

## **Module 2.7.3 – Summary of Clinical Efficacy**

REMICADE<sup>®</sup> (infliximab)

Pediatric Ulcerative Colitis

Date: 11 Nov 2010

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Centocor Research & Development, Inc.\*

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## Abbreviations and Definition of Terms

|        |                                                                                                               |
|--------|---------------------------------------------------------------------------------------------------------------|
| ACT    | <u>A</u> ctive <u>U</u> lcerative <u>C</u> olitis <u>T</u> rial                                               |
| 5-ASA  | 5-aminosalicylate                                                                                             |
| AZA    | azathioprine                                                                                                  |
| CI     | Confidence interval                                                                                           |
| CMH    | Cochran-Mantel-Haenszel                                                                                       |
| CRP    | C-reactive Protein                                                                                            |
| CSR    | Clinical Study Report                                                                                         |
| IMPACT | <u>I</u> nfliximab <u>M</u> ultinational <u>P</u> soriatic <u>A</u> rthritis <u>C</u> ontrolled <u>T</u> rial |
| 6-MP   | 6-mercaptopurine                                                                                              |
| MTX    | methotrexate                                                                                                  |
| NA     | not applicable                                                                                                |
| P.Eq   | prednisone equivalent                                                                                         |
| PK     | pharmacokinetic(s)                                                                                            |
| PUCAI  | pediatric ulcerative colitis activity index                                                                   |
| q#w    | every # weeks                                                                                                 |
| SAP    | Statistical Analysis Plan                                                                                     |
| SAS    | Statistical Analysis Software™                                                                                |
| SCE    | Summary of Clinical Efficacy                                                                                  |
| SCP    | Summary of Clinical Pharmacology                                                                              |
| SD     | standard deviation                                                                                            |
| UC     | ulcerative colitis                                                                                            |
| US     | United States                                                                                                 |

# 1 Background and Overview of Clinical Efficacy

This Summary of Clinical Efficacy presents a summary of the efficacy data for REMICADE® (infliximab) in support of the application for the pediatric ulcerative colitis (UC) indication.

Infliximab was approved in the US in 2005 and in Europe and Canada in 2006 for the treatment of moderate to severely active UC in adult patients, based on data from C0168T37 (ACT 1) and C0168T46 (ACT 2). The results of these studies provided clinically important and statistically significant evidence that infliximab, at 5 mg/kg at Weeks 0, 2, 6 followed by 5 mg/kg every 8 weeks (q8w), is an effective treatment for the induction and maintenance of clinical response, clinical remission, mucosal healing, as well as reducing corticosteroid use in subjects with moderately to severely active UC who had an inadequate response to conventional therapies (Rutgeerts et al, 2005). Additionally, adult subjects treated with infliximab were less likely than those receiving placebo to undergo colectomy through 54 weeks (Sandborn et al, 2009). In open-label extensions of both ACT studies, subjects on infliximab maintained their clinical benefit for up to 3 years, including avoidance of corticosteroid treatment, with a safety profile consistent with current labeling.

The proposed efficacy indication for infliximab for the treatment of pediatric UC is based on a Phase 3 clinical study in pediatric subjects with UC (C0168T72) and supported by 2 Phase 3 studies in adults with UC, ACT 1 and ACT 2.

An overview of the Phase 3 pediatric clinical study, C0168T72, and the two Phase 3 clinical studies in adults, ACT 1 and ACT 2, is presented in the remainder of Section 1, which also includes an overview of the efficacy analyses. The efficacy results from the individual studies are summarized in Section 2, while the comparison of efficacy data across studies is presented in Section 3. Analysis of clinical information relevant to dosing is presented in Section 4 and persistence of efficacy is described in Section 5.

## 1.1 Overview of C0168T72

Study C0168T72 was a Phase 3, randomized, open-label, parallel-group, multicenter study to assess the safety and efficacy of induction and maintenance infliximab 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  $\geq 2$ ), despite receiving current adequate treatment with 6-mercaptopurine (6-MP), azathioprine (AZA), corticosteroids, and/or 5-aminosalicylate (5-ASA) compounds, or have had previous unsuccessful treatment with, or intolerance to, 6-MP, AZA, corticosteroids, and/or 5-ASA compounds. All subjects were required to have UC confirmed by biopsy. A total of 60 pediatric subjects were to be enrolled at approximately 30 sites in North America and Europe and were to be followed for safety and efficacy through Week 54.



Subjects were allowed to be treated with stable doses of corticosteroids, 6-MP/AZA, methotrexate (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 3 exceptions: 1) corticosteroids were allowed to be tapered following the Week 0 visit, 2) discontinuation of 6-MP/AZA, or MTX was allowed anytime during the study starting from screening, and 3) subjects who stepped up (ie, increased their infliximab 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.

All subjects were to receive infliximab 5 mg/kg at Weeks 0, 2, and 6. Subjects in clinical response at Week 8, as measured by the Mayo score, were to be randomized in a 1:1 ratio to receive 1 of 2 maintenance treatment regimens: 5 mg/kg infliximab administered q8w through Week 46 (Group I) or q12w through Week 42 (Group II).

Subjects who were nonresponders to induction dosing at Week 8 were to return for a safety evaluation but received no further infusions. During the maintenance treatment phase, subjects who lost response were eligible to increase (step up) their infliximab dose and/or dosing frequency once as described in [Table 1](#); the visit at which the subject stepped up was defined as Week 0S.

The primary endpoint was clinical response at Week 8; see [Section 1.4.2.4.1](#) for the definition of clinical response.

The infliximab dose chosen for the pediatric subjects in C0168T72 was 5 mg/kg as an induction regimen at Weeks 0, 2, and 6, followed by a maintenance treatment regimen of 5 mg/kg either every 8 weeks (q8w) or every 12 weeks (q12w). These maintenance treatment regimens were chosen to determine if the maintenance dose administration interval for pediatric subjects with UC can be longer than the approved interval for adults with UC. The 5 mg/kg dose was chosen based on the safety, efficacy, and PK results from ACT 1 and ACT 2 in adult subjects with UC, which demonstrated similar infliximab efficacy and safety at both 5 mg/kg and 10 mg/kg, and on the PK results from the pediatric Crohn's disease trials.

## **1.2 Overview of C0168T37 (ACT 1) and C0168T46 (ACT 2)**

Both ACT 1 and ACT 2 were randomized, double-blind, placebo-controlled, parallel-group studies, with similar study designs and identical primary and major secondary endpoints. To enter these studies, adult subjects must have had moderately to severely active UC (defined as a Mayo score of 6 to 12, inclusive, at baseline, including an endoscopic subscore  $\geq 2$ ), despite receiving current adequate treatment, or have had previous unsuccessful treatment with, or intolerance of 6-MP, AZA, corticosteroids, and/or, for ACT 2 only, 5-ASA compounds. All subjects were required to have UC confirmed by biopsy.

Subjects in ACT 1 and ACT 2 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 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.

A notable difference between ACT 1 and ACT 2 was that subjects who failed to tolerate or respond to 5-ASA compounds did not qualify for entry into ACT 1, but did qualify for entry into ACT 2. Another difference between the studies was the duration of the studies. ACT 1 safety and efficacy double-blind evaluations were to be completed through Week 54; ACT 2 safety and efficacy double-blind evaluations were completed through Week 30.

In both studies, subjects were to be randomly assigned (1:1:1) to 1 of 3 treatment groups (placebo, 5 mg/kg infliximab, or 10 mg/kg infliximab). Subjects in ACT 1 were to receive study agent at Weeks 0, 2, 6 followed by q8w treatment through Week 46; subjects in ACT 2 were to receive study agent at Weeks 0, 2, 6 followed by q8w treatment through Week 22.

The primary endpoint in both studies was clinical response at Week 8 (see Section 1.4.2.4.1).

