + MTX	**3 mg/kg q8 wks**	**6 mg/kg q8 wks**
Erosion score Mean Median	2.97 0.25	0.31 0.00 p<0.001	0.07 0.00 p<0.001
Joint space narrowing (JSN) score Mean Median	0.57 0.00	0.05 0.00 p<0.001	0.24 0.00 p=0.130
Patients with erosion score=0 at baseline and at Week 54	58% (23/40)	78% (39/50) p=0.037	79% (38/48) p=0.028
Patients with no new erosions in previously uninvolved joints	41% (93/227)	51% (155/306) p=0.027	55% (168/306) p=0.001
Improvement in physical function	n=275	n=354	n=358
Improvement from baseline HAQ from baseline to Week 54 (averaged over time) Mean Median	0.55 0.57	0.70 0.64 p<0.001	0.77 0.76 p<0.001
Change from baseline to Week 54 in SF-36 physical component Mean Median	10.1 8.9	11.7 10.9 p=0.099	13.2 11.8 p=0.003

Study Results

Clinical response

After 54 weeks of treatment, both doses of Remicade® resulted in statistically significantly greater improvement in signs and symptoms compared with MTX alone as measured by the proportion of patients achieving ACR 20, 50, and 70 response. In the combined Remicade® + MTX groups, 15% of patients achieved a major response vs. 8% of patients treated with MTX alone.

Radiographic response

Greater than 90% of patients had at least two evaluable x-rays. Inhibition of progression of structural damage was observed at Week 30 and Week 54 in the Remicade® + MTX groups compared with MTX alone. Remicade® + MTX stopped the progression of joint disease in more patients compared with MTX alone, 97% vs. 86%, respectively. Remicade® + MTX maintained an erosion-free state in a significantly greater proportion of patients than MTX alone, 79% vs. 58%, respectively. Fewer patients in the Remicade® + MTX groups (47%) developed erosions in uninvolved joints compared with MTX alone (59%).

Physical function response

Both Remicade® treatment groups showed statistically significantly greater improvement in HAQ from baseline averaged over time through Week 54 compared with MTX alone; 0.7 for Remicade® + MTX vs. 0.6 for MTX alone ($p<0.001$). There was no worsening in the SF-36 mental component summary score.

Ankylosing Spondylitis

Table 15: Summary of patient demographics for clinical trials in ankylosing spondylitis

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Gender and Race n (%)
P01522	Randomised, double-blind, placebo-controlled phase (0 to 12 weeks) followed by open-label noncomparative phase (12 – 54 weeks)	Phase A: 5 mg/kg infliximab or placebo administered intravenously at weeks 0, 2, and 6 Phase B: open-label 5 mg/kg infliximab administered intravenously at weeks 12 and every 6 weeks up to Week 54	70	39.5 (21 to 61)	46 (66%) male 24 (34%) female Race not available

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Gender and Race n (%)
C0168T51 (ASSERT)	Randomized, double-blind, placebo controlled, multicenter study.	**Stage 1:** placebo (Group 1) or 5 mg/kg infliximab (Group 2) administered intravenously at weeks 0, 2, 6, 12, and 18. **Stage 2:** **Group 1:** Infliximab 5 mg/kg infusions at Weeks 24, 26, 30, and every 6 weeks thereafter through Week 96. **Group 2:** Infliximab 5 mg/kg infusion every 6 weeks through Week 96. Starting at Week 36, if subjects in Group 2 had a BASDAI ≥3 at 2 consecutive visits, they were to receive a 7.5 mg/kg infliximab infusion and continued to receive 7.5 mg/kg infliximab infusions every 6 weeks thereafter through Week 96.	279	39.8 (18 - 74)	**M:** 225 (80.6%) **F:** 54 (19.4%) **Caucasian:** 273 (97.8%) **Black:** 2 (0.7%) **Asian:** 2 (0.7%) **Other:** 2 (0.7%)

The safety and efficacy of Remicade® were assessed in two multicenter, double-blind, placebo-controlled studies in patients with active ankylosing spondylitis (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥4 and spinal pain ≥4 on a scale of 1-10). The study design and demographics of the study population are summarized in Table 15. Disease activity was measured using the Ankylosing Spondylitis Assessment (ASAS) 20 response criteria and/or the BASDAI. Physical function was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI).

The first trial (P01522) evaluated Remicade® in 70 patients with active ankylosing spondylitis. During the 3-month double-blind phase, patients received either 5 mg/kg Remicade® or placebo at Weeks 0, 2, 6 (35 patients in each group). Starting at Week 12, placebo patients were switched to Remicade® and all patients subsequently received 5 mg/kg Remicade® every 6 weeks up to Week 54. The results of this study were similar to those seen in 8 additional investigator-initiated studies of 169 patients with active ankylosing spondylitis. One-year efficacy was assessed at week 54. Fifty-three patients continued in an open-label long-term extension from week 54 to week 102.

In the second trial (ASSERT), 279 patients with ankylosing spondylitis were randomized to receive either placebo (78 patients, Group 1) or 5 mg/kg Remicade® (201 patients, Group 2) at 0, 2, 6, 12 and 18 weeks. At week 24, patients receiving placebo were crossed over to receive 5 mg/kg Remicade® at week 24, 26 and 30 and then every 6 weeks through to week 96; patients in Group 2 continued at 5 mg/kg Remicade® every 6 weeks through to week 96. Starting with the week-36 infusion and continuing through the week-96 infusion, if a patient in Group 2 had a BASDAI ≥3 at 2 consecutive visits, this patient would receive a 7.5 mg/kg infliximab infusion and would continue to receive 7.5 mg/kg infliximab infusions every 6 weeks thereafter through week 96. Patients had a final evaluation at week 102.

The demographics and disease characteristics at baseline for the 2 phase III studies are shown in Table 16.

Table 16: Summary of demographics and disease characteristics at baseline

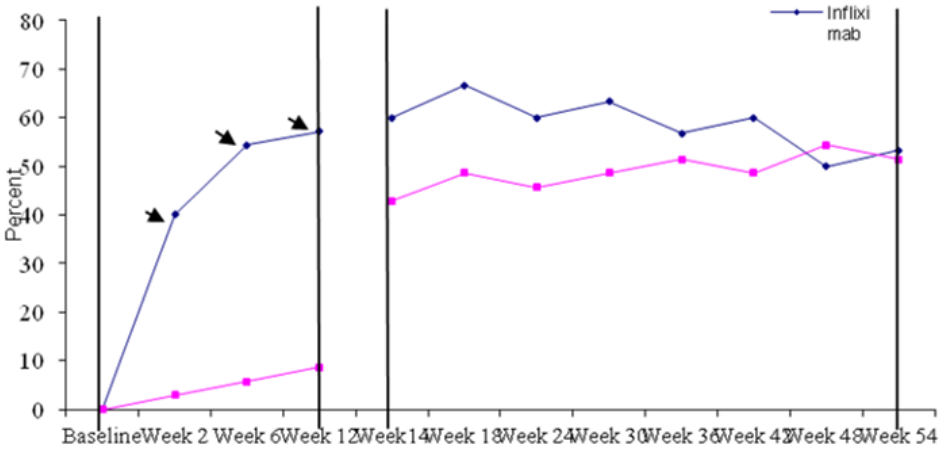
	ASSERT		P01522	
	Placebo	Remicade®	Placebo	Remicade®
Subjects randomized	78	201	35	35
Sex				
Male	87.2%	78.1%	62.9%	68.6%
Female	12.8%	21.9%	37.1%	31.4%
Median age (yrs)	41.0	40.0	38.0	40.0
Median disease duration (yrs)[a]	13.2 [b]	7.7 [b]	14.0	15.0
Median BASDAI (0 – 10)	6.5	6.6	6.3	6.5
Median BASFI (0 – 10)	6.0	5.7	5.1	5.2
SF-36 physical component summary score	30.1	28.8	28.9	30.1
HLA-B27[c]				
Positive	88.5%	86.5%	85.7%	91.4%
Negative	11.5%	13.5%	11.4%	8.6%

[a] Disease duration in ASSERT is diagnosis duration and in P01522 is symptom duration.
[b] Mean disease duration in ASSERT was 11.9 years for the placebo group and 10.1 years for the Remicade® group.
[c] One subject in the placebo group of P01522 was missing HLA-B27 status results at baseline.

Study Results

The primary efficacy endpoint in study P01522 was improvement in signs and symptoms at Week 12, as assessed by the BASDAI. Treatment with Remicade® resulted in significant improvement, with 57% of Remicade®-treated patients achieving at least 50% reduction from baseline in BASDAI score, compared with 9% of placebo patients ($p<0.01$). Improvement was observed at Week 2, and was maintained through Week 54 (Figure 1). At the end of the second year of treatment, 56.6% of patients achieved at least a 50% reduction in BASDAI.

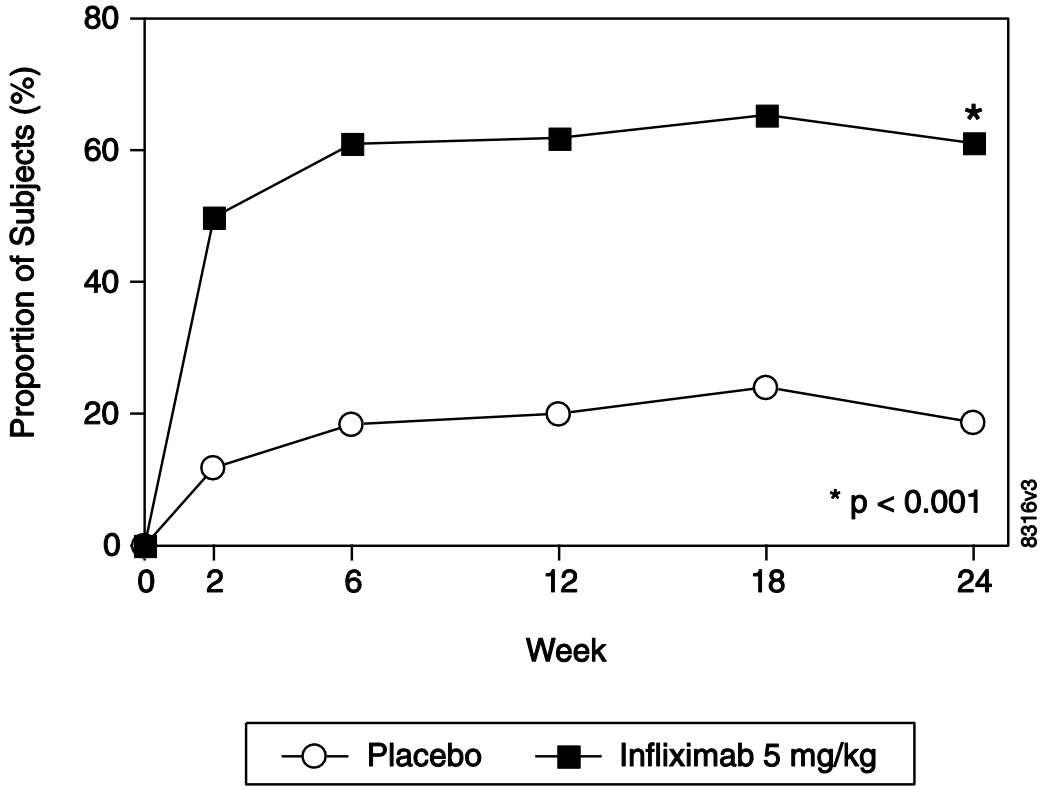
Figure 1: Percentage of subjects with at least 50% improvement in BASDAI score



Arrowed datapoints represent weeks where there were significant differences between the treatments (p<0.01)
Placebo patients were treated with placebo during the double-blind phase and infliximab during the open-label phase.

The primary efficacy endpoint in ASSERT was improvement in signs and symptoms at week 24, as assessed by the ASAS. The proportion of patients achieving an ASAS 20 response at 24 weeks was 61% in the Remicade®-treated group vs. 19% in the placebo group (p<0.001). Improvement was observed at week 2 and continued through week 24 (Figure 2 and Table 17). The percentage of patients achieving an ASAS 20 response at week 102 was 73.9% in the infliximab group.

Figure 2: Proportion of subjects achieving ASAS 20 response over time through Week 24 in ASSERT



At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving Remicade®, compared to 9% and 4%, respectively, for patients receiving placebo (p<0.001, Remicade® vs. placebo). A low level of disease activity (defined as a value <20 [on a scale of 0-100 mm] in each of the four ASAS response parameters) was achieved in 22% of Remicade®-treated patients vs. 1% in placebo-treated patients (p<0.001).

Table 17: Components of Ankylosing Spondylitis Disease Activity

	Placebo (n=78)		Remicade® 5mg/kg (n=201)		
	Baseline	24 Weeks	Baseline	24 Weeks	p-value
ASAS 20 response Criteria (Mean)					
Patient global assessment[a]	6.6	6.0	6.8	3.8	<0.001
Spinal pain[a]	7.3	6.5	7.6	4.0	<0.001
BASFI[b]	5.8	5.6	5.7	3.6	<0.001
Inflammation[c]	6.9	5.8	6.9	3.4	<0.001
Acute Phase Reactants					
Median CRP[d] (mg/dL)	1.7	1.5	1.5	0.4	<0.001
Spinal Mobility (cm, Mean)					
Modified Schober's test[e]	4.0	5.0	4.3	4.4	0.75
Chest expansion[e]	3.6	3.7	3.3	3.9	0.04
Tragus to wall[e]	17.3	17.4	16.9	15.7	0.02
Lateral spinal flexion[e]	10.6	11.0	11.4	12.9	0.03

[a] measured on a VAS with 0="none" and 10="severe"
[b] Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions
[c] Inflammation, average of last 2 questions on the 6 question BASDAI
[d] CRP normal range 0-1.0 mg/dL
[e] Spinal mobility normal values: modified Schober's test: >4 cm; chest expansion: >6 cm; tragus to wall: <15 cm; lateral spinal flexion: >10 cm

Physical function was assessed in both studies using the BASFI. In study P01522, the mean (SD) change at Week 12 from baseline BASFI score was -2.1 (1.6) in patients treated with Remicade® compared to -0.1 (1.8) in the placebo group (p<0.01). In ASSERT the median change (range) at Week 24 from baseline BASFI score was -1.7 (-8.7, 1.8) in patients treated with Remicade® compared to 0.0 (-5.9, 3.0) in the placebo group (p<0.001). The mean (SD) change from baseline was -2.1 (2.2) in patients treated with Remicade® compared to -0.2 (1.7) in the placebo group. The mean (SD) change from baseline through Week 102 in patients treated with Remicade® was -2.7 (2.2) in ASSERT and -2.1 (2.2) in study P01522.

In ASSERT the number of patients who achieved a ≥2 unit improvement in BASFI was also assessed. In the Remicade® group 47.5% of subjects showed a ≥2 units improvement from baseline in BASFI score at Week 24 compared to 13.3% in the placebo group (p<0.001). In the Remicade® group, 80.9% (76/94) of the subjects who showed a ≥2 units improvement at week 24 also showed a ≥2 units improvement at week 102.

The BASFI results are supported by an analysis of the physical component summary score of the SF-36. In ASSERT the median change (range) at Week 24 from baseline SF-36 physical component summary score was 10.2 (-8.5, 37.7) in patients treated with Remicade® compared to 0.8 (-14.1, 21.8) in the placebo group (p<0.001). The mean (SD) change from baseline was 10.8 (9.5) in patients treated with Remicade® compared to 1.5 (7.0) in the placebo group. In study P01522 the mean (SD) change at Week 12 from baseline SF-36 physical component summary score was 10.3 (8.3) in patients treated with Remicade® compared to -0.3 (8.3) in the

placebo group (p<0.01). The mean (SD) change from baseline through Week 102 in patients treated with Remicade® was 12.5 (9.8) in ASSERT and 11.0 (10.4) in study P01522.

Psoriatic Arthritis

Table 18: Summary of patient demographics at baseline; randomized subjects in IMPACT and IMPACT 2

	IMPACT		IMPACT 2	
	Placebo	5 mg/kg	Placebo	5 mg/kg
Subjects randomized	52	52	100	100
Sex				
N	52	52	100	100
Male	30 (57.7%)	30 (57.7%)	51 (51.0%)	71 (71.0%)
Female	22 (42.3%)	22 (42.3%)	49 (49.0%)	29 (29.0%)
Race				
N			100	100
Caucasian	NA	NA	94 (94.0%)	95 (95.0%)
Black	NA	NA	3 (3.0%)	2 (2.0%)
Asian	NA	NA	0 (0.0%)	3 (3.0%)
Other	NA	NA	3 (3.0%)	0 (0.0%)
Age (yrs)				
N	52	52	100	100
Mean±SD	45.2±9.7	45.7±11.1	46.5±11.3	47.1±12.8
Median	46.5	47.0	47.0	46.5
Range	(26, 70)	(22, 72)	(24.0, 71.0)	(18.0, 80.0)
Weight (kg)				
N	52	52	100	100
Mean±SD	81.1±16.0	82.9± 17.6	84.5±20.3	87.9±16.5
Median	81.2	81.0	81.9	86.8
Range	(51, 115)	(49, 120)	(46.8, 175.0)	(56.3, 155.5)
Height (cm)				
N	48	45	99	100
Mean±SD	170.8±9.6	170.4±9.4	169.3±10.0	172.4±9.4
Median	172.5	171.0	168.0	174.0
Range	(149, 192)	(153, 190)	(145.0, 203.0)	(137.0, 193.0)

Safety and efficacy of Remicade® were assessed in a multicenter, double-blind, placebo-controlled study (IMPACT 2) in 200 adult patients with active psoriatic arthritis despite DMARD or NSAID therapy (≥5 swollen joints and ≥5 tender joints) with one or more of the following subtypes: arthritis involving DIP joints (n=49), arthritis mutilans (n=3), asymmetric peripheral arthritis (n=40), polyarticular arthritis (n=100), and spondylitis with peripheral arthritis (n=8).

