Briefing Document for Food and Drug Administration Gastrointestinal Drugs Advisory Committee 21 Jul 2011

REMICADE® (infliximab)

Pediatric Ulcerative Colitis

Date: 14 June 2011

Centocor Research & Development, Inc.*

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Abbreviations

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ACT 1	Active Ulcerative Colitis Trial 1
ACT 2	Active Ulcerative Colitis Trial 2
AE	adverse event
ALT	alanine aminotransferase
ANA	antinuclear antibodies
AS	ankylosing spondylitis
ATC	Anatomical Therapeutic Chemical
AUCτ	area under the plasma concentration-time curve for a dose interval
AZA	azathioprine
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
CRP	C-reactive protein
DBL	database lock
DNA	deoxyribonucleic acid
dsDNA	double-stranded DNA
EU	European Union
FDA	Food and Drug Administration
GI	gastrointestinal
GMS	Global Medical Safety
HBV	hepatitis B virus
HCPs	health care providers
HR	hazard ratio
HSTCL	hepatosplenic T-cell lymphoma
IBD	inflammatory bowel disease
IC	indeterminate colitis
IgG1κ	immunoglobulin G1 kappa
IMPACT	Infliximab Multinational Psoriatic Arthritis Controlled Trial
IV	intravenous
JRA	juvenile rheumatoid arthritis
LE	lupus erythematosus
LTE	long-term extension
mAb	monoclonal antibody
MS	multiple sclerosis
MTX	methotrexate
NHL	non-Hodgkin's lymphoma
OOPD	Office of Orphan Products Development
PCDAI	Pediatric Crohn's Disease Activity Index
PK	pharmacokinetic(s)
PMC	Postmarketing Commitment
PREA	Pediatric Research and Equity Act
PsA	psoriatic arthritis
PSUR	periodic safety update report
PUCAI	Pediatric Ulcerative Colitis Activity Index
q12w	every 12 weeks
q8w	every 8 weeks
QT	QT interval: time from electrocardiogram Q wave to the end of the T wave corresponding to electrical systole

RA	rheumatoid arthritis
REACH	A Randomized, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Anti-TNFα Chimeric Monoclonal Antibody (Infliximab, REMICADE®) in Pediatric Subjects with Moderate to Severe Crohn's Disease
REMS	Risk Evaluation and Mitigation Strategy
RESULTS UC	REMICADE Safety Under Long-term Study in Ulcerative Colitis
SAE	serious adverse event
sBLA	supplemental Biological License Application
t1/2	half-life
TB	tuberculosis
TNFα	tumor necrosis factor alpha
UC	ulcerative colitis
US	United States

Purpose of Document

The purpose of this document is to provide background information on the development program for REMICADE® (infliximab) in the treatment of pediatric patients with moderately to severely active ulcerative colitis (UC), and to review the efficacy, PK, and safety data that support the approval of the product in the target indication.

Regulatory History

Given the low prevalence of pediatric UC, in November 2003, the FDA's Office of Orphan Products Development (OOPD) granted orphan designation to REMICADE for the treatment of pediatric patients with UC.

REMICADE was approved on 15 Sep 2005 for reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active UC who have had an inadequate response to conventional therapy. The approval was based on 30 weeks of data from 2 Phase 3 studies in adult UC patients, ACT 1 and ACT 2. On 13 Oct 2006, REMICADE was further approved for inducing and maintaining clinical remission and mucosal healing, based on 1 year of data from ACT 1 and 24 additional weeks of data from the blinded ACT 2 long-term extension (LTE).

When REMICADE was first approved by the FDA for the treatment of adult patients with UC, the sponsor agreed to a Postmarketing Commitment (PMC) to conduct a pediatric study in UC to fulfill its commitment under the Pediatric Research and Equity Act (PREA).

- During the 10 Nov 2005 pre-Phase 3 meeting to discuss the design of this pediatric study, the FDA indicated that the sponsor should study a pediatric population comparable to that in ACT 1 and ACT 2 (ie, ambulatory patients with moderate to severe UC).

- In subsequent teleconferences, the sponsor and the FDA agreed to:

  - the design of the study, including primary and secondary endpoints,

  - a total enrollment in the study of 60 subjects, and

  - the definition of a positive study (where the lower limit of the 95% confidence interval [CI] for the proportion of subjects in clinical response at Week 8 was greater than 40%).

    - The cut point of 40% was based on the use of pooled data from the placebo groups in the ACT 1 and ACT 2 studies as a "historical control". In the pooled ACT studies, the upper limit of the 95% CI for the proportion of placebo subjects in clinical response at Week 8 was 39.1%, and therefore the cut point for T72 was set at 40%.

  - add the Pediatric Ulcerative Colitis Activity Index (PUCAI) score as a means of assessing efficacy.

- The original protocol was submitted on 29 Mar 2006. The study was initiated 25 Aug 2006 and completed 24 Jun 2010.

- In Aug 2010, the sponsor and the FDA discussed the pending efficacy supplement at a pre-supplemental Biological License Application (sBLA) meeting, at which time the FDA provided guidance on the format and content for the sBLA.

The sponsor filed an sBLA to extend the adult UC indication to the pediatric UC population on 23 Dec 2010. Priority review was requested and granted by the FDA, due to the unmet medical need in this patient population.

1 Executive Summary

Ulcerative colitis, a chronic GI inflammatory disorder, is part of the spectrum of inflammatory bowel disease (IBD) and involves the surface mucosa, crypt epithelium, and submucosa of the colon. Clinically, patients with UC suffer from diarrhea, rectal bleeding, weight loss, abdominal pain, and fever, and may also display prominent extraintestinal manifestations, such as colitic arthritis and ankylosing spondylitis (AS). UC is characterized by a life-long chronic course of remissions and exacerbations.

While the overall clinical features, clinical course of disease, and response to treatment are comparable in pediatric and adult populations with UC, pediatric disease is often more extensive and therefore more severe. Despite this, there are few approved therapeutic options for pediatric UC. The 5-aminosalicylate (5-ASA) compounds are considered first-line therapy, and when these fail corticosteroids are effective for induction of disease remission. The toxicities of long-term treatment with corticosteroids are well established and are of greater concern in children since they adversely impact growth. The only medical option available after 5-ASAs for chronic treatment for moderate to severe pediatric UC is the use of immunosuppressants, most commonly 6-mercaptopurine (6-MP), and azathioprine (AZA), which are not approved for pediatric UC. These agents are associated with serious toxicity, including bone marrow suppression, infection, malignancy (including hepatosplenic T-cell lymphoma [HSTCL]), and teratogenicity. The only alternative for children with UC after these agents fail is colectomy. Colectomy is associated with multiple long-term consequences including incontinence, pouchitis, small bowel obstruction, and infertility. Additionally, it can have significant impact on the physical and emotional development of children. Therefore, there is a high unmet need for an approved therapy that can be prescribed chronically to control moderate to severe pediatric UC before consideration of colectomy.

REMICADE is an anti-tumor-necrosis factor alpha (TNFα) mAb developed as a therapeutic agent for various diseases in which TNFα is thought to mediate chronic inflammation. This antibody is a recombinant IgG1κ, human-murine chimeric mAb that specifically and potently binds and neutralizes TNFα and its membrane-bound precursor.[24] This high-affinity binding prevents the interaction of TNFα with its cellular receptors, thus attenuating inflammatory and other deleterious effects secondary to TNFα overproduction. REMICADE was originally approved in the US on 24 Aug 1998 for moderate to severe Crohn's disease and has subsequently been approved for 14 additional indications in 6 different diseases including reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating steroid use in adult patients with moderately to severely active UC who have had inadequate response to conventional therapy.

The pediatric UC clinical development program for REMICADE consisted of a Phase 3, randomized, open-label, parallel-group, multicenter study in pediatric subjects with UC (T72), supported by data from 2 Phase 3 studies in adult subjects with UC (ACT 1 and ACT 2) and one Phase 3 study in pediatric subjects with Crohn's disease. The T72 study assessed the safety and efficacy of induction and maintenance REMICADE treatment in pediatric subjects aged 6 through 17 years who had moderately to severely active UC (defined as a Mayo score of 6 to 12, inclusive, at baseline, including an endoscopic subscore ≥ 2), despite current adequate treatment, or who had previously failed to respond to or tolerate treatment with 6-MP, AZA, corticosteroids, and/or 5-ASA compounds. A total of 60 pediatric subjects were enrolled at 23 investigational sites in North America and Europe and were followed for safety and efficacy through Week 54. All subjects received an induction regimen of 5 mg/kg REMICADE at Weeks 0, 2, and 6. Subjects in clinical response at Week 8, as measured by the Mayo score, were randomized in a 1:1 ratio to receive 1 of 2 maintenance treatment regimens: 5 mg/kg REMICADE administered every 8 weeks (q8w) through Week 46 or every 12 weeks (q12w) through Week 42. Subjects who were nonresponders to induction dosing at Week 8 received no further infusions. During the maintenance treatment phase, subjects who lost response were eligible to increase (step-up) their REMICADE dose (5 mg/kg q8w → 10 mg/kg q8w) and/or dosing frequency (5 mg/kg q12w → 5 mg/kg q8w or 10 mg/kg q8w) one time.

1.1 Efficacy

T72 met the primary endpoint and demonstrated efficacy based on all major secondary endpoints:

- REMICADE induced clinical response (as measured by the Mayo score) at Week 8 in 44/60 (73.3%) pediatric subjects with UC.
  - Since the lower limit of the 95% CI for the proportion of subjects in clinical response at Week 8 in this study was 62.1%, which is > 40% (ie, greater than the upper limit of the 95% CI for the placebo group in the pooled ACT studies), the criterion for a positive study was met.
- REMICADE induced clinical remission (as measured by the Mayo score, and referred to in this document as "Mayo remission") in 24/60 (40.0%) subjects at Week 8.
- REMICADE induced remission (as measured by the PUCAI score, and referred to in this document as "PUCAI remission") in 17/51 (33.3%) subjects at Week 8.
- At Week 8, 41/60 (68.3%) subjects achieved mucosal healing and 33.3% had normal or inactive disease (as measured by endoscopy).

- At Week 54, a greater proportion of subjects was in PUCAI remission in the q8w group (8/21 [38.1%]) than in the q12w group (4/22 [18.2%]).

- A greater proportion of subjects on corticosteroids at baseline was in PUCAI remission and off corticosteroids at Week 54 in the q8w group (5/13 [38.5%]) than in the q12w group (0/13 [0.0%]).

- There was a substantial reduction from baseline in the average daily corticosteroid dose by Week 8 in all randomized subjects; this reduction in corticosteroid dose was maintained through Week 54 in the q8w group.

Other efficacy measures showed that onset of efficacy was rapid. Reductions in the PUCAI score and partial Mayo score were evident as early as Week 2. The proportion of subjects achieving a clinical response at Week 8 was generally consistent across all subgroups. Summaries of global assessments of change from baseline at Week 8 showed that the majority of subjects, parents/guardians, and physicians assessed subjects' health status as "much better" or "somewhat better." Most subjects who stepped up REMICADE dose and/or dosing frequency during the maintenance phase of the study demonstrated an improvement in disease activity after step-up.

Results of T72 were compared with the ACT 1 and ACT 2 studies and are notable for the similarity of efficacy during the induction and maintenance phases.

- The primary endpoint in T72 and both ACT studies was clinical response at Week 8, as measured by the Mayo score. In T72, REMICADE induced clinical response at Week 8 in 44/60 (73.3%) pediatric subjects with UC, which was similar to the proportion of adult subjects in clinical response at Week 8 in ACT 1 and ACT 2 (66.9%; pooled data from the 5 mg/kg groups).

- In T72, REMICADE induced Mayo remission at Week 8 in 24/60 (40.0%) subjects. This result was comparable to the proportion of adult subjects in clinical remission at Week 8 as measured by the Mayo score (36.4%; pooled data from the 5 mg/kg groups). PUCAI remission was induced in 17/51 (33.3%) subjects in T72.

- Maintenance of PUCAI remission at Week 54 was demonstrated for 8/21 (38.1%) subjects in the q8w group and was comparable with the proportion of adult subjects in clinical remission at Week 54 based on the Mayo score in ACT 1 (34.7% in the 5 mg/kg group). It was demonstrated by Turner et al,[51] as well as in the T72 study, that the PUCAI score is highly positively correlated with the Mayo score.

- In T72, mucosal healing was induced at Week 8 in 41/60 (68.3%) subjects which was consistent with 61.2% of adult subjects in ACT 1 and ACT 2 (pooled data from the 5 mg/kg group). There is also evidence of maintenance of mucosal healing in T72. Nine subjects underwent the optional endoscopy at Week 54. All of these subjects had achieved mucosal healing by their Week 8 visit, and at their Week 54 visit, 8/9 subjects were still in mucosal healing. At Week 54 in ACT 1, 45.5% of adult subjects in the 5 mg/kg group were in mucosal healing.

- In T72, 5/13 (38.5%) subjects receiving corticosteroids at baseline were in PUCAI remission and off corticosteroids at Week 54 in the q8w group, demonstrating the ability of REMICADE to eliminate corticosteroid use in children. This is consistent with 25.7% of the adult subjects in the 5 mg/kg group in ACT 1 who were in clinical remission at Week 54 and not receiving corticosteroids at Week 54.

1.2 Clinical Pharmacology

Pharmacokinetic results in pediatric UC subjects were generally consistent with those observed in adult subjects with UC as well as in pediatric subjects with Crohn's disease (REACH). The maintenance dosing regimen of 5 mg/kg REMICADE q8w resulted in higher infliximab exposure over time when compared with 5 mg/kg REMICADE q12w. Population PK analysis showed that the variability of infliximab PK was influenced by bodyweight, serum albumin levels, and immunogenicity. There was no apparent impact of either age (once body weight was adjusted for) or concomitant immunomodulator use on the PK of infliximab in this study.

When considering the relationship between serum concentration and efficacy, analyses of T72, ACT 1, and ACT 2 studies suggest that there is an apparent relationship between serum infliximab concentration and clinical efficacy endpoints. Higher infliximab exposure was associated with higher rates of clinical response, mucosal healing, and remission at Week 8 and with higher remission rates at Weeks 30 and 54.

Pharmacokinetic and exposure-response modeling confirmed exposure-dependent clinical response and remission in both pediatric and adult subjects with UC. Modeling and simulation indicated that the 5 mg/kg induction dose regimen can achieve clinical response in a majority of pediatric subjects with UC (and be at least as efficacious as in adult subjects with UC who received 5 or 10 mg/kg induction regimens). Similarly, pharmacokinetic and exposure-response modeling confirmed that pediatric subjects who received the 5 mg/kg q8w maintenance dosing regimen were expected to achieve a remission rate comparable to that of adult subjects with UC.

1.2.1 Dose Rationale

Based on the overall evaluation of the efficacy and safety data from studies of infliximab in pediatric subjects with UC, pediatric subjects with Crohn's disease, and adult subjects with UC, in addition to the PK analysis in pediatric and adult subjects with UC, the proposed dosing regimen of infliximab in UC is an induction regimen of 5 mg/kg administered as an IV infusion at Weeks 0, 2, and 6 followed by maintenance IV infusions of 5 mg/kg infliximab q8w. This proposed infliximab dose regimen in pediatric UC is supported by the following:

- A majority of subjects who received the induction dose regimen (ie, 5 mg/kg at Weeks 0, 2, 6) achieved clinical response and mucosal healing in C0168T72.
- Compared to adult subjects with UC, a similar proportion of subjects on the 5 mg/kg q8w maintenance regimen achieved remission.
- Exposure-response modeling showed that an induction regimen of 5 mg/kg at Weeks 0, 2, 6 followed by a maintenance dose regimen of 5 mg/kg q8w will achieve clinical response and remission rates comparable to adult subjects with UC.
- The safety profiles across the clinical studies were generally consistent.

1.3 Safety

REMICADE was generally well tolerated by pediatric subjects in T72 with moderately to severely active UC. The safety profile appears to be consistent with that reported in other studies of REMICADE.

- Through Week 54, 57/60 (95.0%) treated subjects had 1 or more AEs. The system-organ class with the highest incidence of AEs was GI system disorders (36/60 [60.0%]), and worsening UC was the most common AE (27/60 [45.0%]). The overall proportion of subjects with AEs was the same in the q8w and q12w groups; however, it is noteworthy that worsening UC occurred in a greater proportion of subjects in the q12w group (15/23 [65.2%]) than in the q8w group (8/22 [36.4%]).
- The number of treated subjects with 1 or more SAEs was 14/60 (23.3%); the only SAE reported in 2 or more subjects was worsening UC (9/60 [15.0%]). The proportion of subjects with SAEs was similar in the q8w and q12w groups (4/22 [18.2%] and 5/23 [21.7%], respectively), and no noteworthy differences in SAEs were observed.

- Through Week 54 in T72, 13/60 (21.7%) subjects discontinued study agent because of an AE. Worsening UC was the most common AE resulting in discontinuation of study agent (10/60 [16.7%]). The proportion of subjects who discontinued study agent was higher in the q12w group (6/23 [26.1%]) than in the q8w group (3/22 [13.6%]).

- No deaths, malignancies, serious neurologic events, opportunistic infections, TB, or congestive heart failure were reported. No subjects had a serious infusion reaction, possible delayed hypersensitivity reaction, or anaphylactic reaction.

- Of the treated subjects with appropriate samples for analysis of antibodies to infliximab, 4/52 (7.7%) were positive for antibodies to infliximab at any time during the study.

REMICADE has been marketed since 1998 with an estimated cumulative commercial exposure of over 1.5 million patients. Of those, an estimated 22,922 (1.5%) were younger than 18 years of age, including an estimated 17,262 treated for Crohn's disease and an estimated 1581 treated for UC. This postmarketing experience, together with clinical studies, has clearly established the safety profile of REMICADE, which is generally consistent with other TNFα blockers. The main category of AE associated with their use is infections (including TB and opportunistic infections). Other notable categories of AEs observed with TNFα blockers are malignancies (including lymphoma, pediatric malignancies, and leukemia), hepatotoxicity, congestive heart failure, hematologic toxicity, neurologic or demyelinating events, autoimmune disorders, administration reactions, anaphylactic reactions, and delayed hypersensitivity reactions.

Key comparisons for the T72 safety profile include 112 pediatric subjects with Crohn's disease treated with 5 mg/kg REMICADE in the Phase 3 REACH study and 242 adult subjects with UC treated with 5 mg/kg REMICADE in the pooled Phase 3 ACT 1 and ACT 2 studies. Considering AEs, SAEs and events of special interest including colectomies, the T72 safety data are generally consistent with safety data from the REACH and ACT studies and are consistent with current REMICADE labeling. No new safety concerns emerged regarding the proposed use of REMICADE in the pediatric UC population.

Supportive long-term safety is provided from the ongoing pediatric IBD registries and postmarketing reviews. In the IBD registries, in which patients with Crohn's disease rather than patients with UC currently make up the majority, the analyses show that there are no unexpected safety findings, and that the AEs represent known effects of REMICADE treatment and of the diseases under study. The overall postmarketing safety review of AEs reported for REMICADE-exposed pediatric patients supports the conclusion that the safety profile of REMICADE in the pediatric population is generally consistent with that seen in the adult population and with current labeling. Of particular

concern in the pediatric population are the warnings regarding the risk of pediatric malignancy in general and HSTCL in particular that have been added to the REMICADE label.

1.4 Benefits and Risks Conclusions

The proposed indication for pediatric UC is identical to the FDA-approved REMICADE adult UC indication, with the proposed wording change as follows (highlighted in bold text):

> REMICADE is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in **adult and pediatric** patients with moderately to severely active disease who have had an inadequate response to conventional therapy

The overall clinical features, clinical course of the disease, and response to treatment are comparable in pediatric and adult populations with UC, with pediatric disease often more extensive and therefore more severe than adult disease. There are no approved pharmacologic treatment options for children with UC who have failed to respond to conventional therapy. When pharmacologic treatment is no longer effective in managing UC disease, the only alternative is colectomy which is associated with notable morbidity and mortality, particularly in children, in terms of their quality of life, physical and emotional development at a critical age of personality development, and for girls, the probability of reduction of fertility later in life. As such, there is a need for a safe and efficacious treatment option for pediatric patients with moderate to severe UC.

The T72 study provided clinically important evidence that REMICADE was efficacious in pediatric subjects with UC, with efficacy at least as good as that observed in adults. When the 2 maintenance regimens used in T72 were compared in terms of efficacy and safety, the q8w regimen resulted in better remission rates, while maintaining a similar safety profile. REMICADE was generally well-tolerated in this study. No new safety concerns emerged regarding the proposed use of REMICADE in the pediatric UC population. In addition to routine pharmacovigilance, the sponsor has in place significant risk minimization activities including a medication guide, multiple approaches to healthcare provider education, and long-term registries including 2 large, ongoing, prospective pediatric registries, DEVELOP and the Pediatric IBD Collaborative Research Group Registry. These registries will accumulate extensive information about pediatric IBD, including UC, and the benefits and risks of REMICADE treatment.

Therefore, considering the unmet need in the pediatric UC population, the demonstrated efficacy in T72 of REMICADE in pediatric UC that was consistent with the efficacy in adult UC, and the established safety profile of REMICADE, the benefit-risk ratio is considered positive for the treatment of pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

2 Product Development Rationale

2.1 Pharmacologic Class

REMICADE is a chimeric human-murine IgG1κ subclass mAb that binds with high affinity to the soluble and transmembrane forms of human TNFα and inhibits TNFα bioactivity. REMICADE is classified according to the Anatomical Therapeutic Chemical (ATC) Classification System as a TNFα inhibitor (ATC code: L04AB02).

2.2 Proposed Label Revision

REMICADE is approved for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active UC who have had an inadequate response to conventional therapy. The recommended dose of REMICADE is 5 mg/kg given as an IV induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg q8w thereafter for the treatment of moderately to severely active UC in adults.

This document provides data in support of expanding the use of REMICADE at the recommended dosing for adult UC to pediatric patients with moderately to severely active UC who have had an inadequate response to conventional therapy.

The sponsor proposes the following changes to the UC indication and recommended dosing in the approved REMICADE label (shown in bold text below).

- REMICADE is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in **adult and pediatric** patients with moderately to severely active UC who have had an inadequate response to conventional therapy.

- The recommended dose of REMICADE is 5 mg/kg given as an IV 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 **adult and pediatric patients with** moderately to severely active UC.

2.3 Global Experience with REMICADE

2.3.1 Clinical Experience

Through 23 Feb 2011, over 6000 adult subjects across 6 different diseases have been exposed to REMICADE in company-sponsored clinical studies. These subjects included 1304 patients with rheumatoid arthritis (RA), 1427 patients with Crohn's disease, 275 with AS, 293 with psoriatic arthritis (PsA), 493 with UC, and 1373 with plaque psoriasis.

Additionally, 289 pediatric patients have been exposed to REMICADE in multiple dose clinical studies: 112 in pediatric Crohn's disease, 60 in pediatric UC, and 117 in juvenile rheumatoid arthritis (JRA).

2.3.2 Approved Indications

REMICADE was originally approved in the US on 24 Aug 1998 for moderate to severe Crohn's disease and has achieved 14 additional approvals for indications in 6 different diseases. It has gained marketing approvals in 103 countries worldwide, including countries in North America, Europe, Asia, Latin America, the Middle East, and the Pacific Rim.

In the US, REMICADE is indicated for the following:

Crohn's Disease: approved in

- 1998 for reducing the signs and symptoms in patients with moderately to severely active Crohn's disease, and for reducing the number of draining enterocutaneous fistula(s) in patients with fistulizing Crohn's disease.
- 2002 for inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease.
- 2003 for maintaining fistula closure in patients with fistulizing Crohn's disease.

Rheumatoid Arthritis: approved in

- 1999 for reduction in signs and symptoms of RA in patients who have had an inadequate response to methotrexate (MTX).
- 2000 for inhibition of progression of structural damage in patients who have had an inadequate response to MTX.
- 2002 for improving physical function in patients with moderately to severely active RA who have had an inadequate response to MTX.
- 2004 for the treatment of patients with earlier stage RA with moderate to severe disease and not previously treated with MTX.

Ankylosing Spondylitis: approved in

- 2004 for the treatment of active AS.

Psoriatic Arthritis: approved in

- 2005 for reducing signs and symptoms of active arthritis in patients with PsA.
- 2006 for inhibiting the progression of structural damage of active arthritis and improving physical function in patients with PsA.

Ulcerative Colitis: approved in

- 2005 for reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating steroid use in adult patients with moderately to severely active UC who have had inadequate response to conventional therapy.
- 2006 for inducing and maintaining clinical remission and mucosal healing.

Pediatric Crohn's Disease: approved in

- 2006 for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active Crohn's disease.

Plaque Psoriasis: approved in

- 2006 for the treatment of adult patients with chronic severe (ie, extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

2.3.3 Safety Profile of the Pharmacological Class

REMICADE is a biological TNFα blocker. The categories of AEs associated with the use of drugs in this pharmacological class have been well-documented in clinical studies and postmarketing use. The main category of AE associated with their use is infections (including TB and opportunistic infections). Other notable categories of AEs observed with TNFα blockers are malignancies (including lymphoma, pediatric malignancies, and leukemia), hepatotoxicity, congestive heart failure, hematologic toxicity, neurologic or demyelinating events, autoimmune disorders, administration reactions, anaphylactic reactions, and delayed hypersensitivity reactions.

The clinical safety experience with REMICADE indicates that, in general, the safety profile of REMICADE is consistent with the established safety profile of TNFα blockers.

2.3.4 REMICADE Safety Profile

The class of TNFα blockers has a complex safety profile. REMICADE was the first mAb marketed in its class and the sponsor has consistently monitored the safety profile

closely and coordinated with the FDA to inform prescribers and patients about REMICADE.

The estimated cumulative commercial patient exposure to REMICADE in the US and worldwide as of 23 Feb 2011 is presented in Table 1. The estimated exposure in patients < 18 years of age as of Dec 2010 is 14,724 patients in the US and 22,922 patients worldwide.

Table 1: Estimated cumulative commercial patient exposure to REMICADE in the US and worldwide (as of 23 Feb 2011)

	US	Worldwide
Cumulative since first launch, 24 Aug 1998	**849,127**	**1,537,395**
Rheumatoid arthritis	433,420	736,593
Crohn's disease	250,533	499,823
Ulcerative colitis	72,865	107,524
Psoriatic arthritis	42,280	73,613
Ankylosing spondylitis	20,490	70,391
Psoriasis	16,758	35,645
Other	12,781	13,806

Important aspects of the safety profile of REMICADE are described below.

Serious Infections

- Serious and sometimes fatal infections due to bacterial, mycobacterial, viral, invasive fungal, or other opportunistic pathogens have been reported in patients receiving TNFα blockers.