### **1.3 Summary of Study Designs**

A tabular listing of studies described in this submission is included in [Module 5.2](#). The study designs and populations in C0168T72, ACT 1, and ACT 2 are summarized in [Table 1](#).

| <b>Table 1 Study designs and populations; C0168T72, ACT 1, and ACT 2</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                 |
|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Design Element                                                           | C0168T72                                                                                                                                                                                                                                                                                                                                                                                                                                | ACT 1                                                                                                                                                                                                                                                                                          | ACT 2                                                                                                                                                                                                                                                                                                           |
| Blinding/control                                                         | Randomized, open label                                                                                                                                                                                                                                                                                                                                                                                                                  | Randomized, double blind, placebo controlled                                                                                                                                                                                                                                                   | Randomized, double blind, placebo controlled                                                                                                                                                                                                                                                                    |
| Population                                                               | Pediatric subjects 6 through 17 years old who had moderately to severely active UC (defined as a Mayo score of 6 to 12, inclusive, at baseline, including an endoscopic subscore $\geq 2$ ), despite current adequate treatment or who had failed to respond to or tolerate treatment with 6-MP, AZA, corticosteroids, and/or 5-ASA compounds.                                                                                          | In adults, who had moderately to severely active UC (defined as a Mayo score of 6 to 12, inclusive, at baseline, including an endoscopic subscore $\geq 2$ ), despite current adequate treatment or who had failed to respond to or tolerate treatment with 6 MP, AZA, and/or corticosteroids. | In adults, who had moderately to severely active UC (defined as a Mayo score of 6 to 12, inclusive, at baseline, including an endoscopic subscore $\geq 2$ ), despite current adequate treatment or who had failed to respond to or tolerate treatment with 6-MP, AZA, corticosteroids, and/or 5-ASA compounds. |
| Dosing regimen                                                           | Infliximab 5 mg/kg at Weeks 0, 2, and 6.<br>Responders at Week 8 randomized to 5 mg/kg q8w through Week 46 (Group I) or q12w through Week 42 (Group II).<br>Step up to 10 mg/kg q8w for subjects in Group I who lost response and for subjects in Group II who lost response $\leq 8$ weeks from previous infusion.<br>Step up to 5 mg/kg q8w for subjects in Group II who lost response $> 8$ but $< 12$ weeks from previous infusion. | Placebo or infliximab 5 mg/kg or 10 mg/kg at Weeks 0, 2, 6, then q8w through Week 46                                                                                                                                                                                                           | Placebo or infliximab 5 mg/kg or 10 mg/kg at Weeks 0, 2, 6, then q8w through Week 22                                                                                                                                                                                                                            |



| <b>Table 1 Study designs and populations; C0168T72, ACT 1, and ACT 2</b> |                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                               |                                                                                                                                                                                                               |
|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Design Element                                                           | C0168T72                                                                                                                                                                                                                                                                                                   | ACT 1                                                                                                                                                                                                         | ACT 2                                                                                                                                                                                                         |
| Corticosteroid Taper                                                     | Week 0                                                                                                                                                                                                                                                                                                     | Week 8                                                                                                                                                                                                        | Week 8                                                                                                                                                                                                        |
| Length of followup                                                       | 54 weeks                                                                                                                                                                                                                                                                                                   | 54 weeks                                                                                                                                                                                                      | 30 weeks                                                                                                                                                                                                      |
| Primary endpoint                                                         | Clinical response at Week 8                                                                                                                                                                                                                                                                                | Clinical response at Week 8                                                                                                                                                                                   | Clinical response at Week 8                                                                                                                                                                                   |
| Major secondary endpoints                                                | <ol style="list-style-type: none"> <li>1. Remission at Week 54 (based on the pediatric ulcerative colitis activity index [PUCAI])</li> <li>2. Clinical remission at Week 8 (based on the Mayo score)</li> <li>3. Remission at Week 8 (based on the PUCAI)</li> <li>4. Mucosal healing at Week 8</li> </ol> | <ol style="list-style-type: none"> <li>1. Clinical remission at Week 8.</li> <li>2. Mucosal healing at Week 8.</li> <li>3. Clinical response at Week 30.</li> <li>4. Clinical remission at Week 30</li> </ol> | <ol style="list-style-type: none"> <li>1. Clinical remission at Week 8.</li> <li>2. Mucosal healing at Week 8.</li> <li>3. Clinical response at Week 30.</li> <li>4. Clinical remission at Week 30</li> </ol> |
| Other important endpoints                                                | <p>Corticosteroid reduction through Week 54</p> <p>Change in height status at Week 54</p>                                                                                                                                                                                                                  | <p>Clinical remission at Week 54</p> <p>Mucosal healing at Week 54.</p> <p>Clinical response at Week 54.</p> <p>Corticosteroid reduction through Week 54</p>                                                  | <p>Corticosteroid reduction through Week 30</p>                                                                                                                                                               |
| Endoscopies                                                              | Sigmoidoscopy or colonoscopy at screening and at Weeks 8 and 54, (Week 54 sigmoidoscopy encouraged but not required)                                                                                                                                                                                       | Sigmoidoscopy or colonoscopy at screening, and at Weeks 8, 30, and 54                                                                                                                                         | Sigmoidoscopy or colonoscopy at screening and at Weeks 8 and 30.                                                                                                                                              |

## 1.4 Overview of Efficacy Analyses

### 1.4.1 Data Presentation

In Section 2 of this document, a summary of the efficacy results from the C0168T72, ACT 1, and ACT 2 studies are presented separately. This summary includes the results

from the analyses of the primary and major secondary endpoints from each study, as well as other key efficacy endpoints, such as reduction in corticosteroid use over time. In addition, for each of the studies, a summary of the relationship between efficacy and PK, as well as between efficacy and antibody to infliximab status is provided.

For C0168T72, analysis of the demographic and baseline disease characteristics, as well as the efficacy endpoints based on the induction phase of the study (through Week 8 when all subjects received the same treatment) includes 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) are included in the analyses. The data are presented for each treatment group (infliximab 5 mg/kg q8w and infliximab 5 mg/kg q12w). Analyses of the subjects who stepped up are also provided and are presented by step-up treatment group.

Subgroup analyses by age groups of 6 to 11 and 12 to 17 years old were also presented for the following efficacy endpoints in C0168T72: Mayo score at baseline and at Week 8, clinical response at Week 8, clinical remission at Week 8, remission at Weeks 8 and 54, and mucosal healing at Week 8.

To demonstrate that the pediatric ulcerative colitis activity index (PUCAI) and Mayo score assessments provide consistent evaluations of UC disease activity, Pearson correlation coefficients and scatter plots of the PUCAI score versus the Mayo score at baseline and at Week 8 were also performed and presented.

For ACT 1 and ACT 2, the demographic and baseline disease characteristics, and efficacy analyses include all subjects randomized at Week 0. The data are presented for each treatment group (placebo, 5 mg/kg infliximab, and 10 mg/kg infliximab) and for the combined infliximab treatment group. ACT 1 data are provided through Week 54 and ACT 2 through Week 30.

Section 3 presents descriptive comparisons between the pediatric study (C0168T72) and the adult ACT studies. Data from C0168T72 and ACT 1 and ACT 2 were not pooled due to the differences in populations being studied (ie, pediatric versus adult subjects) and the differences in the study designs. C0168T72 was an open-label study in which responders to induction dosing were randomized to receive treatment with 2 different dosing intervals, whereas ACT 1 and ACT 2 were double-blind studies in which subjects remained on the dose to which they were randomized (at Week 0) for the duration of the study (see Section 1.1 and Section 1.2). For selected endpoints at Week 8, as presented in the submission for the adult UC indication ([UC Week 30, SCE](#)), efficacy data from the ACT studies were pooled due to the similarities in subject population and study design.

The descriptive comparisons of C0168T72 with ACT 1 and ACT 2 were made by examining the proportion of subjects in clinical response at Week 8 (the primary endpoint in all 3 studies), the proportions of subjects in clinical remission at Week 8, and the proportion of subjects with mucosal healing at Week 8. In addition, descriptive comparisons between the pediatric and adult UC subjects are presented for the proportion



of subjects in clinical remission at Week 54, and for subjects who were receiving corticosteroids at baseline, the proportion of subjects in clinical remission and not receiving corticosteroids at Week 54, in addition to reductions in corticosteroid use over time. For the Week 54-endpoint comparisons, the data from C0168T72 are compared with only the data from ACT 1, since ACT 1 has data through Week 54, whereas ACT 2 has data only through Week 30. For all these analyses, the data from the infliximab 5 mg/kg treatment group in the ACT studies is used for comparison with C0168T72 because that is the dose used in C0168T72. For comparisons of the data during the maintenance phase, data from the 5 mg/kg q8w treatment group in the C0168T72 study are used. Results from the placebo treatment group in the ACT studies are included for reference.

For each of the primary and major secondary endpoints in C0168T72, the proportion of subjects meeting the respective endpoint, along with the associated 95% CI, is summarized and displayed in 2 ways. First, the data from C0168T72 is presented with the pooled ACT (ACT 1 and ACT 2) data for placebo and the 5 mg/kg Infliximab treatment group. In the second display, the data from the individual ACT studies (ACT 1 and ACT 2) for the placebo and 5 mg/kg infliximab treatment groups are displayed. The Week 8 endpoints are also depicted by figures that display the proportion of subjects meeting each endpoint in C0168T72 and also in the infliximab 5 mg/kg treatment group in each of the ACT studies, as well as for the pooled ACT studies.