Patients also had plaque psoriasis with a qualifying target lesion ≥2 cm in diameter. Forty-six percent of patients continued on stable doses of methotrexate (≤25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg Remicade® or placebo at Weeks 0, 2, 6, 14, and 22 (100 patients in each group). At Week 16, placebo patients with <10% improvement from baseline in both swollen and tender joint counts were switched to Remicade® induction (early escape). At Week 24, all placebo-treated patients crossed over to Remicade® induction. Dosing continued for all patients through Week 46. At Week 38, patients in the randomized Remicade® treatment group with <20% improvement from baseline in the combined swollen and tender joint counts were to have their Remicade® dose increased to 10 mg/kg (dose escalation).

IMPACT and IMPACT 2 demographic information of the study populations are summarized in Table 18.

Study Results

Clinical response

Treatment with Remicade® resulted in improvement in signs and symptoms, as assessed by the ACR criteria, with 58% of Remicade®-treated patients achieving ACR 20 at Week 14, compared with 11% of placebo-treated patients ($p<0.001$). The response was similar regardless of concomitant use of methotrexate. Improvement was observed as early as Week 2. At 6 months, the ACR 20/50/70 responses were achieved by 54%, 41%, and 27%, respectively, of patients receiving Remicade® compared to 16%, 4%, and 2%, respectively, of patients receiving placebo. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and spondylitis with peripheral arthritis subtypes.

Compared to placebo, treatment with Remicade® resulted in improvements in the components of the ACR response criteria, as well as in dactylitis and enthesopathy (Table 19). The clinical response was generally maintained through Week 54, and positive results were also observed in placebo-treated patients who crossed over to Remicade® therapy.

The results of this study were similar to those seen in an earlier multicenter, randomized, placebo-controlled study (IMPACT) of 104 patients with psoriatic arthritis. Improvement in signs and symptoms were also generally sustained in that study through 98 weeks in the subset of patients who continued during the second year open-label extension.

Table 19: Components of ACR 20 and percentage of patients with 1 or more joints with dactylitis and percentage of patients with enthesopathy at baseline and Weeks 24 and 54

	Placebo → Remicade® 5 mg/kg[a]			Remicade® 5mg/kg		
Patients Randomized	(n=100)			(n=100)		
	Baseline	Week 24	Week 54	Baseline	Week 24[b]	Week 54
No. of Patients	100	100	91	100	100	100
Parameter (medians)						
No of Tender Joints[c]	24	20	8	20	6	7
No. of Swollen Joints[d]	12	9	3	12	3	3
Pain[e]	6.4	5.6	2.0	5.9	2.6	2.6
Physician's Global Assessment[e]	6.0	4.5	1.1	5.6	1.5	1.1
Patient's Global Assessment[e]	6.1	5.0	2.5	5.9	2.5	2.8
Disability Index (HAQ-DI)[f]	1.1	1.1	0.5	1.1	0.5	0.5
CRP (mg/dL)[g]	1.2	0.9	0.5	1.0	0.4	0.4
% Patients with 1 or more digits with dactylitis	41	33	15	40	15	16
% Patients with enthesopathy	35	36	20	42	22	21

[a] placebo-treated patients crossed over to Remicade® at Week 24
[b] p<0.001 for percent change from baseline in all components of ACR 20 at Week 24, p<0.05 for % of patients with dactylitis, and p=0.004 for % of patients with enthesopathy at Week 24
[c] Scale 0-68
[d] Scale 0-66
[e] Visual Analog Scale (0=best, 10=worst)
[f] Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)
[g] Normal range 0-0.6 mg/dL

Improvement in PASI in patients with baseline body surface area (BSA) ≥3% (n=87 placebo, n=83 Remicade®) was achieved at Week 14, regardless of concomitant methotrexate use, with 64% of Remicade®-treated patients achieving at least 75% improvement from baseline vs. 2% of placebo-treated patients; improvement was observed as early as Week 2. At 6 months, the PASI 75 and PASI 90 responses were achieved by 60% and 39%, respectively, of patients receiving Remicade® compared to 1% and 0%, respectively, of patients receiving placebo. The PASI response was generally maintained through Week 54, and positive results were also observed in placebo-treated patients who crossed over to Remicade® therapy.

A post-hoc analysis of major clinical response (defined as achieving an ACR 70 response at all visits for a continuous 24 week period during the study) in IMPACT 2 and IMPACT, revealed that 12.1% of Remicade®-treated patients were in major clinical response at Week 54. Due to the shorter period of placebo treatment (24 weeks or less), placebo-treated patients were assumed to have had a major clinical response if they achieved an ACR 70 response at the last visit on placebo. Two percent of placebo-treated patients achieved an ACR 70 response at the last visit before receiving Remicade® (p=0.006).

In the IMPACT study, 30.8% of patients randomized to Remicade® at baseline achieved a major clinical response during the 2-year study. In contrast, 0.0% of patients in the placebo group achieved an ACR 70 response at the last visit before receiving Remicade® therapy (p<0.001).

Radiographic response

Structural damage in both hands and feet was assessed radiographically by the change from baseline in the van der Heijde-Sharp (vdH-S) score, modified by the addition of hand DIP joints. The total modified vdH-S score is a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in the hands and feet. Table 20 summarizes the mean and median change scores at Weeks 24 and 54. Differences in mean changes at Week 24 indicated that significantly more progression in structural damage was observed in the placebo group (mean=0.82 total score) than in the Remicade® group (mean=-0.70 total score). The median change from baseline was 0.00 for both treatment groups. Overall, between-group differences were statistically significant for the total score (p<0.001) and the erosion (p<0.001) and JSN (p=0.013) component scores.

The Remicade®-treated patients continued to demonstrate inhibition of structural damage at Week 54 (mean change from baseline in total score=-0.94, p=0.001). Improvement in the placebo group was also demonstrated after these patients crossed over from placebo to Remicade® treatment, as evidenced by a decrease in their total modified vdH-S score from 0.82 at Week 24 to 0.53 at Week 54. Between-group differences were also statistically significant for the erosion (p<0.001) and JSN (p=0.047) component scores.

Table 20: Radiographic response at Weeks 24 and 54

	Placebo → Remicade® 5 mg/kg[a]	Remicade® 5 mg/kg
Subjects randomized	100	100
Change from baseline at Week 24		
Total modified vdH-S score		
N	100	100
Mean±SD	0.82±2.62	-0.70±2.53
Median	0.00	0.00
IQ range	(0.00, 0.50)	(-0.80, 0.00)
Range	(-4.50, 12.68)	(-15.00, 4.00)
p-value		<0.001
Erosion score		
N	100	100

	Placebo → Remicade® 5 mg/kg[a]	Remicade® 5 mg/kg
Mean±SD	0.51±1.68	-0.56±2.09
Median	0.00	0.00
IQ range	(0.00, 0.50)	(-0.51, 0.00)
Range	(-3.00, 9.00)	(-12.00, 3.00)
p-value		<0.001
JSN score		
N	100	100
Mean±SD	0.31±1.29	-0.14±0.81
Median	0.00	0.00
IQ range	(0.00, 0.00)	(0.00, 0.00)
Range	(-2.50, 9.51)	(-4.00, 2.50)
p-value		0.013
Change from baseline at Week 54		
Total modified vdH-S score		
N	100	100
Mean±SD	0.53±2.60	-0.94±3.40
Median	0.00	0.00
IQ range	(0.00, 0.00)	(-0.50, 0.00)
Range	(-6.13, 12.12)	(-29.00, 3.00)
p-value		0.001
Erosion score		
N	100	100
Mean±SD	0.42±2.02	-0.61±2.16
Median	0.00	0.00
IQ range	(0.00, 0.00)	(-0.50, 0.00)
Range	(-3.81, 12.12)	(-18.00, 2.00)
p-value		<0.001
JSN score		
N	100	100
Mean±SD	0.11±0.97	-0.33±1.37
Median	0.00	0.00
IQ range	(0.00, 0.00)	(0.00, 0.00)
Range	(-3.00, 6.01)	(-11.00, 1.00)
p-value		0.047

	Placebo → Remicade® 5 mg/kg[a]	Remicade® 5 mg/kg
[a] placebo crossed over to Remicade® at Week 24		

Radiographic progression was defined as a worsening from baseline in the modified vdH-S score that was greater than the smallest detectable change (SDC) at Week 24. The SDC captures changes greater than measurement error. Significantly more patients in the placebo group (12.0%) had radiographic progression compared with the proportion of patients in the Remicade® group (3.0%; p=0.017). Similarly, significant treatment group differences in favor of Remicade® were found for radiographic progression based on erosion scores (12.0% of placebo patients vs. 2.0% of Remicade® patients; p=0.006) and JSN scores (11.0% vs. 1.0%; p=0.003).

In addition to the analyses based on the change in vdH-S score, and to confirm the radiographic benefit in an individual patient, a radiographic assessment was also done on a subset of patients based on the clinical judgment of the readers, instead of the detailed scoring system.

In the IMPACT study, all radiographic observations of structural damage were from patients at Week 50 who had films of the same hands and feet taken at baseline and Week 50. Although there was no radiographic evaluation at the end of the placebo-controlled period, the IMPACT data showed no radiographic progression from baseline at Week 50 in both treatment groups as measured by changes in the total modified vdH-S scores.

Physical function

Remicade®-treated patients demonstrated improvement in physical function as assessed by HAQ (median percent improvement in HAQ score from baseline to Week 14 and 24 of 42.9% for Remicade®-treated patients vs. 0.0% for placebo-treated patients, p<0.001). The median HAQ score at baseline was 1.1 in each treatment group. These responses were maintained through Week 54 in the Remicade®-treated patients, and positive results were also observed in the placebo-treated patients who crossed over to Remicade® therapy.

Remicade® treatment results in a clinically meaningful response in HAQ scores. During the placebo-controlled portion of the trial (24 weeks), 54.0% of Remicade®-treated patients achieved a ≥0.3 units decrease in HAQ compared to 22% of placebo-treated patients (p<0.001). The durability of this response was demonstrated through Week 54. In Remicade®-treated patients who achieved >0.3 units decrease in HAQ at Week 14, 74.1% were able to maintain the decrease at Week 54. Over 90% of Remicade®-treated patients who achieved >0.3 units decrease in HAQ at both Weeks 14 and 24, were able to maintain the response at Week 54.

In the IMPACT study conducted in 104 patients with psoriatic arthritis, over 84% of Remicade®-treated patients who achieved ≥0.3 units decrease in HAQ at the end of 1 year and entered the year 2 extension were able to maintain the response at Week 98.

Remicade® treated patients also demonstrated improvement in health-related quality of life as measured by the physical and mental component summary scores of the SF-36 (median change from baseline to Week 14 of 8.7 and 2.1 for Remicade®-treated patients, respectively, vs. 1.0 and 0.5, respectively, for placebo-treated patients). Median baseline scores for the physical component summary score were 32.5 and 29.8 for the Remicade® and placebo groups, respectively; median baseline mental component summary scores were 47.0 and 49.7 for the Remicade® and placebo groups, respectively. These responses were maintained through

Week 54 in the Remicade®-treated patients, and positive results were also observed in the placebo-treated patients who crossed over to Remicade® therapy.

Active Crohn's Disease

Table 21: Summary of patient demographics for clinical trials in active Crohn's disease

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Gender and Race n (%)
T16	Randomised, double-blind, placebo-controlled, single dose-ranging	Single dose of 5 mg/kg, 10 mg/kg, or 20 mg/kg infliximab or placebo administered intravenously	108	37.7 (20 to 65)	55 (51%) male 53 (49%) female 108 (100%) Caucasian
T21 (ACCENT I)	Randomised, double-blind, placebo-controlled	Induction therapy: Infliximab 5 mg/kg administered intravenously at Week 0 Maintenance therapy: Placebo at Weeks 2 and 6, then every 8 weeks to Week 46 Infliximab 5 mg/kg at Weeks 2 and 6, then every 8 weeks to Week 46 Infliximab 5 mg/kg at Weeks 2 and 6, then 10 mg/kg every 8 weeks to Week 46	573 randomized; 580 enrolled	37 (18 to 76)	239 (42%) male 334 (58%) female 549 (96%) Caucasian 12 (2%) Black 5 (1%) Asian 7 (1%) Other

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Gender and Race n (%)
T67 (SONIC)	Phase 3b, multicenter, randomized, double-blind, active - controlled	Group I: Placebo infusions administered at Weeks 0, 2, 6, then every 8 weeks and AZA daily (2.5 mg/kg) Group II: Infliximab infusions (5 mg/kg) administered at Weeks 0. 2. 6, then every 8 weeks and placebo daily Group III: Infliximab infusions (5 mg/kg) administered at Weeks 0, 2, 6 then every 8 weeks and AZA daily (2.5 mg/kg)	Main study (entered/ completed): 508 /318 Group I: 170/86 Group II: 169/111 Group III: 169/121 Study extension (entered/ completed): Group I: 75/67 Group II: 97/85 Group III: 108/90	Main study 36.3 (18-80) Study extension: 36.9 (18-80)	Main Study: M: 262 (52%) F: 246 (48%) 435 Caucasian (92.8%) 21 Black (4.5%) 2 Asian (0.4%) 11 Other (2.3%)

The safety and efficacy of single and multiple doses of Remicade® were assessed in two randomised, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active Crohn's disease [Crohn's Disease Activity Index (CDAI) 220 and 400]. Patients receiving aminosalicylates, corticosteroids and/or immunomodulatory agents were permitted. The safety and efficacy of Remicade® was also assessed in a randomized, double-blind, active - controlled clinical study (SONIC) in immunomodulator - naïve adult patients with moderate to severe Crohn's disease (CDAI ≥220 and ≤450). A summary of the design and subject demographics of the three studies is presented in Table 21.

Study Results

In the single-dose trial of 108 patients (T16), 16% of placebo patients achieved a clinical response (decrease in CDAI 70 points) at Week 4 vs. 81% of patients receiving 5 mg/kg Remicade® ($p<0.001$). Additionally, 4% of placebo patients and 48% of patients receiving 5 mg/kg Remicade® achieved clinical remission (CDAI<150) at Week 4 (Table 22).

Table 22: Number of patients achieving clinical response or clinical remission at Week 4 following a single intravenous infusion

Parameter	Placebo	5 mg/kg Remicade®	p-value[a]
Number of patients achieving clinical response[b]	4/25 (16%)	22/27 (81%)	<0.001
Number of patients achieving clinical remission[c]	1/25 (4%)	13/27 (48%)	<0.01

[a] two-sided Fisher's Exact test
[b] 70-point reduction in CDAI
[c] reduction in CDAI to below 150 points

In a multidose trial (ACCENT I), 580 patients received 5 mg/kg at Week 0. Patients assessed by the investigator to be in clinical response (decrease in CDAI score of ≥25% and ≥70 points) at Week 2 were randomized to one of three treatment groups; the placebo maintenance group received placebo at Weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then 10 mg/kg every 8 weeks. The co-primary endpoints were the proportion of patients in clinical remission (CDAI <150) at Week 30 and time to loss of response through Week 54. Corticosteroid taper was permitted after Week 6. The results for the two co-primary endpoints and key secondary endpoints are summarized in Table 23.