- Among opportunistic infections, TB, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly reported, were frequently disseminated, and were often observed in patients taking concomitant immunosuppressants.

- Cases of reactivation of TB or new TB infections have been observed with REMICADE, including in patients who have previously received treatment for latent or active TB.

Malignancies

- The potential role of TNFα blocker therapy in the development of malignancies is not known.

- In the controlled portions of clinical studies of some TNFα blockers including REMICADE, more malignancies (excluding lymphoma and nonmelanoma skin cancer) have been observed in patients receiving those TNFα blockers compared with control patients.

  - The most common malignancies were breast, colorectal, and melanoma.

  - The rate of malignancies among REMICADE-treated patients was similar to that expected in the general population, whereas the rate in control patients was lower than expected.

- In the controlled portions of clinical studies of all TNFα blockers, more cases of lymphoma have been observed among patients receiving TNFα blockers compared with control patients.

  - In the combined clinical study population for RA, Crohn's disease, PsA, AS, UC, and plaque psoriasis, the rate of lymphomas was approximately 4-fold higher than expected in the general population.

  - Patients with Crohn's disease, RA, or plaque psoriasis, particularly those 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 TNFα blocker therapy.

- Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNFα blockers (initiation of therapy ≤ 18 years of age), including REMICADE.

  - Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma (NHL). 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 TNFα blocker therapy. Most of the patients were receiving concomitant immunosuppressants.

- Postmarketing cases of HSTCL, a rare type of T-cell lymphoma, have been reported in patients treated with TNFα blockers including REMICADE. These cases have had a very aggressive disease course and have been fatal.
  - All reported REMICADE cases have occurred in patients with Crohn's disease or UC, and the majority occurred in adolescent and young adult males.
  - All of these patients had received treatment with the immunosuppressants AZA or 6-MP concomitantly with REMICADE at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to REMICADE or REMICADE in combination with these other immunosuppressants.
- Cases of acute and chronic leukemia have been reported with postmarketing TNFα blocker use in RA and other indications. Even in the absence of TNFα blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Hypersensitivity

- REMICADE has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases.
- Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of infusion.
- In some cases, serum sickness-like reactions (fever, rash, headache, sore throat, myalgia, polyarthralgia, hand and facial edema, and/or dysphagia) have been observed in patients after initial REMICADE therapy (ie, as early as after the second dose), and when therapy was reinstituted following an extended period without treatment.
  - These reactions were associated with a marked increase in antibodies to infliximab, loss of detectable serum concentrations of infliximab, and possible loss of drug efficacy.

Infusion-related Reactions

- An infusion reaction was defined in clinical studies as any AE occurring during an infusion or within 1 to 2 hours after an infusion. The rate of infusion reactions in REMICADE-treated subjects was approximately twice that of placebo-treated subjects.
- Adverse effects during administration of REMICADE have included flu-like symptoms, headache, dyspnea, hypotension, transient fever, chills, GI symptoms, and skin rashes. Anaphylaxis might occur at any time during infusion.

Neurological Events

- REMICADE and other TNFα blockers have been associated in rare cases with CNS manifestation of systemic vasculitis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disorders, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome.

Autoimmunity

- Treatment with REMICADE may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome.

Vaccinations

- No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving TNFα blocker therapy.

- It is recommended that live vaccines not be given concurrently with REMICADE.

- Pediatric patients should be brought up to date with all vaccinations prior to initiating REMICADE therapy.

Use with Other Biologic Immunosuppressants

- The combination of REMICADE and anakinra, abatacept, or tocilizumab is not recommended. In clinical studies, concurrent administration of TNFα blockers and anakinra or abatacept has been associated with an increased risk of infections, including serious infections, compared with TNFα blockers alone, without increased clinical benefit.

- Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection.

Hepatitis B Virus Reactivation

- Use of TNFα blockers, including REMICADE, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, this has been fatal.

  - The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation.

Hepatotoxicity

- Severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholestasis, have been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune hepatitis has been diagnosed in some of these cases.

- Severe hepatic reactions occurred between 2 weeks to more than 1 year after initiation of REMICADE; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation.

Patients with Heart Failure

- REMICADE has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options.

Hematologic Events

- Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE. The causal relationship remains unclear.

2.4 Relevant Scientific Background

2.4.1 Ulcerative Colitis

Inflammatory bowel disease is a chronic GI inflammatory disorder which encompasses UC, Crohn's disease, and indeterminate colitis (IC).[33,35,46] Ulcerative colitis and Crohn's disease differ primarily in the portions and layers of the bowel that are involved. Ulcerative colitis involves the surface mucosa, crypt epithelium, and submucosa of the colon, while Crohn's disease can involve any area of the GI tract from the mouth to the rectum and involves not only the bowel mucosa, but deeper layers of the bowel.[46]

Clinically, patients with UC suffer from diarrhea, rectal bleeding, weight loss, abdominal pain, and fever, and may also display prominent extraintestinal manifestations, such as colitic arthritis and AS.[15,46] UC is characterized by a life-long chronic course of remissions and exacerbations, with at least 15% of patients having an acute attack requiring hospitalization at some time during their illness.[52,54] Traditionally, the management of a severe exacerbation has been dependent on IV steroids; however, up to 40% of patients fail to respond resulting in colectomy during that admission.[21] Even for those patients who respond to steroids, approximately 25% become steroid dependent, and an additional approximately 20% to 30% will require a colectomy at 1 year.[7] It is known that patients with long-standing UC have an increased risk of developing colorectal cancer.[5]

The overall estimate of the prevalence of adult and pediatric UC is 690,000 people in North America and 1 million people in Europe.[31] In the US, the estimated prevalence of pediatric UC (children younger than 20 years) is 28 (95% CI: 26-30) per 100,000 lives, while the estimated prevalence of adult UC is 238 (95% CI: 234-241) per 100,000 lives.[23] Given the low prevalence of pediatric UC, in November 2003, the FDA's OOPD granted orphan designation to REMICADE for the treatment of pediatric patients with UC.

2.4.2 Comparison of Pediatric UC and Adult UC

While UC disease is quite similar in adult and pediatric patients in terms of overall disease pathology and progression, pediatric-onset UC is typically distinguished from adult-onset UC by a greater prevalence of extensive disease (or pancolitis; up to 80% to 90% in pediatric patients compared with approximately 25% in adults patients), and therefore a greater prevalence of moderate to severe disease (approximately 60% in pediatric patients compared with approximately 45% in adult patients[28]).[20,44,53]

Treatment paradigms are similar in adult and pediatric UC, with only a few prospective trials available in pediatrics, but all with similar results to adult trials. Outcome remains the most significant driver of treatment options, and in children, disease activity is the most important outcome measure.[44]

2.4.3 Other Important Considerations for Pediatric Patients with UC

It is important to examine the consequences of UC in all aspects of children's lives, not just the GI manifestations reviewed above. When considering the psychiatric impact of the disease, a meta-analytic review of different chronic diseases suggested that IBD had the most profound effect on mental health of all the medical diseases reviewed.[29] Engstrom and Lindquist found that psychiatric disorder, assessed with a well-validated psychiatric interview, was 4 times as frequent in children with IBD (60%) as in a group of healthy children (15%).[6] Studies have shown that relapses of IBD can profoundly affect patients' quality of life in the academic environment.[34] One study found that 57% of 70 patients with IBD reported total absences of ≥ 2 months, and 21% reported that relapses of IBD prevented examination participation or negatively impacted results.[9] The heterogeneity of the illness and the wide spectrum of disease severity make generalizations inappropriate; nevertheless, the observations in individual studies are disturbing and demand that greater attention be paid to the psychological impact of IBD on young patients[12] and point to the obvious need for effective therapies.

When medical treatment is no longer effective in managing UC disease, proctocolectomy is the only alternative.[3] Although colectomy is curative in the sense of removing the diseased organ, it is associated with notable morbidity and mortality in both adults[8,27] and

children. While pediatric patients who undergo colectomy have similar rates and types of complications as adults,[10] the impact on a pediatric patient's quality of life and physical and emotional development at a critical age of personality development is profound.[47] Furthermore, there is an association of colectomy with a reduction in the probability of conception in females undergoing pouch procedure,[30] an important consideration when considering an indication in a pediatric population

In summary, the impact of UC on children's lives reaches far beyond GI effects and extraintestinal manifestations. Medical intervention in pediatric UC must address these as well as the psychiatric and social impact of the disease.

2.4.4 Treatment of Pediatric UC

2.4.4.1 Medical Therapy and Unmet Medical Need

The overall goal of treatment for UC is to induce remission in acute, active disease and to maintain disease remission.[36] Treatment of UC consists mainly of anti-inflammatory and immunosuppressive therapies and is progressive according to the patient's disease severity and response to therapy.[25,36] However, few drug therapies are approved for use in the treatment of pediatric UC (Table 2).

Table 2: Drug therapies approved or routinely used clinically in the treatment of pediatric UC

Class/ Drug	Approved in US for Pediatric UC	Safety/Tolerability (Warning and Precaution Section)
Aminosalicylates		
Sulfasalazine	Yes	• Hypersensitivity reactions • Blood disorder (agranulocytosis, aplastic anemia, other blood dyscrasias) • Irreversible neuromuscular and central nervous system changes • Fibrosing alveolitis • Oligospermia and infertility (male) • Renal toxicity • Hepatotoxicity • Diarrhea • Exacerbation of the symptoms of UC
Mesalamine	No	
Olsalazine	No	
Balsalazide	Yes	

Table 2: Drug therapies approved or routinely used clinically in the treatment of pediatric UC

Class/ Drug	Approved in US for Pediatric UC	Safety/Tolerability (Warning and Precaution Section)
Corticosteroids Prednisone Methylprednisolone Cortisone	 Yes Yes Yes	• Osteoporosis • Growth retardation • Avascular necrosis • Cushing syndrome • Hypertension • Glucose intolerance • Adrenal insufficiency • Pancreatitis
Immunomodulators Methotrexate	 No	• Risk of infections including fatal opportunistic infections (pneumocystis carinii pneumonia) • Bone marrow suppression • Malignant lymphomas, tumor lysis syndrome in patients with rapidly growing tumors • Heptatotoxicity, fibrosis and cirrhosis • Diarrhea and ulcerative stomatitis • Soft tissue necrosis and osteonecrosis (when given concomitantly with radiotherapy) • Toxicity in lung, kidney, liver, and GI • Hypersensitivity pneumonitis • Teratogenicity (death and/or congenital anomalies) in females and males
Azathioprine	No	• Risk of neoplasia, including HSTCL • Mutagenic potential in both male and female • Hematologic toxicities (severe leukopenia, thrombocytopenia, macrocytic anemia, and/or pancytopenia) • Bone marrow suppression • Serious infections
6-Mercaptopurine	No	• Bone marrow toxicity • Hepatotoxicity • Immunosuppression
Mycophenolate mofetil	No	• Lymphoma • Infections • Neutropenia • Congenital malformation (female users of childbearing potential)
Cyclosporine	No	• Infection • Lymphoma and other neoplasms • Hypertension • Nephrotoxicity • Renal dysfunction including structural kidney damage

Table 2: Drug therapies approved or routinely used clinically in the treatment of pediatric UC

Class/ Drug	Approved in US for Pediatric UC	Safety/Tolerability (Warning and Precaution Section)
Tacrolimus	No	• Infection • Malignancy and lymphoproliferative disorder • Insulin-dependent post-transplant diabetes mellitus (PTDM) in kidney transplant patients • Nephrotoxicity • Hyperkalemia • Neurotoxicity • Anaphylactic reactions • Wound healing complications, renal function impairment, and PTDM in heart transplant patients
Antibacterials Metronidazole	No	• Central and peripheral nervous system effects • More prominent candidiasis symptoms • Low dose with caution in patients with severe hepatic disease
Biologic agents REMICADE	No	• Serious infections including active TB, opportunistic infections, invasive fungal infections, sepsis, etc. • Malignancies • Hepatosplenic T-cell lymphoma • Hepatitis B virus reactivation • Hepatotoxicity • Heart failure • Cytopenias • Hypersensitivity • Demyelinating disease • Lupus-like syndrome
Adalimumab	No	• Serious infections including TB, opportunistic infections, bacterial sepsis, invasive fungal infections • Lymphoma and other malignancies • Anaphylaxis and serious allergic reactions • Hepatitis B virus reactivation • Demyelinating disease, exacerbation or new onset • Cytopenias, pancytopenia • Heart failure • Lupus-like syndrome • Autoimmunity • Neurologic events

Treatment of mild to moderate disease in children, because it is almost always more extensive, typically starts with oral 5-ASA, such as mesalamine, olsalazine, sulfasalazine, and balsalazide with or without antibiotics.[36,41]

For those patients who do not respond to treatment with 5-ASA or for those with moderate or moderate to severe disease, corticosteroids are the first-line treatment for inducing disease remission despite their associated adverse effects. Short-term clinical response to corticosteroids in pediatric patients with newly diagnosed UC is generally good, and a large multicenter prospective study showed that the corticosteroid failure rate in pediatric patients with UC was 29%.[50] However, approximately 45% of pediatric patients who initially responded to corticosteroids either became steroid-dependent[20] or required surgery.[48] Corticosteroids are avoided if possible after induction as their potential adverse effects can be significant in pediatric patients (already negatively impacted by the underlying illness) due to their impact on growth[14] and other morbidities associated with persistent corticosteroid usage.[40,44] Consequently, children with a new diagnosis of UC are often started on corticosteroids with a taper over 2 months.

For those patients who are corticosteroid-refractory or corticosteroid intolerant, the calcineurin inhibitor, cyclosporine[41], and REMICADE[25] may be used in the acute setting. Immunomodulators such as thiopurines (AZA/6-MP) or MTX are used to maintain remission in patients who have been successfully induced by corticosteroids (or other acute treatment alternative options). None of these agents are approved for use in pediatric UC.

Cyclosporine, when used in children with severe, refractory UC who are unresponsive to IV corticosteroids is typically given for 3 to 4 months (ie, not as a maintenance therapy), and is associated with side effects including hypertrichosis, paraesthesis, hypertension, hypomagnesaemia, nephrotoxicity, hepatotoxicity, diabetes, infection, and several neurological problems (seizures, confusion, cortical blindness, and speech and motor disturbances). Deaths and anaphylaxis have also occurred. Prophylaxis against opportunistic infection is suggested when using cyclosporine.[2] There remain several unresolved issues regarding the optimal dose and administration regimens of cyclosporine and, even when effective initially, many of those who respond relapse quickly and require colectomy.

The thiopurines 6-MP and AZA can take as long as 3 months to work, may only be partially effective, and can result in neutropenia, pancytopenia, pancreatitis, nephrotoxicity, and hepatotoxicity in some patients.[1,3,4,49] Frequent blood count monitoring is mandatory at the beginning of therapy and regular blood count and liver enzyme testing should continue throughout treatment with thiopurines. In addition, their use is associated with an increased risk in adults of lymphoma.[22] Furthermore, a very rare and rapidly fatal lymphoproliferative disorder (HSTCL), has been reported in mostly

young adult male patients with IBD (predominantly Crohn's disease) who were treated with thiopurines.[26]

In summary, effective medical therapies to treat pediatric UC are limited in number and remain largely unapproved and unmonitored in this indication. Therefore, there is a high unmet need for an approved therapy that can be prescribed chronically to control moderate to severe pediatric UC.

2.4.4.2 Treatment of Adult Versus Pediatric UC

Although there have been no randomized, placebo-controlled studies in pediatric patients with UC specifically assessing the induction or maintenance of remission by the agents used to treat adult UC, treatment of pediatric UC generally follows the same treatment paradigm that is used to treat adult UC[44,49] (Figure 1).

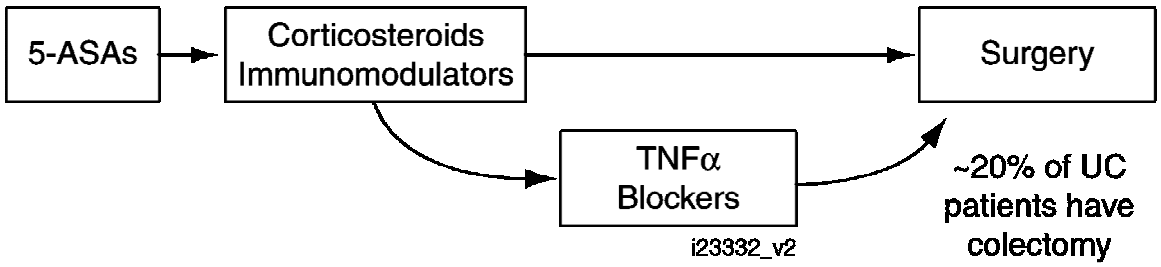


Figure 1: Treatment paradigm for UC

In addition, many of the agents that are approved to treat adult patients with UC are used off-label in many countries. Drug therapies approved or routinely used clinically in the treatment of pediatric UC in the US are presented in Table 2.

2.4.4.3 Surgical Therapy

When medical treatment is no longer effective in managing UC disease, proctocolectomy is the only alternative.[3] The rate of colectomy in pediatric patients ranges from 9% to 46%[17,49] with the cumulative probability reportedly similar between pediatric and adult patients.[28]

Although colectomy is curative in the sense of removing the diseased organ, it is associated with notable morbidity and mortality in both adults[8,27] and children. Complications of colectomy when associated with ileoanal anastomosis with pouch surgery (the preferred option) include pouchitis (acute or chronic), leak, cuffitis, reduced

female fertility, poor functional result including nocturnal stool leakage, and perioperative mortality.[8,27]

While pediatric patients who undergo colectomy have similar rates and types of complications as adults,[10] the impact on a pediatric patient's quality of life, physical and emotional development at a critical age of personality development is profound.[47] Furthermore, there is an association of colectomy with a reduction in the probability of conception in females undergoing pouch procedure.[30] Another complicating factor which is particularly important in the pediatric setting is that emergency surgery for colitis may be needed and this may have resultant negative implications for physical and emotional health. Unplanned colectomy in children can be complicated by the presence of high dose corticosteroid therapy, poor nutrition, and psychologic maladjustment to the colectomy and temporary ileostomy (and resultant negative body image). For these reasons, there is interest in additional, rapid onset, medical therapy to treat UC that is unresponsive to high dose IV corticosteroids.[18]

2.5 Clinical Development Program

The pediatric UC clinical development program for REMICADE consisted of a Phase 3, randomized, open-label, parallel-group, multicenter study in 60 pediatric subjects with UC (T72), supported by data from 2 Phase 3 studies in adult subjects with UC (ACT 1 and ACT 2) and a Phase 3 study in pediatric subjects with Crohn's disease (REACH).

- Efficacy analyses are based upon data from T72, and supported by data from ACT 1 and ACT 2.
- Pharmacokinetics and immunogenicity analyses are based upon data from T72, and supported by data from ACT 1, ACT 2, and REACH.
- Primary safety analyses are based upon data from T72, and supported by data from ACT 1, ACT 2, and REACH. In addition, further supportive safety data from the following are presented:
  - RESULTS UC (T62) long-term safety follow-up study in pediatric subjects with UC.
  - Postmarketing registries in pediatric IBD (DEVELOP and Pediatric IBD Collaborative Research Group Registry).

A description of the Phase 3 REMICADE clinical studies analyzed in support of the pediatric UC indication is presented in Table 3.

Table 3: Description of REMICADE Phase 3 clinical studies analyzed in support of the pediatric UC indication

Study Total Follow-up # of Subjects	Disease Entry Criteria	Treatment Groups
Pediatric UC		
C0168T72 (T72) 54 weeks (antibody assessment at Week 62) 60 subjects enrolled; 45 randomized at Week 8	Mayo score of 6 to 12, inclusive, at baseline, including an endoscopic subscore ≥ 2	All subjects: 5 mg/kg REMICADE Weeks 0, 2, 6 Week 8 • Responders randomized (1:1) to: –5 mg/kg REMICADE q8w through Week 46 (n = 22) –5 mg/kg REMICADE q12w through Week 42 (n = 23) • Nonresponders discontinued from study agent Step-up at loss of response: • 5 mg/kg REMICADE q8w → 10 mg/kg q8w (n = 9) • 5 mg/kg REMICADE q12w → 10 mg/kg q8w (n = 8) • 5 mg/kg REMICADE q12w → 5 mg/kg q8w (n = 6)
Adult UC		
C0168T37 (ACT 1) 54 weeks (antibody assessment at Week 66) Long-term extension (LTE) up to 3 years 364 randomized subjects	Mayo score of 6 to 12, inclusive, at baseline, including an endoscopic subscore ≥ 2	Subjects randomized at Week 0 (1:1:1) to: • Placebo (n = 121) • 5 mg/kg REMICADE (n = 121) • 10 mg/kg REMICADE (n = 122) Study agent: Weeks 0, 2, 6; q8w through Week 46
C0168T46 (ACT 2) 30 weeks (antibody assessment at Week 42) LTE up to 3 years 364 randomized subjects	Mayo score of 6 to 12, inclusive, at baseline, including an endoscopic subscore ≥ 2	Subjects randomized at Week 0 (1:1:1) to: • Placebo (n = 123) • 5 mg/kg REMICADE (n = 121) • 10 mg/kg REMICADE (n = 120) Study agent: Weeks 0, 2, 6, 14, 22
Pediatric Crohn's Disease		
C0168T47 (REACH) 54 weeks (antibody assessment at Week 62) LTE up to 3 years 112 subjects enrolled; 103 randomized at Week 10	Pediatric Crohn's Disease Activity Index score of > 30	All subjects: 5 mg/kg REMICADE Weeks 0, 2, 6 Week 10 • Responders randomized (1:1) to: –5 mg/kg REMICADE q8w through Week 46 (n = 52) –5 mg/kg REMICADE q12w through Week 42 (n = 51) • Nonresponders discontinued from study agent Cross-over at loss of response: • 5 mg/kg REMICADE q8w → 10 mg/kg q8w (n = 10) • 5 mg/kg REMICADE q12w → 10 mg/kg q8w (n = 13) • 5 mg/kg REMICADE q12w → 5 mg/kg q8w (n = 12)

2.5.1 Pediatric UC (T72)

2.5.1.1 Study Population

The T72 study was a Phase 3, randomized, open-label, parallel-group, multicenter study to assess the safety and efficacy of induction and maintenance REMICADE treatment in pediatric subjects aged 6 through 17 years who had moderately to severely active UC (defined as a Mayo score of 6 to 12, inclusive, at baseline, including an endoscopic subscore ≥ 2), despite current adequate treatment or who had previously failed to respond to or tolerate treatment with 6-MP, AZA, corticosteroids, and/or 5-ASA compounds. A total of 60 pediatric subjects were enrolled at 23 sites in North America and Europe and were to be followed for safety and efficacy through Week 54.

2.5.1.2 Study Design

- All subjects were to receive an induction regimen of 5 mg/kg REMICADE at Weeks 0, 2, and 6.

- Subjects in clinical response at Week 8, as measured by the Mayo score, were to be randomized in a 1:1 ratio to receive 1 of 2 maintenance treatment regimens: 5 mg/kg REMICADE administered q8w through Week 46 or q12w through Week 42.

- Subjects who were nonresponders to induction dosing at Week 8 were to return for a final safety evaluation (8 weeks after their last study agent administration) but receive no further infusions.

- During the maintenance treatment phase, subjects who lost response were eligible to increase (step-up) their REMICADE dose (5 mg/kg q8w → 10 mg/kg q8w) and/or dosing frequency (5 mg/kg q12w → 5 mg/kg q8w if loss of response was > 8 but < 12 weeks from the previous REMICADE infusion or 10 mg/kg q8w if loss of response was ≤ 8 weeks from the previous REMICADE infusion) one time.

- Subjects were allowed to be treated with stable doses of corticosteroids, 6-MP/AZA, MTX, or 5-ASA compounds during the study, provided they were on a stable dose prior to screening. Subjects were to remain on the stable doses of their baseline concomitant UC medications throughout the study, with the following exceptions:

  - Corticosteroids were allowed to be tapered following the Week 0 visit

  - Discontinuation of 6-MP/AZA or MTX was allowed anytime during the study starting from screening

  - Subjects who stepped up after losing response were allowed to change their dose of, or initiate treatment with, corticosteroids, 6-MP/AZA, MTX, or 5-ASA compounds if they failed to regain response or if they lost response again.

An overview of the T72 study is presented in Figure 2.

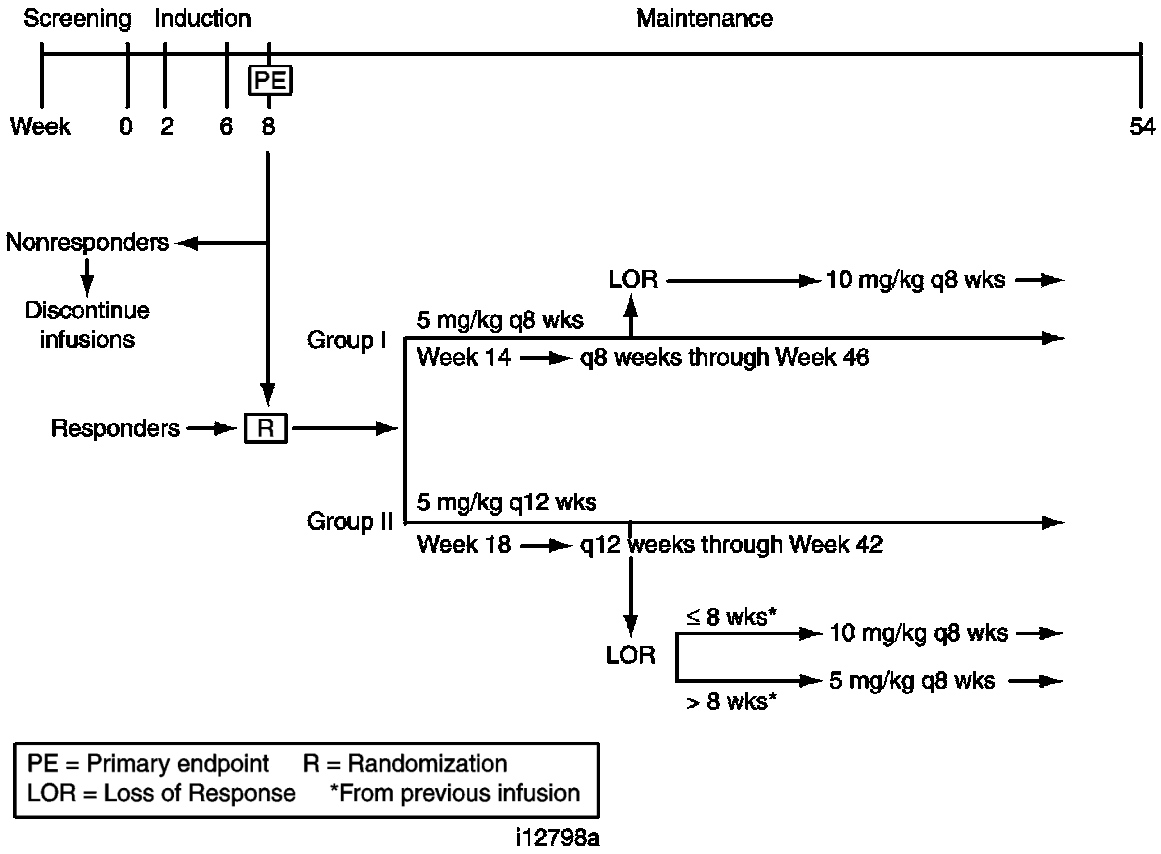


Figure 2: T72 study schema

2.5.1.3 Primary and Major Secondary Endpoints

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, at Week 8.