To support the comparison of remission at Week 54 based on the PUCAI score in C0168T72 with clinical remission at Week 54 in ACT 1 based on the Mayo score, the following data presentations are provided. Note that for all of these analyses, only the data from ACT 1 are used since these are the data used in the comparison at Week 54. In the first presentation, the Mayo scores at baseline and Week 8 are compared using side-by-side comparisons between the infliximab 5 mg/kg groups in C0168T72 and ACT 1. Further side-by-side summaries of C0168T72 and ACT 1 through Week 54 are made for the partial Mayo scores using subjects from the infliximab 5 mg/kg q8w treatment group in each study.

Finally, subgroup analyses examining the effect of the use of baseline concomitant immunomodulators (ie, 6-MP/AZA, or MTX) on selected efficacy endpoints in C0168T72 and the ACT studies are provided in [Section 3.2.7](#).

## **1.4.2 Efficacy Assessments and Definitions**

### **1.4.2.1 Mayo Score**

The efficacy tool used to assess clinical response, clinical remission, and mucosal healing was the Mayo score. 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.

#### 1.4.2.2 PUCAI Score

Because of the low acceptability of repeated endoscopies in pediatric patients, the sigmoidoscopies at Week 54, at step-up, and at early discontinuation, which were originally required, were made optional. Because the endoscopy was optional at Week 54, the Mayo score, for which the endoscopy is 1 of its 4 subscores, could no longer be used as the primary assessment tool for efficacy at Week 54. Instead, with health authority agreement, the validated PUCAI score (Turner et al, 2007), a tool for assessing disease activity in pediatric subjects with UC that does not include an endoscopic assessment, was used to assess efficacy.

The PUCAI has been shown by (Turner et al, 2007) to be a valid, highly reliable, and responsive index with which to assess disease activity in subjects with pediatric UC. Turner et al (2007) applied a rigorous approach to the development and validation of the PUCAI score using a panel of 36 pediatric inflammatory bowel disease experts, 2 adequately powered prospective cohorts of pediatric patients with UC (a multicenter cohort of 157 patients for development, and a separate cohort of 48 patients for validation), and robust statistical and judgmental methods. The PUCAI is easy to score, has clear and accurate gradations and definitions, and the individual subscores of the PUCAI score, as well as the total PUCAI score, have been shown to have excellent interobserver reliability (a measure reflecting reproducibility of the score over different raters). The PUCAI was also shown to be a very responsive index (a measure reflecting the ability of the score to detect accurately the change in disease activity over time and to discriminate between those who improve and those who do not), even during short term follow-up periods and, therefore, suitable for longitudinal assessments in clinical trials. Turner et al (2007) reported that the correlation between the PUCAI score and the full Mayo score was high ( $r = 0.95$ ,  $p < 0.001$ ), as was the correlation between the PUCAI score and colonoscopic appearance ( $r = 0.77$ ,  $p < 0.001$ ). They also determined that a version of the PUCAI score containing a sigmoidoscopy item (which was similar to the Mayo score endoscopy item), added little to the clinical items in terms of validity and in explaining the total variance. Turner et al (2007) concluded that the rigorously developed PUCAI can be confidently used to differentiate accurately the disease activity states and to assess change over time, without the need for colonoscopic assessment.



The PUCAI score is relevant for use in C0168T72 for many reasons, most notably, that the PUCAI was developed and validated for use in the same population of subjects that are studied in C0168T72, namely pediatric subjects with UC. The pediatric patients used in the development and validation of the PUCAI score had very similar demographic and baseline disease characteristics when compared with those in C0168T72. The PUCAI score is also relevant for use in C0168T72 because of its ability to accurately differentiate the disease activity states without the need for an endoscopic assessment. [Turner et al \(2007\)](#) determined that a PUCAI score of < 10 can be used to distinguish between active and inactive disease status (ie, those in remission vs those not in remission). For these reasons, it is expected that the assessment of the disease activity based on the PUCAI score at Week 54 accurately discriminates between those in remission at Week 54 and those not in remission at Week 54 in C0168T72. Furthermore, based on the results in [Turner et al \(2007\)](#) demonstrating that the PUCAI score and the full Mayo score are highly correlated, it is expected that the assessment of remission at Week 54 based on the PUCAI score would have been consistent with the assessment of remission based on the Mayo score, had the endoscopy score actually been available.

The PUCAI score was added as a measure of efficacy in Amendment 1 of the protocol and was to be collected at every visit at which a partial Mayo score was obtained. For subjects who enrolled before the approval of Amendment 1, the PUCAI scores at timepoints prior to the approval of 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 ([C0168T72 CSR, Appendix 1 \[Protocol, Appendix 7\]](#)):

- Abdominal pain (0 to 10 points)
- Rectal bleeding (0 to 30 points)
- Stool consistency (0 to 10 points)
- Number of stools in a 24-hour period (0 to 15 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 \(2007\)](#) specified that a PUCAI score of 35 to 64 indicates moderate disease activity, a score of  $\geq 65$  indicates severe disease activity, a decrease of 20 points is a minimally clinically important change, and a score < 10 indicates remission.

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 to be diagnosed in remission. This same rectal bleeding requirement does not apply when defining remission based on the full Mayo score, since

the definition of clinical remission based on the full Mayo score allows for the possibility that the subject still has streaks of blood in the stool less than half the time.

### **1.4.2.3 IMPACT-III**

Quality of life was assessed for subjects aged 10 through 17 years using the IMPACT-III questionnaire (see C0168T72 CSR, Protocol [Appendix 1] Attachment 5). IMPACT-III is an inflammatory bowel disease-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.

### **1.4.2.4 Endpoint Definitions**

#### **1.4.2.4.1 Clinical Response**

In C0168T72, ACT 1, and ACT 2, clinical response was based on the Mayo score and was defined as a decrease from baseline in the Mayo score by  $\geq 30\%$  and  $\geq 3$  points, accompanied by a decrease in the rectal bleeding subscore of  $\geq 1$  or a rectal bleeding subscore of 0 or 1.

#### **1.4.2.4.2 Clinical Remission**

In C0168T72, ACT 1, and ACT 2, clinical remission was based on the Mayo score and was defined as a Mayo score  $\leq 2$  points, with no individual subscore  $> 1$ . According to this definition, subjects in clinical remission must have had a rectal bleeding subscore of 0 or 1.

#### **1.4.2.4.3 Remission**

In C0168T72, remission was based on the PUCAI score and was defined as a PUCAI score  $< 10$ .

#### **1.4.2.4.4 Mucosal Healing**

In C0168T72, ACT 1, and ACT 2, mucosal healing was determined from the endoscopy subscore of the Mayo score and was defined as an endoscopy subscore of 0 or 1. Normal or inactive disease was defined as an endoscopy subscore of 0.

### **1.4.3 Statistical Methods**

In C0168T72, descriptive statistics, such as the mean, median, SD, range, and the interquartile range are used to summarize continuous variables. Categorical data are summarized using counts and percentages. The comparison of remission at Week 54 between the 2 maintenance treatment groups was analyzed using the chi-square test. As noted in the protocol, this comparison is not adequately powered to show a difference



between maintenance treatment groups; however, testing was performed for this endpoint based on a request from a health authority. No interim analysis was planned or performed, and statistical testing was performed at the  $\alpha = 0.05$  (2-sided) level using SAS version 9.1. See [C0168T72 CSR, Appendix 1 \(SAP\)](#) for additional information on the analysis plan for this study.

In ACT 1 and ACT 2, statistical comparisons were made between the combined infliximab and placebo treatment groups, as well as between the individual infliximab and placebo treatment groups. For categorical variables, counts and percentages were used to describe the data. To compare the proportion of subjects achieving a specified endpoint (eg, clinical remission) between treatment groups, chi-square tests or Cochran-Mantel-Haenszel (CMH) chi-square tests were used, as appropriate. In cases of rare events, Fisher's exact test was used for treatment comparisons. Continuous variables were summarized with the sample size, mean, SD, median, interquartile range, and range (minimum and maximum). Treatment group comparisons were performed using an analysis of variance on the van der Waerden normal scores ([Conover, 1980](#)). Nominal p-values are presented.

All statistical testing was 2-sided and used a 0.05 level of significance using SAS version 8.02.

For C0168T72 and ACT 1 and ACT 2, treatment failure and missing data rules were applied (Section [1.4.3.1](#) and Section [1.4.3.2](#), respectively).