Table 23: Efficacy results of study T21 (ACCENT I) in active Crohn's disease: Patients randomized as responders

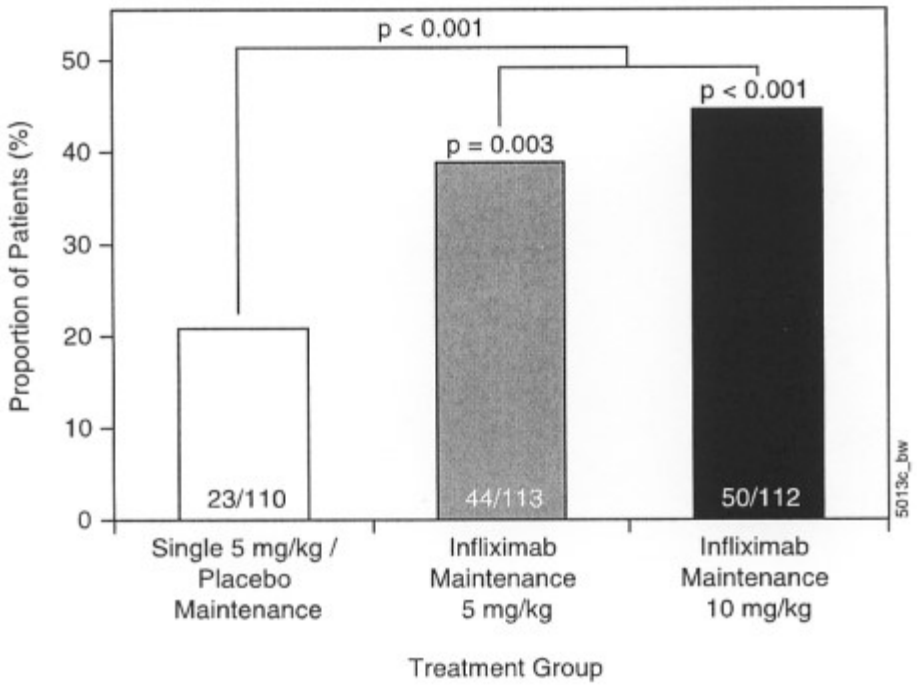
Parameter	Placebo	Remicade® Maintenance		
		5 mg/kg	10 mg/kg	Combined
Number of patients achieving clinical remission[a] at Week 30	23/110 (21%)	44/113 (39%) p=0.003	50/112 (45%) p<0.001	94/225 (42%) p<0.001
Median time to loss of response[b] through 54 (weeks)	19	38 p=0.002	>54 p<0.001	46 p<0.001
IBDQ median change from baseline at Week 30	12	24 p=0.015	30 p=0.001	28 p=0.001
Proportion of patients in clinical remission[a] and not receiving steroids at Week 30 (patients not on steroids at baseline)	6/56 (11%)	18/58 (31%) p=0.008	21/57 (37%) p=0.001	39/115 (34%) p=0.001

[a] reduction in CDAI to below 150 points
[b] reduction in CDAI score of >25% and >70 points

At Week 2, 58% (335) of 573 randomized patients were assessed by the investigator to be in clinical response. A significantly greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved clinical remission at Week 30, compared with patients in the placebo maintenance group (Figure 3) and similar results were seen at Week 54. Patients in the infliximab maintenance groups had significantly longer time to loss of response than patients in the placebo maintenance group (p<0.001). The median time to loss of response was

46 weeks in the combined infliximab maintenance group versus 19 weeks in the placebo maintenance group. Eighty-nine percent (50/56) of patients who lost clinical response on infliximab 5 mg/kg every eight week maintenance dosing, responded to a 10 mg/kg infliximab infusion.

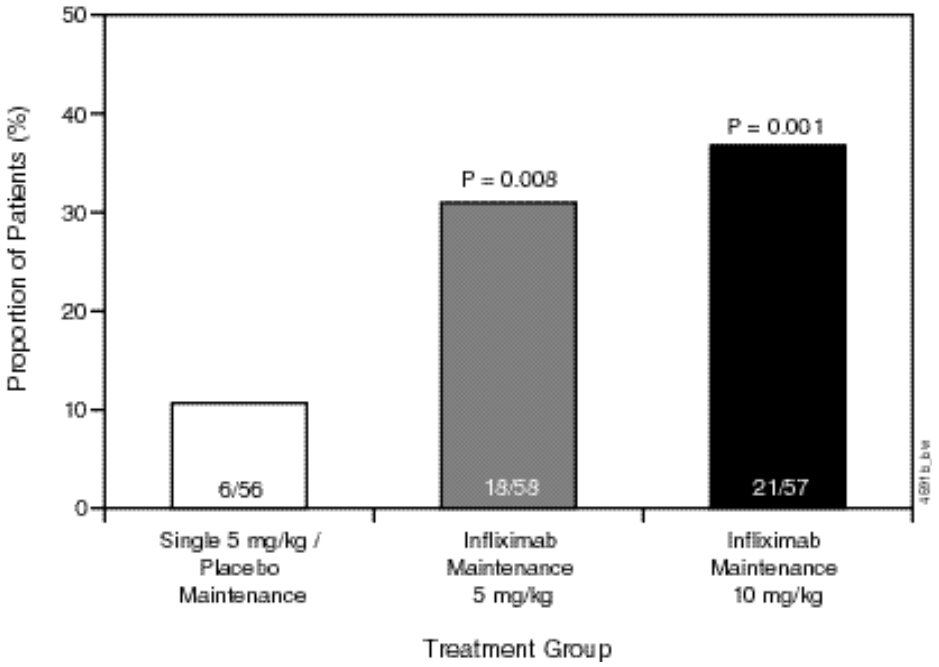
Figure 3: Proportion of patients who were in clinical remission (CDAI<150) at Week 30. Patients included all those randomized as responders.



Improvement in health-related quality of life was assessed using the SF-36 and the disease-specific Inflammatory Bowel Disease Questionnaire (IBDQ). Median improvement from baseline in IBDQ score was significantly greater in the 5 mg/kg (p=0.015) and 10 mg/kg (p=0.001) maintenance groups compared to the placebo maintenance group at Week 30 with similar results at Week 54.

As shown in Figure 4 for patients receiving corticosteroids at baseline, the proportion of these patients in clinical remission and not receiving corticosteroids at Week 30 was 31% for the 5 mg/kg maintenance group and 37% for the 10 mg/kg maintenance group, compared with 11% of patients in the placebo maintenance group (p=0.008 and p=0.001, for the 5 mg/kg and 10 mg/kg maintenance groups, respectively). By Week 22, the median corticosteroid dose at baseline (20 mg/day) was reduced to 10 mg/day in the placebo maintenance group; in the infliximab maintenance group it was reduced to 0 mg/day, indicating that at least 50% of these patients were able to discontinue steroid use. Results were similar at Week 54.

Figure 4: Proportion of patients who were in clinical remission (CDAI <150) and were not receiving corticosteroid at Week 30. Patients included all those randomized as responders.



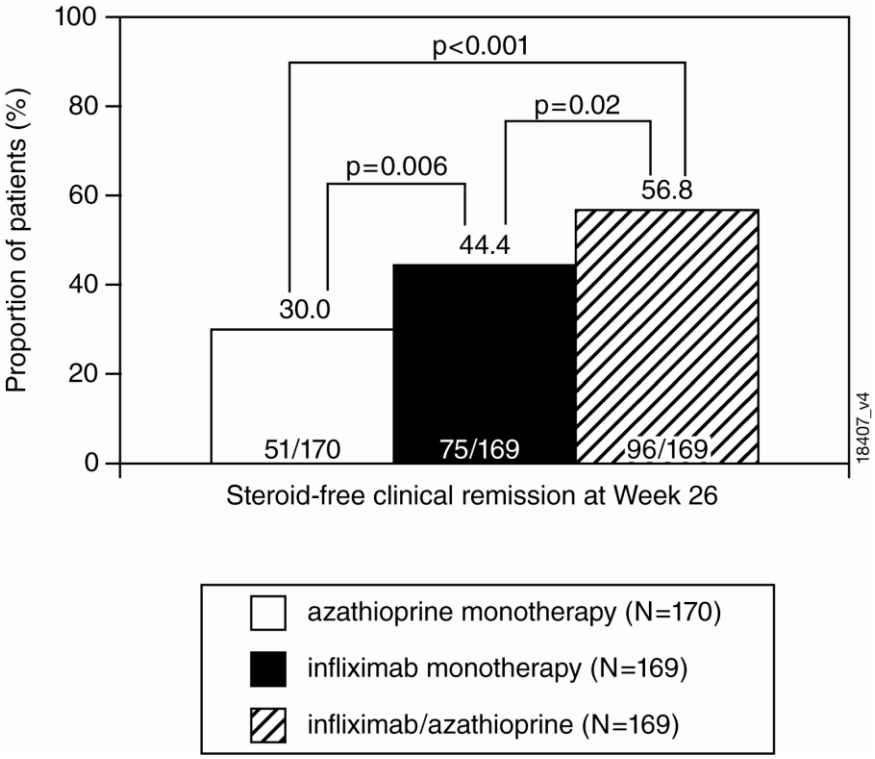
In a subset of patients who had mucosal ulceration at baseline and who participated in an endoscopic substudy, 10 of 32 patients in the infliximab maintenance group had endoscopic evidence of mucosal healing compared with 0 of 17 patients in the placebo group at Week 10. Of the infliximab treated patients showing mucosal healing at Week 10, 7 of 19 patients also showed mucosal healing at 54 weeks.

The safety and efficacy of Remicade® were assessed in a randomized, double-blind, 30-week study (SONIC) in 508 adult patients with moderate to severe Crohn's disease (CDAI ≥220 and ≤450) naïve to biologics and immunomodulators such as azathioprine (AZA). Two Remicade® treatment regimens; Remicade® combination therapy (Remicade® 5 mg/kg at 0, 2, 6 weeks then every 8 weeks plus a comparator [azathioprine (AZA) 2.5 mg/kg daily]) and Remicade® monotherapy (Remicade® 5 mg/kg at 0, 2, 6 weeks then every 8 weeks plus placebo capsules), were compared to the comparator [azathioprine (AZA) 2.5 mg/kg daily]) alone. Of the 318 randomized patients who completed the study through Week 30, 280 patients entered a double-blind study extension to evaluate the long-term efficacy and safety of Remicade® and/or AZA through Week 54. Patients were permitted to take concomitant doses of corticosteroids and/or aminosalicylates; 42% and 54% of patients, respectively, were taking these medications at study start.

A significantly greater proportion of patients receiving Remicade® combination therapy or Remicade® monotherapy achieved the primary endpoint of corticosteroid-free clinical remission (defined as patients in clinical remission [CDAI of <150] who had not taken oral systemic

corticosteroids [prednisone or equivalent] for at least 3 weeks and had not taken budesonide at a dose >6 mg/day for at least 3 weeks) at Week 26 compared to patients receiving AZA monotherapy (Figure 5).

Figure 5: Proportion of patients in corticosteroid-free clinical remission at Week 26 – all patients randomized in SONIC



At Week 50, 35% (*P*=0.028) of patients in the Remicade® monotherapy treatment group and 46% (*P*<0.001) of patients in the Remicade® combination treatment group were in corticosteroid-free clinical remission compared to 24% of patients in the AZA monotherapy arm.[9]

At Week 26 and 50, comparable numbers of patients remained corticosteroid free for ≥3 weeks in the three treatment groups.

Among the 508 patients randomized in SONIC, 309 patients had mucosal ulcerations at baseline (as determined by a video endoscopy). Of these patients, significantly more patients receiving Remicade® as combination therapy achieved mucosal healing (defined as the complete absence of mucosal ulcerations in the colon and terminal ileum as assessed by video endoscopy) at Week 26 compared to patients receiving AZA alone (43.9%; 47/107 vs. 16.5%; 18/109; p<0.001). More patients receiving Remicade® as monotherapy achieved mucosal healing than those receiving AZA alone (30.1%; 28/93 vs.16.5%; 18/109; p=0.02).

[9] When controlling the overall Type I error rate of 0.05 using the Bonferroni multiple comparisons method, the *P* value considered to be statistically significant was set at 0.008 (2-sided).

Fistulising Crohn's Disease

Table 24: Summary of patient demographics for clinical trials in Fistulising Crohn's Disease

Study #	Study design	Dosage, route of administration, and duration	Study subjects (n)	Mean age (years) (range)	Gender
T20	Randomised, double-blind, placebo-controlled.	5 mg/kg Remicade®, 10 mg/kg Remicade® or placebo administered intravenously at Weeks 0, 2 and 6.	94	37 (18 to 63)	47% male 53% female
ACCENT II	Randomised, double-blind, placebo-controlled.	5 mg/kg Remicade®, administered intravenously at Weeks 0, 2 and 6 followed by 5 mg/kg Remicade® or placebo maintenance dosing every 8 weeks through Week 46.	306	39 (18 to 78)	51% male 49% female

The safety and efficacy of Remicade® were assessed in two randomised, double-blind, placebo controlled studies. These studies, T20 and T26 (ACCENT II), included patients with fistulising Crohn's disease with fistula(s) that were of at least 3 months duration. Concurrent use of stable doses of corticosteroids, 5-ASA, antibiotics, methotrexate (MTX), 6-mercaptopurine (6-MP) and/or azathioprine (AZA) was permitted.

A summary of patient demographics and design of the two studies is presented in Table 24. In ACCENT II, patients may have been enrolled with rectovaginal fistulas as well as draining enterocutaneous (perianal, abdominal) fistula(s). At Week 14 in ACCENT II, patients in fistula response (defined as ≥50% reduction from baseline in the number of draining fistulas) at both Weeks 10 and 14 were randomised separately from those not in response to receive either placebo or 5 mg/kg Remicade® maintenance dosing at Week 14 and then every eight weeks through Week 46.

Study Results

Table 25 presents the results of the primary and secondary endpoints of study T20. In addition to these results, the median time to onset of response and median duration of response in Remicade® treated patients in the T20 study were 2 and 12 weeks, respectively.

Table 25: Results of study T20 in fistulizing Crohn's disease[a]

Primary Endpoint	Placebo	Remicade®
≥50% reduction from baseline in the number of draining fistulas for at least 2 consecutive visits	8/31 (26%)	**5 mg/kg:** 21/31 (68%), p=0.002 **10 mg/kg:** 18/32 (56%), p=0.021 **Combined:** 39/63 (62%), p=0.002
Secondary Endpoint		
Closure of all fistulas	4/31 (13%)	**5 mg/kg:** 20/31 (65%), p≤0.001 **10 mg/kg:** 13/32 (41%), p=0.022 **Combined:** 33/63 (52%), p≤0.001
[a] all p-values are compared to placebo		

The primary endpoint of ACCENT II study was the time from randomization to loss of fistula response among patients who were in fistula response at Week 14. At the time of randomization (Week 14), 69% (195/282) of patients were in fistula response. A significantly longer time to loss of fistula response was seen in the Remicade® maintenance group compared with the placebo maintenance group (p<0.001, Figure 6). The median time to loss of fistula response following randomization was >40 weeks for patients in the Remicade® maintenance group compared with 14 weeks for patients in the placebo maintenance group. Subgroup analyses of the proportion of patients in fistula response at Week 54 showed that Remicade® maintenance was significantly better than placebo maintenance for patients with baseline CDAI ≥150. The analyses also suggested that Remicade® maintenance was better than placebo maintenance for patients with baseline CDAI<150; however, these analyses were based on a small number of patients and the results were not significant.

Figure 6: Fistula response over time

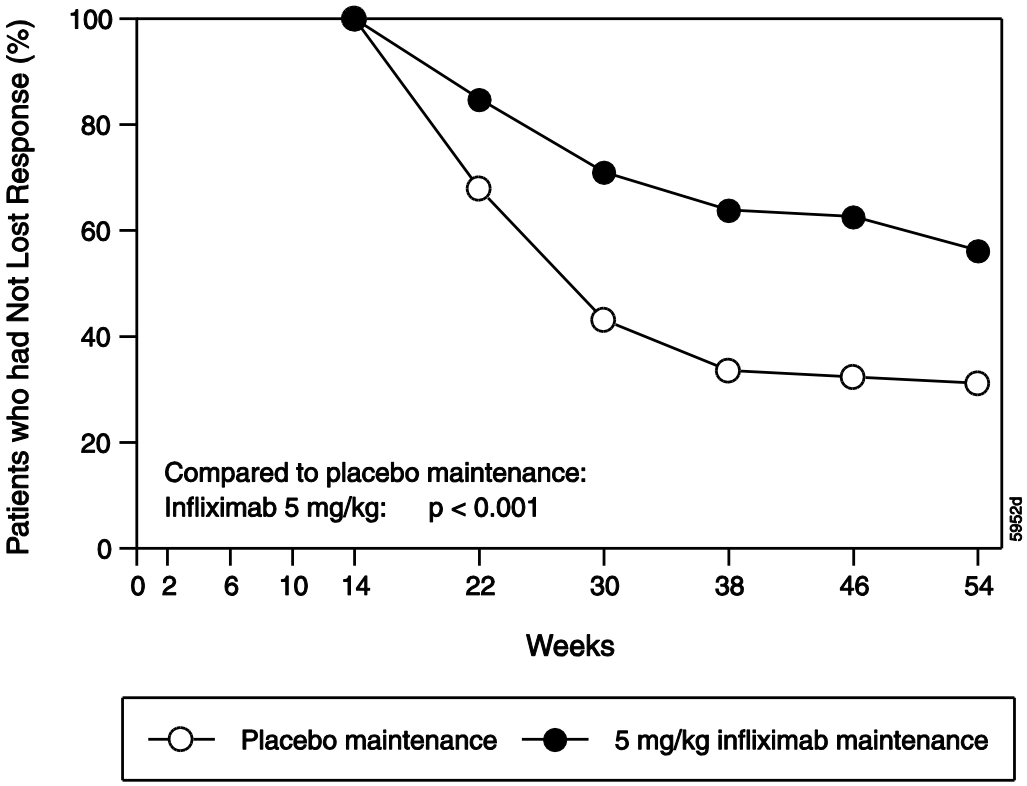


Table 26: Number of patients randomized as responders who lost fistula response by category

	Placebo Maintenance	Remicade® Maintenance
Patients randomized	99	96
Patients who lost fistula response	61 (62%)	40 (42%)
Loss of response category		
Reduction from baseline in number of draining fistulas that was <50% over 4 weeks or more	16 (16%)	13 (14%)
Change in medication	31 (31%)	19 (20%)
Surgical procedure for Crohn's disease	0 (0%)	1 (1%)
Crossover to treatment with increased dose of Remicade®	13 (13%)	7 (7%)
Discontinuation due to lack of efficacy	1 (1%)	0 (0%)

The results of secondary endpoints in ACCENT II are presented in Table 27.