The major secondary endpoints were:

- Clinical remission at Week 8, defined as a Mayo score ≤ 2 points, with no individual subscore > 1, at Week 8 (referred to as "Mayo remission" in this document).
- Remission at Week 8, defined as a PUCAI score < 10 points at Week 8 (referred to as "PUCAI remission" in this document).

- Mucosal healing at Week 8, defined as an endoscopy subscore of 0 or 1 at Week 8.
- PUCAI remission at Week 54.

2.5.1.4 Efficacy Outcomes

2.5.1.4.1 Mayo Score

The efficacy tool used to assess clinical response, Mayo remission, and mucosal healing at Week 8 was the Mayo score.[45] The Mayo score consists of the following 4 UC-related subscores:

- Stool frequency
- Rectal bleeding
- Findings of endoscopy
- Physician's global assessment

Each subscore was rated on a scale from 0 to 3, indicating normal (0) to severe (3) activity. The Mayo score was calculated as the sum of the 4 subscores and thus ranged from 0 to 12. The partial Mayo score is the Mayo score without the endoscopy subscore and ranged from 0 to 9. A Mayo score of 6 to 10 indicates moderate disease, whereas a Mayo score of 11 to 12 indicates severe disease.

2.5.1.4.2 PUCAI

Due to the issues associated with performing repeated endoscopies in pediatric subjects, the protocol was amended to make the Week 54 sigmoidoscopy optional and to add the validated PUCAI score,[51] a tool for assessing disease activity in pediatric subjects with UC that does not include an endoscopic assessment, as a measure of efficacy during the maintenance phase. For subjects who enrolled prior to the protocol amendment, the PUCAI scores at timepoints prior to the amendment were not retrospectively collected; these subjects were considered evaluable for PUCAI from the first visit at which the PUCAI score was obtained.

The PUCAI score is comprised of 6 subscores:

- Rectal bleeding (0 to 30 points)
- Number of stools in a 24-hour period (0 to 15 points)
- Stool consistency (0 to 10 points)
- Abdominal pain (0 to 10 points)
- Nocturnal bowel movement (0 to 10 points)
- Activity level (0 to 10 points)

The PUCAI score was calculated as the sum of the 6 subscores and thus ranged from 0 to 85, with lower scores indicating less severe disease. Turner et al specified that a PUCAI score of 35 to 64 indicates moderate disease activity, a score of ≥ 65 indicates severe disease activity, a decrease of 20 points is a minimally clinically important change, and a score < 10 indicates remission.[51] Turner et al also demonstrated that the full Mayo score and the PUCAI score are highly correlated ($r = 0.95$, $p < 0.001$).[51]

It should be noted that the use of the PUCAI to define remission is a higher hurdle to obtain compared with remission measured by the Mayo score because of the requirement for the absence of rectal bleeding for PUCAI remission but not for Mayo remission.

2.5.1.4.3 Patient-Reported Outcomes

Quality of life was assessed for subjects aged 10 through 17 years using the IMPACT III questionnaire.[13,38,37] IMPACT III is an IBD-specific questionnaire for pediatric patients comprising 35 questions, each scored from 1 to 5; total scores range from 35 to 175, with higher scores indicating better quality of life.

2.5.1.4.4 Global Assessments

Global assessments of change from baseline were performed at Week 8 by the subject, parent/guardian, and physician; each is a 5-point scale used to assess the change from baseline in the subject's health status from the perspective of the subject, the parent/guardian, and the physician.

2.5.2 Adult UC (ACT 1 and ACT 2)

2.5.2.1 Study Population

ACT 1 and ACT 2 were Phase 3 randomized, double-blind, placebo-controlled, parallel-group multicenter studies to assess the safety and efficacy of induction and maintenance REMICADE treatment in adult subjects who had moderately to severely active UC (defined as a Mayo score of 6 to 12, inclusive, at baseline, including an endoscopic subscore ≥ 2), despite current adequate treatment or who had previously failed to respond to or tolerate treatment with 6-MP, AZA, corticosteroids, and/or 5-ASA compounds (ACT 2 only). All subjects were required to have UC confirmed by biopsy. In both ACT 1 and ACT 2, 364 subjects were randomized.

2.5.2.2 Study Design

- Subjects were to be randomly assigned (1:1:1) to 1 of 3 treatment groups: placebo, 5 mg/kg REMICADE, or 10 mg/kg REMICADE.

- Subjects in ACT 1 were to receive study agent at Weeks 0, 2, and 6, followed by q8w treatment through Week 46; subjects in ACT 2 were to receive study agent at Weeks 0, 2, 6, 14, and 22.

- Subjects were allowed to be treated with stable doses of corticosteroids, 6-MP/AZA, or 5-ASA compounds during the study, provided they were on a stable dose prior to baseline. Subjects were to remain on the stable doses of their baseline concomitant UC medications throughout the study, with the exception of corticosteroids, which were allowed to be tapered following the Week 8 visit.

- Safety and efficacy double-blind evaluations were to be completed through Week 54 in ACT 1 and through Week 30 in ACT 2.

- Importantly, in ACT 1 and ACT 2, subjects remained on the dose to which they were randomized (at Week 0) for the duration of the study whereas in T72, only responders to induction dosing were randomized to maintenance treatment. Because of the differences in the study designs between the ACT studies and C0168T72, different analysis populations were used in the maintenance analyses in each study. In ACT 1 and 2, the analysis population was all randomized subjects and in C0168T72 the analysis population was all subjects randomized as responders.

Overviews of ACT 1 and ACT 2 are presented in Figure 3 and Figure 4.

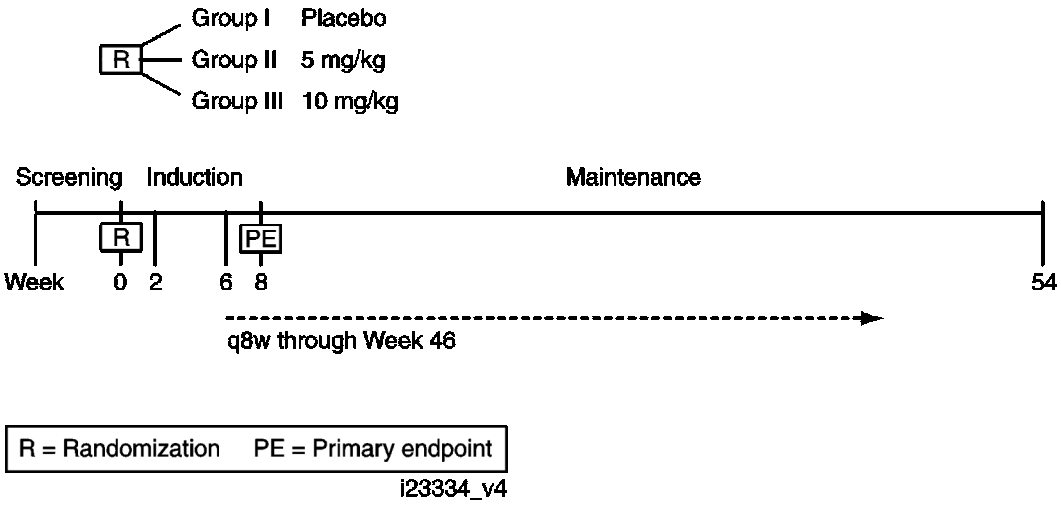


Figure 3: ACT 1 study schema

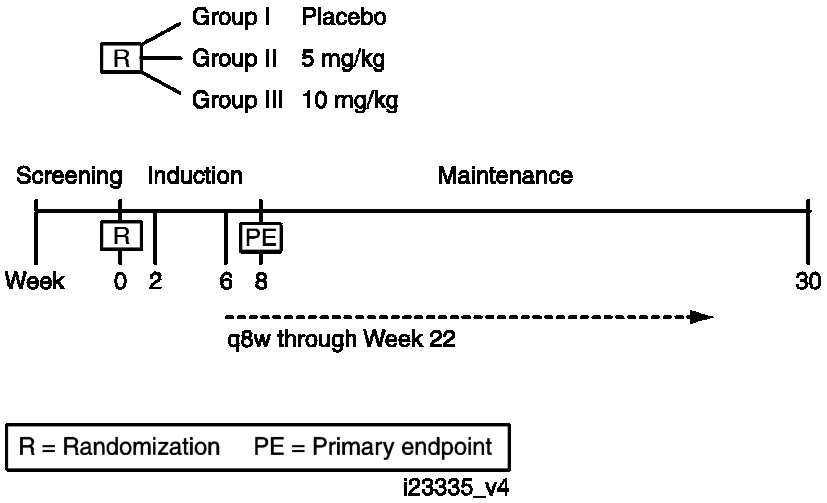


Figure 4: ACT 2 study schema

2.5.2.3 Primary and Major Secondary Endpoints

The primary endpoints were the same in ACT 1 and ACT 2. 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 ≥ 1 or a rectal bleeding subscore of 0 or 1.

The major secondary endpoints were:

- Mayo remission at Week 8, defined as a Mayo score ≤ 2 points, with no individual subscore > 1, at Week 8.
- Mucosal healing at Week 8, defined as an endoscopy subscore of 0 or 1 at Week 8.
- Clinical response at Week 30, defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, with a decrease in the rectal bleeding subscore ≥ 1 or a rectal bleeding subscore of 0 or 1, at Week 30.
- Mayo remission at Week 30, defined as a Mayo score ≤ 2 points, with no individual subscore > 1, at Week 30.

Other key endpoints for ACT 1 were:

- Mayo remission at Week 54.
- Mucosal healing at Week 54.

2.5.3 Pediatric Crohn's Disease (REACH)

2.5.3.1 Study Population

REACH was a Phase 3, randomized, open-label, parallel-group, multicenter study to assess the safety and efficacy of induction and maintenance REMICADE treatment in pediatric subjects aged 6 through 17 years who had moderate to severe Crohn's disease (defined as a Pediatric Crohn's Disease Activity Index [PCDAI] score of > 30) despite current adequate treatment with AZA, 6-MP, or MTX. A total of 112 subjects were enrolled in 34 investigational sites located in North America, Western Europe, and Israel.[16]

2.5.3.2 Study Design

- All subjects were to receive an induction regimen of 5 mg/kg REMICADE at Weeks 0, 2, and 6.

- The primary endpoint was clinical response at Week 10 (defined as a decrease from baseline in the PCDAI score of ≥ 15 points and a total PCDAI score of ≤ 30 points). Subjects in clinical response at Week 10 were to be randomized in a 1:1 ratio to receive 1 of 2 maintenance treatment regimens: 5 mg/kg REMICADE administered q8w through Week 46 or q12w through Week 42.

- Subjects who were nonresponders to induction dosing at Week 10 were to return for a final safety evaluation (8 weeks after the last study agent administration) but receive no further infusions.

- During the maintenance treatment phase, subjects who lost response were eligible to cross-over as follows: 5 mg/kg q8w → 10 mg/kg q8w; 5 mg/kg q12w → 5 mg/kg q8w if loss of response was > 8 but < 12 weeks from the previous REMICADE infusion; or 5 mg/kg q12w →10 mg/kg q8w if loss of response was ≤ 8 weeks from the previous REMICADE infusion.

- Subjects were required to be on stable doses of 6-MP/AZA or MTX prior to screening, and were allowed to be treated with stable doses of corticosteroids or 5-ASA compounds during the study provided they were on a stable dose prior to screening. Subjects were to remain on stable doses of their baseline concomitant UC medications throughout the study, with the following exceptions:

  - Corticosteroids were allowed to be tapered following the Week 2 visit

  - Subjects who crossed-over (ie, increased their REMICADE dose and/or dosing frequency) after losing response were allowed to change their dose of, or initiate treatment with, corticosteroids, 6-MP/AZA, MTX, or 5-ASA compounds if they failed to regain response or if they lost response again.

An overview of the REACH study is presented in Figure 5.

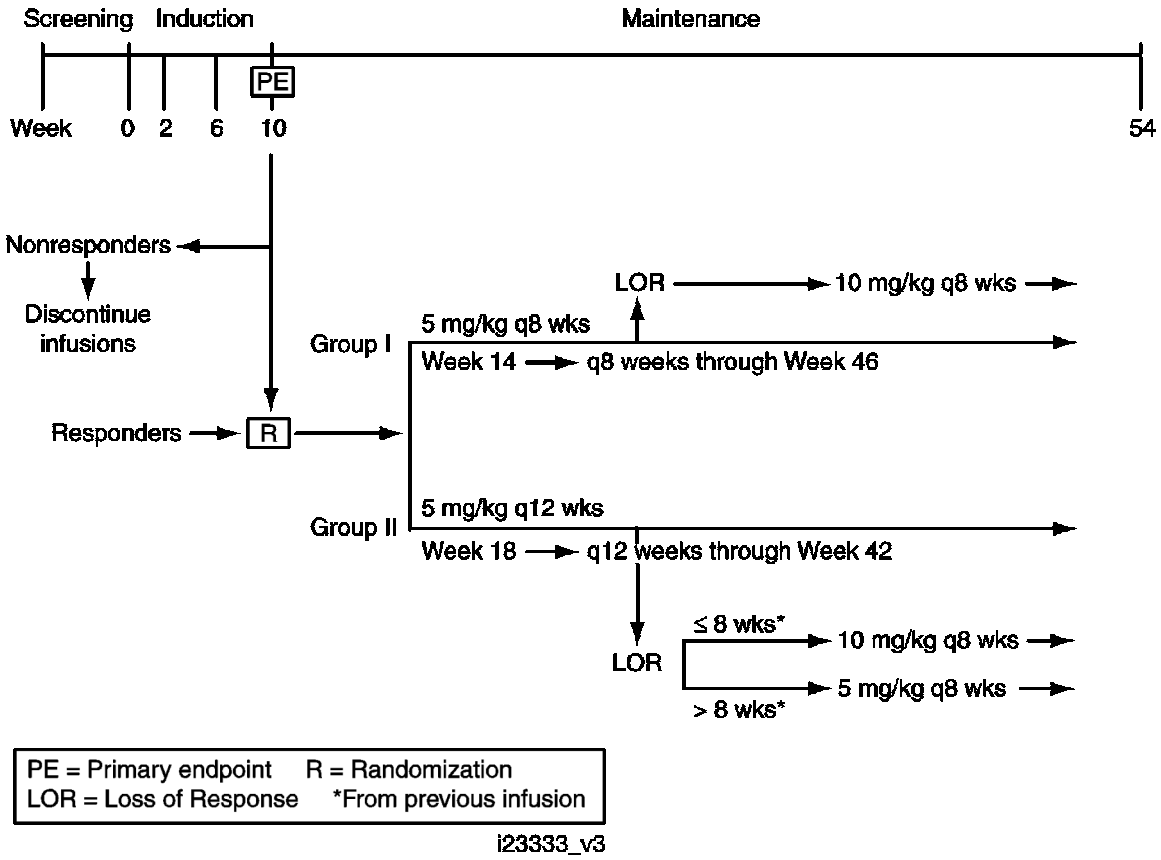


Figure 5: REACH study schema

2.6 Subject Demographics and Baseline Disease Characteristics

2.6.1 T72

Subject demographics, baseline disease characteristics, and concomitant UC medications in T72 are included in Table 4 and summarized below.

- Twenty-eight (46.7%) male and 32 (53.3%) female subjects were enrolled; 49 (81.7%) were Caucasian. The median age was 14.5 years, median weight was 50.80 kg, and median height was 159.65 cm. Subjects in the group that was not randomized at Week 8 were younger and weighed less than subjects in the groups that were randomized at Week 8.

- Among all treated subjects, the median duration of UC disease was 1.35 years and the median C-reactive protein (CRP) level was 0.3 mg/dL; 46 (76.7%) subjects had extensive disease as indicated by endoscopy. The median Mayo score was 8.0, and the median PUCAI score was 55.0.

- All of the 60 treated subjects (100%) were receiving concomitant medications for UC at baseline, including oral or parenteral corticosteroids 37 (61.7%) or immunomodulators or 5-ASA compounds (32 [53.3%] for each). A higher proportion of subjects in the group that was not randomized at Week 8 were receiving aminosalicylates at baseline.

In general, demographics, baseline disease characteristics, and concomitant UC medications were similar between the q8w and q12w groups.

2.6.2 Comparison of T72, REACH, ACT 1, and ACT 2

A summary of subject demographics, baseline disease characteristics, and concomitant medication use for T72, REACH, ACT 1, and ACT 2 is presented in Table 4.

Table 4: Summary of demographics, clinical disease characteristics, and concomitant medications at baseline; treated subjects in T72 and REACH, and randomized subjects in ACT 1 and ACT 2

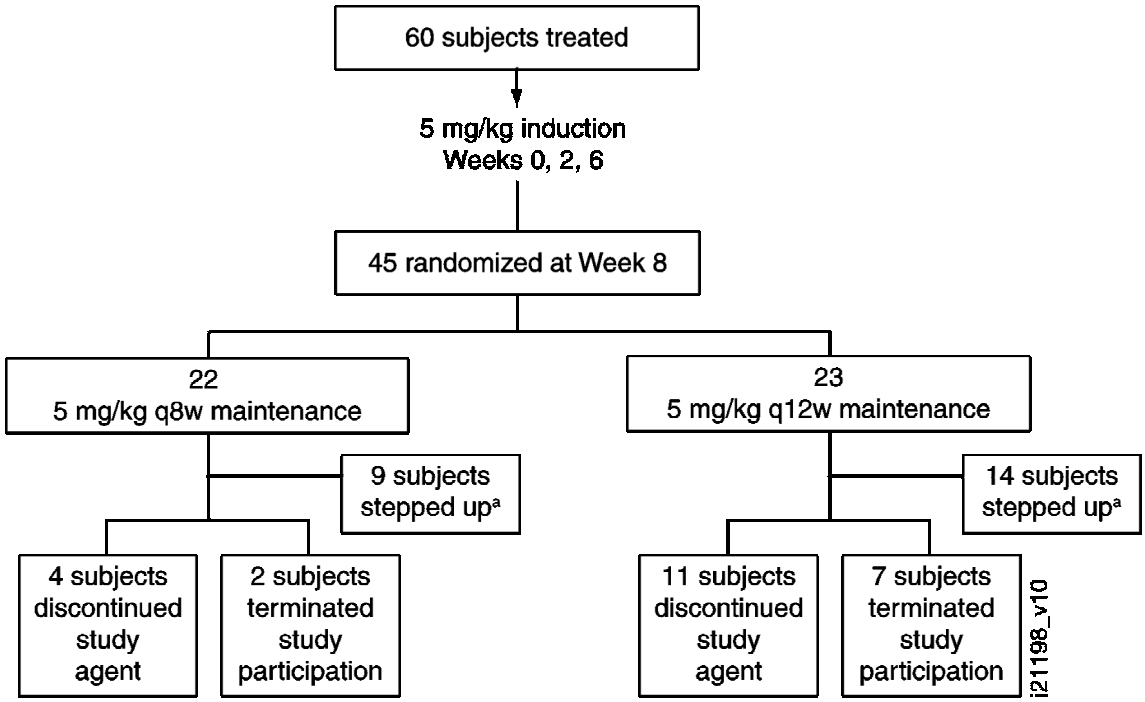
	T72	REACH	ACT 1	ACT 2
Number of subjects	60	112	364	364
Median age (years)	14.5	13.0	40.0	38.0
Female	53.3%	41.1%	39.0%	40.9%
Caucasian	81.7%	83.9%	93.4%	94.5%
Median weight (kg)	50.8	42.0	76.5	75.0
Disease duration (years)				
Median	1.4	1.6	4.7	4.9
Extent of disease				
Extensive (pancolitis)	76.7%	NA	45.6%	39.9%
Proportion of subjects with severe disease (Mayo score)	10%	NA	12.4%	10.2%
Concomitant UC/Crohn's disease medications				
Corticosteroids	61.7%	34.8%	61.0%	51.1%
6-MP/AZA/MTX	53.3%	98.2%	48.9%	42.9%
5-ASA compounds	53.3%	52.7%	69.5%	74.7%
Median Mayo/PCDAI score[a]	8	40	8	8
Median CRP (mg/dL)/erythrocyte sedimentation rate ([ESR] mm/h)[b]	0.3	36.0	0.8	0.7

[a] Mayo score is for the T72 and ACT studies and PCDAI score is for the REACH study.
[b] CRP is for the T72 and ACT studies and ESR is for the REACH study.

- Overall, given the differences between UC and Crohn's disease, the baseline characteristics of subjects in T72 and REACH were generally comparable in terms of race, age, and disease duration.
  - The proportion of subjects receiving baseline 6-MP, AZA, or MTX was higher in REACH compared with T72, per requirement for REACH subjects to maintain a stable dose ≥ 2 weeks prior to screening through Week 54.
- Other than obvious study differences (eg, age, weight, disease duration), the baseline disease characteristics were generally similar between the pediatric and adult populations; however, the proportion of subjects with extensive disease was greater in T72 than in the ACT studies.

2.7 Subject Disposition

The disposition of treated subjects in T72 is shown in Figure 6.



[a] Stepped up: Received higher dose (5 mg/kg q8 → 10 mg/kg q8) or shorter frequency (5 mg/kg q12 → 10 mg/kg q8 or 5 mg/kg q8)

Figure 6: Disposition of treated subjects in T72

- A greater proportion of subjects randomized at Week 8 discontinued study agent in the q12w group (47.8%) than in the q8w group (18.2%).

- A total of 23 subjects stepped up to a different regimen during the course of the study. More subjects stepped up in the q12w group (60.9%) than in the q8w group (40.9%). Most subjects who stepped up did so by Week 22 (18 [78.3%]).

3 Overview of Efficacy

Analyses of efficacy are based upon data from T72 and supported by data from ACT 1 and ACT 2.

Efficacy Analysis Considerations

- For T72, analysis of the efficacy endpoints based on the induction phase of the study (through Week 8 when all subjects received the same treatment) included all treated subjects. For analyses of data during the maintenance phase (ie, beyond Week 8), only subjects randomized at Week 8 (ie, those who were in clinical response at Week 8) were included in the analyses.

- For ACT 1 and ACT 2, analyses were based on randomized subjects. Data for the 5 mg/kg group is presented for comparison with the 5 mg/kg group in T72. Data from the placebo group is also provided. In general, the data from ACT 1 and ACT 2 were combined for analysis; however, for endpoints beyond Week 30, only ACT 1 data were used.

- In the T72 and ACT studies, the following rules were applied to most endpoints:

  - Treatment failure

    - Subjects who discontinued study agent due to lack of therapeutic effect, had a colectomy or ostomy, or had protocol-prohibited medication changes were considered to be a treatment failure from the time of the event until the end of the study.

    - In addition, subjects who stepped up in T72 were considered treatment failures from the point of step-up.

    - For dichotomous endpoints occurring after the treatment failure event, subjects were considered to not have achieved the endpoint. For continuous endpoints, the baseline value was carried forward from the time of the treatment failure event through the end of the study.

- Missing data
  - Subjects with missing data for dichotomous endpoints were considered to not have achieved the endpoint. For continuous endpoints, subjects with missing data had the last observation carried forward.

3.1 T72

3.1.1 Key Efficacy Endpoints

A summary of results for the key efficacy endpoints in T72 is presented in Table 5.

Table 5: Summary of key efficacy endpoints in T72

Primary Endpoint	
Subjects in clinical response at Week 8	**73.3% (44/60)**
95% CI	(62.1%, 84.5%)
Major Secondary Endpoints	
Subjects in Mayo remission at Week 8	40.0% (24/60)
Subjects in PUCAI remission at Week 8	33.3% (17/51)
Subjects in mucosal healing at Week 8	68.3% (41/60)
Subjects in PUCAI remission at Week 54	27.9% (12/43)
Subjects in the q8w group	38.1% (8/21)
Subjects in the q12w group	18.2% (4/22)
p-value	0.146
Other Key Endpoint	
Subjects in PUCAI remission at Week 54 and not receiving corticosteroids at Week 54 (of subjects on corticosteroids at baseline)	19.2% (5/26)
Subjects in the q8w group	38.5% (5/13)
Subjects in the q12w group	0.0% (0/13)

3.1.1.1 Primary Endpoint - Clinical Response at Week 8

The protocol-specified criterion for determining that REMICADE is effective in the treatment of UC in pediatric subjects was met. The criterion specified that the lower limit of the 95% CI for the proportion of pediatric subjects in clinical response at Week 8 must be > 40%. This cut point of 40% was based on the use of pooled data from the placebo groups in the ACT 1 and ACT 2 studies as a "historical control." In the pooled ACT studies, the upper limit of the 95% CI for the proportion of placebo subjects in clinical response at Week 8 was 39.1%, and therefore the cut point for T72 was set at 40%.

- Of the 60 treated subjects, 73.3% were in clinical response at Week 8 (Table 5). The criterion for a positive study was met because the lower limit of the 95% CI for the proportion of subjects in clinical response at Week 8 was 62.1% (ie, > 40%).

- The proportion of subjects achieving a clinical response at Week 8 was generally consistent across the subgroups (demographics, baseline disease characteristics, baseline medications), particularly among subjects who were or were not receiving corticosteroids, immunomodulators (6-MP/AZA or MTX), and 5-ASAs at baseline (Table 6).