### **1.4.3.1 Treatment Failure Rules**

In C0168T72, ACT 1, and ACT 2, treatment failure rules were applied for all efficacy endpoints unless otherwise specified (see [C0168T72 CSR, Section 3.11.2.3](#), [ACT 1 30 Week CSR, Section 6.3.1.2](#) and [ACT 2 30 Week CSR, Section 6.3.1.2](#)). Subjects who had any of the following events were considered to be treatment failures in the analysis from the time point that the treatment failure occurred until the end of the study:

1. Colectomy (partial or full) or ostomy.
2. Discontinuation of study agent due to unsatisfactory therapeutic effect (in C0168T72) or due to lack of efficacy (in ACT 1 and ACT 2).
3. Protocol-prohibited medication changes (see [C0168T72 CSR, Appendix 11](#); also refer to [ACT 1 30 Week CSR, Appendix 11 \[SAP\]](#) and [ACT 2 30 Week CSR, Appendix 11 \[SAP\]](#)).
4. Step-up (only applies to subjects in C0168T72).

Treatment failure rules were applied in the analyses as follows. For dichotomous endpoints, subjects with a treatment failure prior to the designated analysis timepoint were considered not to have met the endpoint. For continuous endpoints, subjects with a



treatment failure had their baseline values (at Week 0) assigned from the time of the treatment failure onward. Treatment failure rules overrode other data-handling rules.

Treatment failure rules were not applied for the following endpoints in C0168T72:

- Global assessment of change from baseline at Week 8
- Height status
- Improvement after step-up
- Mucosal healing at Week 54

### **1.4.3.2 Missing Data Rules**

In addition to the treatment failure rules, missing data rules were also applied. In general, for subjects with missing observations, unless otherwise specified, the last observation was carried forward for continuous endpoints. Subjects were considered as not achieving the respective endpoints for dichotomous endpoints.

The Mayo score was calculated if at least 1 of the subscores was available from the visit at which the Mayo score was to be measured. For missing subscores, the last available value for that particular subscore was carried forward to compute a full Mayo score. If all 4 subscores were missing, the Mayo score was not calculated and was considered missing for that visit.

The PUCAI score was calculated only when 3 or more of the 6 subscores were available from the visit at which the PUCAI score was to be measured. For missing subscores, the last available value for that subscore was carried forward to compute the PUCAI score. If more than 3 subscores were missing, the PUCAI score could not be calculated and was considered missing for that visit.

## **2 Summary of Results of Individual Studies**

### **2.1 C0168T72**

#### **2.1.1 Demographics and Baseline Disease Characteristics**

A total of 60 subjects were enrolled at 23 sites in the United States, Canada, the Netherlands, and Belgium. At Week 8, 45 subjects were randomized as responders (22 and 23 in the q8w and q12w maintenance treatment groups, respectively) and the remaining 15 discontinued study agent.

Overall, 23 subjects stepped up. More subjects stepped up in the q12w maintenance treatment group than in the q8w maintenance treatment group (60.9% vs 40.9%). A total of 9 subjects in the q8w maintenance treatment group stepped up to 10 mg/kg q8w. Of

the 14 subjects in the q12w group who stepped up, 8 who lost response  $\leq 8$  weeks from the previous infusion stepped up to 10 mg/kg q8w, and 6 who lost response  $> 8$  but  $< 12$  weeks from previous infusion stepped up to 5 mg/kg q8w. Most subjects who stepped up did so by Week 22 (18 [78.3%]).

A higher proportion of subjects discontinued study agent in the 5 mg/kg q12w maintenance treatment group (47.8%) than in the 5 mg/kg q8w maintenance treatment group (18.2%). A greater proportion of subjects in the q12w group compared with the q8w group discontinued study agent due to AEs (26.1% in the q12w group [all due to worsening of UC] compared with 13.6% in the q8w group [only [REDACTED] due to worsening of UC]) or to unsatisfactory therapeutic effect (17.4% in the q12w group compared with 4.5% in the q8w group).

Of the 23 subjects who stepped up, 11 (47.8%) discontinued study agent; most of which (9 subjects) were originally randomized to the q12w maintenance treatment group.

Of the 60 subjects enrolled, 28 (46.7%) were male, 32 (53.3%) were female, and 81.7% were Caucasian. The median age was 14.5 years, median weight was 50.80 kg, and median height was 159.65 cm. Of the treated subjects, 15 were 6 to 11 years old and 45 were 12 to 17 years old.

Subjects who were not randomized at Week 8 were younger and weighed less than subjects in the groups that were randomized at Week 8 (median age 12.0 vs 15.0 years and median weight 40.80 kg vs 51.20 kg, respectively).

Baseline demographics were similar between the 2 randomized treatment groups (C0168T72 CSR, Table 3).

Among all treated subjects, the median duration of UC disease was 1.35 years and the median CRP level was 0.3 mg/dL; 76.7% (46) of subjects had extensive disease as indicated by endoscopy. The median Mayo score was 8.0 (C0168T72 CSR, Attachment 1.8). The median PUCAI score was 55.0 (C0168T72 CSR, Attachment 1.9).

Baseline disease characteristics were similar in the groups that were and were not randomized at Week 8. However, a higher proportion of subjects in the group that was not randomized (73.3%) reported obvious blood with stool most of the time for the Mayo rectal bleeding subscore, compared with 46.7% in the group that was randomized (C0168T72 CSR, Attachment 1.8).

Baseline disease characteristics were generally similar between the maintenance treatment groups (C0168T72 CSR, Attachment 1.8 and C0168T72 CSR Attachment 1.9). However, the median duration of disease was longer in the q8w maintenance treatment group (1.8 years) than in the q12w maintenance treatment group (1.1 years). More subjects in the q12w maintenance treatment group than the q8w maintenance treatment group reported 5 or more stools more than normal (13 and 7 subjects, respectively) on the Mayo stool frequency subscore; more subjects in the q8w group than the q12w group



reported obvious blood with stool most of the time (13 and 8 subjects, respectively) for the Mayo rectal bleeding subscore.

All of the 60 treated subjects were receiving concomitant medications for UC at baseline, including oral or parenteral corticosteroids (61.7%) or immunomodulators or 5 ASA compounds (53.3% for each; C0168T72 CSR, Table 5).

The use of concomitant medications at baseline was generally similar between the groups that were and were not randomized at Week 8 with the exception of aminosalicylate use. In the group that was not randomized at Week 8, 66.7% of subjects were receiving aminosalicylates at baseline, versus 48.9% in the randomized group.

The use of concomitant medications for UC at baseline was similar between the maintenance treatment groups (C0168T72 CSR, Table 5).

## 2.1.2 Primary Efficacy Endpoint

The primary endpoint was clinical response at Week 8, which was defined as a decrease from baseline in the Mayo score by  $\geq 30\%$  and  $\geq 3$  points, with a decrease in the rectal bleeding subscore of  $\geq 1$  or a rectal bleeding subscore of 0 or 1. This endpoint was the primary endpoint in the original and amended protocol.

Of the 60 subjects treated, 44 (73.3%) were in clinical response at Week 8, with a 95% CI of 62.1% to 84.5% (C0168T72 CSR, Table 7). Because the lower limit of the 95% CI for the proportion of pediatric subjects in clinical response at Week 8 in this study was 62.1% ( $> 40\%$ ), the protocol-specified criterion for determining that infliximab is effective in the treatment of UC in pediatric subjects was met. The criterion of  $> 40\%$  for C0168T72 was based on the use of pooled data from the placebo groups in the ACT 1 and ACT 2 studies as a “historical control.” Because the upper limit of the 95% CI for the proportion of placebo subjects in clinical response at Week 8 in the pooled ACT studies was 39.1% (Appendix 1.1), the cutoff point for C0168T72 was set at 40%. The primary endpoint was robust to changes in analysis rules regarding missing data and treatment failure rules (C0168T72 CSR, Section 6.2.1).

## 2.1.3 Secondary Efficacy Analyses

### 2.1.3.1 Major Secondary Efficacy Analyses

In Amendment 1 of the protocol, changes were made to the original protocol-specified major secondary endpoints. As stated previously, the endoscopy at Week 54, which was originally required, was made optional. Thus, the original protocol-specified major secondary endpoints of clinical remission at Week 54 and clinical response at Week 54, which were based on the Mayo score, were no longer able to be assessed in all subjects. In this same protocol amendment, the PUCAI score was added as an assessment of efficacy. Due to these changes, 2 of the 4 major secondary endpoints were changed. The



first major secondary endpoint, while still an assessment of remission at Week 54, was changed to be based on the PUCAI score instead of the Mayo score. Because the assessment of maintenance of remission was changed to be based on the PUCAI score, an assessment of remission at Week 8 based on the PUCAI score was added as a major secondary endpoint, and replaced the major secondary endpoint of clinical response at Week 54. Clinical remission at Week 8 (based on the Mayo score) and mucosal healing at Week 8 were major secondary endpoints in both the original and amended protocol.