Table 27: Results of study T26 (ACCENT II) in fistulising Crohn's disease[a]

Secondary Endpoints	Placebo Maintenance	Remicade® Maintenance
Number of patients with all fistulas closed at Week 30	26/98 (27%)	46/96 (48%), p=0.002
Number of patients with all fistulas closed at Week 54	19/98 (19%)	33/91 (36%), p=0.009
Median duration of fistula closure	23 weeks	40 weeks, p<0.001
Number of patients developing new fistulas	19/99 (19%)	14/96 (15%), p=0.391
Number of patients with all fistulas closed at every week from Week 22 to Week 54	16/99 (16%)	23/96 (24%), p=0.174
Number of patients in CDAI response at Week 30 [b]	9/31 (29%)	17/33 (52%), p=0.067
Number of patients in CDAI response at Week 54 [b]	2/31 (7%)	12/33 (36%), p=0.004
Number of patients in CDAI remission at Week 30 who were not in remission at baseline [b]	11/57 (19%)	24/57 (42%), p=0.008
Number of patients in CDAI remission at Week 54 who were not in remission at baseline [b]	6/57 (11%)	17/57 (30%), p=0.010
Number of patients in CDAI remission at Week 30 who were in remission at baseline [b]	18/40 (45%)	26/39 (67%), p=0.053
Number of patients in CDAI remission at Week 54 who were in remission at baseline [b]	15/40 (38%)	21/39 (54%), p=0.145
Median IBDQ improvement from baseline at Week 30[c]	4	14, p=0.002
Median IBDQ improvement from baseline at Week 54 [c]	5	10, p=0.029
Mean number of hospitalizations per patients	0.31	0.11, p=0.021
Mean number of surgeries and procedures per patients	1.26	0.65, p=0.111

[a] all p-values are compared to placebo
[b] CDAI response is a reduction from baseline CDAI score of ≥25% and ≥70 points in patients with a baseline score of ≥220. CDAI remission is a CDAI score of <150 points. The possible range for CDAI scores is from 0 to >750.
[c] The possible range for IBDQ scores is from 32 to 224. ACCENT II did not specify a minimally important difference for change in IBDQ score.

Patients who responded to treatment and subsequently lost their fistula response in ACCENT II were eligible to cross over to treatment with Remicade® at 5 mg/kg, if receiving placebo, or to a

higher dose of Remicade® (10 mg/kg), if receiving Remicade®. For patients who lost fistula response, treatment with an increased dose tended to re-establish fistula response.

Reduction in average daily corticosteroid dose was greater in the Remicade® maintenance group compared with the placebo maintenance group at all time points.

In the ACCENT II study, there was no difference between maintenance arms for proportions of patients with newly diagnosed fistula-related abscesses. The adverse event proctalgia was reported more frequently in subjects receiving Remicade® maintenance compared with placebo maintenance.

Active Crohn's Disease in Pediatric Patients

Table 28: Summary of patient demographics for clinical trials in active pediatric Crohn's disease

Study #	Study Design	Dosage, route of administration and duration	Study Subjects (n)	Mean age (range)	Gender and Race n (%)	
T55	Phase 1 Open-label, single-dose study	Single intravenous infusion of 5 mg/kg infliximab	6	9.5 (9.0 – 11.0)	4 (66.7%) 2 (33.3%) 6 (100.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)	female male Caucasian Black Asian Other
T23	Phase 1/2 Randomised, dose-blinded, single-dose study with an open-label retreatment extension	Single intravenous infusion of 1 mg/kg, 5 mg/kg, or 10 mg/kg infliximab Retreatment extension: up to 8 intravenous infusions of 5 mg/kg infliximab over a 48-week period	21 8 / 21	14.6 (11.0-17.0)	6 (28.6%) 15 (71.4%) 19 (90.5%) 2 (9.5%) 0 (0.0%) 0 (0.0%)	female male Caucasian Black Asian Other
T47	Phase 3 Randomised, open-label study of induction and maintenance therapy	Intravenous infusions of infliximab 5 mg/kg for all patients at weeks 0, 2, and 6 Patients in clinical response at week 10 randomised to maintenance treatment with intravenous infusions of 5 mg/kg infliximab either q8 weeks or q12 weeks	112 103 / 112	13.3 (6.0 – 17.0)	46 (41.1%) 66 (58.9%) 94 (83.9%) 15 (13.4%) 1 (0.9%) 2 (1.8%)	female male Caucasian Black Asian Other

The safety and efficacy of Remicade® was assessed in a randomised, single-dose, multicenter Phase 2 study (T23) of 21 pediatric patients who were 11 to 17 years old (median age 15.0) with active Crohn's disease (median Pediatric Crohn's Disease Activity Index [PCDAI] of 43) despite use of corticosteroids or immunomodulators (57% were receiving 6-MP or AZA and an additional 14% were receiving MTX; and 91% were receiving corticosteroids at study entry). Eight of the 21 pediatric patients enrolled in T23 participated in its extension. The safety and efficacy of Remicade® were also assessed in a randomised, multiple-dose, open-label, multicenter Phase 3 study (REACH) in 112 pediatric patients 6 to 17 years old (median age 13.0 years) with moderately to severely active Crohn's disease (median PCDAI of 40) and an inadequate response to conventional therapies. In REACH, all subjects were required to be on a stable dose of 6-MP, AZA, or MTX (35% were also receiving corticosteroids at baseline).

A summary of patient demographics and design of the REACH trial is presented in Table 28.

Study Results

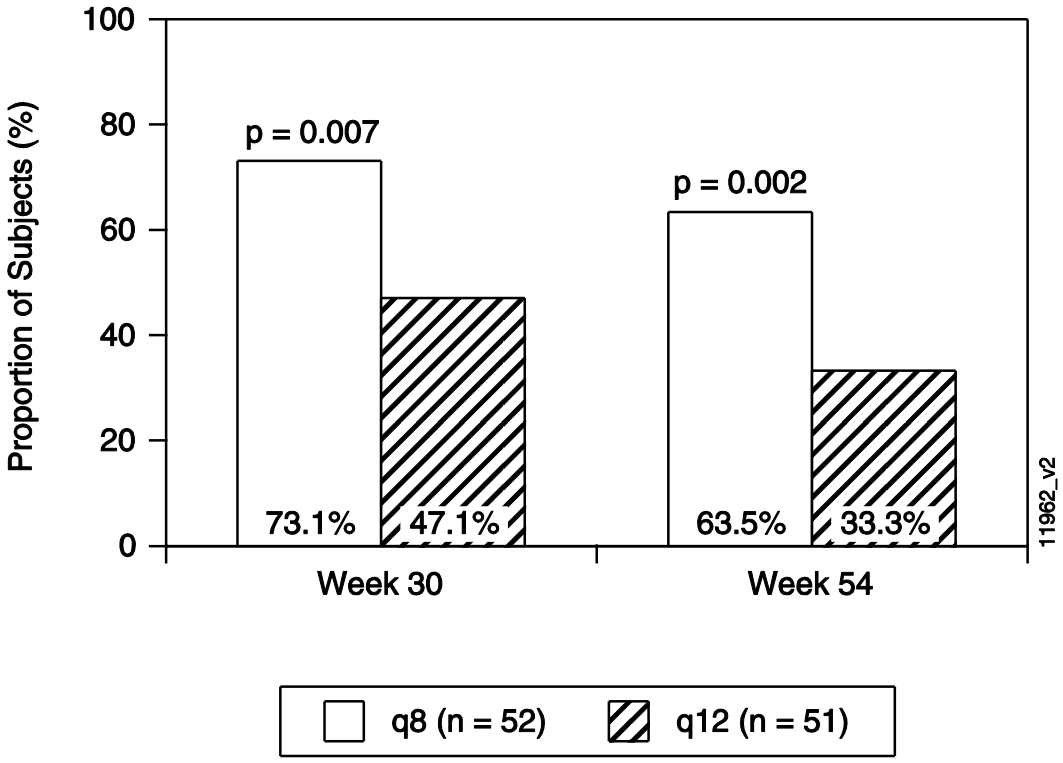
In the Phase 2 single-dose trial (T23) of 21 pediatric patients, all patients achieved a clinical response (decrease in CDAI ≥70 points or decrease in PCDAI ≥10 points) at some point in the 20 weeks following the single dose of Remicade®. Clinical remission, defined as a reduction in the modified CDAI score to below 150 points or a reduction in the PCDAI to below 10 points, was achieved in 10 patients (47.6%; 16.7% in the 1 mg/kg, 57.1% in the 5 mg/kg, and 62.5% in the 10 mg/kg Remicade® treatment groups). All 7 patients who had fistulising disease had their fistulas closed at a minimum of 1 evaluation visit.

In the Phase 3 multidose trial (REACH), 112 patients received 5 mg/kg Remicade® at weeks 0, 2, and 6. Patients assessed by the investigator to be in clinical response (defined as a decrease from baseline in the PCDAI score of ≥15 points and total PCDAI score of ≤30 points) at week 10 (n=103) were randomised to 1 of 2 treatment groups and received either 5 mg/kg infliximab q8 weeks or q12 weeks as a maintenance treatment regimen. If response was lost during maintenance treatment, crossing over to a higher dose (10 mg/kg) or shorter dosing interval (q8 weeks) was allowed.

In REACH, the proportion of patients achieving clinical response at week 10 was 88.4% (99/112) compared with 66.7% (128/192) in adults (ACCENT I). Similarly, the proportion of patients achieving clinical remission, defined as a PCDAI score of ≤10 points, at week 10 was 58.9% (66/112) compared with 39.1% (75/192) in adults (ACCENT 1).

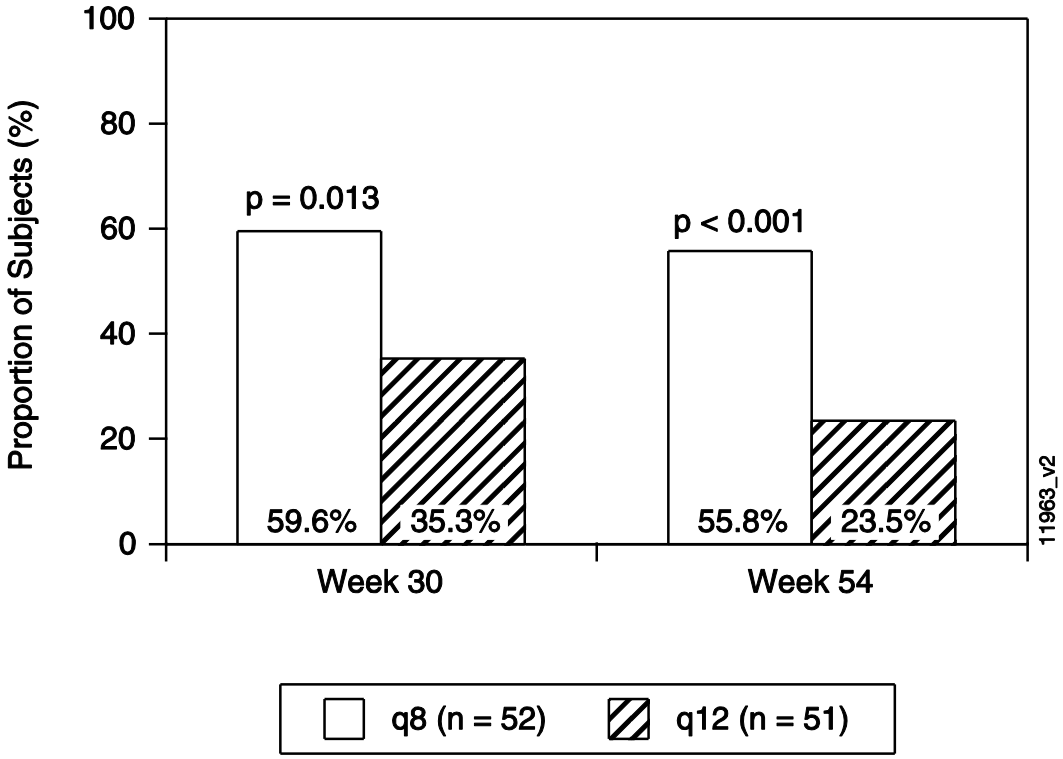
In REACH, at weeks 30 and 54, the proportion of patients in clinical response was determined for both maintenance treatment groups (Figure 7). At week 30, the proportion of patients in clinical response was significantly higher in the q8 week (73.1%, 38/52) than in the q12 week maintenance treatment group (47.1%, 24/51; p=0.007). At week 54, the proportion of patients in clinical response was also significantly higher for subjects in the q8 week (63.5%, 33/52) than in the q12 week maintenance treatment group (33.3%, 17/51; p=0.002).

Figure 7: Clinical response at Weeks 30 and 54 – Remicade® 5 mg/kg q8 weeks and Remicade® 5 mg/kg q12 weeks



At week 30 of the REACH trial, the proportion of patients in clinical remission was significantly higher in the q8 week maintenance treatment group (59.6%, 31/52) than in the q12 week maintenance treatment group (35.3%, 18/51; p=0.013). At week 54, the proportion of patients in clinical remission was also significantly higher for patients in the q8 week (55.8%, 29/52) than in the q12 week (23.5%, 12/51; p<0.001) maintenance treatment groups (Figure 8).

Figure 8: Clinical remission at Weeks 30 and 54 – Remicade® 5 mg/kg q8 weeks and Remicade® 5 mg/kg q12 weeks



For randomised patients in REACH, the average daily corticosteroid dose was significantly lower than baseline at weeks 10, 30, and 54. The proportion of patients able to discontinue corticosteroids while in remission at week 30 was 45.8% and 33.3% for the q8 week and q12 week maintenance groups, respectively. At week 54, the proportion of patients able to discontinue corticosteroids while in remission was 45.8% and 16.7% for the q8 and q12 week maintenance groups, respectively. In both groups, the average corticosteroid dose decreased so that half of the patients had discontinued corticosteroids by their first maintenance visit (week 14 for the q8 week and week 18 for the q12 week maintenance treatment group) (Figure 9).

Figure 9: Summary of median daily corticosteroid (prednisone equivalent) dose (mg/kg/day) through Week 54; randomized subjects taking corticosteroids at baseline

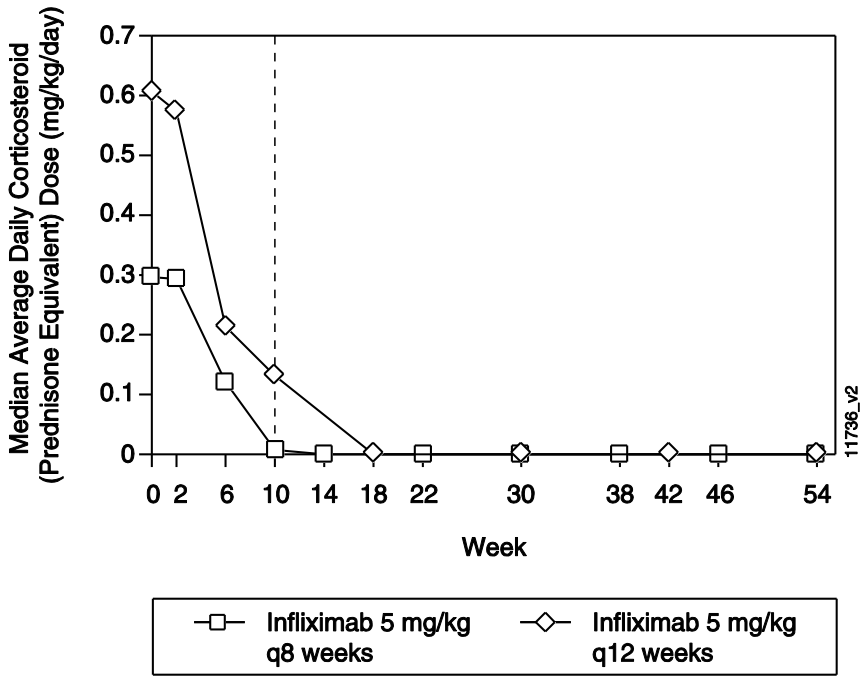


Table 29 presents the results of the primary and secondary endpoints of the REACH trial.