Table 6: Number of subjects in clinical response as measured by the Mayo score at Week 8 with exact 95% CIs by baseline concomitant medications; treated subjects in T72

Concomitant medication	Receiving at baseline	Not receiving at baseline
Corticosteroids (parenteral or oral)		
n	37/60	23/60
Subjects in clinical response	78.4% (29/37)	65.2% (15/23)
95% CI	(61.8%, 90.2%)	(42.7%, 83.6%)
Immunomodulators (6-MP/AZA/MTX)		
n	32/60	28/60
Subjects in clinical response	71.9% (23/32)	75.0% (21/28)
95% CI	(53.3%, 86.3%)	(55.1%, 89.3%)
5-ASA		
n	32/60	28/60
Subjects in clinical response	68.8% (22/32)	78.6% (22/28)
95% CI	(50%, 83.9%)	(59.1%, 91.7%)
Corticosteroids (parenteral or oral) or immunomodulators (6-MP/AZA/MTX)		
n	52/60	8/60
Subjects in clinical response	75.0% (39/52)	62.5% (5/8)
95% CI	(61.1%, 86%)	(24.5%, 91.5%)

3.1.1.2 Major Secondary Endpoints

3.1.1.2.1 Mayo Remission at Week 8

- Of the 60 treated subjects, 40% were in Mayo remission at Week 8 (Table 5 and Figure 7).

3.1.1.2.2 PUCAI Remission at Week 8

- Of the 51 subjects evaluable for PUCAI at Week 8, 33.3% were in PUCAI remission (Figure 7 and Figure 8).

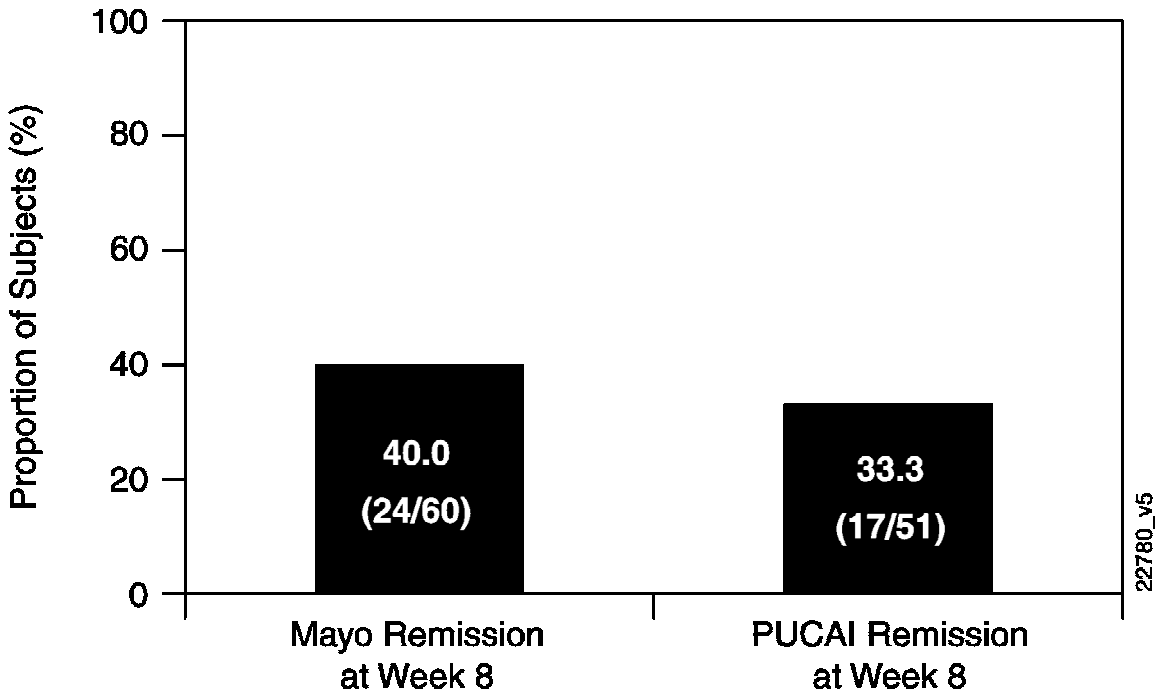


Figure 7: Proportion of subjects in Mayo and PUCAI remission at Week 8; treated subjects in T72

3.1.1.2.3 Mucosal Healing at Week 8

- Of the 60 treated subjects, 41 (68.3%) were in mucosal healing at Week 8 (Table 5); 20 (33.3%) had an endoscopy subscore of 0 (indicating normal or inactive disease).

3.1.1.2.4 PUCAI Remission at Week 54

- The proportion of randomized subjects in PUCAI remission at Week 54 was 27.9% ([12/43]; Table 5). A notably greater proportion of subjects was in remission at Week 54 in the q8w group (38.1% [8/21]) than in the q12w group (18.2% [4/22], p = 0.146; Table 5 and Figure 8). Note that this comparison was not adequately powered to show a difference between groups.
  - The proportion of subjects in PUCAI remission at Week 30 was also higher in the q8w group (40.0% [8 of 20 subjects]) than in the q12w group (19.0% [4 of 21 subjects]; Figure 8).

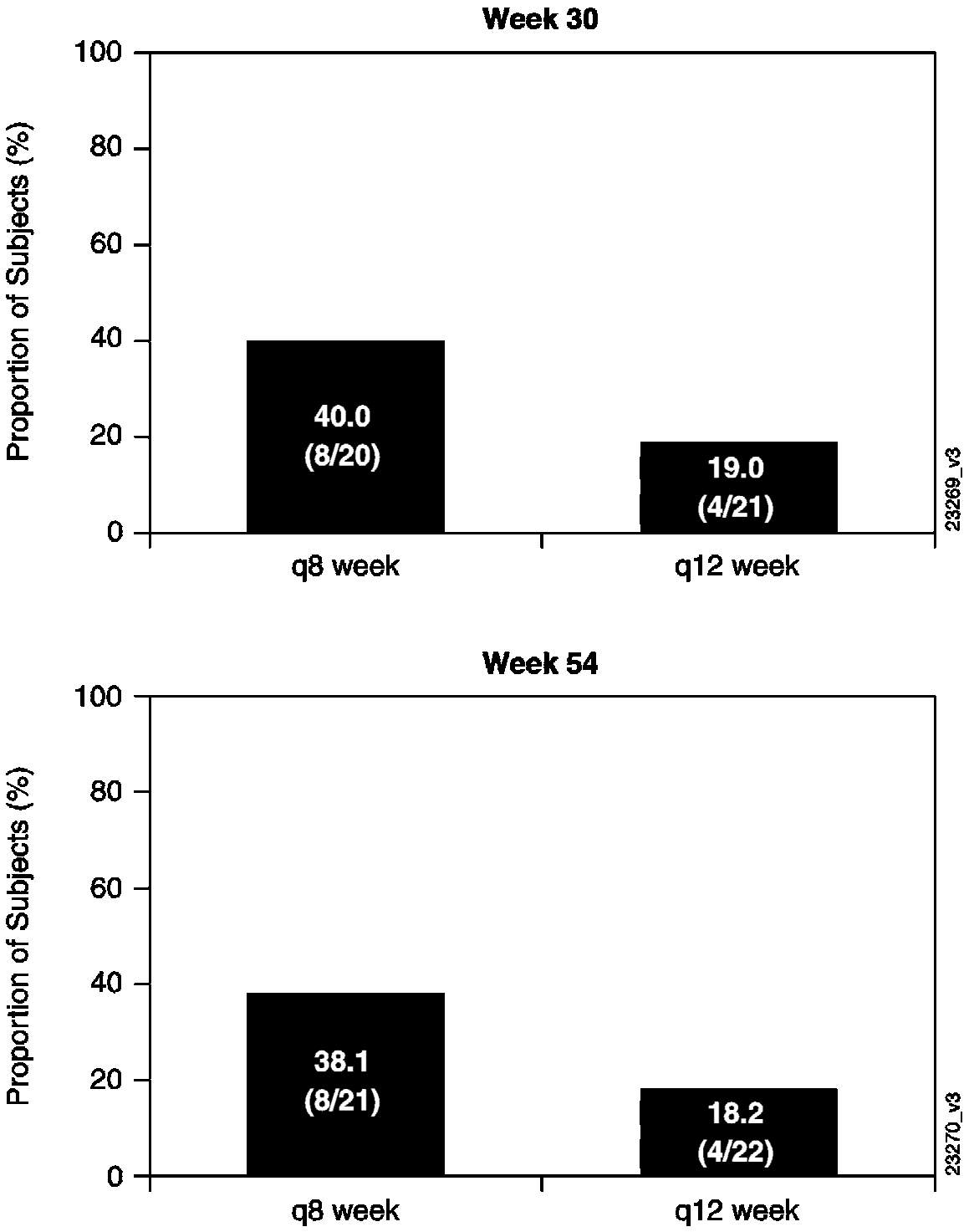


Figure 8: Proportion of subjects in PUCAI remission at Weeks 30 and 54; randomized subjects in T72

3.1.2 Other Efficacy Endpoints

3.1.2.1 Corticosteroid Use and PUCAI Remission at Week 54

- The proportion of randomized subjects receiving corticosteroids at baseline, in PUCAI remission at Week 54, and not receiving corticosteroids at Week 54 was greater in the q8w group (38.5%) than in the q12w group (0.0%; Table 5 and Figure 9).
  - The proportion of randomized subjects receiving corticosteroids at baseline, in PUCAI remission at Week 30, and not receiving corticosteroids at Week 30 was also greater in the q8w group (41.7%) than in the q12w group (7.7%; Figure 9).

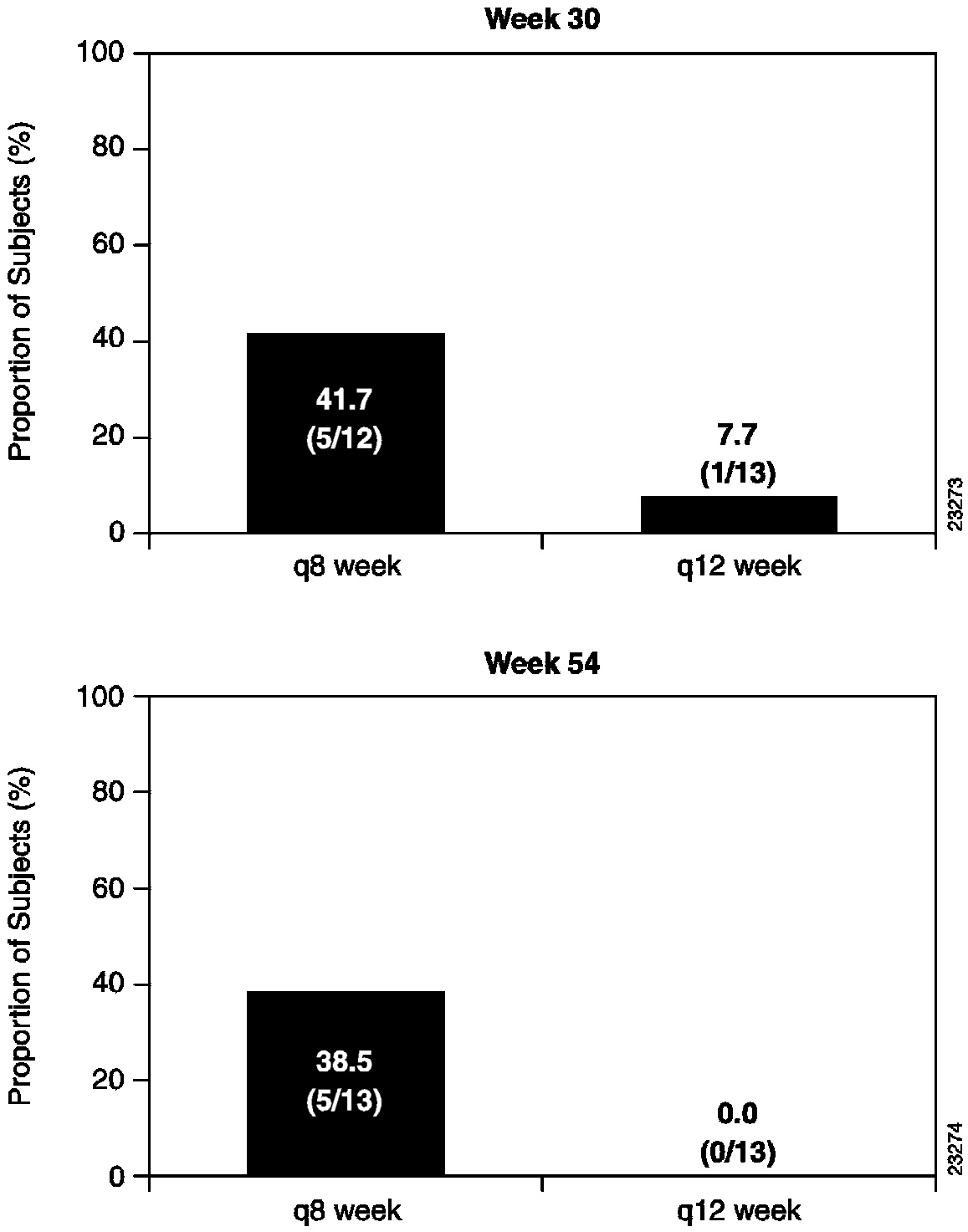


Figure 9: **Proportion of randomized subjects receiving corticosteroids at baseline, in PUCAI remission, and not receiving corticosteroids at Weeks 30 and 54; randomized subjects in T72**

3.1.2.2 Corticosteroid Reduction Over Time

For subjects receiving corticosteroids at baseline, a substantial reduction in the median average daily corticosteroid dose had occurred by Week 8 in both the q8w and q12w groups (Figure 10); this substantial reduction was maintained through Week 54 in the q8w group but not in the q12w group.

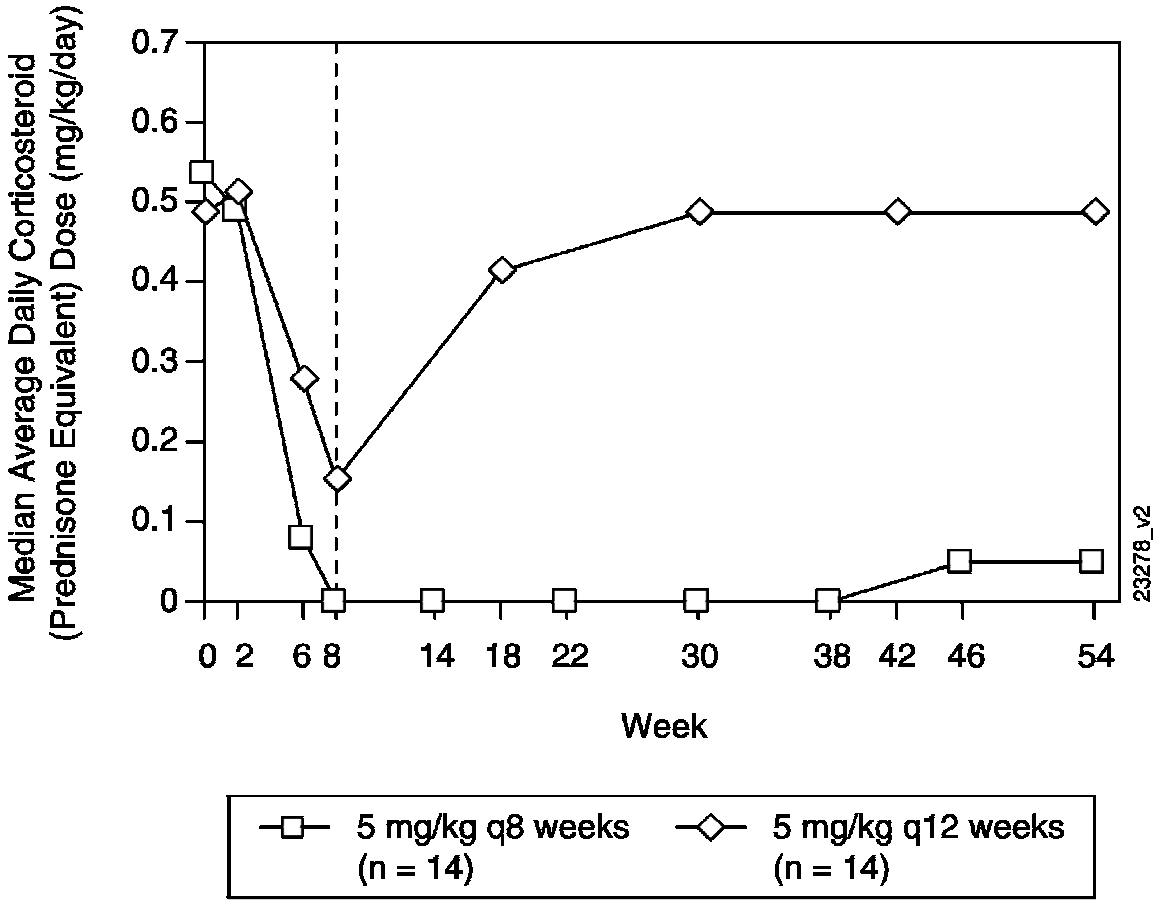


Figure 10: Median average daily corticosteroid (prednisone equivalent) dose (mg/kg/day) through Week 54; randomized subjects receiving corticosteroids at baseline in T72

3.1.2.3 Mucosal Healing at Week 54

Due to the issues associated with performing repeated endoscopies in pediatric subjects, the T72 protocol was amended to make the Week 54 sigmoidoscopy optional. Of the 9 randomized subjects who underwent an endoscopy at Week 54, all 9 had achieved mucosal healing at Week 8, and 8 (3 of 4 in the q8w group and all 5 in the q12w group) demonstrated persistence of mucosal healing at Week 54; 6 had an endoscopy subscore of 0 (indicating normal or inactive disease).

3.1.2.4 Mayo and Partial Mayo Scores Over Time

- In all randomized subjects, a substantial reduction in the Mayo score (median reduction of 5.0 from median baseline score of 8.0) was observed at Week 8.

- In all randomized subjects, a substantial reduction in the partial Mayo score was observed as early as Week 2 (median reduction of 3.0 from median baseline score of 6.0); this substantial reduction was maintained through Week 54 in the q8w group but not in the q12w group (Figure 11).

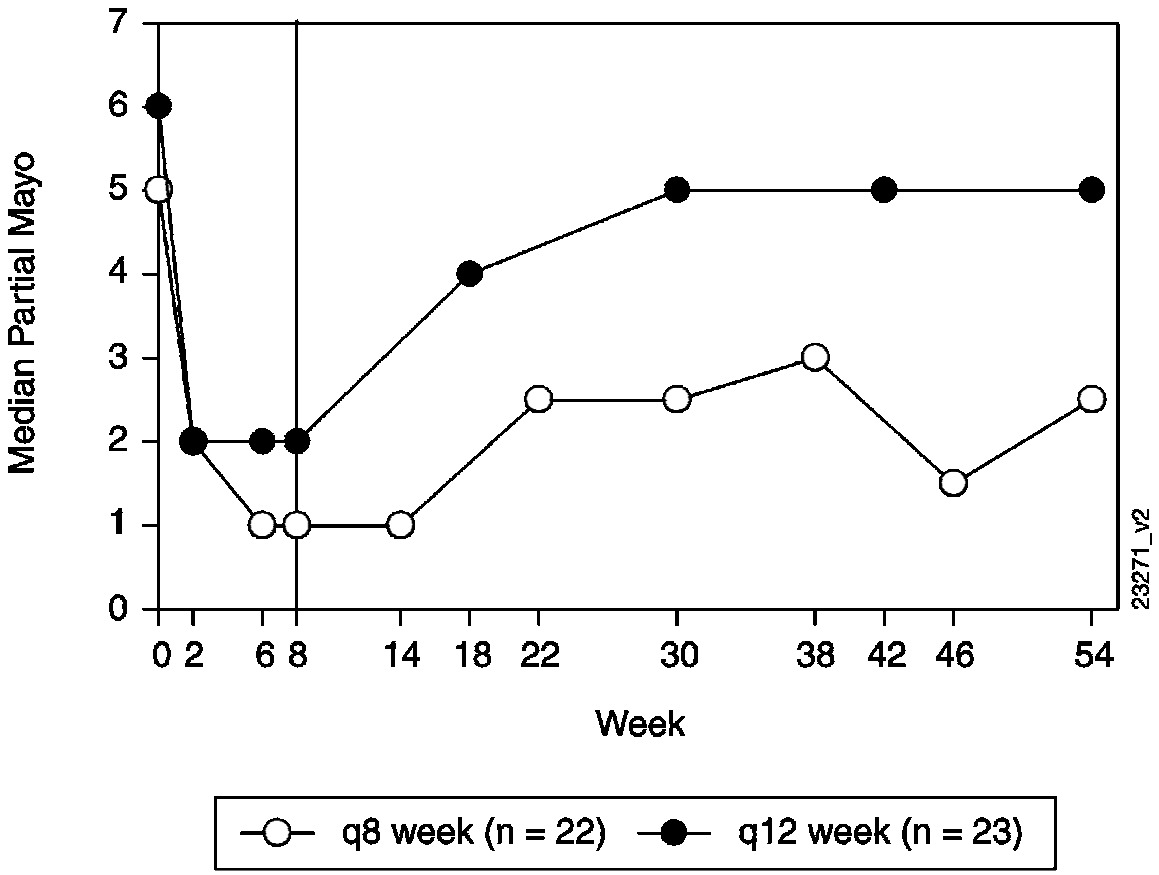


Figure 11: Median partial Mayo score through Week 54; randomized subjects in T72

3.1.2.5 PUCAI Over Time

- In subjects randomized at Week 8, a substantial reduction in the PUCAI was observed as early as Week 2 (median reduction of 35.0 from median baseline score of 55.0); this reduction was maintained in the q8w group with a median reduction of 30.0 at

Week 54, but not in the q12w group where the median change from baseline at both Week 30 and Week 54 was 0.0.

- At least 50% of subjects in the q8w group had a clinically meaningful change (≥ 20 point decrease in PUCAI) at Week 54.[51]

3.1.2.6 Correlation Between Mayo Score and PUCAI

A high positive correlation was observed between the Mayo score and the PUCAI score at baseline (0.749, $p < 0.001$) and Week 8 (0.878, $p < 0.001$; Figure 12). This result is consistent with the correlation between the Mayo score and the PUCAI described in Turner et al[51] ($r = 0.95$, $p < 0.001$). Further, of the 51 subjects evaluable for both the Mayo score and the PUCAI score at Week 8, the remission status based on the 2 measures was the same for 45 (88.2%) of the subjects, indicating that the 2 measures provide consistent results. The remaining 6 subjects had PUCAI and Mayo scores that were both near the cut point used to define remission.

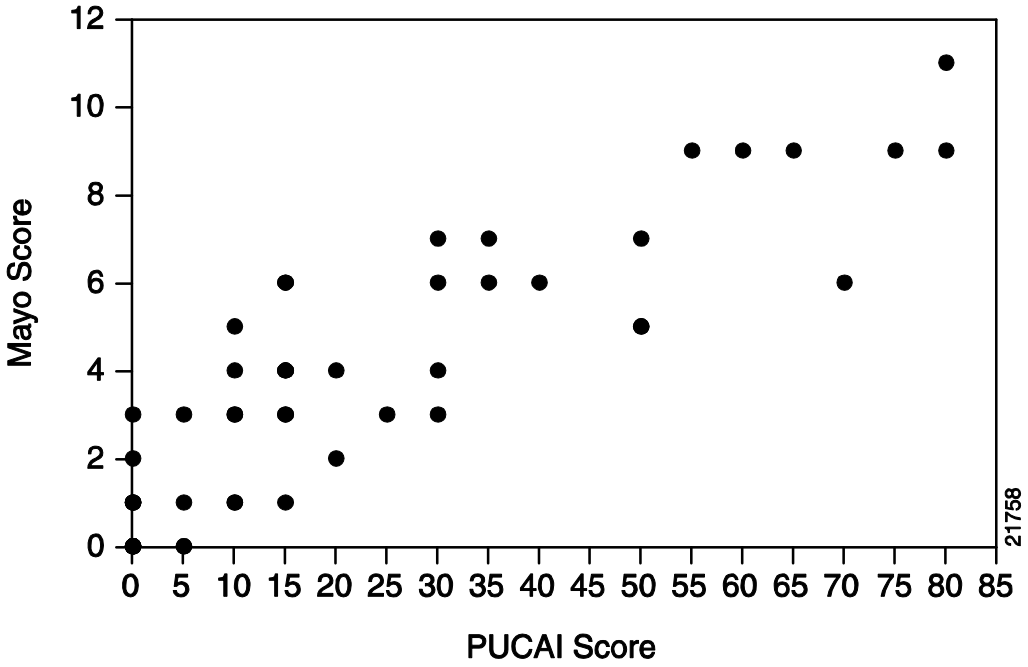


Figure 12: Scatter plot of Mayo score vs PUCAI at Week 8; treated subjects in T72

3.1.2.7 Step-up Treatment

Of the 45 subjects randomized at Week 8, 23 had their treatment regimen stepped up. Most subjects who stepped up their REMICADE dose and/or dosing frequency during the

maintenance phase of the study demonstrated an improvement in disease activity after step-up; however, these results are based on a small number of subjects who may have altered their concomitant medications after stepping up (Figure 13).

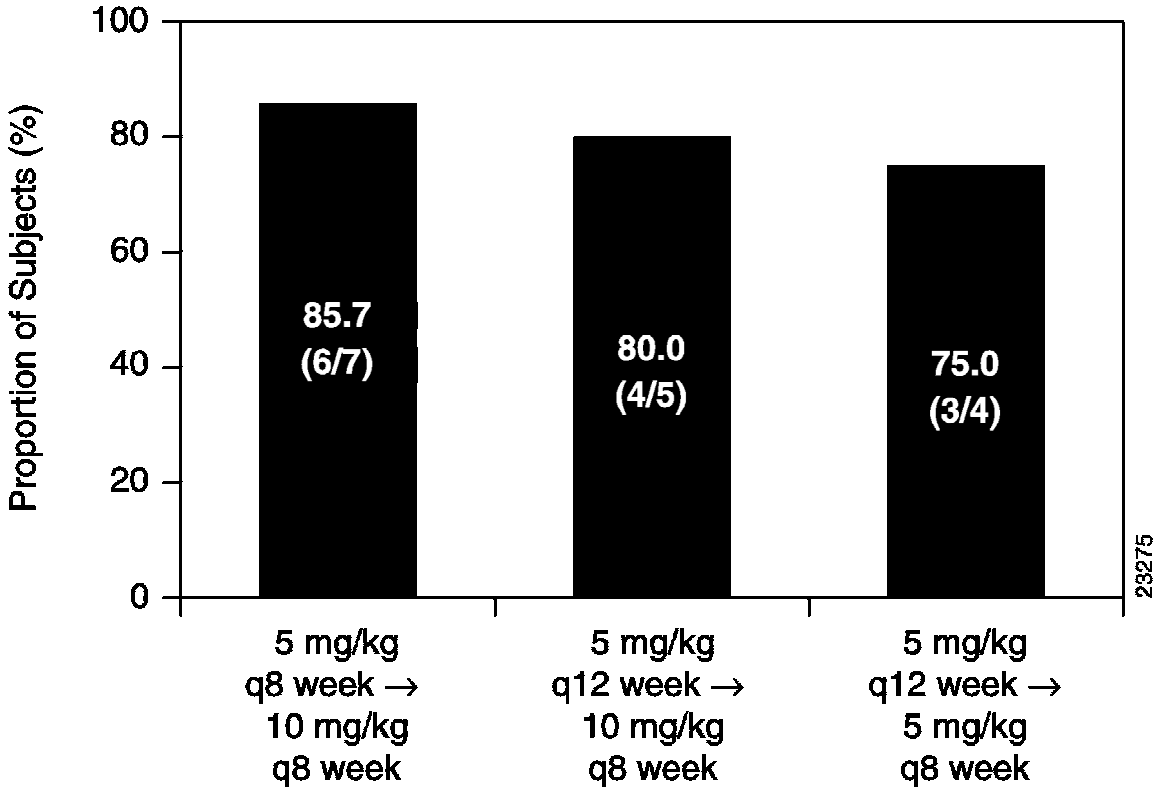


Figure 13: Proportion of subjects who demonstrated an improvement in the partial Mayo score (decrease of ≥ 2 points) 8 weeks after their first step-up dose; randomized subjects in T72

3.1.2.8 IMPACT III at Week 8

For the 54 treated subjects who completed the IMPACT III (quality of life) questionnaire[37] at baseline, improvement in the IMPACT III score was observed at Week 8 (median change of 15 points from median baseline score of 108.5). While the change in IMPACT III score that corresponds to clinically relevant improvement in disease activity has not been externally validated in pediatric UC, it has been reported that an increase of 10.8 points correlated with clinical improvement in pediatric Crohn's disease.[39]

3.1.2.9 Global Assessments

Fifty-four treated subjects and parents/guardians and 55 physicians completed a global assessment of change from baseline at Week 8; 52 subjects (96.3%), 51 (92.7%) physicians, and 52 (96.3%) parents/guardians assessed the change as "much better" or "somewhat better" (Figure 14).