The results of the major secondary endpoint analyses are presented below in order of importance. The analysis of the first major secondary endpoint involves a comparison between the q8w and the q12w maintenance treatment groups in the proportion of subjects in remission at Week 54 based on the PUCAI score. Although not specifically stated in the protocol, the intent was that this endpoint would be tested if the primary endpoint was considered positive. The analyses for the remaining 3 major secondary endpoints (ie, clinical remission at Week 8 based on the Mayo score, remission at Week 8 based on the PUCAI score, and mucosal healing at Week 8), consist solely of descriptive (not comparative) statistics since these endpoints are based on data from the single-arm induction period of the study (through Week 8) where all subjects were receiving the same treatment (ie, infliximab 5 mg/kg at Weeks 0, 2, and 6). Because there was only one statistical hypothesis test for the major secondary endpoints, corresponding to the first major secondary endpoint of remission at Week 54, and only descriptive statistics are provided for the other 3 major secondary endpoints, the Type 1 error is controlled over the major secondary endpoints. Furthermore, since the first major secondary endpoint was tested sequentially after the primary endpoint, the overall Type 1 error for the study is controlled at the 0.05 level of significance.

#### **2.1.3.1.1 Remission at Week 54 (PUCAI Score)**

The proportion of randomized subjects in remission (as measured by the PUCAI score) at Week 54 was 27.9% (12 of 43 subjects). A notably greater proportion of subjects was in remission at Week 54 in the q8w maintenance treatment group (38.1% [8 of 21 subjects]) than in the q12w maintenance treatment group (18.2% [■ of 22 subjects]  $p = 0.146$ ; C0168T72 CSR, Table 8).

Notably, the proportion of subjects in remission at Week 30 was also higher in the q8w maintenance treatment group (40.0% [8 of 20 subjects]) than in the q12w maintenance treatment group [■ of 21 subjects]).

#### **2.1.3.1.2 Clinical Remission at Week 8 (Mayo Score) and Remission at Week 8 (PUCAI Score)**

Of the 60 subjects treated with infliximab, 24 (40.0%) were in clinical remission as measured by the Mayo score at Week 8.

Of the 51 subjects evaluable for PUCAI at Week 8, 17 (33.3%) were in remission as measured by the PUCAI at Week 8 (C0168T72 CSR, Attachment 3.5).

#### **2.1.3.1.3 Mucosal Healing at Week 8**

Of the 60 subjects treated with infliximab, 41 (68.3%) were in mucosal healing at Week 8 (C0168T72 CSR, Attachment 3.6). Twenty subjects (33.3%) had an endoscopy subscore of 0 (indicating normal or inactive disease) at Week 8 (C0168T72 CSR, Attachment 3.7).

### **2.1.3.2 Other Secondary Efficacy Analyses**

#### **2.1.3.2.1 Corticosteroid Analyses**

Analyses of the reduction in corticosteroid use over time and the proportion of subjects in clinical remission at Week 54 and not receiving corticosteroids at Week 54 were prespecified in the original protocol. In the amended protocol, these same corticosteroid analyses are specified, with the exception that the remission at Week 54 analysis is now based on the PUCAI score instead of the Mayo score. It was not necessary to account for multiplicity for these corticosteroid analyses since no hypothesis testing was performed.

Of the 45 subjects who were randomized to a maintenance treatment regimen at Week 8, 28 (62.2%) were receiving corticosteroids at baseline. The number of subjects receiving corticosteroids was the same (14 subjects) in each group, and the median average daily prednisone equivalent (P.Eq) corticosteroid dose at baseline, was similar in each group (0.54 mg/kg/day vs 0.49 mg/kg/day in the 5 mg/kg q8w and q12w treatment groups, respectively [C0168T72 CSR, Attachment 3.18]). Note that all analyses of corticosteroid dose are standardized by body weight, and are based on the average corticosteroid dose over the 6 days prior to a study visit.

##### **2.1.3.2.1.1 Corticosteroid Elimination Over Time**

For subjects receiving corticosteroids at baseline, a substantial reduction in average daily corticosteroid use had occurred by Week 8 in both the q8w and q12w maintenance treatment groups. The median value for the q8w group was 0.0 mg/kg/day by Week 8 and remained 0.0 mg/kg/day until Week 54 when a slight increase to 0.05 mg/kg/day was observed (C0168T72 CSR, Attachment 3.17). Although the reduction in the q12w treatment group at Week 8 was not as large as the reduction observed in the q8w treatment group, the median value in the q12w treatment group was further reduced to 0.04 mg/kg/day by their first maintenance treatment visit at Week 18. By Week 54, however, the average daily corticosteroid use had returned to baseline levels in the q12w treatment group.



### 2.1.3.2.1.2 Corticosteroid Use and Remission at Week 54

The proportion of randomized subjects who were receiving corticosteroids at baseline and who were in remission (based on the PUCAI score) at Week 54 and not receiving corticosteroids at Week 54 was greater in the q8w maintenance treatment group (38.5%, 5 of 13 subjects) than in the q12w maintenance treatment group (0.0%, 0 of 13 subjects, C0168T72 CSR, Attachment 3.19). For this analysis, subjects with missing data for corticosteroid use at Week 54 had their last value carried forward to Week 54. This method of imputation of corticosteroid dose did not have an effect on the analysis. Because of the method of data collection, missing data did not occur while subjects were being followed in the study since values from the previous visit were assumed to be maintained until a change in the corticosteroid dose was recorded. Subjects who discontinued the study had missing data from the time of study discontinuation until Week 54. Of the 28 subjects who were receiving corticosteroids at baseline, 12 subjects discontinued the study prior to Week 54 and thus do not have corticosteroid data at Week 54. Therefore, for these 12 subjects, their last corticosteroid dose was carried forward to Week 54. Because these subjects discontinued the study, however, they also do not have an evaluation of the PUCAI score at Week 54, and therefore these subjects are considered not to be in remission at Week 54. Since all of the subjects with missing data for corticosteroids are not in remission at Week 54, the analysis of the proportion of subjects in remission without corticosteroids at Week 54 is the same regardless of how the missing data for corticosteroids are handled because to meet this endpoint subjects must be in remission at Week 54 **and** not be receiving corticosteroids at Week 54.

Appendix 1.2 provides an expanded analysis of the Week 54 remission and corticosteroid results described above. In particular, for both the subset of subjects receiving corticosteroids at baseline and also those not receiving corticosteroids at baseline, analyses for all 4 combinations of remission status at Week 54 (in remission vs not in remission) and corticosteroid status at Week 54 (receiving corticosteroids vs not receiving corticosteroids) are provided. It is notable that all 12 subjects who were in remission at Week 54 (8 in the q8w treatment group and 4 in the q12w treatment group) were also not receiving corticosteroids at Week 54. This includes 5 of 13 subjects in the q8w treatment group who were receiving corticosteroids at baseline, as well as 3 of 8 and 1 of 9 subjects in the q8w and q12w treatment groups, respectively, who were not receiving corticosteroids at baseline.

When examining the subjects in the q8w treatment group who were not in remission at Week 54, the majority of the subjects (11 of 13) were not receiving corticosteroids at Week 54. This includes 6 of 8 subjects who were receiving corticosteroids at baseline and all 5 subjects who were not receiving corticosteroids at baseline. Of subjects in the q12w treatment group who were not in remission at Week 54, approximately half of the subjects (8 of 18) were not receiving corticosteroids at Week 54. This includes 6 of 13 subjects who were receiving corticosteroids at baseline and 2 of 5 who were not receiving corticosteroids at baseline.



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#### 2.1.3.2.2 Mayo Scores

The median baseline Mayo score in all randomized subjects was 8.0 (7.5 and 8.0 in the q8w and q12w maintenance treatment groups, respectively). A substantial reduction in the Mayo score was observed by Week 8 (median reduction of 5.0 [6.0 and 5.0 in the q8w and q12w groups, respectively]). For the 9 randomized subjects who underwent an endoscopy at Week 54, a median reduction from baseline in the Mayo score of 6.0 was observed in the q8w group, while the median reduction in the Mayo score at Week 54 was 0.0 in the q12w group (C0168T72 CSR, Attachment 3.13).