Table 29: Results of study T47 (REACH) in pediatric patients with Crohn's disease (all randomised subjects)

Primary and Secondary Endpoints	Remicade®		
	q8 weeks	q12 weeks	Combined
Number of subjects in clinical response [a]			
Week 10 (**Primary Endpoint)**			99/112 (88.4%) [e]
Week 30	38/52 (73.1%)	24/51 (47.1%), p=0.007 [b]	62/103 (60.2%)
Week 54	33/52 (63.5%)	17/51 (33.3%), p=0.002 [b]	50/103 (48.5%)
Number of subjects in clinical remission [c]			
Week 10			66/112 (58.9%) [e]
Week 30	31/52 (59.6%)	18/51 (35.3%), p=0.013 [b]	49/103 (47.6%)
Week 54	29/52 (55.8%)	12/51 (23.5%), p<0.001 [b]	41/103 (39.8%)
Number of subjects in clinical remission [c] off corticosteroids			
Week 30	11/24 (45.8%)	4/12 (33.3%), p=0.473 [b]	15/36 (41.7%)
Week 54	11/24 (45.8%)	2/12 (16.7%), p=0.086 [b]	13/36 (36.1%)
Mean improvement from baseline in daily corticosteroid (P.Eq) dose (mg/kg/day)			
Week 10	-	-	0.3, p<0.001 [d]
Week 30	-0.3	-0.5, p=0.449 [b]	0.4, p<0.001 [d]
Week 54	-0.3	-0.5, p=0.434 [b]	0.4, p=0.001 [d]
Mean improvement from baseline in IMPACT III			
Week 10	-	-	23.9, p<0.001 [d]
Week 30	-	-	21.1, p<0.001 [d]
Week 54	-	-	24.3, p<0.001 [d]

Primary and Secondary Endpoints	Remicade®		
	q8 weeks	q12 weeks	Combined
Mean improvement from baseline in z-score			
Week 30	-	-	0.3, p<0.001 [d]
Week 54	-	-	0.5, p<0.001 [d]
Number of subjects with at least 0.5 SD improvement in z-score			
Week 30	8/23 (34.8%)	2/15 (13.3%)	10/38 (26.3%)
Week 54	10/23 (43.5%)	3/15 (20.0%)	13/38 (34.2%)
Number of subjects with at least 1.0 SD improvement in z-score			
Week 30	1/23 (4.3%)	0/15 (0%)	1/38 (2.6%)
Week 54	3/23 (13.0%)	1/15 (6.7%)	4/38 (10.5%)

[a] Clinical response is defined as a decrease from baseline in the PCDAI score of at least 15 points with a total score of no more than 30 points.
[b] p-values are comparing the q8 and q12 week maintenance treatment groups using a chi-square test.
[c] Clinical remission is defined as a PCDAI score of ≤10 points.
[d] p-values are comparing the post baseline measurement with the baseline measurement using a paired t-test.
[e] All treated subjects.

The incidence of infections at Week 10 and at Week 54 was reported as numerically greater in the q8 week maintenance treatment group than in the q12 week maintenance treatment group, however, the incidence of serious infections were similar.

The extent to which patients were affected by their bowel disease was assessed using IMPACT III (a questionnaire with a possible score ranging from 35 to 175 specifically developed and validated for use in pediatric inflammatory bowel disease) in a subset of North American patients. Significant improvement from baseline in the IMPACT III score was observed at week 10 (23.9 for randomised subjects and 22.9 for treated subjects, p<0.001) and at weeks 30 and 54 (21.1 and 24.3, for all randomised subjects, respectively, p<0.001 for all time points) in patients treated with Remicade®.

The height z-score is a measure of the deviation of the pediatric patient's height from the expected height for a population of the same age and gender. By week 54, in children with a delayed bone age who had received 5 mg/kg of infliximab q8 weeks (n=23 at baseline), 43.5% had improved their height z-score by at least ½ standard deviation, and 13.0% had improved their height z-score by at least 1 standard deviation by week 54 (based on the reference population).

Plaque Psoriasis

Table 30: Summary of demographics at baseline; randomized subjects in EXPRESS, and EXPRESS II

	EXPRESS	EXPRESS II
Subjects randomized	378	835
Sex		
N	378	835
Male	268 (70.9%)	554 (66.3%)
Female	110 (29.1%)	281 (33.7%)
Race		
N	378	835
Caucasian	369 (97.6%)	773 (92.6%)
Black	2 (0.5%)	19 (2.3%)
Asian	4 (1.1%)	23 (2.8%)
Other	3 (0.8%)	20 (2.4%)
Age (yrs)		
N	378	835
Mean±SD	42.8±11.9	44.0±12.7
Median	42.0	44.0
IQ range	(34.0, 51.0)	(34.0, 53.0)
Range	(19.0, 76.0)	(18.0, 80.0)
Weight (kg)		
N	375	835
Mean±SD	86.6±19.8	91.9±22.8
Median	86.0	88.9
IQ range	(73.2, 96.5)	(76.0, 104.0)
Range	(43.0, 162.3)	(44.3, 184.2)
Height (cm)		
N	377	835
Mean±SD	172.6±10.0	171.8±9.8
Median	173.0	172.0
IQ range	(166.0, 180.0)	(165.0, 179.0)
Range	(145.0, 194.0)	(137.0, 200.0)

The safety and efficacy of Remicade® were assessed in two randomized double-blind placebo-controlled studies in adults with chronic, stable plaque psoriasis involving ≥10% BSA, a minimum PASI score of 12, and who were candidates for systemic anti-psoriatic therapy or

phototherapy. Patients with guttate, pustular, or erythrodermic psoriasis were excluded from the study. No concomitant anti-psoriatic therapies were allowed during the study, with the exception of low-potency topical corticosteroids on the face and groin after Week 10. Demographic information for both study populations are summarized in Table 30.

The EXPRESS study evaluated 378 patients who received placebo or Remicade® at a dose of 5 mg/kg at Weeks 0, 2, and 6 (induction therapy), followed by maintenance therapy every 8 weeks through Week 22. At Week 24, the placebo group crossed over to Remicade® induction therapy (5 mg/kg), followed by maintenance therapy every 8 weeks (placebo/Remicade® group) through Week 46. Patients originally randomized to Remicade® continued to receive Remicade® 5 mg/kg every 8 weeks through Week 46.

The EXPRESS II study evaluated 835 patients who received placebo or Remicade® at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6 (induction therapy). At Week 14, within each dose, patients in the two Remicade® groups were randomized to either scheduled (every 8 weeks) or as needed (PRN) maintenance treatment through Week 46. At Week 16, the placebo group crossed over to Remicade® induction therapy (5 mg/kg), followed by maintenance therapy every 8 weeks through Week 46.

The primary endpoint was the proportion of patients who achieved a reduction in score of at least 75% from baseline at Week 10 by the Psoriasis Area and Severity Index (PASI 75). The PASI is a composite score that takes into consideration both the fraction of body surface area affected and the nature and severity of psoriatic changes within the affected regions (induration, erythema, and scaling).

In EXPRESS, other evaluated outcomes included the proportion of patients who achieved a score of “cleared” or “minimal” by the Static Physician’s Global Assessment (sPGA) and the proportion of patients with a reduction of PASI of at least 90% from baseline. The sPGA is a 6 category scale ranging from “5=severe” to “0=cleared” indicating the physician’s overall assessment of the psoriasis severity focusing on induration, erythema, and scaling. Treatment success of “cleared” or “minimal” consisted of none or minimal elevation in plaque, up to faint red coloration in erythema, and none or minimal fine scale over <5% of the plaque.

EXPRESS II evaluated the proportion of patients who achieved a score of “clear” or “excellent” by the Relative Physician’s Global Assessment (rPGA) and the proportion of patients with a reduction of PASI of at least 90% from baseline. The rPGA is a 6 category scale ranging from “6=worse” to “1=clear” that was assessed relative to baseline. Overall lesions were graded with consideration to the percent of body involvement as well as overall induration, scaling, and erythema. Treatment success of “clear” or “excellent” consisted of some residual pigmentation (Wornoff’s ring may be present) to marked improvement (nearly normal skin texture; some erythema may be present).

Patients in all treatment groups and in both studies had a median baseline PASI score ranging from 17 to 22. In EXPRESS, the percentage of patients with baseline sPGA classifications ranged from 52% for moderate, 36% for marked, and 2% for severe. Across all treatment groups, the percentage of patients who previously received systemic therapy for psoriasis was 71% in EXPRESS and 55% in EXPRESS II; and those who previously received UVB ranged from 65% to 71% in EXPRESS, and 50% to 55% in EXPRESS II.

Study Results

In both studies, at Week 10, more patients randomized to Remicade® 3 mg/kg or 5 mg/kg than placebo achieved PASI 75 (Table 31 and Table 32). By Week 6, in EXPRESS II, 78% and 48% of patients on 3 mg/kg Remicade® achieved a PASI 50 and 75 respectively and across both studies, 88-90% and 56-62% of patients on 5 mg/kg Remicade® achieved a PASI 50 and PASI 75 respectively. At Week 10, the individual components of the PASI (induration, erythema, and scaling) contributed comparably to the overall treatment- associated improvement in PASI. In addition, most patients in all Remicade® treatment groups achieved an assessment of minimal/cleared on the sPGA or excellent/clear on the rPGA when compared with placebo.

In both studies, at Week 10, significant improvement from baseline was seen among the Remicade®-treated group compared to the placebo group in the condition specific Dermatology Life Quality Index (DLQI) and the general health status questionnaire SF-36.

Table 31: PASI and sPGA[b] responses at Weeks 10, 24, and 50 (EXPRESS)

	Placebo	5 mg/kg Remicade®
	(n=77)	(n=301)
Week 10	77	301
PASI 90	1 (1.3%)	172 (57.1%)
PASI 75	2 (2.6%)	242 (80.4%)[a]
PASI 50	6 (7.8%)	274 (91.0%)
Week 24	77	276
PASI 90	1 (1.3%)	161 (58.3%)
PASI 75	3 (3.9%)	227 (82.2%)[a]
PASI 50	5 (6.5%)	248 (89.9%)
Week 50	N/A	281
PASI 90	N/A	127 (45.2%)
PASI 75	N/A	170 (60.5%)
PASI 50	N/A	193 (68.7%)
sPGA of minimal or cleared		
Week 10	3 (3.9%)	242 (82.9%)[a]
Week 24	2 (2.6%)	203 (73.6%)
Week 50	N/A	149 (53.0%)

[a] p<0.001 compared with placebo
[b] Static Physician's Global Assessment
N/A – Not applicable; Note no data is available for placebo group due to patients crossing over to Remicade® prior to Week 50.

Table 32: PASI and rPGA[b] responses at Week 10 (EXPRESS II)

	Placebo	3 mg/kg infliximab	5 mg/kg infliximab
	(n=208)	(n=313)	(n=314)
Week 10			
PASI 50	17 (8.2%)	270 (86.3%)	291 (92.7%)
PASI 75	4 (1.9%)	220 (70.3%)[a]	237 (75.5%)[a]
PASI 90	1 (0.5%)	116 (37.1%)	142 (45.2%)
rPGA of excellent or clear			
Week 10	2 (1.0%)	217 (69.8%)[a]	234 (76.0%)[a]

[a] p<0.001 compared with placebo
[b] Relative Physician's Assessment

In EXPRESS, at Weeks 24 and 50, 82% and 61% of patients respectively achieved a PASI 75. At Week 50, 45% achieved a PASI 90. Among PASI 75 responders at Week 10, 89% achieved a PASI 75 and 65% achieved a PASI 90 at Week 24. At Week 50, 65% of PASI responders achieved a PASI 75 and 50% achieved a PASI 90.

In EXPRESS, the Nail Psoriasis Severity Index (NAPSI) evaluated 4 components of nail matrix disease and 4 components of nail bed disease with scores ranging from 0 to 8, with a higher score representing more severe disease. The median baseline NAPSI score was 4. Maximum improvement in the Remicade® group occurred at Week 24 with a median improvement of 2 compared to 0 in the placebo group. At Week 50, in the infliximab group, the median improvement of 2 in NAPSI was maintained.

In EXPRESS II, among the 4 maintenance regimens, response was best maintained in the 5 mg/kg Remicade® every 8 weeks group. At Weeks 26 and 50, 78% and 55% respectively achieved a PASI 75. At Weeks 26 and 50, 56% and 34% respectively achieved a PASI 90. Among PASI 75 responders at Week 10 in the 5 mg/kg every 8 weeks group, 83% maintained a PASI 75 and 61% a PASI 90 at Week 26. At Week 50, 60% maintained a PASI 75 and 40% a PASI 90.

The median duration of maintaining PASI 75 among Week 10 PASI responders after induction therapy in the PRN groups was between 12 to 16 weeks.

In both EXPRESS and EXPRESS II, a post hoc analysis was performed to evaluate patients achieving a major clinical response as defined by maintaining ≥90% improvement in PASI at consecutive visits for at least 24 weeks. In EXPRESS, 36% and in EXPRESS II, 31% of patients in the 5 mg/kg every 8 week maintenance group achieved a major clinical response.

In EXPRESS II, response to retreatment was evaluated in patients who were randomized as responders at Week 14 in the PRN groups and subsequently lost response after a 12-40 week gap of therapy. Approximately 67% of patients in the 3 mg/kg PRN group and 84% of patients in the 5 mg/kg PRN group regained response.

Efficacy and safety of Remicade® treatment beyond 12 months has not been evaluated in patients with plaque psoriasis.

Ulcerative Colitis

Table 33: Summary of patient demographics for clinical trials in ulcerative colitis

Study #	Study Design	Dosage, route of administration and duration	Study Subjects (n)	Mean age (range)	Gender and Race n (%)
T37 (ACT 1)	Randomised, multicentre, double-blind, placebo-controlled, parallel-group study in patients with moderately to severely active UC despite current or historical treatment with standard therapy	Remicade® 5 mg/kg, 10/mg/kg, or placebo administered intravenously at Weeks 0, 2, and 6, followed by additional infusions every 8 weeks thereafter through Week 46	364	41.9 (18.0, 81.0)	222 (61.0%) male 142 (39.0%) female 340 (93.4%) Caucasian 6 (1.6%) Black 4 (1.1%) Asian 14 (3.8%) Other
T46 (ACT 2)	Randomised, multicentre, double-blind, placebo-controlled, parallel-group study in patients with moderately to severely active UC despite current or historical treatment with standard therapy	Remicade® 5 mg/kg, 10/mg/kg, or placebo administered intravenously at Weeks 0, 2, and 6, followed by additional infusions every 8 weeks thereafter through Week 22	364	40.0 (18.0, 82.0)	215 (59.1%) male 149 (40.9%) female 344 (94.5%) Caucasian 8 (2.2%) Black 5 (1.4%) Asian 7 (1.9%) Other

The safety and efficacy of Remicade® were assessed in two multicentre, randomized, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2) with an inadequate response to conventional therapies. Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. In both studies, patients were randomized at week 0 to receive either placebo, 5 mg/kg Remicade®, or 10 mg/kg Remicade® at Weeks 0, 2, 6, and every 8 weeks thereafter through week 46 in ACT 1 and at weeks 0, 2, 6, and every 8 weeks thereafter through week 22 in ACT 2. Corticosteroid taper was permitted after Week 8. The study design and demographics of the study population for the two trials are summarized in Table 33.

In the first study (ACT 1), 364 patients were randomized who were on current treatment or had failed to respond to or tolerate oral corticosteroids, 6-mercaptopurine (6-MP) or azathioprine (AZA). Patients randomized in the second study (ACT 2) (n=364) were on or had failed to respond to or tolerate oral corticosteroids, 6-MP, AZA, or aminosalicylates. In both studies, baseline concomitant medications for ulcerative colitis were generally similar across treatment groups. However, because of differences in entry criteria, there were more subjects in ACT 2 (25.8%) than in ACT 1 (11.3%) who were solely taking aminosalicylates for their ulcerative colitis.

In both studies, clinical response and clinical remission were defined based on the Mayo score, which consists of four subscores: stool frequency, rectal bleeding, findings of endoscopy, and physician's global assessment. Each subscore is rated on a scale from 0 to 3, indicating normal (0) to severe (3) activity. The Mayo score is the sum of the 4 subscores. Clinical response was defined as a decrease from baseline in the Mayo score of ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1. Clinical remission was defined as a Mayo score ≤2 points, with no individual subscore >1.

Clinical Response, Clinical Remission and Mucosal Healing

In both the ACT 1 and ACT 2 studies, a significantly greater percentage of patients in the Remicade® groups were in clinical response at Week 8 (the primary endpoint) when compared to placebo (Figure 10). Table 34 and Table 35 present the primary and secondary endpoints of the ACT 1 and ACT 2 studies, respectively.