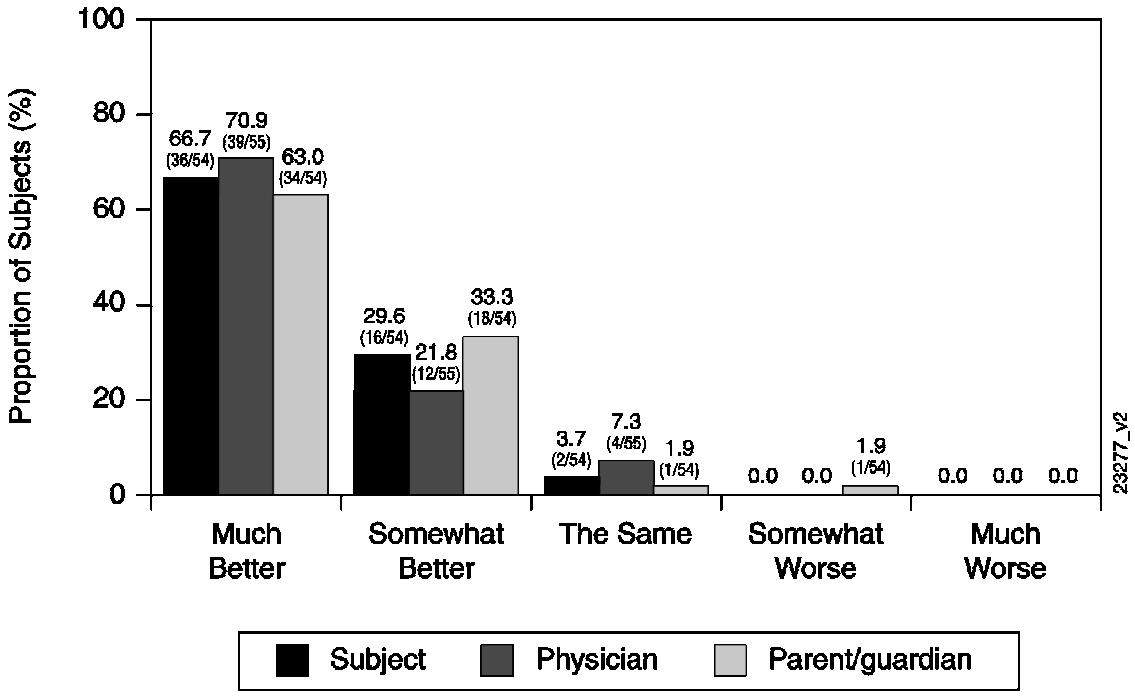


Figure 14: Global assessment of change from baseline at Week 8 in T72

3.1.2.10 Subgroup Analysis

Analyses of key endpoints were performed based on the age groups of 6 to 11 and 12 to 17 years (Table 7). Overall, although some differences were noted between the age groups, efficacy was observed in both age groups and no consistent pattern indicating greater efficacy in one of the age groups was apparent. Differences between the age groups are difficult to assess because of the small sample sizes, particularly in the 6 to 11 years age group (n = 15).

Table 7: Summary of efficacy by age group; treated subjects in T72

	6 to 11 years	12-17 years
Subjects treated	15	45
Median baseline Mayo score	8.0	8.0
Median Week 8 Mayo score	3.0	3.0
Subjects in clinical response at Week 8	9 (60.0%)	35 (77.8%)
Subjects in Mayo remission at Week 8	7 (46.7%)	17 (37.8%)
Subjects in mucosal healing at Week 8	8 (53.3%)	33 (73.3%)
Subjects in PUCAI remission at Week 8	4/12 (33.3%)	13/39 (33.3%)
Subjects in the q8w group in PUCAI remission at Week 54	3/5 (60.0%)	5/16 (31.3%)
Subjects in the q12w group in PUCAI remission at Week 54	0/4 (0.0%)	4/18 (22.2%)

3.2 ACT 1 and ACT 2

Both ACT 1 and ACT 2 produced clinically important and statistically significant evidence that REMICADE is an effective treatment for the induction and maintenance of clinical response, clinical remission, and mucosal healing, as well as reducing corticosteroid use, in subjects with moderately to severely active UC despite receiving current adequate treatment, or having had previous unsuccessful treatment with, or intolerance of 6-MP, AZA, corticosteroids, and/or, for ACT 2 only, 5-ASA compounds.[42] Additionally, subjects treated with REMICADE were less likely than those receiving placebo to undergo colectomy through 54 weeks.[43]

A summary of the key efficacy endpoints for the placebo and 5 mg/kg groups in ACT 1 and ACT 2 is presented in Table 8.

Table 8: Summary of key efficacy endpoints in ACT 1 and ACT 2

	ACT 1		ACT 2	
	Placebo	REMICADE 5 mg/kg	Placebo	REMICADE 5 mg/kg
Subjects randomized	121	121	123	121
Primary Endpoint				
Subjects in clinical response at Week 8	45 (37.2%)	84 (69.4%)	36 (29.3%)	78 (64.5%)
p-value		< 0.001		< 0.001
Major Secondary Endpoints				
Subjects in Mayo remission at Week 8	18 (14.9%)	47 (38.8%)	7 (5.7%)	41 (33.9%)
p-value		< 0.001		< 0.001
Subjects in mucosal healing at Week 8	41 (33.9%)	75 (62.0%)	38 (30.9%)	73 (60.3%)
p-value		< 0.001		< 0.001
Subjects in clinical response at Week 30	36 (29.8%)	63 (52.1%)	32 (26.0%)	57 (47.1%)
p-value		< 0.001		< 0.001
Subjects in Mayo remission at Week 30	19 (15.7%)	41 (33.9%)	13 (10.6%)	31 (25.6%)
p-value		0.001		0.003
Other Key Endpoints				
Subjects in clinical remission at Week 54	20 (16.5%)	42 (34.7%)	NA[a]	NA[a]
p-value		0.001		
Subjects in mucosal healing at Week 54	22 (18.2%)	55 (45.5%)	NA[a]	NA[a]
p-value		< 0.001		
Randomized subjects with corticosteroids at baseline	79	70	60	60

Table 8: Summary of key efficacy endpoints in ACT 1 and ACT 2

	ACT 1		ACT 2	
	Placebo	REMICADE 5 mg/kg	Placebo	REMICADE 5 mg/kg
Subjects in Mayo remission at Week 30 and not receiving corticosteroids at Week 30	8 (10.1%)	17 (24.3%)	2 (3.3%)	11 (18.3%)
p-value		0.030		0.010
Subjects in Mayo remission at Week 54 and not receiving corticosteroids at Week 54	7 (8.9%)	18 (25.7%)	NA[a]	NA[a]
p-value		0.006		

[a] Data through Week 30 only for ACT 2.

3.3 Comparison of Efficacy Between T72 and the ACT Studies

A summary of key efficacy endpoints in T72 and the pooled ACT studies is presented in Table 9. In addition, for the induction endpoints of clinical response, clinical remission, and mucosal healing at Week 8, Figure 15 provides the point estimates and corresponding 95% CIs for T72 and also for the 5 mg/kg REMICADE group and the placebo group in the pooled ACT studies.

Table 9: Summary of key efficacy endpoints in T72 and the ACT studies

	REMICADE 5 mg/kg	
	T72	**ACT studies**
Clinical response at Week 8	**73.3%** (44/60)	**66.9%** (162/242)
95% CI	(62.1%, 84.5%)	(61.0%, 72.9%)
Mayo remission at Week 8	**40.0%** (24/60)	**36.4%** (88/242)
95% CI	(27.6%, 52.4%)	(30.3%, 42.4%)
PUCAI remission at Week 8	**33.3%** (17/51)	NA
95% CI	(20.4%, 46.3%)	
Mucosal healing at Week 8	**68.3%** (41/60)	**61.2%** (148/242)
95% CI	(56.6%, 80.1%)	(55.0%, 67.3%)
Median Mayo score at Week 8[b]	**3.0** (n = 60)	**3.0** (n = 121)
Remission at Week 54[a,b,c]	**38.1%** (8/21)	**34.7%** (42/121)
95% CI	(17.3%, 58.9%)	(26.2%, 43.2%)
Remission at Week 54 and not receiving corticosteroids at Week 54[a,b,c,d]	**38.5%** (5/13)	**25.7%** (18/70)
Mucosal healing at Week 54[a,b]	(3/4)	**45.5%** (55/121)
Median partial Mayo score at Week 54[a,b]	**2.5** (n = 22)	**3.0** (n = 121)

[a] 5 mg/kg q8w
[b] ACT 1 only
[c] Based on the PUCAI score for T72 and the Mayo score for ACT 1.
[d] Among subjects on corticosteroids at baseline.

3.3.1.1 Clinical Response

- The proportions of subjects in clinical response at Week 8 were similar among the pediatric and adult subjects with UC in the 5 mg/kg REMICADE groups, with overlapping CIs (Table 9, Figure 15), despite corticosteroid taper beginning at t Week 0 in T72 versus Week 8 in the ACT studies. In addition, there is a

separation between T72 and the placebo group in the ACT studies, as evidenced by the non-overlapping CIs.

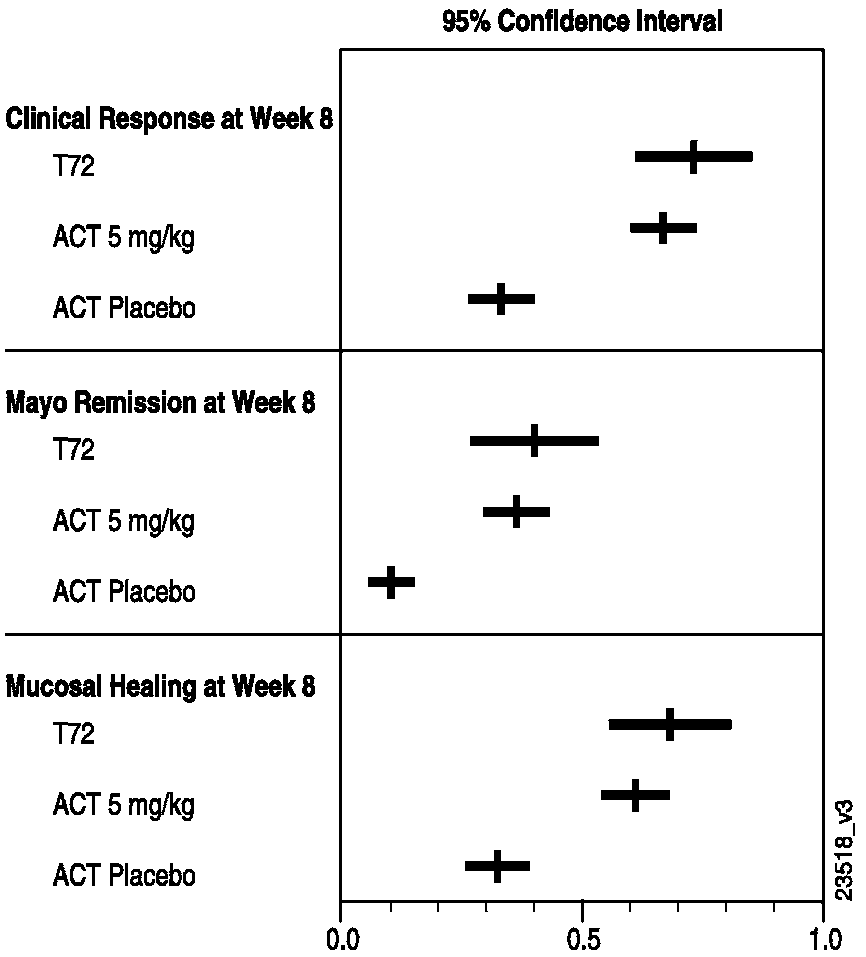


Figure 15: Point estimates and 95% CIs for the proportions of subjects in clinical response, clinical remission, and mucosal healing at Week 8 for T72 and also for the 5 mg/kg REMICADE group and the placebo group in the pooled ACT studies

- Of the 9 pediatric subjects who had the optional endoscopy at Week 54 in T72, 5 (3 of 4 in the q8w group) were considered to be in clinical response at Week 54. In the adult subjects in ACT 1, 45.5% in the 5 mg/kg REMICADE group were in clinical response at Week 54.

3.3.1.2 Remission

3.3.1.2.1 Mayo Remission at Week 8

The proportions of subjects in Mayo remission at Week 8 were similar among the pediatric and adult subjects with UC in the 5 mg/kg REMICADE groups, with overlapping CIs (Table 9, Figure 15). In addition, a separation is evident between T72 and the placebo group in the ACT studies.

3.3.1.2.2 Remission at Week 54

The proportion of pediatric subjects in the REMICADE 5 mg/kg q8w group in T72 who were in PUCAI remission at Week 54 (38.1% [8/21]) was similar to the proportion of adult subjects in the REMICADE 5 mg/kg q8w group in ACT 1 who were in Mayo remission at Week 54 (34.7% [42/121]). Due to differences in the study designs for T72 and ACT 1, a sensitivity analysis was performed where remission at Week 54 was assessed in subjects who were in clinical response at Week 8. The results of this analysis were consistent with the results presented above. It is noted that the assessments of remission at Week 54 in the T72 and ACT 1 studies are based on a different efficacy tool (ie, the PUCAI score for T72 and the Mayo score for ACT 1). However, it was demonstrated by Turner et al, as well as in the T72 study, that the rigorously developed and validated PUCAI score is highly positively correlated with the Mayo score.[51] In addition, it was shown that the remission statuses based on the PUCAI score and the Mayo score at Week 8 were in agreement for 88% of subjects. Thus, assessments of remission based on these 2 tools are expected to be consistent.

3.3.1.3 Mucosal Healing

- The proportions of subjects in mucosal healing at Week 8 were similar among the pediatric and adult subjects with UC in the 5 mg/kg REMICADE groups, with overlapping CIs (Table 9, Figure 15). In addition, a separation is evident between T72 and the placebo group in the ACT studies.

- Of the 9 subjects in T72 who underwent the optional endoscopy at Week 54, all had achieved mucosal healing at Week 8, and 8 (3 of 4 in the q8w group and all 5 in the q12w group) were still in mucosal healing at Week 54. At Week 54 in ACT 1, 45.5% of adult subjects in the 5 mg/kg REMICADE group were in mucosal healing.

3.3.1.4 Mayo and Partial Mayo Scores

- The median Mayo scores were very similar between T72 and the REMICADE 5 mg/kg group in ACT 1 at baseline and at Week 8 (Table 9).

- The median partial Mayo scores for T72 (5 mg/kg q8w group) and ACT 1 (5 mg/kg q8w group) were very similar through Week 54 (Table 9 and Figure 16). In both studies, the median partial Mayo score decreased quickly during induction. This decrease was generally maintained during maintenance treatment.

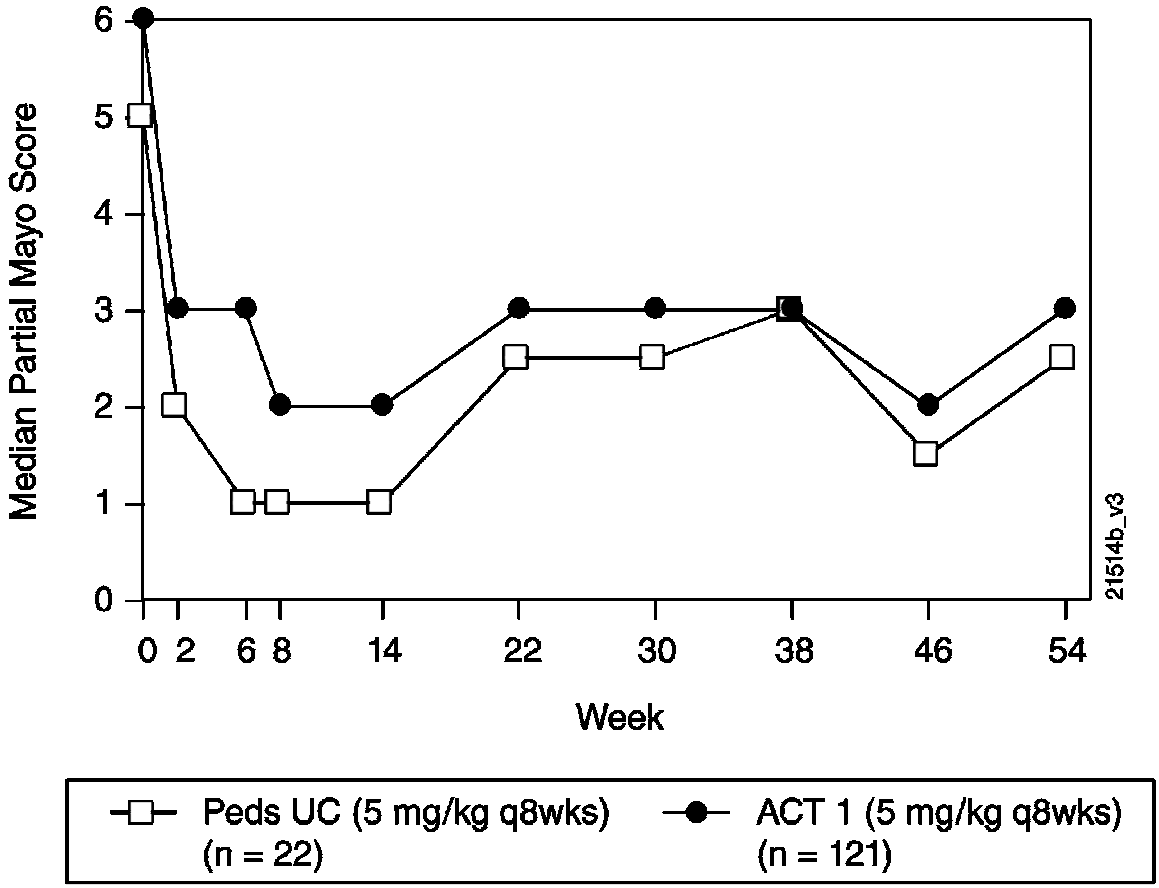


Figure 16: Median partial Mayo score through Week 54; randomized subjects in the 5 mg/kg q8w group in T72 and ACT 1

3.3.1.5 Corticosteroid Reduction Over Time

Although the specific reductions in corticosteroid use cannot be compared between T72 and ACT 1 because the corticosteroid doses in T72 were adjusted for body weight, substantial reductions in the corticosteroid dose were observed in the REMICADE 5 mg/kg q8w group in both of these studies (from 0.54 mg/kg/day to 0.0 mg/kg/day by Week 8 in T72 and from 20 mg/day to 5 mg/day by Week 22 in ACT 1) for subjects on corticosteroids at baseline; these substantial reductions were maintained through Week 54.

3.3.1.6 Corticosteroid Use and Remission at Week 54

The proportion of subjects in the REMICADE 5 mg/kg q8w group in T72 who were receiving corticosteroids at baseline and who were in PUCAI remission and not receiving corticosteroids at Week 54 was 38.5% (5 of 13 subjects). Although based on a small number of subjects, this result is consistent with the proportion of adult subjects in the REMICADE 5 mg/kg q8w group in ACT 1 who were receiving corticosteroids at baseline and who were in Mayo remission and not receiving corticosteroids at Week 54 (25.7%).

3.4 Summary of Efficacy

A Phase 3 randomized, open label multicenter pediatric study established the efficacy of REMICADE for the treatment of moderate to severe UC in pediatric subjects in both inducing and maintaining multiple efficacy endpoints. Data in the pediatric study were consistent with data from the ACT 1 and ACT 2 adult studies in moderate to severe UC. These studies demonstrated:

- REMICADE was effective in inducing clinical response and remission (as measured by the Mayo and PUCAI scores).
  - Clinical response was induced at Week 8 in a similar proportion of pediatric subjects and adult subjects (pooled data from the ACT 1 and ACT 2 studies).
  - The proportion of subjects achieving a clinical response at Week 8 in T72 was generally consistent across the subgroups (demographics including age, baseline disease characteristics, and baseline medications), particularly among subjects who were or were not receiving corticosteroids, immunomodulators (6-MP/AZA or MTX), and 5-ASAs at baseline.
  - Mayo remission was induced at Week 8 in a similar proportion of pediatric subjects as in adult subjects, and in the T72 study, the proportion of subjects in PUCAI remission at Week 8 was similar to the proportion of subjects in Mayo remission at Week 8.
- REMICADE was effective in inducing mucosal healing evaluated by endoscopy.
  - Mucosal healing was induced at Week 8 in a similar proportion of pediatric and adult subjects. Furthermore, maintenance of mucosal healing at Week 54 was demonstrated in the ACT 1 study as well as in 8 of 9 pediatric subjects in the T72 study who had an endoscopy at Week 54.

- REMICADE maintained efficacy though Week 54 as evaluated by PUCAI remission, partial Mayo score, and remission without corticosteroid use.
  - Maintenance of PUCAI remission in T72 was higher in the 5 mg/kg q8w group compared to the 5 mg/kg q12w group.
  - Maintenance of PUCAI remission at Week 54 in pediatric subjects in the REMICADE 5 mg/kg q8w group was consistent with maintenance of Mayo remission in adult subjects in the ACT 1 study.
  - Consistent with results in ACT 1, reductions in the partial Mayo score obtained during the induction phase were maintained through Week 54 in the REMICADE 5 mg/kg q8w group in T72.
  - Consistent proportions of pediatric and adult subjects were in remission and not receiving corticosteroids at Week 54 in T72 and ACT 1, for subjects in the REMICADE 5 mg/kg q8w groups who were receiving corticosteroids at baseline. In addition, substantial reductions in corticosteroid dose were observed in both the pediatric and adult UC populations through Week 54.

4 Overview of Clinical Pharmacology

Pharmacokinetics and immunogenicity analyses are based upon data from T72, and supported by data from ACT 1, ACT 2, and REACH.

Pharmacokinetics and Immunogenicity Analysis Considerations

- All 60 subjects in T72 who received at least 1 dose of REMICADE and had at least 1 measurable PK concentration were included in the population PK analysis. In the T72 serum concentration summaries, data for subjects who stepped-up their REMICADE dose during the maintenance phase were excluded from the point of step-up.
- For the PK analysis, data from ACT 1 and ACT 2 were pooled due to the similarities in subject population and study design, and the 5 mg/kg group is presented as this was the regimen in T72. For the immunogenicity analysis, data from the 5 mg/kg and 10 mg/kg groups in ACT 1 and ACT 2 were pooled.
- All randomized subjects in REACH were to receive baseline immunomodulators per protocol.

4.1 Pharmacokinetics of Infliximab in Pediatric Subjects with UC

4.1.1 Serum Infliximab Concentrations

- Following induction therapy of 5 mg/kg REMICADE at Weeks 0, 2, 6, the median serum peak concentration of infliximab was 115.1 μg/mL.
- During maintenance treatment, the median serum trough infliximab concentration following 5 mg/kg REMICADE q8w was generally higher than that from 5 mg/kg REMICADE q12w.
- An increased dose of infliximab or a more frequent dose administration during step-up led to higher serum infliximab concentration levels.
- There was no apparent impact of age on serum infliximab concentration between the 2 age groups (6 to 11 years versus 12 to 17 years).
- The use of concomitant immunomodulators (ie, 6-MP/AZA/MTX) did not appear to have a significant effect on the serum infliximab concentration in this study.
- Subjects positive for antibodies to infliximab (n = 4) appeared to have low serum trough concentrations.

4.1.2 Population PK Analysis

- Population PK of infliximab in pediatric subjects with UC was well described by a 2-compartment PK model with first-order elimination.
- Median terminal t1/2 of infliximab in pediatric subjects with UC was estimated to be approximately 11 days.
- Body weight and serum albumin levels were identified to be significant covariates to infliximab PK.
- A subject's age and use of immunomodulators had no significant effect on infliximab PK.
- PK simulations showed that steady-state infliximab trough concentrations in subjects who received 5 mg/kg REMICADE q12w were lower than those in subjects receiving 5 mg/kg REMICADE q8w.
  - The lower exposure (particularly lower trough serum infliximab concentrations) in subjects who received 5mg/kg REMICADE q12w may explain why a lower

proportion of these subjects achieved remission during maintenance compared to subjects in the 5 mg/kg q8w group.

4.2 Comparative Pharmacokinetics of Infliximab in Pediatric UC, Pediatric Crohn's Disease, and Adult UC

A summary of PK parameters in the T72, REACH, and ACT studies is presented in Table 10.

Table 10: Summary of infliximab 5 mg/kg PK parameters in the T72, REACH, and ACT studies

	T72	REACH	ACT studies
Median peak serum concentration during induction (µg/mL)[a]	115.1[b]	108.7[b]	131.6[b]
Median trough serum concentration during maintenance at Week 30 (µg/mL)[a]	1.9	1.8	2.5
Median t1/2 (days)	10.8	10.7	11.7[c]

a Data are presented for the 5 mg/kg q8w group.
b At Week 2.
c Derived from data only in ACT 1.