In all randomized subjects, improvement from the median baseline value of 6.0 was observed as early as Week 2 for the partial Mayo score (the median reduction from baseline was 3.0). At Week 8, the median reduction from baseline was 4.0 (overall and in each maintenance treatment group). During the maintenance phase of the study, the substantial reduction in the partial Mayo score was maintained in the q8w maintenance treatment group, with a median reduction from baseline of 3.0 at Week 54. However, the improvement in the partial Mayo score was not maintained in the q12w maintenance treatment group; at both Week 30 and Week 54, the median change from baseline in the q12w group was 0.0 (C0168T72 CSR, Attachment 3.14; C0168T72 CSR, Attachment 3.15).

#### 2.1.3.2.3 PUCAI Scores

In the group of subjects randomized at Week 8, the median PUCAI score at baseline was 55.0 (50.0 and 57.5 in the q8w and q12w maintenance treatment groups, respectively). Reductions in the PUCAI score were evident as early as Week 2, when the median reduction from baseline in the PUCAI score was 35.0. By Week 8, the median decrease in the PUCAI score was 45.0 (40.0 in the q8w and 47.5 in the q12w group). During the maintenance phase of the study, the substantial reduction in the PUCAI score was maintained in the q8w group, with a median reduction from baseline of 30.0 at Week 54. However, the improvement in the PUCAI score was not maintained in the q12w group; at both Week 30 and Week 54, the median change from baseline was 0.0. C0168T72 CSR, Attachment 3.9 summarizes baseline and change from baseline in the PUCAI score through Week 54.

Turner et al (2007) described a decrease of  $\geq 20$  points in the PUCAI score as a clinically meaningful change. Using this criterion, at least 50% of the subjects in the 5 mg/kg infliximab q8w maintenance treatment group had a clinically meaningful change at Week 54 since the median reduction from baseline at Week 54 for the PUCAI score was 30.0 points.

#### 2.1.3.2.4 Correlation Between Mayo and PUCAI

To assess for consistency in the evaluation of efficacy based on the full Mayo score and the PUCAI score, scatterplots of the full Mayo score versus the PUCAI score and also

correlations between these 2 measures were produced for baseline and Week 8. At baseline a high positive correlation was observed between the full Mayo score and the PUCAI score (0.749,  $p < 0.001$ ; Table 2), which is reflected in the scatterplot (Appendix 1.3), where higher PUCAI scores are generally associated with higher full Mayo scores. Notably, from the scatterplot it is also evident that, with the exception of [REDACTED] subjects, those who were classified as having moderate to severe UC by the full Mayo score (ie, Mayo scores  $\geq 6$ ) were also classified as having moderate to severe UC by the PUCAI score (PUCAI scores  $\geq 35$ ). In the [REDACTED] subjects for whom the Mayo score met the criteria for moderate to severe disease but the PUCAI score did not, the full Mayo score was on the low end of the range of scores for the moderate category (6 for [REDACTED] subjects and 7 for [REDACTED] and the PUCAI scores for these subjects, although outside of the moderate-to-severe range, were also low. Note that [REDACTED] did not meet the criteria for moderate to severe disease by the full Mayo score also did not meet the criteria by the PUCAI score (Mayo score of 5 and PUCAI score of 10).

At Week 8, the correlation between the full Mayo score and the PUCAI score (0.878,  $p < 0.001$ ; Table 2) was higher than the correlation seen at baseline. Again, this high positive correlation was reflected in the scatterplot (Appendix 1.4), where lower values of the PUCAI score were generally associated with lower values of the full Mayo score. This result is consistent with the correlation between the full Mayo score and the PUCAI score described in Turner et al (2007).

In summary, a high positive correlation exists between the full Mayo score and the PUCAI score at both baseline and Week 8. Therefore, the efficacy assessments based on these 2 measures would be expected to produce consistent results.

**Table 2 Summary of Pearson's correlation coefficient between PUCAI and Mayo score at baseline and at Week 8; treated subjects in C0168T72**

|                                                                     | n  | Correlation | p-Value   |
|---------------------------------------------------------------------|----|-------------|-----------|
| Correlation between PUCAI and Mayo score at baseline                | 49 | 0.749       | $< 0.001$ |
| Correlation between PUCAI and Mayo score at Week 8 <sup>a,b,c</sup> | 51 | 0.878       | $< 0.001$ |

<sup>a</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect had their baseline value carried forward.

<sup>b</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to a lack of efficacy had their baseline value carried forward.

<sup>c</sup> Subjects with insufficient data had their last value carried forward.

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#### 2.1.3.2.5 Mucosal Healing at Week 54

As noted previously, endoscopy was optional at Week 54. Of the subjects still participating in the study at Week 54, 9 agreed to have an endoscopy for the Mayo score at that visit. All of these subjects had achieved mucosal healing at their Week 8 visit.

At the Week 54 visit, 8 (88.9%) of the 9 subjects were still in mucosal healing [REDACTED] in the q8w group and all 5 in the q12w group), with 6 of the subjects (66.7%; [REDACTED] in the q8w group and [REDACTED] of 5 in the q12w group) having normal or inactive disease (endoscopy subscore of 0, [Appendix 1.5](#)).

#### 2.1.3.2.6 Clinical Response at Week 54

Of the pediatric subjects who had an endoscopy at Week 54, 55.6% (5 of 9 subjects [REDACTED] in the q8w treatment group and [REDACTED] of 5 in the q12w treatment group]) were considered to be in clinical response at Week 54 (C0168T72 CSR, [Attachment 3.12](#)).

#### 2.1.3.2.7 Improvement After Step-up

During the maintenance treatment phase, subjects who lost response were eligible to increase (step up) their infliximab dose and/or dosing frequency one time; the visit at which the subject stepped up was defined as Week 0S. An assessment of the ability to regain clinical response (based on the full Mayo score) after step up was not directly feasible in C0168T72 because of the need for endoscopy data in the clinical response definition. As a means of assessing efficacy after stepping up to a higher dose or more frequent dose interval, the proportions of step-up subjects who demonstrated improvement based on the partial Mayo score and the PUCAI score were summarized for each step-up treatment group. Improvements based on the partial Mayo score was defined as a decrease in the partial Mayo score of  $\geq 2$  points from the Week 0S visit. Improvement based on the PUCAI score was defined as a decrease in the PUCAI score of  $\geq 20$  points from the Week 0S visit ([Turner et al, 2007](#)). These analyses were based on observed data, thus treatment failure and missing data rules were not applied.

Of the 45 randomized subjects, 23 stepped up. Six of these subjects discontinued and [REDACTED] completed the study prior to their Week 8S visit. Of the 16 subjects who had a Week 8S visit, 13 (81.3%) demonstrated improvement based on the partial Mayo score at this visit. A similar proportion of subjects demonstrated improvement in each step-up group ([Appendix 1.6](#)). Fewer subjects (7 [53.8%] of 13) demonstrated improvement based on the PUCAI score at Week 8S ([Appendix 1.7](#)).

Of the step-up subjects who remained in the study at Week 54, 9 (90.0%) of 10 had demonstrated improvement based on the partial Mayo score and all 9 subjects (with an evaluable PUCAI score at Week 54) demonstrated improvement based on the PUCAI score.

In summary, most subjects who stepped up infliximab dose and/or dosing frequency during the maintenance phase of the study demonstrated an improvement in disease activity. However, these results should be interpreted with caution as they are based on a small number of subjects. Furthermore, these subjects were allowed to alter their concomitant medications after stepping up, which could confound the evaluation of the effect of the step-up regimen.

#### **2.1.3.2.8 IMPACT III at Week 8**

The IMPACT III score ranges from 35 to 175. A higher IMPACT III score indicates a better quality of life; a change toward a higher score indicates improvement (Otley et al, 2005; Otley et al, 2008). A total of 54 treated subjects completed the IMPACT III questionnaire at baseline, with a median score of 108.5. At Week 8, improvement from baseline in the IMPACT-III score was observed, with a median change of 15 points (C0168T72 CSR, Attachment 3.29). 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 in IMPACT-III score correlated with clinical improvement in pediatric Crohn's disease based on the pediatric Crohn's disease activity index (Otley et al, 2006).

#### **2.1.3.2.9 Global Assessments**

Among the 60 treated subjects, 54 subjects and parents/guardians and 55 physicians completed a global assessment of change from baseline at Week 8; 36 subjects (66.7%) said that they felt much better. Physician and parent/guardian global assessments of change from baseline at Week 8 were similar: 39 (70.9%) and 34 (63.0%), respectively, assessed the change as much better.

Summaries of global assessment scores through Week 8 showed that 81.7% of all treated subjects assessed their health status as very good or fair at Week 8, whereas only 41.7% had assessed their health status as fair at baseline (no subjects had assessed their health status as very good). Parent/guardian assessments of subject health status were similar: approximately 80% assessed subject health status as very good or fair at Week 8, versus 33.3% who assessed it as fair at Week 0 (again, no parent/guardian had assessed subject health status as very good).