Table 34: Efficacy results of study T37 (ACT 1) in ulcerative colitis

		Remicade®	
	Placebo	**5 mg/kg**	**10 mg/kg**
Patients randomized	n=121	n=121	n=122
Parameter			
Primary Endpoint			
Clinical response at Week 8 n (%)	45 (37.2%)	84 (69.4%) p<0.001	75 (61.5%) p<0.001
Secondary Endpoints			
Clinical response at Week 30 n (%)	36 (29.8%)	63 (52.1%) p<0.001	62 (50.8%) p=0.002
Clinical response at Week 54 n (%)	24 (19.8%)	55 (45.5%) p<0.001	54 (44.3%) p<0.001
Clinical remission at Week 8 n (%)	18 (14.9%)	47 (38.8%) p<0.001	39 (32.0%) p=0.002
Clinical remission at Week 30 n (%)	19 (15.7%)	41 (33.9%) p=0.001	45 (36.9%) p<0.001
Clinical remission at Week 54 n (%)	20(16.5%)	42 (34.7%) p=0.001	42 (34.4%) p=0.001
Mucosal healing at Week 8 n (%)	41 (33.9%)	75 (62.0%) p<0.001	72 (59.0%) p<0.001
Mucosal healing at Week 30 n (%)	30 (24.8%)	61 (50.4%) p<0.001	60 (49.2%) p<0.001
Mucosal healing at Week 54 n (%)	22 (18.2%)	55 (45.5%) p<0.001	57 (46.7%) p<0.001
Subjects receiving corticosteroids at baseline, in clinical remission and not receiving corticosteroids at Week 30	8 (10.1%)	17 (24.3%) p=0.030	14 (19.2%) p=0.125

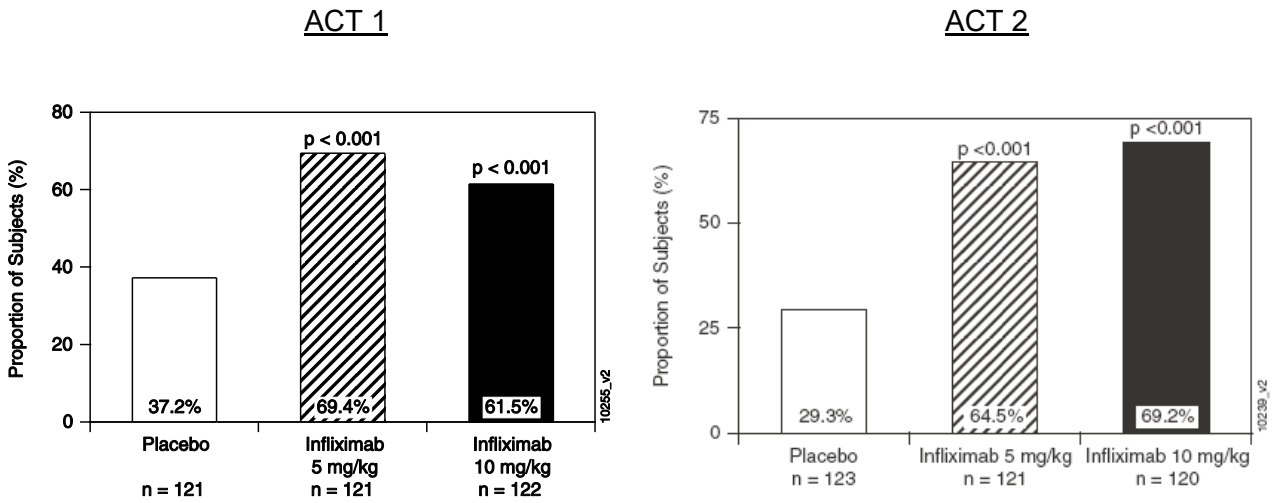
		Remicade®	
	Placebo	**5 mg/kg**	**10 mg/kg**
Subjects receiving corticosteroids at baseline, in clinical remission and not receiving corticosteroids at Week 54	7 (8.9%)	18 (25.7%) p=0.006	12 (16.4%) p=0.149
Subjects in sustained response through Week 54 (clinical response at Weeks 8, 30 and 54)	17 (14.0%)	47 (38.8%) p<0.001	45 (36.9%) p<0.001
Subjects in sustained remission through Week 54 (clinical remission at Weeks 8, 30 and 54)	8 (6.6%)	24 (19.8%) p=0.002	25 (20.5%) p=0.002
Median change from baseline in IBDQ at Week 8	16	39 p<0.001	33 p=0.001
Median change from baseline in IBDQ at Week 30	0	27 p=0.002	31 p=0.004
Median change from baseline in IBDQ at Week 54	0	26 <0.001	19 <0.001

Table 35: Efficacy results of study T46 (ACT 2) in ulcerative colitis

		Remicade®	
	Placebo	**5 mg/kg**	**10 mg/kg**
Patients randomized	n=123	n=121	n=120
Parameter			
Primary Endpoint			
Clinical response at Week 8 n (%)	36 (29.3%)	78 (64.5%) p<0.001	83 (69.2%) p<0.001
Secondary Endpoints			
Clinical response for the Week 30 n (%)	32 (26.0%)	57 (47.1%) p<0.001	72 (60.0%) p<0.001
Clinical remission at Week 8 n (%)	7 (5.7%)	41 (33.9%) p<0.001	33 (27.5%) p<0.001
Clinical remission at Week 30 n (%)	13 (10.6%)	31 (25.6%) p=0.003	43 (35.8%) p<0.001
Mucosal healing at Week 8 n (%)	38 (30.9%)	73 (60.3%) p<0.001	74 (61.7%) p<0.001
Mucosal healing at Week 30 n (%)	37 (30.1%)	56 (46.3%) p=0.009	68 (56.7%) p<0.001
Subjects receiving corticosteroids at baseline, in clinical remission and not receiving corticosteroids at Week 30	2 (3.3%)	11 (18.3%) p=0.010	18 (27.3%) p<0.001
Subjects in sustained response through Week 30 (clinical response at both Week 8 and Week 30)	19 (15.4%)	50 (41.3%) p<0.001	64 (53.3%) p<0.001
Subjects in sustained remission through Week 30 (clinical remission at both Week 8 and Week 30)	3 (2.4%)	18 (14.9%) p<0.001	27 (22.5%) p<0.001
Median change from baseline in IBDQ at Week 8	7	38 p<0.001	33 p<0.001
Median change from baseline in IBDQ at Week 30	0	20 p=0.005	32 p<0.001

In both studies, a significantly greater percentage of patients in both Remicade® groups achieved clinical response, clinical remission and mucosal healing than patients in the placebo groups (Table 36). Each of these effects was maintained through the end of each trial (through Week 54 in ACT 1, and through Week 30 in ACT 2). In addition, a greater proportion of patients in the Remicade® groups (approximately twice as many) demonstrated sustained response and sustained remission than patients in the placebo groups.

Figure 10: Proportion of randomized subjects in clinical response at Week 8 (primary endpoint) in ACT 1 and ACT 2



In both ACT 1 and ACT 2, a significantly greater proportion of patients treated with 5 mg/kg or 10 mg/kg infliximab experienced clinical response at Week 30 compared to placebo treatment (Table 36). In addition, the proportion of patients in sustained response (i.e., were in clinical response at both Week 8 and Week 30) in the Remicade® groups was approximately twice as large as the proportion of patients in sustained response in the placebo group.

In ACT 1, the proportion of patients in clinical response at Week 54 and the proportion of patients in sustained response through Week 54 (i.e., clinical response at Weeks 8, 30 and 54) was significantly greater in the Remicade®-treated subjects compared to placebo-treated subjects (Table 36).

Table 36: Proportion of subjects in clinical response, and in sustained response

	ACT 1			ACT 2		
		Remicade®			Remicade®	
	Placebo	5 mg/kg	10 mg/kg	Placebo	5 mg/kg	10 mg/kg
Subjects randomized	121	121	122	123	121	120
Subjects in clinical response at Week 8	37.2%	69.4%	61.5%	29.3%	64.5%	69.2%
p-value		<0.001	<0.001		<0.001	<0.001
Subjects in clinical response at Week 30	29.8%	52.1%	50.8%	26.0%	47.1%	60.0%
p-value		<0.001	0.002		<0.001	<0.001
Subjects in sustained response through Week 30 (clinical response at Weeks 8 and 30)	23.1%	48.8%	45.9%	15.4%	41.3%	53.3%
p-value		<0.001	<0.001		<0.001	<0.001
Subjects in clinical response at Week 54	19.8%	45.5%	44.3%	NA	NA	NA
p-value		<0.001	<0.001			
Subjects in sustained response through Week 54 (clinical response at Weeks 8, 30 and 54)	14.0%	38.8%	36.9%	NA	NA	NA
p-value		<0.001	<0.001			

In ACT 1 through Week 46, a total of 46.7% of subjects discontinued study infusions, 62.0% of placebo-treated and 39.1% of Remicade®-treated subjects. The most common reason for discontinuation of study infusions was lack of efficacy, which occurred in nearly twice as many placebo-treated subjects as Remicade®-treated subjects (46.3% vs. 24.3%, respectively). Overall, in ACT 2, 29.1% of subjects discontinued study infusions prior to Week 22. In particular, 45.5% of placebo-treated subjects and 20.7% of Remicade®-treated subjects discontinued study infusions. As was observed with ACT 1, the most common reason for discontinuation of study infusions in ACT 2 was lack of efficacy, which occurred in 32.5% of placebo-treated and 16.6% of Remicade®-treated subjects.

In ACT 1 and ACT 2, response to Remicade® was consistently greater compared to placebo across all Mayo subscores at Week 8 and Week 30 and Week 54 (ACT 1 only) (Table 37).

Table 37: Proportion of subjects in ACT 1 and ACT 2 with Mayo subscores indicating no disease activity or mild disease

	ACT 1			ACT 2		
		Remicade®			Remicade®	
	Placebo	5 mg/kg	10 mg/kg	Placebo	5 mg/kg	10 mg/kg
	(n=121)	(n=121)	(n=122)	(n=123)	(n=121)	(n=120)
Stool frequency						
Baseline	16.5%	16.5%	9.8%	13.0%	15.7%	16.7%
Week 8	34.7%	59.5%	58.2%	31.7%	62.8%	59.2%
Week 30	34.7%	51.2%	52.5%	30.9%	50.4%	53.3%
Week 54	31.4%	52.1%	50.8%	NA	NA	NA
Rectal bleeding						
Baseline	53.7%	39.7%	47.5%	43.1%	57.0%	45.8%
Week 8	73.6%	86.0%	80.3%	63.4%	81.8%	85.0%
Week 30	65.3%	73.6%	71.3%	56.9%	75.2%	80.0%
Week 54	62.0%	69.4%	67.2%	NA	NA	NA
Physician's global assessment						
Baseline	4.1%	5.8%	2.5%	3.3%	5.0%	3.3%
Week 8	43.8%	73.6%	63.9%	35.0%	68.6%	65.8%
Week 30	35.5%	57.0%	54.9%	35.0%	54.5%	62.5%
Week 54	26.4%	52.9%	53.3%	NA	NA	NA
Findings of endoscopy						
Baseline	0.0%	0.0%	0.0%	0.8%	0.0%	1.7%
Week 8	33.9%	62.0%	59.0%	31.7%	60.3%	62.5%
Week 30	25.6%	51.2%	51.6%	32.5%	50.4%	59.2%
Week 54	20.7%	49.6%	50.8%	NA	NA	NA

In ACT 1 and ACT 2, at Week 8 and at Week 30, a significantly greater proportion of subjects in the Remicade®-treated group experienced clinical remission compared to placebo ($p \leq 0.003$ for all comparisons) (Table 38). Remission was sustained (i.e., in clinical remission at both Week 8 and Week 30) in more subjects receiving Remicade® compared to placebo. Of patients treated with corticosteroids at baseline, a significantly greater proportion of patients in the Remicade®-treated groups in ACT 1 and ACT 2 were in clinical remission at Week 30 and able to discontinue corticosteroids compared to the placebo-treated patients (22.3% versus 7.2%, respectively).

In ACT 1, the proportion of subjects in clinical remission at Week 54 and the proportion of subjects in sustained remission through Week 54 (i.e., were in clinical remission at Weeks 8, 30, and 54) was significantly greater in the Remicade®-treated subjects compared to the placebo-treated subjects. Approximately twice the proportion of subjects in the Remicade®-treated groups were in clinical remission at Week 54 and able to discontinue corticosteroids compared to the placebo-treated subjects (Table 38).

Table 38: Proportion of subjects in clinical remission, in sustained remission, and in clinical remission and not receiving corticosteroids

	ACT 1			ACT 2		
		Remicade®			Remicade®	
	Placebo	5 mg/kg	10 mg/kg	Placebo	5 mg/kg	10 mg/kg
Subjects randomized	121	121	122	123	121	120
Subjects in clinical remission at Week 8	14.9%	38.8%	32.0%	5.7%	33.9%	27.5%
p-value		<0.001	0.002		<0.001	<0.001
Subjects in clinical remission at Week 30	15.7%	33.9%	36.9%	10.6%	25.6%	35.8%
p-value		0.001	<0.001		0.003	<0.001
Subjects in sustained remission through Week 30 (clinical remission at Weeks 8 and 30)	8.3%	23.1%	26.2%	2.4%	14.9%	22.5%
p-value		0.001	<0.001		<0.001	<0.001
Subjects in clinical remission at Week 54	16.5%	34.7%	34.4%	NA	NA	NA
p-value		0.001	0.001			
Subjects in sustained remission through Week 54 (clinical remission at Weeks 8, 30, and 54)	6.6%	19.8%	20.5%%	NA	NA	NA
p-value		0.002	0.002			
Subjects on corticosteroids at baseline	79	70	73	60	60	66
Subjects in clinical remission at Week 30 able to discontinue corticosteroid use	10.1%	24.3%	19.2%	3.3%	18.3%	27.3%
p-value		0.030	0.125		0.010	<0.001
Subjects in clinical remission at Week 54 able to discontinue corticosteroid use	8.9%	25.7%	16.4%	NA	NA	NA
p-value		0.006	0.149	NA	NA	NA

Mucosal healing was defined as an endoscopy subscore (from the Mayo score) of 0 or 1. At Weeks 8, 30 and 54 in ACT 1 and at Weeks 8 and 30 in ACT 2, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg dose groups achieved mucosal healing compared to patients in the placebo group (Table 39). The proportion of subjects with mucosal healing was similar between the 2 Remicade® dose groups in the two studies.

Table 39: Proportion of subjects with mucosal healing

	ACT 1			**ACT 2**		
		Remicade®			**Remicade®**	
Mucosal Healing[1]	**Placebo**	**5 m/kg**	**10 mg/kg**	**Placebo**	**5 mg/kg**	**10 mg/kg**
Subjects randomized	121	121	122	123	121	120
at Week 8	33.9%	62.0%	59.0%	30.9%	60.3%	61.7%
p-value		<0.001	<0.001		<0.001	<0.001
at Week 30	24.8%	50.4%	49.2%	30.1%	46.3%	56.7%
p-value		<0.001	<0.001		0.009	<0.001
at Week 54	18.2%	45.5%	46.7%	NA	NA	NA
p-value		<0.001	<0.001			

[1] The proportion of subjects with mucosal healing may not equal the proportion of subjects with a value of 0 or 1 for the findings of endoscopy Mayo subscore. This is due to different data handling rules being used in the two analyses.

Health-related quality of life was assessed in ACT 1 and ACT 2 using the IBDQ and the SF-36. The IBDQ is a questionnaire specifically designed for subjects with inflammatory bowel disease. The SF-36 is a generic health status questionnaire that has been widely used in various diseases and conditions to assess patients' physical and mental well being.

The median total IBDQ scores at baseline were similar among the treatment groups. At both Week 8 and Week 30 in ACT 1 and ACT 2, and at Week 54 in ACT 1, the combined Remicade® treatment group had a median improvement from baseline that was greater than that observed in the placebo treatment group ($p<0.001$ for all comparisons) (Table 40). Similar improvements were also observed in all 4 dimensional (i.e. bowel, emotional, systemic and social) scores of the IBDQ ($p\leq0.015$ for all comparisons between the combined Remicade®-treatment group and the placebo treatment group). At both Week 8 and Week 30 in ACT 1 and ACT 2 and Week 54 in ACT 1, subjects in the combined Remicade® treatment group had greater improvement in the physical and mental component summary scores of the SF-36 compared with the placebo treatment group ($p\leq0.044$ for all comparisons) (Table 40**Error! Reference source not found.**).