Serum peak infliximab concentrations observed at Week 2 in the T72, REACH, and ACT studies are presented in Figure 17; steady state trough serum infliximab concentrations at Week 30 are presented in Figure 18.

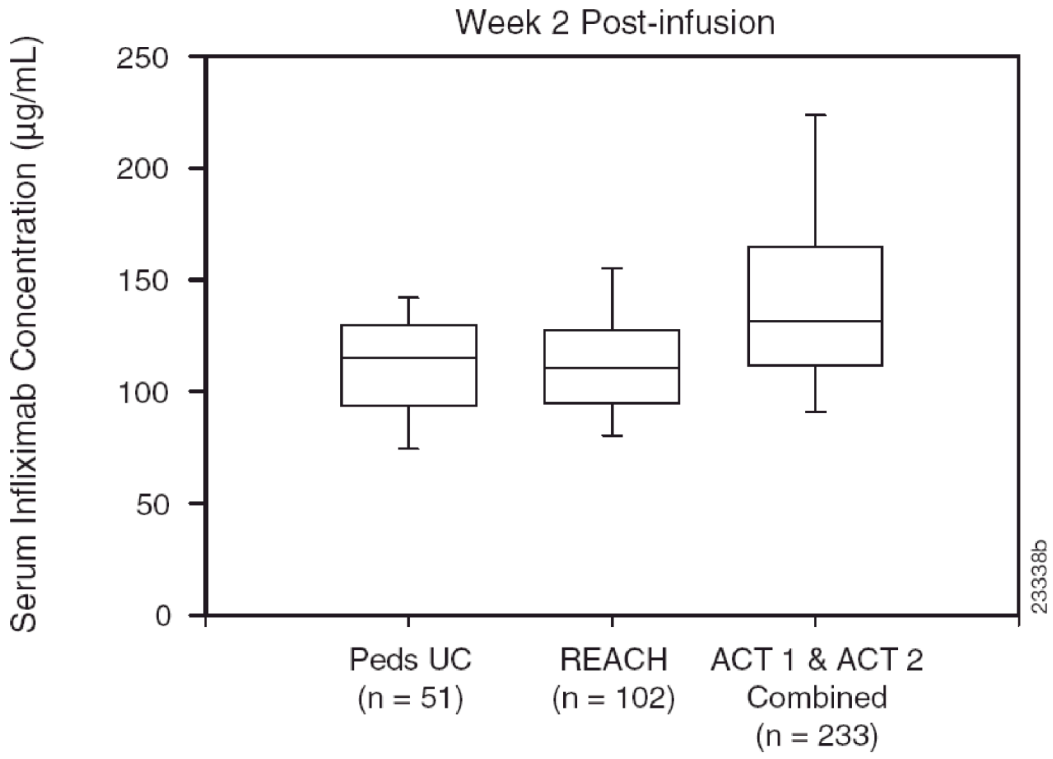


Figure 17: **Serum infliximab concentrations (µg/mL) 1 hour postinfusion at Week 2; treated subjects in the 5 mg/kg groups in T72, REACH, and ACT 1 and ACT 2 combined.** The top and bottom of each box indicate the 25th and 75th percentiles. The solid line within the box denotes the median. The central vertical lines (whiskers) extend from the edge of the box to the 10th and 90th percentiles.

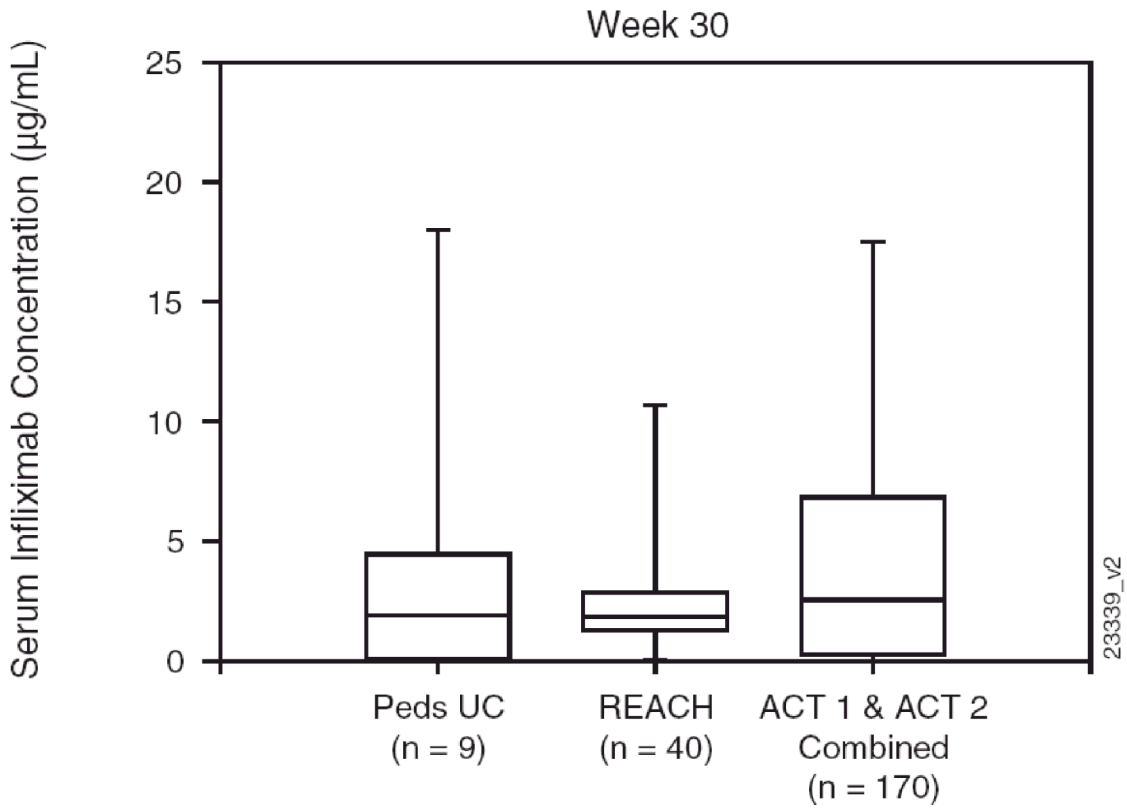


Figure 18: **Serum infliximab concentrations at Week 30; subjects in the 5 mg/kg q8w groups in T72, REACH, and ACT 1 and ACT 2 combined.**
The top and bottom of each box indicate the 25th and 75th percentiles. The solid line within the box denotes the median. The central vertical lines (whiskers) extend from the edge of the box to the 10th and 90th percentiles.

4.2.1 Infliximab Pharmacokinetics in Pediatric Subjects with UC Versus Pediatric Subjects with Crohn's Disease

- Serum infliximab concentrations (peak and steady-state trough concentrations) were similar in pediatric subjects with UC and pediatric subjects with Crohn's disease (Table 10, Figure 17, Figure 18).

- Elimination half-lives were also similar in these 2 pediatric populations (approximately 11 days in both pediatric UC and pediatric Crohn's disease subjects).

4.2.2 Infliximab Pharmacokinetics in Pediatric Subjects with UC Versus Adult Subjects with UC

- Serum infliximab concentrations in pediatric subjects with UC were slightly lower than those in adult subjects with UC (Table 10, Figure 17, Figure 18).

- There was substantial overlap in infliximab exposure between adult and pediatric subjects with UC, although median area under the curve for a dosing interval (AUCτ) at steady-state in pediatric subjects was approximately 20% lower than that in adult subjects following 5 mg/kg REMICADE q8w.

- The difference in infliximab serum concentration between pediatric subjects and adult subjects with UC was small considering the PK variability observed with infliximab in these clinical studies.

Overall, infliximab pharmacokinetics (eg, serum infliximab concentrations and elimination t1/2) were generally comparable between pediatric and adult subjects with UC.

4.3 Exposure-Response Relationship of Infliximab with UC

4.3.1 Relationship between Serum Infliximab Concentration and Efficacy in Pediatric and Adult Subjects with UC

Analyses of PK and efficacy data from the T72, ACT 1, and ACT 2 studies suggest that there is an apparent relationship between serum infliximab concentration and clinical efficacy endpoints in pediatric and adult subjects with UC.

- Higher serum infliximab concentrations at Week 8 were associated with a higher clinical response rate in both pediatric and adult subjects with UC (Figure 19). Similar results were observed for other efficacy endpoints (eg, mucosal healing and remission during induction therapy with infliximab).

- During maintenance therapy, higher steady-state trough infliximab concentrations were associated with higher remission rates at Week 30 and Week 54 in both pediatric and adult subjects with UC.

- Although subjects with the lowest 25% of serum infliximab concentrations had the lowest clinical response rates, more than half of these subjects were in clinical response (Figure 20).

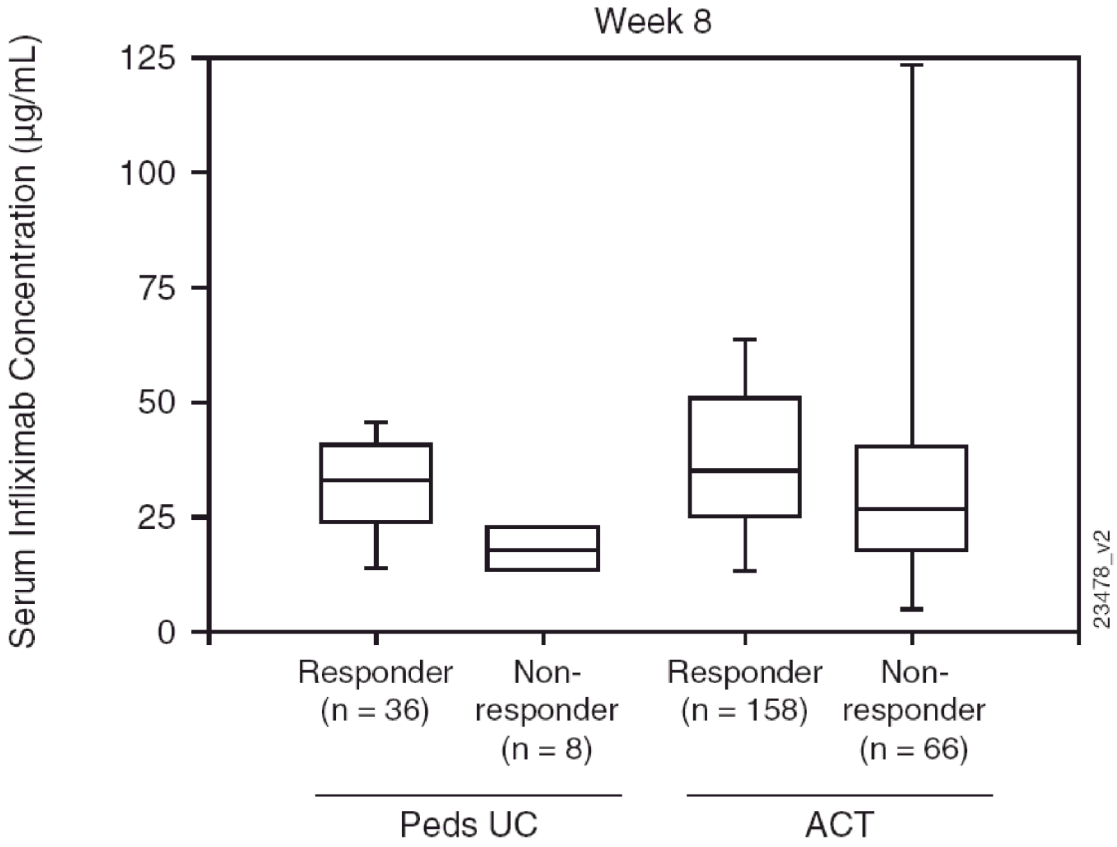


Figure 19: **Serum infliximab concentrations at Week 8 by responder status; subjects in the 5mg/kg groups in T72 and ACT 1 and ACT 2 combined.**
The top and bottom of each box indicate the 25th and 75th percentiles. The solid line within the box denotes the median. The central vertical lines (whiskers) extend from the edge of the box to the 10th and 90th percentiles.

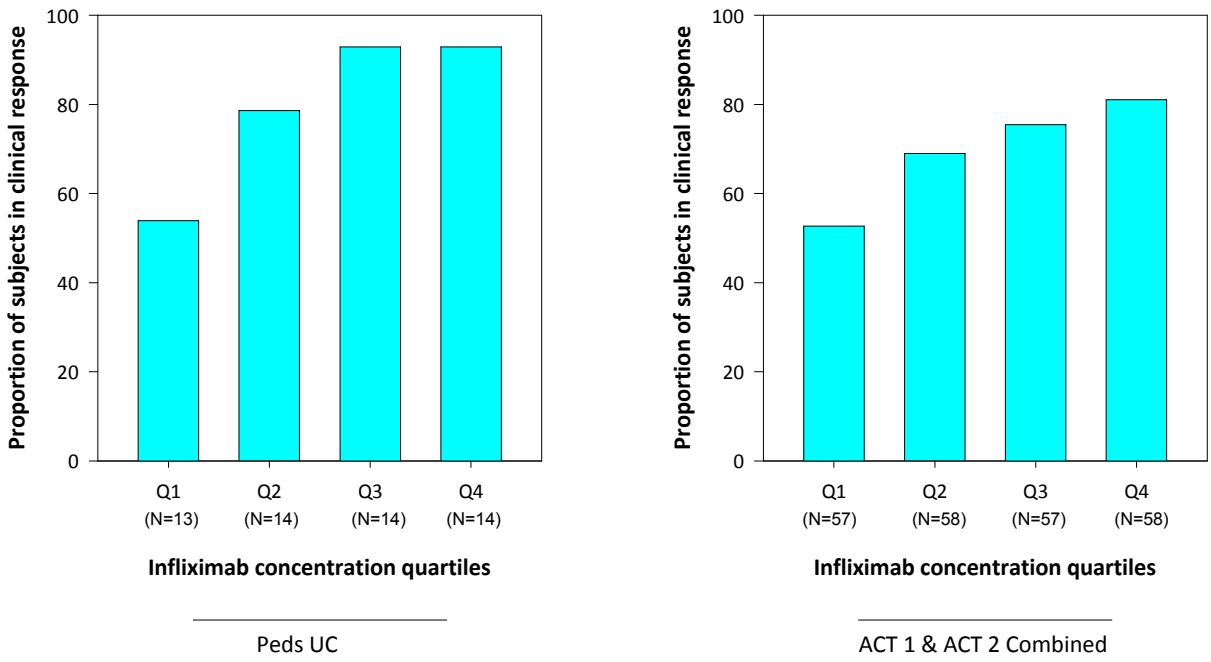


Figure 20: **Proportion of subjects in clinical response at Week 8 by serum infliximab concentration quartiles for subjects in the 5 mg/kg groups in T72 and ACT 1 and ACT 2 combined.**
For pediatric subjects with UC: Q1 < 18.1 µg/mL; Q2 ≥18.1 to <28.9 µg/mL; Q3 ≥ 28.9 to <41.1 µg/mL; Q4 ≥ 41.1 µg/mL. For adult subjects with UC: Q1 < 21.29 µg/mL; Q2 ≥ 21.29 to < 33.02 µg/mL; Q3 ≥ 33.02 to < 47.88 µg/mL; Q4 ≥47.88 µg/mL.

4.3.2 Exposure-Response Relationship of Infliximab in Pediatric and Adult Subjects with UC

Exposure-response modeling is commonly used to evaluate the relationship between a drug's concentration and its subsequent pharmacological action. This can be useful in the process of selecting safe and efficacious doses in a target population. Exposure-response modeling is especially important in dose selection for pediatric patients because pediatric studies tend to provide sparse data which may make dose selection particularly challenging for a pediatric indication. Exposure-response modeling can leverage information from other studies (especially adult studies in the same indication) which may help to more accurately predict the expected pharmacological response to a given level of drug exposure in a pediatric population.

Exposure-response analyses were conducted for infliximab in pediatric and adult subjects with UC and the results of these analyses (presented below) provide further evidence about the relationship between infliximab PK exposure and observed efficacy endpoints.

- Exposure-response modeling confirms exposure-dependent clinical response and remission in both pediatric and adult subjects with UC (Figure 21).

- Modeling and simulation indicates that the 5 mg/kg induction dose regimen can achieve clinical response in a majority of pediatric subjects with UC (at least as efficacious as in adult subjects with UC who received 5 or 10 mg/kg induction regimens).

- Similarly, pediatric subjects who receive the 5 mg/kg q8 w maintenance dosing regimen are expected to achieve a remission rate comparable to that of adult subjects with UC.

The above exposure-response results should be interpreted with care because of some differences between the study designs in the pediatric (T72) and adult (ACT 1 and ACT 2) studies. In addition relatively few numbers of subjects were available for these analyses during maintenance in T72.

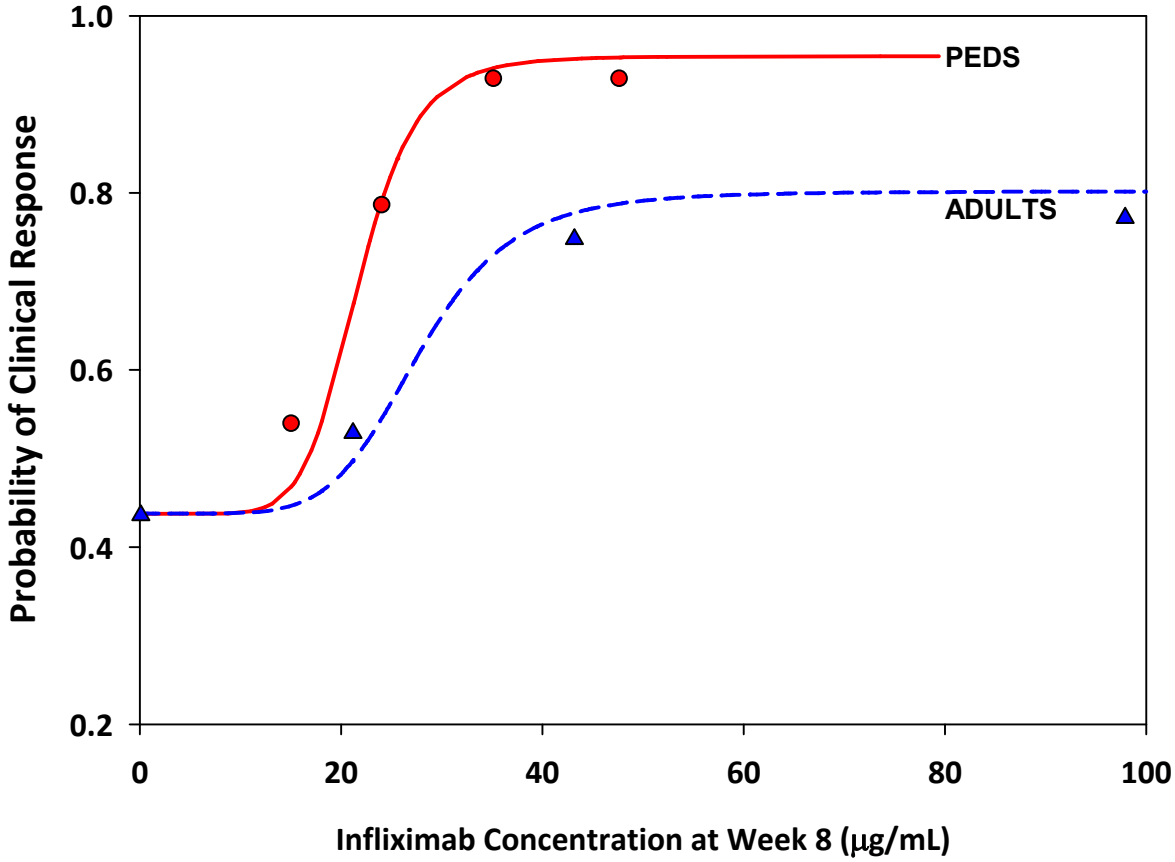


Figure 21: **Infliximab exposure-response relationship for pediatric (T72) and adult (ACT 1 & ACT 2) subjects with UC.**
The solid and dashed lines represent the predicted probabilities of response from a nonlinear logistic regression fit for the pediatric and adult subjects, respectively. The clinical response rates for the pediatric subjects (closed circles) and adult subjects (closed triangles) in each of the respective quartiles of infliximab concentrations at Week 8 are plotted at the midpoint values of the respective infliximab concentrations at Week 8.

4.4 Dose Rationale for REMICADE in Pediatric UC

In T72, induction doses of 5 mg/kg REMICADE at Weeks 0, 2, and 6 followed by a 5 mg/kg q8w maintenance dosing regimen was selected for evaluation in pediatric subjects with UC because this was the approved dose regimen of REMICADE in pediatric subjects with Crohn's disease and adult subjects with UC. Additionally, a maintenance dose of 5 mg/kg q12w was evaluated to explore the possibility of a lower maintenance dose.

Based on the overall evaluation of the efficacy and safety data from studies of REMICADE in pediatric subjects with UC, pediatric subjects with Crohn's disease, and adult subjects with UC, in addition to the PK analysis in pediatric and adult subjects with UC, the proposed dosing regimen of REMICADE in UC is an induction regimen of 5 mg/kg administered as an IV infusion at Weeks 0, 2 and 6 followed by maintenance IV infusions of 5 mg/kg REMICADE q8w. The proposed REMICADE dose regimen in pediatric UC is supported by the following:

- The majority of subjects who received the induction dose regimen (ie, 5 mg/kg at Weeks 0, 2, 6) achieved clinical response and mucosal healing in T72. A similar proportion of subjects achieved clinical response and mucosal healing in the ACT studies.
- Compared with adult subjects with UC, a similar proportion of subjects on the 5 mg/kg q8w maintenance regimen achieved remission.
- Exposure-response modeling showed that an induction regimen of 5 mg/kg at Weeks 0, 2, 6 followed by a maintenance dose regimen of 5 mg/kg q8w will achieve clinical response and remission rates comparable to adult subjects with UC.
- The safety profiles across the clinical studies were generally consistent.

4.5 Antibodies to Infliximab

A summary of the incidence of antibodies to infliximab in the T72, REACH, and ACT studies is presented in Table 11.

Table 11: Summary of antibodies to infliximab in T72, REACH, and the ACT studies

	T72[a]	REACH[a]	ACT 1[a]	ACT 2[b]
Subjects treated	60	112	243	241
Subjects with appropriate samples	52	105	229	188
Subjects positive for antibodies to infliximab	4 (7.7%)	3 (2.9%)	14 (6.1%)	12 (6.4%)

[a] Antibodies to infliximab assessed at Week 54, (8 weeks after last infusion of REMICADE).
[b] Antibodies to infliximab assessed at Week 30, (8 weeks after last infusion of REMICADE)

The incidence of antibodies to infliximab was low and consistent across T72, ACT 1, ACT 2, and REACH, after accounting for the differences in the use of concomitant immunomodulators which have been shown to decrease the incidence of antibodies to

infliximab. Approximately 40% to 50% of subjects in T72, ACT 1, and ACT 2 compared with approximately 98% of subjects in REACH received concomitant immunomodulators.

4.6 Summary of PK and Antibodies to Infliximab

The PK and immunogenicity results presented above demonstrate the following:

- PK results in pediatric UC subjects were generally consistent with those observed in Crohn's disease subjects (REACH) as well as in adult UC subjects (ACT 1 and ACT 2).

- Population PK modeling and simulation shows that substantial overlap exists for infliximab systemic exposure between adult and pediatric subjects with UC, albeit there is a trend towards slightly lower infliximab concentration in pediatric UC subjects.

- Population PK analysis shows that the variability of infliximab PK was influenced by bodyweight, serum albumin levels, and immunogenicity. There was no apparent impact of either age or concomitant immunomodulator use on the PK of infliximab.

- The maintenance dosing regimen of 5 mg/kg REMICADE q8w resulted in higher infliximab exposure over time when compared to 5 mg/kg REMICADE q12w.

- There is an apparent relationship between serum infliximab concentration and clinical efficacy endpoints in pediatric and adult subjects with UC. Higher infliximab exposure was associated with higher rates of clinical response, mucosal healing, and remission at Week 8 and with higher remission rates at Weeks 30 and 54.

- The proportion of subjects who tested positive for antibodies to infliximab through Week 54 was low (7.7%) in T72, and consistent with that (6.1% in ACT 1 and 6.4% in ACT 2) in adult subjects with UC.

- The comparable infliximab exposure (relative to pediatric subjects with Crohn's disease and adult subjects with UC), together with the efficacy and safety data, support the use of 5 mg/kg REMICADE administered at Weeks 0, 2, and 6, followed by a maintenance regimen of 5 mg/kg REMICADE q8w thereafter for the treatment of UC in pediatric subjects.

5 Overview of Safety

Primary safety analyses are based upon data from:

- T72
- ACT 1 and ACT 2
- REACH

Supportive long-term safety data from the following are presented:

- RESULTS UC long-term safety follow-up study in pediatric subjects with UC
- Postmarketing registries in pediatric IBD (DEVELOP and Pediatric IBD Collaborative Research Group Registry)
- Postmarketing review of pediatric AE reports

Safety Analysis Considerations

- Safety data from the ACT studies were pooled due to the similarities in subject population and study design. For comparison purposes, since the T72 and REACH studies included only a 5 mg/kg group, only pooled data for the 5 mg/kg group in the ACT studies are presented.
- For T72, REACH, and the ACT studies, the safety analyses are presented through Week 54 and include all treated subjects. In the pooled data for the ACT studies, data through Week 54 of ACT 2 include the main study (Weeks 0 to 30) and through Week 24 of the study extension (Weeks E-0 to E-24); study agent administration remained blinded through Week E-24. For T72 and REACH, data for subjects who stepped up/crossed over were included according to the treatment regimen received prior to step-up/cross-over.
- All subjects in the T72 and REACH pediatric studies were treated with REMICADE; therefore, the incidence of AEs in a control group of subjects with pediatric UC or pediatric Crohn's disease (who were receiving currently available therapy) was not available for comparison. Additionally, since subjects and physicians in T72 and REACH were not blinded to maintenance group, data may be confounded by biases in data collection and/or interpretation. Finally, because of the small numbers of subjects in T72 and REACH, comparisons between studies should be interpreted with caution.

5.1 Safety in T72

5.1.1 Extent of Exposure

Through Week 54, for the 60 treated subjects, the average number of REMICADE administrations received was 6; the median total dose received was 30.1 mg/kg; and the average duration of follow-up was 38.0 weeks.

5.1.2 Analyses of Adverse Events

5.1.2.1 All Adverse Events

Table 12 presents AEs occurring in ≥ 10% of treated subjects through Week 54.