Summaries of global assessment scores through Week 54 (C0168T72 CSR, Attachment 3.27) showed similar changes among all randomized subjects, although the differences moderated somewhat as the study progressed. The percentage of subjects who assessed their health status as very good or fair was 40% at Week 0, 91.1% at Week 8, 60.0% at Week 30, and 57.8% at Week 54. Parent/guardian assessments were comparable.



#### **2.1.3.2.10 Height Status**

In the 8 randomized subjects who had at least a 1-year delay in bone age, an increase in height was observed, as measured by age- and gender-specific z-scores (a measure of the deviation of the subjects' height from the expected height for a population of the same age and gender). The median z-score at baseline was -0.36 and the median change from baseline was 0.08 at Week 30 and 0.25 at Week 54 (C0168T72 CSR, Attachment 3.23; C0168T72 CSR, Attachment 3.24). These results should be interpreted with caution because of the small sample size.

### **2.1.4 Subgroup Analyses**

Analyses were performed to examine the consistency of clinical response at Week 8 across subgroups defined by demographic, baseline disease characteristics, and by concomitant medications. The proportion of subjects achieving a clinical response at Week 8 was generally consistent across the subgroups (C0168T72 CSR, Attachment 3.4). Of particular interest, among the 32 subjects who were receiving immunomodulators at baseline, 71.9% were in clinical response at Week 8 and among the 28 subjects who were not receiving immunomodulators at baseline, 75.0% were in clinical response at Week 8. In addition, among pediatric subjects who were or were not receiving corticosteroids and who were or were not receiving 5-ASAs at baseline, a similar proportion of subjects in each group were in clinical response at Week 8 (C0168T72 CSR, Attachment 3.4). Additional analyses based on immunomodulator use at baseline are presented in Section 3.2.7.

Subgroup analyses based on the age groups of 6 to 11 and 12 to 17 years old were performed for the following efficacy endpoints: Mayo score, clinical response, clinical remission, remission, and mucosal healing and are summarized in Table 3.

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

**Table 3 Summary of efficacy by age group; treated subjects in C0168T72**

|                                                              | Infliximab 5 mg/kg |            |
|--------------------------------------------------------------|--------------------|------------|
|                                                              | Ages 6-11          | Ages 12-17 |
| Subjects treated                                             | 15                 | 45         |
| Baseline Mayo score                                          |                    |            |
| Median                                                       | 8.0                | 8.0        |
| Week 8 Mayo score <sup>a,b</sup>                             |                    |            |
| Median                                                       | 3.0                | 3.0        |
| Subjects in clinical response at Week 8 <sup>c, d</sup>      | 9 (60.0%)          | 35 (77.8%) |
| Subjects in clinical remission at Week 8 <sup>c, d</sup>     | 7 (46.7%)          | 17 (37.8%) |
| Subjects in mucosal healing at Week 8 <sup>c, d</sup>        | 8 (53.3%)          | 33 (73.3%) |
| Subjects with evaluable PUCAI scores at Week 8 <sup>e</sup>  | 12                 | 39         |
| Subjects in remission at Week 8 <sup>c, d</sup>              | 4 (33.3%)          | 13 (33.3%) |
| Subjects with evaluable PUCAI scores at Week 54 <sup>f</sup> |                    |            |
| q8wk treatment group                                         | 5                  | 16         |
| Subjects in remission at Week 54 <sup>c, d</sup>             |                    | 5 (31.3%)  |
| q12wk treatment group                                        | 4                  | 18         |
| Subjects in remission at Week 54 <sup>c, d</sup>             | 0 (0.0%)           | 4 (22.2%)  |

<sup>a</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect had their baseline value carried forward.

<sup>b</sup> Subjects with insufficient data had their last value carried forward.

<sup>c</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in clinical response, or in clinical remission (based on Mayo score), or in remission (based on PUCAI score), or in mucosal healing.

<sup>d</sup> Subjects with insufficient data are considered to not be in clinical response or in clinical remission (based on Mayo score), or in remission (based on PUCAI score), or in mucosal healing.

<sup>e</sup> Evaluable subjects are subjects with their first PUCAI evaluated on or prior to Week 8.

<sup>f</sup> Evaluable subjects are subjects with their first PUCAI evaluated on or prior to Week 54.

Table derived from: RE500:Appendix 1.8; Appendix 1.9; Appendix 1.10; Appendix 1.11 ; Appendix 1.12;Appendix 1.13

## 2.1.5 Efficacy and Pharmacokinetics

To relate clinical efficacy with exposure to infliximab, the association between the median improvement from baseline in the Mayo score at Week 8 and the PUCAI score at



Week 8, and serum infliximab concentration at Week 8 was evaluated. Serum infliximab concentrations at Week 8 were categorized into 4 ranges (based on the data quartiles in micrograms per milliliter): < 19.69, 19.69 to < 27.71, 27.71 to < 39.57, and ≥ 39.57 (C0168T72 CSR, Section 6.7). Overall, it appears that subjects who achieved higher serum infliximab concentrations at Week 8 generally had greater efficacy as measured by the Mayo (C0168T72 CSR, Attachment 3.32) and PUCAI (C0168T72, Attachment 3.33) scores.

### 2.1.6 Efficacy and Antibodies to Infliximab

The relationship between antibody to infliximab status and the proportion of subjects in remission at Week 54 was evaluated to determine the potential influence of antibodies to infliximab on efficacy (C0168T72 CSR, Section 6.6). Among the 45 randomized subjects, only [REDACTED] (all in the q8w maintenance treatment group) were positive for antibodies to infliximab. [REDACTED] subjects [REDACTED] was in remission at Week 54. Among the subjects who were negative for antibodies to infliximab, [REDACTED] of 9 achieved remission. The proportion of subjects who were inconclusive for antibodies to infliximab and who were in remission was slightly lower (8 [24.2%] of 33 subjects in remission at Week 54 C0168T72 CSR, Attachment 3.31). Because only [REDACTED] were positive for antibodies to infliximab, no conclusions can be made regarding the relationship between antibody positive status and clinical efficacy measures.

## 2.2 ACT 1

### 2.2.1 Demographics and Baseline Disease Characteristics

In ACT 1, 364 subjects were randomized (1:1:1) to receive either infliximab (5 mg/kg or 10 mg/kg) or placebo. The baseline demographic characteristics were similar across the treatment groups (ACT 1 CSR, Table 5). Among all subjects, 61.0% were men, 93.4% were Caucasian, and the median age was 40.0 years.

Among all randomized subjects, the median duration of UC was 4.7 years, the median Mayo score was 8.0, 30.8% were refractory to corticosteroids, the median CRP concentration was 0.8 mg/dL, and 45.6% had extensive disease (ACT 1 Week 30 CSR, Attachment 1.11). Although the clinical disease characteristics at baseline were generally similar across the treatment groups, the 10 mg/kg infliximab treatment group had a longer median duration of disease (5.9 years) than either the 5 mg/kg infliximab (4.1 years) or placebo (4.4 years) treatment groups. A similar proportion of subjects across all treatment groups were receiving each UC medication at baseline. A total of 94.0% of randomized subjects were receiving an UC medication at baseline with 61.0% receiving corticosteroids, 48.9% receiving 6-MP or AZA, and 69.5% receiving 5-ASA compounds.

## 2.2.2 Primary Efficacy Endpoint (Clinical Response at Week 8)

The proportion of subjects reaching the primary endpoint of clinical response at Week 8 was significantly greater in the infliximab treatment groups than in the placebo treatment group. At Week 8, 65.4% of subjects in the combined infliximab treatment group and 37.2% of subjects in the placebo treatment group were in clinical response ( $p < 0.001$ , [ACT 1 Week 30 CSR, Attachment 3.1](#)). The proportion of subjects in clinical response at Week 8 in the individual infliximab treatment groups were similar to each other and both were superior to the placebo treatment group (5 mg/kg 69.4%,  $p < 0.001$  and 10 mg/kg 61.5%,  $p < 0.001$ , [ACT 1 Week 30 CSR, Figure 3](#)).

## 2.2.3 Secondary Efficacy Analyses

### 2.2.3.1 Clinical Remission Through Week 54

The proportions of subjects in clinical remission are reported in the [ACT 1 54-week CSR, Table 5](#). The proportions of subjects reaching the major secondary endpoints of clinical remission at Weeks 8 and 30 were significantly greater for each infliximab treatment group than for the placebo treatment group ( $p \leq 0.002$  for all comparisons). At Week 8, 35.4% of subjects in the combined infliximab group were in clinical remission compared with 14.9% of subjects in the placebo group. At Week 30, 35.4% of subjects in the combined infliximab group were in clinical remission compared with 15.7% of subjects in the placebo group. The proportions of subjects in clinical remission at Week 8 were 38.8% and 32.0%, respectively, in the 5 mg/kg and 10 mg/kg infliximab treatment groups, while at Week 30, 33.9% and 36.9%, respectively, were in clinical remission.