Table 40: Summary [mean (median)] of baseline and change from baseline in total IBDQ score and physical and mental component summary scores of SF-36

	ACT 1		ACT 2	
	Placebo	Remicade®*, p-value	Placebo	Remicade®*, p-value
Subjects randomized	121	243	123	241
IBDQ				
Total				
Baseline	123 (121)	127 (127)	125 (127)	128 (127)
Change at Week 8	21 (16)	39 (36), <0.001	20 (7)	37 (34), <0.001
Change at Week 30	18 (0)	34 (27), <0.001	18 (0)	34 (29), <0.001
Change at Week 54	13(0)	32 (23), <0.001	NA	NA
SF-36				
Physical component summary				
Baseline	36.5 (35.9)	38.0 (37.8)	39.0 (39.1)	39.5 (39.5)
Change at Week 8	4.5 (1.4)	6.2 (5.0), 0.042	2.9 (0.0)	6.5 (5.2), <0.001
Change at Week 30	3.4 (0.0)	5.7 (2.6), 0.044	2.6 (0.0)	5.3 (4.6), 0.007
Change at Week 54	2.7 (0.0)	6.0 (2.5), 0.002	NA	NA
Mental component summary				
Baseline	39.5 (38.8)	41.2 (42.7)	39.3 (39.0)	40.3 (42.3)
Change at Week 8	3.1 (0.0)	6.1 (3.6), 0.020	3.0 (0.0)	6.2 (3.2), 0.003
Change at Week 30	3.1 (0.0)	5.9 (1.8), 0.012	4.4 (0.0)	6.5 (3.5), 0.021
Change at Week 54	1.3 (0.0)	5.1 (0.0), 0.001	NA	NA
*5 & 10 mg/kg Infliximab Groups Combined				

From baseline through Week 30 in the pooled data from ACT 1 and ACT 2, the mean number of ulcerative colitis-related hospitalizations was 50% lower in the combined Remicade® treatment group than in the placebo treatment group (9 versus 18 hospitalizations per 100 subjects, p=0.005). No notable differences were observed between the 5 mg/kg and 10 mg/kg Remicade® treatment groups, both of which had a significantly lower mean number of ulcerative colitis-related hospitalizations than the placebo treatment group (p≤0.030). A similar benefit was seen through 54 weeks in ACT 1.

Time to first ulcerative colitis-related hospitalization was longer in the combined Remicade® treatment group than in the placebo treatment group in both the ACT 1 and ACT 2 studies.

Upon completion of 54 weeks in ACT 1 or 30 weeks in ACT 2, patients who in the opinion of the investigator would benefit from further study agent were eligible to enter a study extension for up to 3 years. Patients who received study agent within ACT 1 or ACT 2 were encouraged to participate in a long term safety follow-up observational study, upon completion of or discontinuation from either UC study or its extension. Patients who did not have complete follow-up through 54 weeks following their first study infusion in either ACT 1 or ACT 2 and who

did not participate in the long term safety follow up study were encouraged to participate in a substudy of each ACT study to retrospectively collect targeted information on ulcerative colitis related hospitalizations and surgical procedures, including colectomy.

Time to colectomy was measured in all patients who participated in the UC studies through 54 weeks from their first study infusion. Colectomy data was pooled from ACT 1 and ACT 2 (including retrospective substudy data collections), the ACT 2 Extension, and the long term safety follow-up study. Complete follow-up data on colectomy were collected on 630 of the 728 ACT patients; 98 patients (13.5%) had incomplete follow-up data. Among the 630 patients with complete follow-up, complete colectomy follow-up was obtained retrospectively in 37 patients. The proportion of patients who underwent colectomy at any time within 54 weeks following the first infusion were: 11.6 % (28/242) in the 5 mg/kg infliximab group, 7.4% (18/242) in the 10 mg/kg infliximab group, and 14.8% (36/244) in the placebo group.

Ulcerative Colitis in Pediatric Patients

Table 41: Summary of patient demographics for clinical trials in pediatric ulcerative colitis

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Median age (range)	Gender and Race n (%)
T72	Phase 3 multi-center, randomized, open-label, parallel-group	Intravenous infusions of infliximab 5 mg/kg for all patients at weeks 0, 2, and 6 Patients in clinical response at week 8 randomised to maintenance treatment with intravenous infusions of 5 mg/kg infliximab either q8 weeks through week 46 or q12 weeks through week 42.	60 6 of 15 (6-11 years of age) and 23 of 45 (12-17 years of age) completed the study	14.5 years (6.0-17.0)	Gender: Male 28 (46.7) Female 32 (53.3) Race: Caucasian 49 (81.7) Black 5 (8.3) Asian 3 (5.0) Other 3 (5.0)

The safety and efficacy of Remicade® were assessed in a multi-center, randomized, open-label, parallel-group Phase 3 clinical study in 60 pediatric patients aged 6 through 17 years (median age 14.5 years) with moderately to severely active ulcerative colitis (Mayo score of 6 to 12; Endoscopic subscore ≥ 2) with an inadequate response to conventional therapies (Study Peds UC). At baseline 53% of patients were receiving immunomodulator therapy (6-MP/AZA/MTX), 53% of patients were receiving aminosalicylates and 62% of patients were receiving corticosteroids. Discontinuation of immunomodulators and corticosteroid taper were permitted after Week 0.

All patients received an induction regimen of 5 mg/kg infliximab at Weeks 0, 2, and 6. Patients (15) who did not respond to Remicade® at Week 8 received no further drug and returned for safety follow-up. At Week 8, 45 patients were randomized in a 1:1 ratio to one of two maintenance treatment regimens: 5 mg/kg infliximab every 8 weeks (q8 week) through Week 46 or every 12 weeks (q12 week) through Week 42.

A summary of patient demographics and design of the pediatric ulcerative colitis study is presented in Table 41.

The primary endpoint was clinical response at Week 8, defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, with a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.

Major secondary endpoints included clinical remission measured by the Mayo score at Week 8 and remission by the Pediatric Ulcerative Colitis Activity Index (PUCAI) score at Week 8 and Week 54, and mucosal healing at Week 8. For patients receiving corticosteroids at baseline, reduction in median corticosteroid use, and remission combined with elimination of corticosteroid use at Week 54 were evaluated as pre-specified analyses but not designated as primary or secondary efficacy endpoints.

Study Results

Clinical Response, Clinical Remission and Mucosal Healing

Of the 60 patients treated, 44 (73.3%) were in clinical response at Week 8 (95% CI: 62.1%, 84.5%). The proportions of patients achieving clinical response at Week 8 were similar between those taking concomitant immunomodulators at baseline (72%) and those not taking concomitant immunomodulators at baseline (75%).

Clinical remission was defined by a Mayo score of ≤ 2 points, with no individual subscore > 1. Remission was also defined by a PUCAI score of <10 points. At Week 8, infliximab induced clinical remission in 40% (24/60) of patients as measured by the Mayo score and in 33.3% (17/51) of patients as measured by the PUCAI score.

The proportion of patients in remission at Week 54 as measured by the PUCAI score was 38% (8/21) in the q8 week maintenance treatment group and 18% (4/22) in the q12 week maintenance treatment group.

Nine out of 22 patients in the 5 mg/kg q8 week group required dose escalation to 10 mg/kg q8 week.

Mucosal healing was defined as an endoscopy subscore (from the Mayo score) of 0 or 1. At Week 8, 68.3% (41/60) of patients were in mucosal healing with 33.3% (20/60) having an endoscopy subscore of 0 (indicating normal or inactive disease).

Overall, although some differences were noted between the age groups in the efficacy measures examined, efficacy was observed in both age groups and no consistent pattern indicating greater efficacy in one of the age groups was apparent. The differences between the 6 to 11 and the 12 to 17 year old age groups, however, are difficult to assess because of the small sample sizes, particularly in the 6 to 11 year old age group (15 patients).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicity

Acute and Multiple Dose Toxicity

Since the chimpanzee is the only species to have similar cross-reactivity as humans, safety studies in this species provide the most relevant safety information on infliximab administration to humans. Although infliximab does not inhibit rat TNFα, single dose and one-week repeat dose toxicity studies were performed only to evaluate potential non-specific effects.

In the rat studies, minimal and reversible hepatic changes (Kupffer cell and hepatocellular hyperplasia) and slight reduction in erythrocyte count, hemoglobin and hematocrit values were observed at single doses ≥10 mg/kg and at seven daily doses ≥10 mg/kg/day. These changes are not the result of the pharmacodynamic effects of the antibody because infliximab does not neutralize the cytotoxicity of rat TNFα. They are likely the result of a normal rat reticuloendothelial system response to the administration of large doses of chimeric (human-murine) antibody, a completely foreign protein to this test animal. Thus, the infliximab-related hematologic and hepatic effects observed in the rat are not considered relevant to humans.

A number of safety studies with infliximab in chimpanzees were conducted. The results of these studies showed that infliximab was well tolerated at doses up to 30 mg/kg/day for at least 3 consecutive days and at doses up to 15 mg/kg/day for at least 5 days. No infliximab-related signs of toxicity, including abnormal hepatic or hematologic effects, similar to the findings in rats, were observed during these chimpanzee studies. Based on the results of these studies it is demonstrated that single doses of infliximab up to 30 mg/kg, which is 6 times the proposed single dose for humans (5 mg/kg), can be administered without producing overt signs of toxicity. In addition, infliximab has been administered to chimpanzees in single doses up to 30 mg/kg and up to a total dosage of 90 mg/kg (30 mg/kg/dose X 3 doses) over three consecutive days without producing overt signs of toxicity, which is approximately 3.5-6.0 times the proposed total dosage for humans of 15 mg/kg (5 mg/kg/dose X 3 doses) administered at 0, 2 and 6 weeks for closure of fistula(s) and for moderate to severe Crohn's disease treatment (5 mg/kg/dose X 5 doses) at 8 week intervals.

Since infliximab does not cross react with species other than chimpanzees, a 6 month toxicity study was performed using cV1q anti-mouse TNFα monoclonal antibody, a murine analog of human anti-TNFα. One hundred and twenty mice received weekly intravenous doses of (control), 10 or 40 mg/kg of cV1q. Each group was further divided into necropsy groups: Interim (Week 13), Main (Week 26), and Recovery (Week 39). There were no effects of cV1q treatment on clinical observations, body weight, food consumption, hematology, serum chemistry and ophthalmology evaluations. There were no pathological findings considered treatment-related. Therefore, the no-observed-adverse-effect-level (NOAEL) is greater than 40 mg/kg. The clinical significance of the results of toxicity studies with specific anti-TNFα monoclonal antibody tested in homologous system is uncertain.

Carcinogenicity

No findings suggestive of carcinogenic or mutagenic activity were observed in laboratory studies (in vivo and in vitro) performed with infliximab, nor have any carcinogenic or mutagenic effects been associated with any of the excipients used to formulate infliximab.

Human lymphocytes were used to evaluate in vitro the potential of infliximab to induce chromosomal aberrations. In the Salmonella typhimurium - Escherichia coli-microsome plate assay, infliximab was evaluated for its potential ability to induce reverse mutations. Potential clastogenic effects were determined in vivo using the mouse micronucleus test. Infliximab did not exhibit mutagenic activity in any one of the 3 assays.

Infliximab does not cause generalised suppression of immune system function. Analysis indicated that differential white blood cell counts (WBC) from chimpanzees treated with high doses of infliximab were minimally effected.

Reproductive and Developmental Toxicity

Reproductive and developmental non-clinical toxicity studies have not been performed with infliximab because the species cross-reactivity of infliximab is limited to chimpanzees. Based on the lack of cross-reactivity, standard reproductive/developmental toxicity studies (Segments I, II, and III) in rats and rabbits are considered inappropriate to provide relevant information on the potential of infliximab to produce adverse reproductive or developmental effects in humans.

Comprehensive developmental toxicity studies with a surrogate anti-mouse TNFα monoclonal antibody (cV1q) were performed in mice. Analogous to infliximab, cV1q specifically binds and neutralises mouse TNFα. These developmental toxicity studies showed that cV1q, administered intravenously at 10 or 40 mg/kg/dose to pregnant mice on days 6 and 12 of gestation, produced no maternal or developmental toxicity. The clinical significance of the results of the developmental toxicity studies with a species-specific anti-TNFα monoclonal antibody tested in a homologous system is uncertain. Infliximab should be given to a pregnant woman only if clearly needed (see 7.1.1 Pregnant Women).

An additional fertility and general reproductive toxicity study was performed. The male mice received weekly doses of vehicle control, 10 or 40 mg/kg beginning 56 days (8 weeks) before cohabitation and continuing through cohabitation (2 weeks) and the week before sacrifice. The female mice received the same doses weekly beginning 2 weeks prior to cohabitation with males (maximum of 14 days) and on days 0 and 7 of presumed gestation. No toxicologically important effects on estrous cycle, fertility, tubal transport, pregnancy, implantation, development of pre-implantation of embryos of female mice, libido (time to mate), reproductive organ weights and epididymal sperm maturation were observed. The clinical significance of the results of the developmental toxicity studies with a species-specific anti-TNFα antibody tested in a homologous system is uncertain. Infliximab should be given to a pregnant woman only if clearly needed (see 7.1.1 Pregnant Women).

Special Toxicology

Local Tolerance

The local irritancy potential of infliximab at a concentration of 5 mg/mL was evaluated in rabbits following a single intravenous infusion (3 hours), intramuscular or subcutaneous dose. All 3 routes of administration demonstrated that infliximab was well tolerated and did not produce a degree of irritancy considered clinically significant. Infliximab will be reconstituted and diluted to a concentration that may range from 0.4 to 4.0 mg/mL before infusion. Also, the recommended infusion time is over a period of not less than 2 hours (see 4.4 Administration). Therefore, the infliximab concentration (5 mg/mL) and infusion time (3 hours) evaluated exceeded that recommended to humans.

Host Response to Infliximab

No immune responses were detected in 4 cynomolgus monkeys following 4 treatments with infliximab and evaluated for 14 weeks after the final treatment. In Tg197 transgenic mice, infliximab was often immunogenic. However, in normal mice, multiple administrations of infliximab appeared to be tolerogenic. The relevance of these studies to infliximab immunogenicity in humans is uncertain since: infliximab is a predominantly foreign protein in these species, the animals which were typically treated did not exhibit symptoms of Crohn's disease, the animals were not treated with relevant concomitant medications for inflammatory bowel disease, and often did not possess TNFα that could be recognised by infliximab.

In Vitro Human Tissue Cross-Reactivity

Two in vitro cross-reactivity studies were performed on normal, adult human tissue specimens. In the first study, reactivity was observed in Kupffer's cells of the liver, macrophages in the lymph nodes and mononuclear cells in the skin and kidney. Reactivity in these organs was anticipated and considered physiologic because of the presence of TNFα in these cells. A second in vitro cross-reactivity study on normal human tissues was performed using an improved, more sensitive assay system to detect infliximab. In this study, reactivity was observed with mononuclear and stromal cells in many tissues. This reactivity was consistent with the known cell and tissue expression patterns for TNFα. No unanticipated cross-reactivity with other cells and tissues was observed.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrREMICADE®
Infliximab for injection

Read this carefully before you start taking **Remicade®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Remicade®**.

Serious Warnings and Precautions

- Serious infections, including sepsis, tuberculosis, legionellosis (a serious form of bacterial pneumonia), listeriosis (an infection that usually develops after eating food contaminated by bacteria called listeria) and opportunistic infections (such as systemic fungal, viral, and bacterial infections), have been reported in patients, especially those 65 years and older, receiving Remicade® and other similar medicines. Some patients with these infections have died. Prior to treatment with Remicade®, you should tell your doctor if you have a chronic infection, a history of recurrent infection, or if you have lived in or traveled to an area where infections called histoplasmosis, coccidioidomycosis or blastomycosis are common. These infections are caused by fungus that can affect the lungs or other parts of your body. Ask your doctor if you don't know if these infections are common in the area in which you have lived or traveled. If you develop an infection during treatment with Remicade®, you should tell your doctor right away.

- Prior to treatment with Remicade®, you should tell your doctor if you have had tuberculosis, or if you have been exposed recently to anyone who might have tuberculosis, or if you have any other reason to believe you may be at risk for tuberculosis. Your doctor will evaluate you for tuberculosis and may begin treatment for tuberculosis before you are treated with Remicade®.

- Treatment with Remicade® must be interrupted if you develop a serious infection or sepsis. Tell your doctor if you have any symptoms of an infection (for example, fever, fatigue, cough, flu-like symptoms, or pain) while you are taking Remicade® and for 6 months after you receive the medicine. If you need surgery, tell your doctor that you have taken Remicade®.

- Lymphoma and other cancers, which may result in death, have been reported in children and teenage patients taking TNF- blockers, including Remicade®. Some patients who have received TNF-blockers, including Remicade® have developed a rare type of cancer called hepatosplenic T-cell lymphoma. Of these patients, most were teenage or young adult males and most had either Crohn's disease or ulcerative colitis. This type of cancer often results in death. Almost all patients had also received drugs known as azathioprine or 6-mercaptopurine in addition to TNF-blockers. You should also tell your doctor if you have had or develop lymphoma or other cancers while you are taking Remicade®.

What is Remicade® used for?

Remicade® is a medicine that is used in people with moderate to severe rheumatoid arthritis (in combination with methotrexate) and ankylosing spondylitis. Your doctor has chosen to treat your rheumatoid arthritis with Remicade® because you have moderately to severely active rheumatoid arthritis. Your doctor has chosen to treat your ankylosing spondylitis with Remicade® because you have had an inadequate response to other treatments or because you cannot tolerate other treatments.