Table 12: Number of subjects with 1 or more treatment-emergent adverse events (with frequency of >= 10%) through Week 54 by WHOART system-organ class and preferred term; treated subjects in T72

	REMICADE
Subjects treated[a,b]	60
Avg duration of follow-up (weeks)	38.0
Avg exposure (weeks)	29.4
Subjects with 1 or more adverse events	57 (95.0%)
System-organ class/preferred term	
Gastro-intestinal system disorders	36 (60.0%)
Colitis ulcerative	27 (45.0%)
Abdominal pain	8 (13.3%)
Respiratory system disorders	28 (46.7%)
Upper respiratory tract infection	14 (23.3%)
Pharyngitis	11 (18.3%)
Coughing	6 (10.0%)
Resistance mechanism disorders	20 (33.3%)
Fever	8 (13.3%)
Skin and appendages disorders	14 (23.3%)
Body as a whole - general disorders	12 (20.0%)
Central & peripheral nervous system disorders	11 (18.3%)
Headache	8 (13.3%)
Musculo-skeletal system disorders	7 (11.7%)
Red blood cell disorders	7 (11.7%)
Anemia	6 (10.0%)

[a] Data for subjects who stepped up are included.
[b] Includes data from Week 0 through Week 54.

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- Through Week 54, 57 (95.0%) treated subjects had an AE. The system-organ class with the highest incidence of AEs was GI system disorders, and worsening UC was the most common AE.

- All subjects (100%) in the q8w and q12w groups reported an AE. Table 13 presents AEs occurring in ≥ 10% in either group through Week 54.

Table 13: Number of subjects with 1 or more treatment-emergent adverse events (with frequency of >= 10% in either treatment group) through Week 54 by WHOART system-organ class and preferred term and by maintenance treatment group; randomized subjects by treatment received in T72

	REMICADE 5 mg/kg	
	q8w	q12w
Randomized subjects by treatment received[a,b]	22	23
Avg duration of follow-up (weeks)	50.4	44.6
Avg exposure (weeks)	41.0	34.3
Subjects with 1 or more adverse events	22 (100.0%)	23 (100.0%)
System-organ class/preferred term		
Gastro-intestinal system disorders	12 (54.5%)	16 (69.6%)
Colitis ulcerative	8 (36.4%)	15 (65.2%)
Abdominal pain	3 (13.6%)	2 (8.7%)
Respiratory system disorders	11 (50.0%)	11 (47.8%)
Upper respiratory tract infection	7 (31.8%)	6 (26.1%)
Pharyngitis	4 (18.2%)	4 (17.4%)
Coughing	2 (9.1%)	3 (13.0%)
Resistance mechanism disorders	10 (45.5%)	7 (30.4%)
Fever	6 (27.3%)	1 (4.3%)
Skin and appendages disorders	7 (31.8%)	7 (30.4%)
Central & peripheral nervous system disorders	5 (22.7%)	4 (17.4%)
Headache	3 (13.6%)	3 (13.0%)
Musculo-skeletal system disorders	4 (18.2%)	3 (13.0%)
Red blood cell disorders	4 (18.2%)	3 (13.0%)
Anemia	4 (18.2%)	2 (8.7%)
Body as a whole - general disorders	2 (9.1%)	7 (30.4%)
Pain	0 (0.0%)	4 (17.4%)

Table 13: Number of subjects with 1 or more treatment-emergent adverse events (with frequency of >= 10% in either treatment group) through Week 54 by WHOART system-organ class and preferred term and by maintenance treatment group; randomized subjects by treatment received in T72

	REMICADE 5 mg/kg	
	q8w	q12w
Urinary system disorders	1 (4.5%)	3 (13.0%)
Urinary tract infection	1 (4.5%)	3 (13.0%)
Liver and biliary system disorders	0 (0.0%)	4 (17.4%)

[a] Data for subjects who stepped up are included according to the regimen received prior to step-up.
[b] Includes data from Week 0 through Week 54.

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5.1.2.2 Deaths

No deaths were reported in T72.

5.1.2.3 Serious Adverse Events

Table 14 presents the number of subjects with an SAE through Week 54.

Table 14: Number of subjects with 1 or more treatment-emergent serious adverse events through Week 54 by WHOART preferred term; treated subjects in T72

	REMICADE
Subjects treated[a,b]	60
Avg duration of follow-up (weeks)	38.0
Avg exposure (weeks)	29.4
Subjects with 1 or more serious adverse events	14 (23.3%)
Preferred terms	
Colitis ulcerative	9 (15.0%)
Anemia	1 (1.7%)
Cellulitis	1 (1.7%)
Infection	1 (1.7%)
Infection viral	1 (1.7%)
Neutropenia	1 (1.7%)
Pancreatitis	1 (1.7%)
Pharyngitis	1 (1.7%)
Pneumonia lobar	1 (1.7%)
Urinary tract infection	1 (1.7%)

[a] Data for subjects who stepped up are included.
[b] Includes data from Week 0 through Week 54.

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- Through Week 54, 14 (23.3%) treated subjects had an SAE. No individual SAE was reported in more than 1 subject in any treatment group except for worsening UC.
- The proportions of subjects with SAEs were similar in the q8w and q12w groups. Table 15 presents the number of subjects with an SAE by maintenance treatment group through Week 54.

Table 15: Number of subjects with 1 or more treatment-emergent serious adverse events through Week 54 by WHOART preferred term and by maintenance treatment group; randomized subjects by treatment received in T72

	REMICADE 5 mg/kg	
	q8w	q12w
Randomized subjects by treatment received[a,b]	22	23
Avg duration of follow-up (weeks)	50.4	44.6
Avg exposure (weeks)	41.0	34.3
Subjects with 1 or more serious adverse events	4 (18.2%)	5 (21.7%)
Preferred terms		
Colitis ulcerative	2 (9.1%)	3 (13.0%)
Anemia	1 (4.5%)	0 (0.0%)
Cellulitis	1 (4.5%)	0 (0.0%)
Infection	1 (4.5%)	0 (0.0%)
Infection viral	1 (4.5%)	0 (0.0%)
Pancreatitis	1 (4.5%)	0 (0.0%)
Pharyngitis	0 (0.0%)	1 (4.3%)
Urinary tract infection	0 (0.0%)	1 (4.3%)

[a] Data for subjects who stepped up are included according to the regimen received prior to step-up.
[b] Includes data from Week 0 through Week 54.

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5.1.2.4 Other Significant Adverse Events

5.1.2.4.1 Discontinuation of Study Agent Due to Adverse Events

- Through Week 54, 13 (21.7%) subjects discontinued study agent due to an AE. Worsening UC was the most common AE resulting in discontinuation of study agent.

- The proportion of subjects who discontinued study agent due to an AE was higher in the q12w group (26.1%) than in the q8w group (13.6%); all subjects who discontinued study agent due to an AE in the q12w group did so due to worsening UC, compared with only 1 of 3 subjects in the q8w group.

5.1.2.4.2 Infections

- Through Week 54, 31 (51.7%) treated subjects had an infection. Upper respiratory infection was the most common infection.

- Serious infections were reported in 7 (11.7%) subjects: 1 subject in the group that was not randomized at Week 8 (pneumonia), 3 subjects in the q8w group (infection of unknown origin, viral infection, and facial cellulitis) and 3 subjects in the q12w group (pharyngitis, worsening UC, and urinary tract infection). No cases of active TB or serious opportunistic infections were reported.

- The proportions of infections and serious infections were similar in the q8w and q12w groups.

- Most infections required oral or parenteral antimicrobial treatment.

5.1.2.4.3 Malignancies

No malignancies were reported in T72.

5.1.2.4.4 Infusion Reactions

- Through Week 54, 8 (13.3%) treated subjects had an infusion reaction. Of the 340 total infusions, 17 (5.0%) resulted in an infusion reaction.

- Dyspnea was the only infusion reaction reported in more than 1 subject.

- The proportions of subjects experiencing infusion reactions were similar in the q8w and q12w groups and were not impacted by concomitant immunomodulator therapy. In addition, the proportions of infusions resulting in an infusion reaction were similar in the q8w and q12w groups. However, within the q8w group, fewer infusions associated with infusion reactions were reported in subjects on concomitant immunotherapy than in subjects on monotherapy

- No serious infusion reactions were reported. All infusion reactions were mild or moderate in intensity.

5.1.2.4.5 Possible Anaphylactic and Possible Delayed Hypersensitivity (Serum-sickness Like) Reactions

No possible anaphylactic reactions or possible delayed hypersensitivity reactions were reported in T72.

5.1.2.5 Colectomy

In the 54 weeks after their first study administration in T72, 5 (8.3%) pediatric subjects underwent a colectomy:

- 2/15 (13%) subjects not randomized at Week 8
  - 1 subject received 2 induction doses of 5 mg/kg
  - 1 subject received 3 induction doses of 5 mg/kg

- 1/22 (4.5%) subject in the q8w group
  - subject received 3 induction doses of 5 mg/kg and 2 step-up doses of 10 mg/kg

- 2/23 (8.7%) subjects in the q12w group
  - 1 subject received 3 induction doses of 5 mg/kg and 1 step-up dose of 10 mg/kg
  - 1 subject received 3 induction doses of 5 mg/kg, 2 maintenance doses of 5 mg/kg, and 2 step-up doses of 10 mg/kg

5.1.3 Clinical Laboratory Evaluations

5.1.3.1 Clinical Hematology

Through Week 54, the most common markedly abnormal postbaseline hematology laboratory value was a decrease in lymphocytes, occurring in 15 (25.0%) treated subjects; 10 (66.7%) of these subjects received concomitant immunomodulators during the study.

5.1.3.2 Clinical Chemistry

The proportion of treated subjects with markedly abnormal postbaseline chemistry laboratory values was low, and the majority of the values occurred only transiently. Through Week 54, the most common markedly abnormal postbaseline clinical chemistry laboratory value was elevated ALT, occurring in 3 (5.0%) treated subjects.

5.1.4 Other Observations Related to Safety

5.1.4.1 Antibodies to Infliximab and Possible Reactions to Study Agent

Of the 60 subjects in T72, 52 had an appropriate sample for analysis of antibodies to infliximab, and of these 52 subjects, 4 (7.7%) were positive for antibodies to infliximab at any time during the study. Due to this small number, it is not possible to make definitive conclusions regarding the relationship of antibodies to infliximab and infusion reactions, possible anaphylactic reactions, or possible delayed hypersensitivity reactions.

5.1.4.2 Antinuclear Antibodies/Anti-double-stranded DNA Antibodies

Forty-four of 60 treated subjects were evaluated for antinuclear antibodies (ANA); 41 (93.2%) were negative at baseline, 9 (22.0%) of whom were newly positive at any time during the study. Of the 42 subjects evaluated for anti-dsDNA antibodies, all subjects (100%) were negative at baseline and newly positive anti-dsDNA antibodies were detected in 2 (4.8%) subjects. There were no new reports of autoimmune disease through Week 54 of the study. An SAE of lupus erythematosus (LE) syndrome (lupus-like reaction) was reported after Week 54.

5.1.5 Safety in Subgroup Analyses

Safety analyses based on demographic and baseline characteristics, pediatric age group (6 to 11 years and 12 to 17 years), and treatment with REMICADE monotherapy and REMICADE combination therapy (ie, subjects who received concomitant treatment with AZA, 6-MP, or MTX at baseline) were performed.

- Some differences were observed in the proportions of subjects with SAEs and infections based on demographics and baseline disease characteristics; however, the small numbers of subjects in the subgroups make it unlikely that the observed differences have any clinical significance. In general, subjects weighing ≤ 50.8 kg tended to have more SAEs and infections than those weighing > 50.8 kg.

- There were more subjects in the 12 to 17 years age group than in the 6 to 11 years age group (45 [75.0%]) compared with 15 [25.0%], respectively). While the numbers of subjects in each subgroup are too small to make any definitive conclusions about the effect of age on safety events, there were higher proportions of subjects with SAEs, discontinuation of study agent due to AEs, and infections in the younger age group than in the older age group.

- Similar proportions of subjects receiving REMICADE monotherapy and combination therapy experienced AEs; however, more subjects in the monotherapy group experienced SAEs and discontinuation of study agent due to AEs than in the combination therapy group, and these differences were driven primarily by events of worsening UC. Similar proportions of subjects experienced infusion reactions in the monotherapy and combination therapy groups although, as may be expected, fewer infusions resulting in infusion reactions were observed in the combination immunomodulator therapy group than in the monotherapy group.

5.2 Comparison of Safety in T72, REACH, and the ACT Studies

A summary of the key safety data in T72, REACH, and the ACT studies through Week 54 is presented in Table 16.

Table 16: Summary of safety of REMICADE 5 mg/kg in the T72, REACH, and ACT studies through Week 54

	REMICADE 5 mg/kg		
	T72	REACH	ACT Studies[a]
Avg duration of follow-up (weeks)	38.0	47.3	41.1
Subjects with 1 or more AEs	95.0% (57/60)	95.5% (107/112)	86.0% (208/242)
System-organ class with highest incidence of AEs	Gastro-intestinal system disorders	Gastro-intestinal system disorders	Gastro-intestinal system disorders
	60.0% (36/60)	75.0% (84/112)	45.9% (111/242)
Subjects with 1 or more SAEs	23.3% (14/60)	19.6% (22/112)	17.8% (43/242)
Subjects who discontinued study agent because of 1 or more AEs	21.7% (13/60)	10.7% (12/112)	5.8% (14/242)
Subjects with 1 or more infections	51.7% (31/60)	54.5% (61/112)	38.8% (94/242)
Subjects with 1 or more serious infections	11.7% (7/60)	8.0% (9/112)	3.3% (8/242)
Subjects with 1 or more malignancies	0.0% (0/60)	0.0% (0/112)	1.7% (4/242)
Subjects with 1 or more infusion reactions	13.3% (8/60)	17.0% (19/112)	10.7% (26/242)
Subjects with 1 or more possible anaphylactic or possible delayed hypersensitivity (serum-sickness like) reactions	0.0% (0/60)	1.8% (2/112)[b]	0.8% (2/242)[c]

[a] ACT 1 through Week 54; ACT 2 through Week 30, and E0 through E24 of the long-term study extension.
[b] Possible anaphylactic reactions.
[c] Possible delayed hypersensitivity reactions.

- Overall proportions of subjects with AEs and SAEs were consistent in T72 and REACH, and slightly lower in the ACT studies. The GI system-organ class had the highest incidence of AEs across the studies. The most commonly reported AEs were worsening UC (T72 study) and headache (REACH study and 5 mg/kg REMICADE group in the ACT studies). Worsening of the disease was the most commonly reported SAE for all studies.

- The overall proportions of subjects with AEs were the same in the q8w and q12w groups in T72. In T72, AEs of worsening UC occurred in a greater proportion of subjects in the q12w group than in the q8w group. In both T72 and REACH, no noteworthy differences were reported when comparing SAEs in the q8w and q12w groups.

- The proportion of subjects discontinuing study agent due to AEs was higher in T72 than in REACH and the ACT studies. Worsening of the disease under study was the most common AE resulting in discontinuation of study agent, and was more common in the q12w than in the q8w group in T72.

- There were no deaths or malignancies in T72 or REACH. During the ACT main studies, there were no deaths; malignancies were reported in 4 subjects, 3 of whom had been treated with REMICADE.

- When considering the proportions of subjects experiencing infusion reactions and the number of infusions with infusion reactions, they were generally consistent between T72, REACH, and the ACT studies. There were no serious infusion reactions through Week 54 in 5 mg/kg REMICADE-treated subjects in any of the studies.

- No possible anaphylactic reactions or possible delayed hypersensitivity reactions were reported in T72. Two possible anaphylactic reactions were reported in REACH, and 2 possible delayed hypersensitivity reactions were reported in the 5 mg/kg group in the ACT studies.

- The proportion of subjects with infections in T72 was similar to that in REACH and higher than the proportion in the ACT studies. When comparing the proportions of subjects with infections in the q8w and q12w groups, they were similar in T72 and higher in the q8w group in REACH. In all studies, the system-organ class with the highest incidence of infections was respiratory system disorders. The proportion of subjects with serious infections was similar in T72 and REACH, and higher in T72 than the ACT studies.

- When comparing monotherapy and combination therapy across T72 and the ACT studies, no consistent trends were observed in the proportions of REMICADE-treated subjects having AEs, SAEs, and discontinuing study agent due to AEs.

In summary, the safety data from T72 are consistent with safety data from the REACH and ACT studies and are consistent with current REMICADE labeling. No new safety concerns emerged regarding the proposed use of REMICADE in the pediatric UC population.

5.3 Supportive Safety Findings From Long-term Safety Follow-up Studies and Registries

5.3.1 RESULTS UC

Description of RESULTS UC:

- The RESULTS UC (C0168T62) program collects targeted long-term safety data in adult subjects with UC who participated in the ACT 1 or ACT 2 studies, and in pediatric subjects with UC who participated in the T72 study. As of 08 Dec 2010, follow-up data was available for 45 pediatric subjects who participated in T72.

- Data collected in the RESULTS UC program include serious infections, deaths, new malignancies (including colorectal cancer), new autoimmune diseases, and surgical procedures (including colectomy). In addition, information is collected on the signs and symptoms of delayed hypersensitivity (serum sickness-like) reactions following readministration of commercial REMICADE.

- Other than commercial REMICADE, treatments such as immunosuppressants, other commercially available TNFα blockers, and experimental therapies are not always reported in RESULTS UC; this may potentially impact the incidence as well as the severity of AEs reported.

Outcomes for T72 subjects enrolled in RESULTS UC:

- Through 08 Dec 2010, 4 events have been reported in the 45 subjects from T72: new autoimmune disease (Crohn's disease); serious viral infection with cytomegalovirus (CMV) hepatitis; serious bacterial infection with *Campylobacter*; and psoriatic eruption.

- Through 08 Dec 2010, 10 of 45 subjects underwent a partial or total colectomy. This is in addition to the 5 subjects who underwent a colectomy during the T72 study (Section 5.1.2.5). The colectomies occurred predominantly in subjects who were refractory to corticosteroids and immunomodulators and occurred more often in subjects receiving q12w therapy than q8w therapy. Colectomies were generally not conducted in subjects who responded to REMICADE at the end of the T72 study.

  - This colectomy rate (15/60 [25%]) is not inconsistent with colectomy rates for pediatric patients reported in the literature (9% to 46%).[49]

These data, in conjunction with data from other long-term safety follow-up studies of REMICADE, have revealed no new safety trends or concerns. The types of reported events are consistent with what has been observed in clinical studies and are addressed in current REMICADE labeling. Since the data collected in C0168T62 are limited, the

sponsor will approach all T72 investigator sites in the US and Canada to actively recruit subjects from T72 into the ongoing pediatric IBD registry, DEVELOP.

5.3.2 DEVELOP (C0168Z02)

Description of Registry:

- DEVELOP (C0168Z02) is an ongoing, multicenter, prospective, multinational observational registry of long-term safety and clinical status of pediatric patients (< 17 years at the time of enrollment) with IBD, including Crohn's disease, UC, or IC, who have been treated with REMICADE and/or other medical therapies for IBD.

- This company-sponsored registry plans to enroll 5000 patients: 2000 with Crohn's disease who have been exposed to REMICADE; 2000 with Crohn's disease who have received other Crohn's disease treatments only; and 1000 patients with UC (500 who have been exposed to REMICADE and 500 who have received other UC treatments only). There are no treatment assignments, nor restrictions on the use of commercially available medications.

- After enrollment, follow-up data is obtained by the registry physician or designee every 6 months, via a review of the patient's medical records and/or direct contact (ie, preferably an office visit/infusion), and includes: disease characteristics; medications; dose and frequency of REMICADE, other biologics, and immune modulators; clinical status; quality of life; and AEs (including dysplasia and malignancy, infection, and autoimmune disease).

- The first patient was enrolled in May 2007 (in the US). Patient enrollment is expected to take approximately 96 months and patients will be followed for 20 years (anticipated date of final report is 2036). The registry is monitored and is overseen by a Scientific Advisory Panel of 16 internationally-recognized Pediatric IBD leaders.

Registry Objectives:

- The goal of DEVELOP is to prospectively assess the long-term outcomes (ie, safety, clinical status, and quality of life) of pediatric patients with IBD who have been treated with REMICADE and/or other IBD therapies.

- The focus is the occurrence of AEs and SAEs reported in association with REMICADE relative to other approved or commonly prescribed therapies. Particular attention is on SAE's of special interest: mortality, serious infection, TB, malignancy, intestinal dysplasia, new-onset autoimmune disorders (eg, lupus, MS), and pregnancy.

Study Enrollment:

- As of 22 Apr 2011, 2787 patients were enrolled at 57 sites in the US and 20 sites in the EU. The majority of the patients (2389) had Crohn's disease, and 394 were colitis patients (332 with UC and 62 with IC). Note that an amendment to include UC patients was not implemented until mid-2010. The average length of follow-up was approximately 1.33 years.

- Of the 2787 patients, 1534 had been treated with other IBD therapies only and 1253 had previous REMICADE exposure. A total of 95% of patients receiving REMICADE were being dosed q8w. For patients with previous REMICADE exposure, approximately two-thirds were receiving monotherapy and one-third was receiving a concomitant immunomodulator.

Demographics:

- Consistent with the US and EU REMICADE Crohn's disease indication in pediatric patients, REMICADE-exposed patients in DEVELOP have more severe disease activity when compared with patients who have received other treatments only. Specifically, REMICADE-treated patients had a longer duration of disease (3.0 vs. 2.1 years) at the time of enrollment and were more likely to have:
  - been hospitalized in the year prior to enrollment (38% vs. 22%);
  - had a previous bowel resection (12.0% vs 5.4%) or had a stoma (4.0% vs. 1.2%);
  - received total parenteral nutrition (10% vs. 3%);
  - a fistula (20.0% vs 7.2%), stricture (8.2% vs. 3.9%), stenosis (5.5% vs. 1.8%), or abscess (15.0% vs. 6.7%);
  - been previously or currently treated with immunomodulators (83% vs 73%) and/or corticosteroids (81% vs. 69%).

Outcomes:

The available data through 22 April 2011 are summarized below:

- The majority of AEs and SAEs were related to the GI system. While the overall cumulative incidences of AEs and SAEs were similar for the REMICADE-exposed and non-REMICADE-exposed patients, REMICADE-exposed patients had a higher cumulative incidence of infection and serious infection. The incidence of serious infections was evaluated on the basis of whether or not the patient had received REMICADE in the prior 90 days. The DEVELOP Steering Committee specified that infections occurring within 3 months of a REMICADE infusion would be considered potentially related to REMICADE, while infections occurring outside of this time

frame (including infections occurring in patients who had never received REMICADE) would be considered not related to REMICADE. Using these parameters, the incidence of serious infection was 3.2 per 100 patient-years in the REMICADE-exposed group, compared with 2.0 per 100 patient-years in the group exposed to other treatments only. Many of the serious infections in the REMICADE-exposed group were abscesses, likely related to Crohn's disease (eg, intra-abdominal, pelvic, perianal, or gluteal).

- To further assess risk factors for a serious infection, a Cox-proportional hazards regression analysis was conducted. Results showed that the only statistically significant independent predictors of increased risk for serious infection were related to disease severity: hospitalization in the prior year (hazard ratio [HR] 2.14, p=0.003) and physician's global assessment score (HR 1.32, p=0.015). Neither the use of immunomodulators (HR 1.48, p=0.17), prednisone (HR 1.21, p=0.56), nor REMICADE (HR 1.57, p=0.07) were significant predictors of increased risk of serious infection.

- One death (motor vehicle accident) was reported.

- A total of 7 malignancies were reported, including 4 that occurred in patients with exposure to REMICADE (1 each of basal cell carcinoma, acute monoblastic leukemia, melanoma and lymphoproliferative disorder-diffuse lymphadenopathy) and 3 without exposure to REMICADE (1 B-cell lymphoma, 1 Hodgkin's lymphoma, and 1 hematophagic histiocytosis). For each group, the incidence of malignancy has been 0.2 malignancies per 100 patient-years of follow-up.

- No events of colonic dysplasia, TB, MS, or other demyelinating events were reported. There have been 3 reports of pregnancy in patients exposed to REMICADE (including 1 in a partner of a male patient in the registry). Two of the pregnancies resulted in the birth of a healthy infant with no maternal complications. In the third pregnancy, the infant developed laryngomalacia but subsequently did well. There were also 2 pregnancies reported in patients not exposed the REMICADE, both of which ended in elective terminations.

- A total of 7.7% of patients who have received treatment with REMICADE and are participating in the registry's immunogenicity substudy were positive for antibodies to infliximab.

Overall, the severity and type of AEs reported were consistent with those observed in REMICADE clinical studies and in postmarketing experience. AEs of special interest, including malignancy, dysplasia, serious infection, mortality, TB, new autoimmune disorders, and pregnancy, will continue to be actively monitored in DEVELOP.

5.3.3 Pediatric IBD Collaborative Research Group Registry

Description of Registry:

- The Pediatric IBD Collaborative Research Group Registry, initiated in 2002, is a prospective, multicenter, inception cohort study of a subgroup of children newly-diagnosed with IBD. Patients 16 years of age or younger are eligible to enroll.

- No predefined visits, treatments, or procedures are required. At registration, at 30 days post IBD diagnosis (optional), and q3 months, physicians record specific conditions and disease characteristics as well as changes in IBD therapy, disease progression, key events, use of ancillary services, hospitalizations, and laboratory values.[19]

Registry Objective:

- The overall goals include assessment of the natural history of IBD in newly diagnosed (within the past 30 days) pediatric patients, documentation of the variety of treatment regimens used in managing IBD, and assessment of the clinical and humanistic outcomes of treatment in real-world medical practice settings. The registry receives funding support from a number of sources and companies, including the sponsor.

- An active publication schedule and presentation of results at national and international meetings is a goal of the Pediatric IBD Collaborative Research Group Registry (approximately 21 manuscripts and 60 presentations).

- This registry will describe the indications and patterns of use of REMICADE in children ≤ 16 years diagnosed with IBD, examine clinically relevant short- and long-term outcomes after REMICADE therapy, and describe the frequency of SAEs in pediatric patients with IBD treated with REMICADE.

Study Enrollment:

- As of April 2011 (the most recent DBL), 1736 patients (1166 currently active) were enrolled at 24 sites in the US and Canada.

- Approximately two-thirds of the patients have been diagnosed with Crohn's disease, with the remaining having UC or IC. A total of 568 patients (32.7 %) have received REMICADE (447 for Crohn's disease, 98 for UC, and 23 for IC).

Demographics:

- At the time of their first REMICADE infusion, the majority of patients (56.5%) were 10 to 14 years of age. A total of 7697 REMICADE infusions have been administered, with a mean of 13.6 infusions per patient (range 1 to 60). The mean

number of infusions per patient is 14.6, 9.7, and 9.3 for Crohn's disease, UC, and IC, respectively. The 568 REMICADE-treated patients have a total of 1385.3 REMICADE exposure years with a range of 0 (1 infusion only) to 8.3 years and a mean of 2.4 ± 2 years.

Outcomes:

- Since the start of reporting outcomes data (01 Jan 2005) until the DBL for the most recent report in April 2011, 6914 REMICADE infusions were administered. Approximately 3% of these infusions were associated with an infusion reaction. There were 21 delayed hypersensitivity reactions in 11 patients; none required hospitalization.

- One cancer has been reported in a 14 year-old female who had received 8 doses of REMICADE (Stage II Hodgkin's disease, currently in remission). This patient had also received approximately 3 years of 6-MP treatment. This patient was successfully treated and is now 21 years of age; she continues to be in remission per her last oncology note (June 2009).

- One death has been reported during follow-up in an 11 year-old male patient treated with REMICADE. This patient had severe gastroduodenal and colonic disease whose therapy at the time of registry entry included AZA, prednisone, and enteral nutrition. He received 4 doses of REMICADE and approximately 6 months after the last REMICADE dose, suffered cardiac arrest that was secondary to cardiac arrhythmia associated with long time from electrocardiogram Q wave to the end of the T wave corresponding to electrical systole (QT) interval. In retrospect, the patient had suffered what may have been a near miss arrhythmia prior to the diagnosis of Crohn's disease. The primary investigator considered a doubtful relationship between REMICADE treatment and this patient's death.

5.4 Postmarketing Safety

5.4.1 Overview

An estimated 22,922 pediatric patients (< 18 years old) have been exposed to REMICADE through 23 Feb 2011. The sponsor conducted a cumulative review of serious, postmarketing pediatric AE reports with the use of REMICADE through 31 Dec 2010, including spontaneous, solicited, and registry reports.

- The search identified 1501 serious postmarketing pediatric cases with REMICADE. Of those, 1002 were in patients treated for IBD (Crohn's disease 790; UC 164; Other IBD 48). Five hundred and one of the IBD cases were reported in US patients. There were a total of 24 deaths in patients with IBD, including 4 patients with UC.

- The following topics were reviewed:
  - serious infections
  - malignancy (including HSTCL; Sections 5.4.2 and 5.4.3)
  - infusion-related reactions
  - hypersensitivity
  - demyelinating events
  - blood and lymphatic system disorders
  - general disorders
  - immune system disorders
  - respiratory disorders
  - skin disorders

- In addition, the subset of 87 reports in patients with UC in the US was examined.
  - Age ranged from 1 to 17 years with a mean of 13.3 years.
  - The majority of the patients were between the ages 6 to 17 years, and there were similar numbers of females and males.
  - None of the 87 patients had a fatal outcome.
  - The most frequently reported types of AEs among the subset with ages 6 to 17 years were: infusion-related or hypersensitivity reactions and lack of efficacy or exacerbation of UC with REMICADE use.

Overall, the report concluded that the pattern of AEs reported in IBD pediatric patients is consistent with the known safety profile for REMICADE in adult and pediatric patients, and/or reflects the background incidence in the target IBD population. Events observed in children that were described in REMICADE labeling included serious infections, infusion-related and hypersensitivity reactions, and malignancies (including HSTCL). No new safety issues were identified through the evaluation. The benefit-risk of REMICADE for pediatric patients with moderate to severe UC inadequately responding to conventional therapies was positive in appropriately selected patients. Overall, the benefit-risk profile for REMICADE remains favorable when used as directed.

5.4.2 HSTCL

Hepatosplenic T-cell lymphoma is a very rare form of NHL that characteristically occurs in young adult males. These cases have had a very aggressive disease course and have been fatal. Cases have been reported in IBD patients that are associated with the use of thiopurines (including AZA and 6-MP without TNFα blocker exposure), a combination of thiopurines and TNFα blockers (REMICADE and/or HUMIRA), but not with REMICADE alone.[26,32]

Table 17 presents an overview of the 27 cases of HSTCL reported in REMICADE-treated patients cumulatively through 23 Feb 2011. All HSTCL cases reported in Table 17 involved a drug history and/or concomitant use of AZA, 6-MP, or both.

Table 17: Case overview of HSTCL reported cumulatively with REMICADE through 23 Feb 2011

Characteristic		Number of Cases (n=27)
Sex	Male Female	24 3
Age (years) **Mean: 27.9** **Median: 24**	9 to 17 18 to 30 31 to 60	3 15 9
Indication for REMICADE use	Crohn's disease Ulcerative colitis	23 4
Number of infusions	1 to 5 6 to 15 > 15 Unknown	13 2 5 7
Latency from first infusion until diagnosis (years)	< 1 1 to 4 > 4 Unknown	2 11 [a] 10 [a] 5
Latency from last infusion until diagnosis (years)	< 1 1 to 4 > 4 Unknown	10 7 3 7

[a] 1 case reported conflicting information regarding latency category

Of the 27 cases:

- The majority occurred in male patients and there was a tendency for patients to be younger although not necessarily pediatric (median age 24 years). Three cases occurred in the pediatric population.
- All cases of HSTCL occurred in patients with Crohn's disease or UC.
- There was variability in REMICADE exposure regarding the number of infusions received with many patients receiving 5 or less infusions.
- There was variability in the latency from both first and last infusion until diagnosis of HSTCL.

Collectively, these data suggest that the risk factors for HSTCL in IBD patients include IBD itself, male sex, thiopurine exposure, and the combination of thiopurines with TNFα blockers. Mechanistically, 6-MP, and its parent compound, AZA, can cause DNA damage, and both agents have immunosuppressive effects, both properties which may have the potential to increase malignancy risk. While REMICADE and other TNFα blockers are not known to have mutagenic properties, the potential role of TNFα-blocking therapy in the development of malignancies is not known. Caution should be exercised when considering TNFα-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Patients with UC and their physicians need to be well-informed about HSTCL when considering REMICADE therapy, and the option of using REMICADE for the treatment of pediatric UC should be available for appropriately selected patients. This risk is discussed in detail in the REMICADE label.

5.4.3 Pediatric Malignancies

Reports of pediatric malignancy (excluding HSTCL) were reviewed. A search of the sponsor's worldwide safety database for reports of malignancy diagnosed in patients age 22 years or younger and treated with REMICADE at age 18 or younger identified 29 cases. In 69% of the reports, the patients had been treated with REMICADE for IBD, including 1 patient treated for UC. In 86% of the reports, concomitant immunosuppressant use was reported, including 16 patients who were treated with AZA or 6-MP. Of the 29 malignancies reported, 14 were lymphomas (5 NHL, 6 Hodgkin's disease, 3 unspecified), 2 were leukemias (1 lymphocytic leukemia, 1 chronic myeloid leukemia), and 13 were solid tumors (leiomyosarcoma, nephroblastoma, malignant melanoma [2], undifferentiated liver malignancy, basal cell carcinoma, hepatocellular carcinoma, colorectal carcinoma, thyroid cancer [2], malignant brain neoplasm, carcinoid tumor of appendix, malignant neoplasm not specified). At the time of diagnosis, 8 of the children were 2-11 years old, 13 were 12-18 years old, and 8 were 19-22 years old. A fatal outcome was reported for 4 patients.

No specific clustering of malignancy cases was noted, either by age or tumor type. Some of the cases described were known pediatric malignancies, such as sacrococcygeal teratoma, neuroblastoma, and nephroblastoma. A few of the malignancies, however, such as leiomyosarcoma, melanoma, basal cell carcinoma, and colorectal carcinoma, were unusual cancers for a pediatric population. Leukemia and lymphoma are known to occur in children, and immunosuppression is a known risk factor for NHL. It is possible that concomitant exposure to AZA, 6-MP, or MTX and/or the presence of underlying autoimmune diseases were significant contributory factors. While a causal relationship between REMICADE and the development of these pediatric malignancies was not established, in light of the severe nature of these events, information regarding the

possible risk of development of malignancies in the pediatric population was included in the Warnings and Precautions section of the USPI for REMICADE as a class effect for TNFα blockers.

5.5 Worldwide Marketing Experience

REMICADE has been marketed since 24 Aug 1998, and is currently approved in approximately 103 countries for various disease conditions including Crohn's disease, Pediatric Crohn's disease, fistulizing Crohn's disease, RA, AS, PsA, psoriasis, and UC. As of 23 Feb 2011, worldwide exposure was estimated at approximately 1,537,395 patients. Of those, an estimated 22,922 (1.5%) were younger than 18 years of age, including an estimated 17,262 treated for Crohn's disease and an estimated 1581 treated for UC. An extensive safety profile for REMICADE has been developed and documented in periodic safety update reports (PSURs) submitted to health authorities worldwide. The sponsor continues to monitor and report AEs to health authorities throughout the world. There have been no regulatory actions that have led to the withdrawal of this product in any country.

Estimates of patients exposed to REMICADE cumulatively since launch include patients exposed in the setting of commercial use, but not patients exposed to non-commercial drug (Company-sponsored studies and investigator-initiated studies using Company-provided study drug). The patient exposure estimates for commercially used drug are calculated using models. In order to calculate the number of patients exposed, the model used to estimate exposure numbers incorporates known vial sales with current labeled dosages and actual usage patterns identified in physician surveys and other market research. Caveats should be noted when reviewing the methodologies used to estimate exposure numbers. The dose of infliximab varies by indication and sometimes even within indication. Likewise, marketed indications vary by country. Deriving estimates of patient exposure requires making assumptions about both dose and retreatment use by disease and by country. Once the overall estimates are calculated, they can be separated by age group to estimate the pediatric exposure. The US and worldwide exposure estimates by indication are provided in Table 1.

5.6 Postmarketing Safety Surveillance

The sponsor's Global Medical Safety (GMS) department systematically collects all spontaneously reported AEs from multiple sources (eg, patients, physicians, the medical literature, and regulatory authorities). In addition, GMS collects all SAEs from clinical studies, which include but are not limited to interventional studies, registry studies, and other observational studies. Postmarketing safety surveillance includes a comprehensive pharmacovigilance system, which involves proactive signal detection through the

real-time medical assessment of single AE reports and periodic medical evaluation of aggregate safety data. Safety signals are routinely reviewed and evaluated in a cross-functional Safety Management Team as well as on an ad hoc basis, when appropriate.

An extensive safety profile for REMICADE has been established and is documented in PSURs produced every 6 months and submitted to health authorities worldwide. Most recently, PSUR 21 and PSUR 22 were filed to FDA in Oct 2010 and PSUR 23 was filed in May 2011. Since the 2006 approval for pediatric Crohn's disease, each REMICADE PSUR has included a separate section analyzing AEs reported in the pediatric population.

The overall postmarketing safety review of AEs reported for REMICADE for pediatric patients in PSURs 21 through 23 supports the conclusion that the safety profile of REMICADE in the pediatric population is consistent with current labeling. Among all system-organ class observations, ranking first and second in frequency of events reported were the General Disorders and Administration Site Conditions (including infusion-related reactions) and Infections and Infestations.

The sponsor will continue to monitor the entire safety profile including the number of deaths and the number of subjects with a serious infection, delayed hypersensitivity (serum sickness-like) reactions, malignancy, or new autoimmune disease. These risks will be monitored using routine pharmacovigilance activities.

5.7 Risk Minimization

Risk minimization refers to the processes intended to minimize risks of a pharmaceutical or biological product. In the case of REMICADE in the US such processes are described in the Risk Evaluation and Mitigation Strategy (REMS). The specific goals of the REMS are to educate patients about the serious risks associated with REMICADE therapy and to alert and warn health care providers (HCPs) about unrecognized histoplasmosis and other invasive fungal infections associated with TNFα blocker use.

Medication Guide

The patient education is accomplished by the dissemination of the Medication Guide. The Medication Guide is patient labeling, designed to provide patients (and parents) with the information necessary for safe and effective use in lay language. The Medication Guide includes sections entitled:

- What is the most important information I should know about REMICADE?
- What is REMICADE?
- Who should not receive REMICADE?

- What should I tell my doctor before starting treatment with REMICADE?
- How should I receive REMICADE?
- What should I avoid while receiving REMICADE?
- What are the possible side effects of REMICADE?

Key information is highlighted, including the risk of infection including risk factors and symptoms, and the risk of cancer. Other topics include risks of heart failure, liver injury, blood problems, nervous system disorders, allergic reactions, lupus-like syndrome and psoriasis.

In addition, patients are advised when to contact their physician. The Medication Guide also directs the patients to further information: the www.REMICADE.com website and a toll-free telephone number for information about REMICADE. Lastly, it instructs patients how to report side effects to FDA with a toll-free telephone number.

To complement the REMS, the Company provides multiple resources for patients and HCPs to access information about the safety profile of REMICADE.

Additional Approaches to Risk Mitigation via Health Care Provider Education

Responses to Unsolicited Requests for Information

Patients and HCPs are invited to contact the company to learn more about REMICADE and to ask questions. This information can be requested by a toll-free telephone number, by e-mail, or by accessing the sponsor's medical information website. Patients are provided with information from the Medication Guide and advised to contact their HCPs. Health care providers who make unsolicited requests about information that is beyond the scope of the label receive standard or customized responses based on REMICADE data and review of the medical literature.

Clinical Science Liaisons

The sponsor employs field-based scientists (doctoral level or sub-specialty-trained nurses) who regularly visit selected physicians and can respond to unsolicited requests for information.

Medical Education Presentations (National Faculty)

The sponsor organizes educational programs in which trained faculty educate other health care providers about REMICADE, include its safety profile. There are 51 gastroenterologists on the faculty, including 7 pediatric gastroenterologists. The material discussed at these programs focuses on labeled information.

The Medversation Website (www.medversation.com)

Medversation is a website designed to communicate on-label information to HCPs related to REMICADE and the diseases it treats. This includes natural history of the diseases, benefits of therapy, risks of therapy, and a benefit-risk analysis.

Printed Medical Educational Material

These items, often brochures or larger kits of information, are provided to HCPs and to patients in the HCPs offices. They explain on-label information about REMICADE, including important safety information

5.8 Summary of Safety

5.8.1 Phase 3 Clinical Studies

- The safety data from T72 are consistent with safety data from the REACH and ACT studies and are consistent with current REMICADE labeling. No new safety concerns emerged regarding the proposed use of REMICADE in the pediatric UC population.
  - The overall proportions of subjects with AEs and SAEs were similar in T72 and REACH, and slightly lower in the ACT studies.
  - The GI system-organ class had the highest incidence of AEs across the studies and worsening of the disease under study was the most commonly reported SAE and the most common AE resulting in discontinuation of study agent.
  - The proportion of infections and serious infections were similar in T72 and REACH, and were higher than the proportion in the ACT studies.

5.8.2 Long-term Safety Follow-up Study in Pediatric Subjects with UC

- The RESULTS UC data, in conjunction with data from other long-term safety follow-up studies of REMICADE, have revealed no new safety trends or concerns.
  - With over 4 years of follow-up, only 4 events were reported. These events are consistent with what has been observed in clinical studies and are addressed in the current REMICADE labeling.
  - The observed colectomy rate was not inconsistent with rates reported in the literature. Colectomies occurred predominantly in subjects who were refractory to corticosteroids and immunomodulators, and occurred more often in subjects who had received q12w therapy than q8w therapy.

5.8.3 Postmarketing Registries in Pediatric IBD

- The safety of REMICADE in the treatment of pediatric IBD, including pediatric UC, is being assessed in 2 large, ongoing, prospective registries: DEVELOP and the Pediatric IBD Collaborative Research Group Registry. These registries will accumulate extensive information about pediatric IBD, and the benefits and risks of REMICADE treatment.

- The safety and use of REMICADE in these registries appear consistent with REMICADE clinical studies (both pediatric and adult) and REMICADE postmarketing experience. Exposure to REMICADE has been associated with a higher risk of serious infection, consistent with the WARNINGS section of REMICADE prescribing information.

- The most common AEs and SAEs were related to the GI system. There have been no disease- or drug-related deaths and few malignancies with no clear pattern indicating increased risk in association with REMICADE. There have been no cases of colonic dysplasia, TB, MS, or other central demyelinating disorders.

5.8.4 Postmarketing Review of Pediatric AE Reports

- In a cumulative review of serious, postmarketing pediatric AE reports with the use of REMICADE through 31 Dec 2010, the pattern of AEs reported in the IBD pediatric patients was consistent with the known safety profile for REMICADE seen in adult and pediatric patients and/or reflected the background incidence in the target IBD population.

- REMICADE has been marketed since 24 Aug 1998, and is approved in approximately 103 countries. As of 23 Feb 2011, worldwide exposure was estimated at approximately 1,537,395 patients. Of those, an estimated 22,922 (1.5%) were younger than 18 years of age, including an estimated 17,262 treated for Crohn's disease and an estimated 1581 treated for UC.

- The sponsor systematically collects all spontaneously reported AEs from multiple sources. Postmarketing safety surveillance includes a comprehensive pharmacovigilance system, which involves proactive signal detection through the real-time medical assessment of single AE reports and periodic medical evaluation of aggregate safety data. Safety signals are routinely reviewed and evaluated.

- The overall postmarketing safety review of AEs reported for REMICADE for pediatric patients in PSURs 21 through 23 supports the conclusion that the safety profile of REMICADE in the pediatric population is consistent with that seen in the adult population and consistent with current labeling. The sponsor will continue to monitor the entire safety profile of REMICADE and report AEs to health authorities throughout the world.

- Risk minimization includes processes described in the REMS, with the goals of educating patients about the serious risks associated with REMICADE therapy and alerting and warning HCPs about unrecognized histoplasmosis and other invasive fungal infections associated with TNFα blocker use. Additional education is provided by multiple approaches, including direct interactions, written material, and internet-delivered information.

6 Benefits and Risks Conclusions

6.1 Unmet Need

Pediatric UC remains an important orphan disease in children that is associated with substantial physical, developmental, emotional, and psychosocial morbidity. Consequences of the disease and the drugs used to treat the disease can persist into adulthood. While the overall clinical features, clinical course of disease, and response to treatment are comparable in pediatric and adult populations with UC, pediatric disease is often more extensive and therefore more severe.

The largest unmet therapeutic needs for pediatric UC are (i) for therapies that are effective in ameliorating signs and symptoms of the disease in children for whom 5-ASA and/or corticosteroids (the only currently approved therapies) are ineffective and, (ii) once signs and symptoms are controlled, for therapies that maintain clinical response in children inadequately maintained with 5-ASA. While a number of drugs are used clinically in both of these situations, their use is off-label and the benefit-risk ratio remains uncertain. For example, the risks and toxicities of long-term corticosteroid use are well established, and their adverse impact on growth is of great concern in children who have not reached their peak growth. Conventional immunosuppressants such as 6-MP and AZA, also not approved for pediatric UC, are ineffective in a substantial proportion of children with UC and are associated with serious toxicities such as bone marrow suppression, infection, malignancy, including HSTCL, and teratogenicity.

In children who fail medical therapies, the only other option is colectomy. While colectomy removes the underlying source of disease (ie, the colon), it is associated with multiple long-term consequences including incontinence, pouchitis, leak, small bowel obstruction, and reduced female fertility. Additionally, it can have significant impact on the physical and emotional development of children.

Therefore, a high unmet need remains for an approved therapy that can control disease both short-term and long-term in children with moderate to severe UC who have not responded to conventional agents. REMICADE has been demonstrated to fill the need for a chronic therapy in adult patients with UC who have failed conventional therapy. Results of the T72 study show that in pediatric patients with UC who have failed

conventional therapies, the need for a chronic therapy can be filled by REMICADE, before consideration of colectomy.

6.2 Benefits

The T72 trial demonstrated that REMICADE is highly effective in ameliorating the signs and symptoms of moderate to severe pediatric UC in subjects who inadequately responded to conventional therapies. Response was rapid, with substantial reductions in signs and symptoms (as measured by the partial Mayo score) observed by Week 2. At Week 8, almost 75% of subjects achieved the study primary efficacy endpoint of clinical response. Evidence of efficacy was also observed in the proportions of subjects achieving clinical remission and mucosal healing at Week 8, and efficacy was consistently observed across age groups. While the trial was open-label and was not placebo-controlled, it employed a prespecified historical control derived from the placebo groups in the ACT 1 and ACT 2 studies in adult subjects with UC. For the pooled placebo groups of ACT 1 and ACT 2, the placebo-response rate was 33.2%, with the upper limit of the 95% CI at Week 8 of 39.1%. Using this upper limit as the historical control, it is unlikely that the magnitude of response seen in T72 is due to a placebo effect. Moreover, the results of T72 are consistent with the efficacy in the pooled 5 mg/kg REMICADE group in ACT 1 and ACT 2 for response, remission, and mucosal healing at Week 8. Thus, the T72 trial establishes REMICADE as a highly effective therapy for inducing response, remission, and mucosal healing in pediatric UC using an induction dosing regimen of 5 mg/kg at Weeks 0, 2, and 6.

In the pediatric UC subjects who responded to REMICADE, T72 also demonstrated that more subjects randomized to q8w versus q12w infusions of 5 mg/kg of REMICADE maintained remission through 1 year. Additionally, while receiving q8w maintenance REMICADE, a substantial proportion of subjects who required corticosteroids at study entry were able to reduce or even eliminate corticosteroid use. Results are again generally consistent with observations in adults with UC from the ACT 1 and ACT 2 studies. While limited data are available for mucosal healing at Week 54, the strong supportive data from ACT 1 and ACT 2 and overall consistency of data between T72 and the ACT studies across multiple endpoints support maintenance of response, remission, and mucosal healing in children. Combined, these results show that maintenance dosing with REMICADE at 5 mg/kg q8w offers a promising treatment for maintaining long-term control of pediatric UC.

6.3 Risks

REMICADE was generally well tolerated in T72. The types and severity of AEs reported were consistent with those expected in the disease population. No new safety

risks of REMICADE were identified, although the small size of the study limits conclusions that can be drawn about REMICADE safety in pediatric UC. Given the relatively small size of the pediatric UC patient population, as indicated by the Orphan Designation for this clinical development program, it is not feasible to fully characterize the safety profile of REMICADE in this population, and the overall risk profile of REMICADE must be inferred from experience in other populations.

REMICADE has been approved since 1998 and is currently licensed in 103 countries worldwide for 6 different diseases including Crohn's disease and UC. With cumulative commercial use estimated at more than 1.5 million patients globally across all indications, REMICADE's safety profile has been well-characterized. Most relevant for the pediatric UC population, REMICADE was approved in 2006 for the treatment of pediatric Crohn's disease and in cumulative experience, its safety profile has been characterized in almost 23,000 patients with pediatric IBD (most with Crohn's disease, but an estimated 1581 were treated for pediatric UC). Potential risks of REMICADE have been discussed in detail in previous sections of this document. While REMICADE has been associated with serious safety risks, most are infrequent and can be successfully treated if patients are monitored appropriately and side effects are detected early. Educational and support services are in place to facilitate this.

Of the potential risks of REMICADE, the greatest concern in the pediatric population is malignancies. While not observed in the REMICADE clinical studies in pediatric UC or Crohn's disease, malignancies, some fatal, have been reported among children, adolescents, and young adults who received postmarketing treatment with TNFα blockers, including REMICADE. Approximately half of these cases were lymphomas, including Hodgkin's and NHL. Higher rates of lymphomas have been reported in patients with immune-mediated inflammatory disorders, including IBD.[11] Aside from lymphomas, the other cases represented a variety of malignancies, including some rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents, though most of the patients were receiving concomitant immunosuppressants. Given the confounded nature of most reports of malignancy, it is not possible to definitively conclude whether or how REMICADE may have contributed, though this potential risk should be considered by prescribers and patients considering use of REMICADE.

Of particular concern in patients with IBD considering treatment with immunosuppressive agents is HSTCL. Hepatosplenic T-cell lymphoma is a very rare form of NHL that characteristically occurs in young adult males. These cases have had a very aggressive disease course and have been fatal. Trisomy 8 has been found in HSTCL and isochromosome 7q is strongly associated with HSTCL. Cases have been reported in IBD patients that are associated with the use of thiopurines (including AZA and 6-MP

without TNFα blocker exposure), a combination of thiopurines and TNFα blockers (REMICADE and/or HUMIRA), but not with REMICADE alone. The risk of HSTCL in IBD patients receiving thiopurines is estimated to be approximately 1 in 45,000, and the risk in patients receiving both thiopurines and TNFα blockers to be approximately 1 in 22,000. These risks may be higher in young males.[26] Of the 27 cases of HSTCL reported in REMICADE-treated patients cumulatively through 23 Feb 2011, 3 occurred in children. All cases of HSTCL occurred in Crohn's disease or UC patients and involved a drug history and/or concomitant use of AZA, 6-MP, or both. Mechanistically, thiopurine, 6-MP, and its parent compound, AZA, can cause DNA damage, and both agents have immunosuppressive effects, both properties which may have the potential to increase malignancy risk. While REMICADE and other TNFα blockers are not known to have mutagenic properties, the potential role of TNFα-blocking therapy in the development of malignancies is not known. Caution should be exercised when considering TNFα-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy. Collectively, these data suggest that the risk factors for HSTCL in IBD patients include IBD itself, male sex, thiopurine exposure, and the combination of thiopurines with TNFα blockers, though it is not possible to discern their relative contributions. Nonetheless, UC patients and their physicians need to be well-informed about HSTCL when considering REMICADE therapy, and the option of using REMICADE for the treatment of pediatric UC should be available for appropriately selected patients. This risk is discussed in detail in the REMICADE label.

6.4 Benefit-Risk Conclusions

In summary, there remains a high unmet need for medical treatments for pediatric patients with UC who inadequately respond to conventional therapies and for agents that can be administered chronically to maintain disease control. Data presented in this document indicate that REMICADE is highly efficacious in ameliorating the signs and symptoms of pediatric UC in subjects who have inadequately responded to conventional therapies, and response is generally maintained long-term with chronic q8w REMICADE administration. While REMICADE has been associated with serious safety risks, most are infrequent and can be successfully treated if patients are monitored appropriately and side effects are detected early. Fatal or irreversible safety risks associated with REMICADE are rare. Thus, overall, the benefits of REMICADE outweigh the risks and support the proposed indication for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in pediatric patients with moderately to severely active UC who have had an inadequate response to conventional therapy. The data also support the proposed dosing regimen of 5 mg/kg at Weeks 0, 2, and 6, then q8w.

Close monitoring of REMICADE safety in pediatric patients with UC is warranted in the postapproval setting, and a robust plan for monitoring safety has been proposed, including both routine pharmacovigilance measures as well as 2 large ongoing prospective registries.

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