Remicade® is also used in people with moderate to severe plaque psoriasis. Your doctor has chosen to treat your plaque psoriasis with Remicade® because your disease is still active even though you have tried other treatments.

Remicade® is also used in people with active psoriatic arthritis. Your doctor has chosen to treat your psoriatic arthritis with Remicade® because your disease is still active even though you have tried other treatments.

Remicade® is also used in adults, children and teenagers with moderate to severe Crohn's disease or with moderate to severe ulcerative colitis. Your doctor has chosen to treat your Crohn's disease or ulcerative colitis with Remicade® because your disease is still active even though you have tried other treatments.

How does Remicade® work?

Research has shown that in these diseases the body overproduces a substance known as tumour necrosis factor alpha (TNF alpha). The active ingredient in Remicade® is called infliximab. Infliximab is a monoclonal antibody, a type of protein that recognises and binds to other unique proteins. Infliximab binds to and neutralises TNF alpha. Infliximab is made from mouse and human proteins.

Remicade® is a medicine that affects your immune system. Remicade® can lower the ability of your immune system to fight infections.

What are the ingredients in Remicade®?

Medicinal ingredients: Infliximab
Non-medicinal ingredients: Dibasic sodium phosphate dihydrate, monobasic sodium phosphate monohydrate, polysorbate 80, sucrose. No preservatives are present.

Remicade® comes in the following dosage forms:

Remicade® is supplied as lyophilized concentrate for IV injection in individually-boxed single-use vials of 100 mg infliximab.

Vial stopper is free of natural rubber latex.

Tell all doctors involved in your care that you take Remicade®.

Do not use Remicade® if:

- You have a severe infection, such as sepsis (an infection in the bloodstream), abscess,

tuberculosis or other serious infection, you must not take Remicade®.
- You have heart failure that is moderate or severe, you must not take Remicade®.
- You are allergic to infliximab or any ingredient in Remicade® (polysorbate 80, sodium phosphate and sucrose), or if you have a history of allergies to mouse proteins, you should not take Remicade®.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Remicade®. Talk about any health conditions or problems you may have, including if you:

- Congestive heart failure: If you have mild heart failure and you are being treated with Remicade®, your heart failure status must be closely monitored by your doctor. If you develop new or worsening symptoms of heart failure (such as shortness of breath or swelling of your feet), you must contact your doctor immediately.
- Other heart problems: Some patients have experienced a heart attack (some of which led to death), low blood flow to the heart, or abnormal heart rhythm within 24 hours of beginning their infusion of Remicade®. Symptoms may include chest discomfort or pain, arm pain, stomach pain, shortness of breath, anxiety, lightheadedness, dizziness, fainting, sweating, nausea, vomiting, fluttering or pounding in your chest, and/or a fast or a slow heartbeat. Tell your doctor right away if you have any of these symptoms.
- Immediate allergic reactions: Some patients who have received Remicade® have developed allergic reactions, including anaphylaxis. Some reactions can happen while you are getting your infusion or shortly afterwards. Some of these reactions have been serious. The symptoms include hives, difficulty breathing, chest pain and high or low blood pressure. Your doctor may decide to stop Remicade® treatment for severe reactions. Your doctor can prescribe medicines to treat these effects.
- Delayed allergic reactions: Some allergic reactions can occur 3 to 12 days after Remicade® retreatment. The symptoms of this type of delayed reaction include muscle or joint pain with fever or rash. Tell your doctor if you notice any of these symptoms.
- Nervous system diseases: Tell your doctor if you have a disease that affects your nervous system, like multiple sclerosis, neuropathies, Guillain-Barré syndrome, or seizures; or you have been diagnosed with optic neuritis; or if you experience painful and limited eye movements, loss of feeling in the forehead or vision loss (orbital apex syndrome); or any numbness, tingling, or visual disturbances. Some patients have reported that their nervous system disease got worse after receiving Remicade®.
- Autoimmune disease: Some patients treated with Remicade® have developed symptoms that suggest an autoimmune disease called lupus-like syndrome. Tell your doctor if you notice symptoms of lupus-like syndrome, such as, prolonged chest discomfort or pain, shortness of breath, joint pain, or sun-sensitive rash on the cheeks or arms. Your doctor will evaluate your condition and may decide to stop your treatment with Remicade®.
- Liver injury: There have been cases where people taking Remicade® have developed liver problems. Signs that you could be having a problem include: jaundice (skin and eyes turning yellow), dark brown-colored urine, right-sided abdominal pain, fever, and severe fatigue (tiredness). You should contact your doctor immediately if you develop any of these symptoms.
- Previous phototherapy: Tell your doctor if you have had phototherapy (treatment with ultraviolet light or sunlight along with a medicine to make your skin sensitive to light) for psoriasis. In clinical trials, skin cancers were more common in patients who received prior phototherapy.

- Blood Problems: In some instances, patients treated with TNF-blocking agents may develop low blood counts, including a severely decreased number of white blood cells. If you develop symptoms such as persistent fever or infections, bleeding, or bruising, you should contact your doctor right away.
- Stroke: Some patients have experienced a stroke within approximately 24 hours of their infusion of Remicade®. Tell your doctor right away if you have symptoms of a stroke which may include: numbness or weakness of the face, arm or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance or coordination or a sudden, severe headache.
- Hepatitis B: Treatment with TNF-blocking agents such as Remicade® may result in a reactivation of the hepatitis B virus in people who carry this virus. If you have or have had hepatitis B infection or know or suspect you may be a carrier of hepatitis B virus, be sure to tell your doctor about this as this may impact the decision to start or continue treatment with Remicade®. Your doctor should do a blood test for hepatitis B virus before you start treatment with Remicade®.
- Vaccination: Tell your doctor that you have received Remicade® if you need to get a vaccination. It is not known if medicines like Remicade® can interfere with vaccinations. You should not receive live vaccines while you are taking Remicade®. The use of a 'live' vaccine may result in an infection caused by the 'live' vaccine or bacteria contained in the vaccine (when you have a weakened immune system). It is recommended that you be brought up to date with all vaccinations in agreement with current guidelines prior to starting Remicade®.
- Therapeutic infectious agents: Tell your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).
- Pregnancy, breast-feeding and ability to have children: If you are being treated with Remicade®, you must avoid becoming pregnant by using adequate contraception during your treatment and for 6 months after your last Remicade® injection. Tell your doctor if you think you may be pregnant, are breast-feeding, or planning to conceive a child. Your doctor will help you decide whether or not to use Remicade®.
  If you have a baby and you were using Remicade® during your pregnancy, it is important to tell your baby's doctor and other healthcare professionals about your Remicade® use so they can decide when your baby should receive their vaccinations, including live vaccines, such as BCG (used to prevent tuberculosis), rotavirus vaccine or any other live vaccines.
  If you received Remicade® while you were pregnant, your baby may be at higher risk for getting an infection. It is important that you tell your baby's doctors and other healthcare professionals about your Remicade® use before the baby receives any vaccine, including live vaccines such as the BCG vaccine (used to prevent tuberculosis), rotavirus vaccine, or any other live vaccines. Administration of BCG vaccine within 12 months after birth to the baby whose mother received Remicade® while pregnant may result in infection in the newborn with severe complications, including death. For other types of vaccines, discuss with your doctor.
  If you are breast-feeding, it is important that you tell your baby's doctors and other healthcare professionals about your Remicade® use before your baby is given any vaccine. Live vaccines should not be given to your baby while you are breast-feeding unless your baby's doctor recommends otherwise.
  Severely decreased numbers of white blood cells have also been reported in infants born to women treated with Remicade® during pregnancy. If your baby has continual fevers or infections, contact your baby's doctor immediately.
  It is not known if Remicade® can affect your ability to have children in the future.

- Have any surgery planned

Other warnings you should know about:

Reports of a type of blood cancer called lymphoma in patients on Remicade® or other TNF-blockers are rare but occur more often than expected for people in general. People who have been treated for rheumatoid arthritis, Crohn's disease or ankylosing spondylitis for a long time, particularly those with highly active disease may be more prone to develop lymphoma.

Cancers, other than lymphoma, have also been reported. There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death. For children and adults taking TNF-blocker medicines, the chances of getting lymphoma or other cancers may increase.

Some patients treated with Remicade® have developed certain kinds of skin cancer. If any changes in the appearance of the skin or growths on the skin occur during or after therapy, tell your doctor.

Some women being treated for rheumatoid arthritis with Remicade® have developed cervical cancer. For women taking Remicade®, including those over 60 years of age, your doctor may recommend that you continue to be regularly screened for cervical cancer.

Patients with a specific type of lung disease called COPD (Chronic Obstructive Pulmonary Disease) may be at increased risk for cancer with Remicade® treatment. If you have COPD you should discuss with your doctor whether Remicade® is appropriate for you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Remicade®:

- Tell your doctor about all medicines that you have recently taken or are taking during your treatment with Remicade®. These include any other medicines to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or psoriasis. Drugs that may interact with Remicade® include: prescription and non-prescription medicines, vitamins, and herbal supplements.

- Patients with rheumatoid arthritis or Crohn's disease often take other medicines that can cause side effects. Special studies have not been done to determine whether other medicines will react with Remicade®. In studies of Remicade®, patients were also taking antibiotics, antivirals, corticosteroids, mercaptopurine (6MP), azathioprine (AZA), methotrexate (MTX), and aminosalicylates along with Remicade®. Patients who took immunosuppressants, such as methotrexate, corticosteroids, mercaptopurine, azathioprine, had a lower risk of allergic reactions during infusion.

- Especially, tell your doctor if you take KINERET® (anakinra) or ORENCIA® (abatacept). Remicade® should not be taken together with anakinra or abatacept.

- If you have a baby or if you breastfed your baby while you are using Remicade®, tell your baby's doctor about your Remicade® use before the baby receives any live vaccines.

How to take Remicade®:

Remicade® will be given to you by a healthcare professional. The medicine will be given to you through a needle placed in a vein in your arm. This is called an infusion. For adults with ankylosing spondylitis, psoriatic arthritis, or plaque psoriasis, the infusion will take about 2 hours. For children with Crohn's disease or ulcerative colitis, the infusion will take about 2 hours. For adults with rheumatoid arthritis, Crohn's disease or ulcerative colitis, the first 3 infusions will be given over a period of about 2 hours, after the third consecutive 2-hour infusion your doctor may decide to give you the infusion over a 1-hour period. During the infusion you will be monitored for side effects. You must stay for 1 to 2 hours after the infusion so that you can continue to be watched for any reactions to the medicine.

Your doctor may:

- ask you to take other medicines along with Remicade®;
- delay your treatment with Remicade® if you have a surgery planned.

Where I may receive the infusion:

Your doctor will decide where you will receive the infusion. The BioAdvance® Network has been established to facilitate the administration of Remicade®. This network consists of clinics located across Canada that are staffed by qualified healthcare professionals specially trained in the administration of Remicade® infusions. Contact your doctor if you have any questions.

Usual dose:

Rheumatoid Arthritis

The recommended dose of Remicade® is 3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. Remicade® should be given in combination with methotrexate.

Ankylosing Spondylitis

The recommended dose of Remicade® is one initial infusion followed by infusions at 2 and 6 weeks after the first dose. Then you will receive an infusion every 6 to 8 weeks thereafter.

Crohn's Disease and Fistulising Crohn's Disease

Adults
The recommended dose of Remicade® is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderate to severe, active Crohn's disease. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg. Your doctor may consider doing a blood test (therapeutic drug monitoring) to determine how much infliximab is in your blood stream in order to optimize your dose of Remicade®.

Children (9 years of age or older)
The recommended dose of Remicade® for children with moderately to severely active Crohn's disease is 5 mg/kg given as an induction regimen of 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks.

Ulcerative Colitis

Adults
If you are receiving Remicade® for ulcerative colitis, you will receive your first 5 mg/kg dose followed by additional 5 mg/kg doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8 weeks thereafter. Your doctor will monitor your response to Remicade® and may change your dose. Your doctor may consider doing a blood test (therapeutic drug monitoring) to determine how much infliximab is in your blood stream in order to optimize your dose of Remicade®.

Children (6 years of age or older)
The recommended dose of Remicade® for children with moderately to severely active ulcerative colitis is 5 mg/kg given as an induction regimen of 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks.

Psoriatic Arthritis

The recommended dose of Remicade® is 5 mg/kg as an intravenous infusion followed with additional doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. If you show no response at 24 weeks, no additional treatment with Remicade® should be given.

Plaque Psoriasis

The recommended dose of Remicade® is 5 mg/kg given as an intravenous infusion followed with additional 5 mg/kg doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. If you do not show an adequate response at Week 14, after infusions at Weeks 0, 2, and 6, no additional treatment with Remicade® should be given.

Overdose:

Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

If you think you have taken too much Remicade®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget or miss an appointment to receive Remicade®, make another appointment as soon as possible.

What are possible side effects from using Remicade®?

These are not all the possible side effects you may feel when taking Remicade®. If you experience any side effects not listed here, contact your healthcare professional.

Some patients had side effects that caused them to stop Remicade® treatment. The most common reasons were shortness of breath, rash, and headache.

Other common side effects besides the ones already mentioned in this leaflet include abdominal pain, back pain, coughing, diarrhea, dizziness, fatigue, itchiness, pain, upper respiratory infections (such as bronchitis, sinusitis, cold, sore throat), upset stomach, and urinary tract infections. Remicade® may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of Remicade®.

Children and teenagers who took Remicade® in studies for ulcerative colitis had similar side effects as adults with ulcerative colitis. The most common side effects observed in children with ulcerative colitis include: cough and cold symptoms including sore throat, stomach pain, fever, headache and anemia (low red blood cell count). Among patients who took Remicade® for ulcerative colitis in clinical studies, more children had infections as compared with adults, including bladder infections, skin infections, and bronchitis.

Some of the side effects of Remicade® can be serious and may require treatment.

Tell your doctor if you experience any of the effects listed in this leaflet or any other side effects.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Serious infections: symptoms of fever, feel very tired, have a cough or develop flu-like symptoms or develop an abscess.		✓	
Allergic reactions: symptoms, while you are getting your Remicade® infusion or shortly afterwards, of hives (red, raised, itchy patches of skin), difficulty breathing, chest pain and high or low blood pressure or symptoms 3 to 12 days after receiving Remicade® including fever, rash, headache and muscle or joint pain.		✓	
UNCOMMON			
Liver injury: signs that you could be having a problem include: jaundice (skin and eyes turning yellow), dark brown-colored urine, right sided abdominal pain, fever and severe fatigue (tiredness).		✓	

Heart failure: If you have been told that you have a heart problem called congestive heart failure, you will need to be closely monitored by your doctor. New or worse symptoms that are related to your heart condition, including shortness of breath or swelling of your ankles or feet.		✓	
Blood problems: symptoms of fever that doesn't go away, bruising or bleeding very easily or looking very pale.		✓	
Nervous system disorders: signs include changes in your vision (including blindness), seizures, weakness in your arms and/or legs, and numbness or tingling in any part of your body.		✓	
Malignancy: if you have had or develop lymphoma or other cancers, including skin cancers, while you are taking Remicade®.		✓	
Lupus: symptoms may include chest discomfort or pain that doesn't go away, shortness of breath, joint pain, or a rash on the cheeks or arms that gets worse in the sun.		✓	
Paradoxical drug-induced immune disorders: the appearance of new inflammatory symptoms in the skin and/or other organs that are opposite to what should occur when taking this medicine. New symptoms could include but are not limited to: skin rashes, small pus-filled bumps that can spread over the body, shortness of breath, numbness or tingling in any part of your body or fever that doesn't go away.		✓	
RARE			
Skin problems: skin rashes including redness, itching, skin peeling and blistering; Small pus-filled bumps that can spread over		✓	

the body, sometimes with a fever (acute generalized exanthematous pustulosis); Itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes (lichenoid reactions)			
Lung problems: symptoms of new or worsening shortness of breath.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Remicade® is stored in the original package in the refrigerator before use. Do not use beyond the refrigerated expiration date printed on the carton. Only at the location of reconstitution, Remicade® can also be stored in the original carton outside of refrigerated storage up to a maximum of 30°C for a single period of up to 6 months; but not exceeding the refrigerated expiration date printed on the carton. In this situation, write the non-refrigerated expiry date on the carton including month/year and do not return to refrigerated storage again. Discard this medicine if not used by the new expiry date or the expiry date printed on the carton, whichever is earlier. It must be kept out of the reach and sight of children. The vial must be kept sealed. Only a healthcare professional should prepare the medicine before use and administer it to you. It should not be used beyond the expiration date.

If you want more information about Remicade®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (innovativemedicine.jnj.com/canada), or by calling 1-800-567-3331 or 1-800-387-8781.

Information about the BioAdvance® Network can be obtained by contacting Janssen Inc. at:

1-800-567-3331.

This leaflet was prepared by Janssen Inc.
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