In addition, a greater proportion of infliximab-treated subjects were in clinical remission at Week 54 than subjects in the placebo treatment group. The proportion of subjects in clinical remission was significantly greater in the combined infliximab treatment group than in the placebo treatment group (34.6% compared with 16.5%,  $p < 0.001$ ). Similarly, the proportion of subjects in clinical remission in both infliximab treatment groups was also significantly greater than in the placebo treatment group (34.7% in the 5 mg/kg and 34.4% in the 10 mg/kg infliximab treatment groups,  $p = 0.001$  in both instances).

### 2.2.3.2 Mucosal Healing Through Week 54

The proportions of subjects with mucosal healing at Week 8, a major secondary endpoint in ACT 1, and mucosal healing at Weeks 30 and 54 are presented in the [ACT 1 Week 54 CSR, Table 6](#). A greater proportion of subjects in the combined infliximab treatment group had mucosal healing at Weeks 8 (60.5%) and 30 (49.8%) than subjects in the placebo treatment group (33.9% and 24.8% at Weeks 8 and 30, respectively;  $p < 0.001$  for both comparisons). A greater proportion of subjects in the 5 mg/kg infliximab treatment group had mucosal healing at both Week 8 and Week 30 (62.0% and 50.4%, respectively), when compared with the 10 mg/kg infliximab treatment group (59.0% and 49.2%, respectively). At Week 54, more than twice the proportion of subjects in the



combined infliximab group had mucosal healing compared with the placebo treatment group (45.5% in 5 mg/kg, 46.7% in 10 mg/kg, and 46.1% in the combined infliximab treatment groups compared with 18.2% in the placebo treatment group,  $p < 0.001$  for all 3 comparisons).

### 2.2.3.3 Clinical Response Through Week 54

The proportion of subjects in clinical response at Weeks 8, 30, and 54 is shown in [ACT 1 Week 54 CSR, Table 4](#). The proportion of subjects reaching the major secondary endpoint of clinical response at Week 30 were significantly greater in the infliximab treatment groups than in the placebo treatment group. At Week 30, 51.4% of subjects in the combined infliximab treatment group and 29.8% of subjects in the placebo treatment group were in clinical response ( $p < 0.001$ ). A similar proportion of subjects in the 5 mg/kg and 10 mg/kg infliximab treatment groups were in clinical response at Week 30 (52.1% and 50.8%, respectively).

Infliximab continued to provide greater clinical response than placebo at Week 54. The proportion of subjects in clinical response at Week 54 was significantly greater in each infliximab treatment group (45.5% in the 5 mg/kg infliximab treatment group, 44.3% in the 10 mg/kg infliximab treatment group, and 44.9% in the combined infliximab treatment group) than in the placebo treatment group (19.8%,  $p < 0.001$  for all 3 comparisons).

### 2.2.3.4 Corticosteroid Endpoints

#### 2.2.3.4.1 Corticosteroid Dose

The median daily P.Eq corticosteroid dose through Week 54 (presented as mg/day) is shown by treatment group in [Figure 9 of the ACT 1 Week 54 CSR](#). Of subjects who were receiving corticosteroids at baseline, the median daily corticosteroid dose in the combined infliximab treatment group decreased from 20.0 mg/day at baseline to 8.5 mg/day at Week 54. The median daily corticosteroid dose for the placebo treatment group varied from 20.0 mg/day at baseline to 10 mg/day at Weeks 22 and 30, and up to 20 mg/day at Weeks 38, 46, and 54 ([ACT 1 Week 54 CSR, Attachment 3.17](#)). Although both the 5 mg/kg and 10 mg/kg infliximab treatment groups had substantial reductions from baseline in corticosteroid dose, the 5 mg/kg infliximab group had greater reductions (median dose at Week 54 of 5 mg/day) than the 10 mg/kg infliximab group (median dose at Week 54 of 10 mg/day).

#### 2.2.3.4.2 Corticosteroid Use and Clinical Remission

Among subjects who were receiving corticosteroids at baseline, a greater proportion were in clinical remission and not receiving corticosteroids at Week 30 and at Week 54 in the combined infliximab treatment group (21.7% and 21.0%) compared with the placebo treatment group (10.1% and 8.9%,  $p = 0.039$  and  $p = 0.022$ , respectively; [ACT 1](#)

Week 54 CSR, Attachment 3.20). A slightly greater proportion of subjects were in clinical remission and not receiving corticosteroids in the 5 mg/kg than in the 10 mg/kg infliximab treatment group at both visits (24.3% versus 19.2% at Week 30; 25.7% versus 16.4% at Week 54).

### **2.2.3.5 Efficacy and Pharmacokinetics**

To relate clinical improvement with exposure to infliximab, the association between response status and the serum infliximab concentrations at Week 54 was evaluated. Subjects' response status was expressed as 'not in response', 'in response but not in remission', and 'in remission'.

A serum infliximab concentration-response relationship was demonstrated at Week 54, where higher infliximab concentration levels were associated with higher levels of response. At Week 54, for example, the median serum infliximab concentration was greatest in subjects 'in remission' and lowest in subjects 'not in response'. At Week 54, the median infliximab concentrations were 2.1 µg/mL, 5.5 µg/mL, and 6.9 µg/mL for subjects who were not in response, those that were in response but not in remission, and those that were in remission, respectively (ACT 1 54 Week CSR, Section 10.4).

### **2.2.3.6 Efficacy and Antibodies to Infliximab**

An evaluation of antibody to infliximab status through Week 54 versus clinical response and remission at Week 54 was performed to determine the influence of antibodies to infliximab on the efficacy of infliximab. Because the treatment groups were divided further into the subject's antibody to infliximab status, some analyses were based on a limited number of subjects and should be interpreted with caution.

At Week 54, 3 of the 14 (21.4%) antibody positive subjects were in clinical response while [REDACTED] of these subjects were also in clinical remission at Week 54. The proportion of subjects in clinical response at Week 54 was somewhat less among subjects negative for antibodies to infliximab, [REDACTED] of 36 subjects. The incidence of antibody negative subjects in clinical remission at Week 54 was also 8.3%. By comparison, the proportion of subjects inconclusive for antibodies to infliximab who were in clinical response or clinical remission was 103 (57.5%) of 179 and 79 (44.1%) of 179 subjects, respectively, at Week 54 (ACT 1 54 Week CSR, Section 11.5.2.3).

## **2.3 ACT 2**

### **2.3.1 Demographics and Baseline Disease Characteristics**

In ACT 2, 364 subjects were randomized (1:1:1) to receive either infliximab (5 mg/kg or 10 mg/kg) or placebo. The baseline demographic characteristics were generally similar



across the treatment groups (ACT 2 CSR, Table 5). Among all subjects, 59.1% were men, 94.5% were Caucasian, and the median age was 38.0 years.

The clinical disease characteristics at baseline were generally similar across the treatment groups. Among all randomized subjects, the median duration of UC was 4.9 years, the median Mayo score was 8.0, 28.8% were refractory to corticosteroids, the median CRP concentration was 0.7 mg/dL, and 39.9% had extensive disease (ACT 2 CSR, Attachment 1.12). A similar proportion of subjects across all treatment groups were receiving each UC medication at baseline. A total of 95.1% of randomized subjects were receiving a UC medication at baseline with 51.1% receiving corticosteroids, 42.9% receiving 6-MP or AZA, and 74.7% receiving 5-ASA compounds (ACT 2 CSR, Section 8.3.3).

## 2.3.2 Primary Efficacy Endpoint (Clinical Response at Week 8)

The proportion of subjects achieving the primary endpoint of clinical response at Week 8 was 66.8% in the combined infliximab treatment groups versus 29.3% in the placebo treatment group ( $p < 0.001$ , ACT 2 Week 30 CSR, Attachment 3.1). The clinical response rates in the individual infliximab treatment groups were similar to each other and both were superior to the placebo treatment group (5 mg/kg 64.5%,  $p < 0.001$  and 10 mg/kg 69.2%,  $p < 0.001$ , ACT 2 Week 30 CSR, Figure 3).

## 2.3.3 Secondary Efficacy Analyses

### 2.3.3.1 Clinical Remission Through Week 30

A total of 30.7% of subjects in the combined infliximab treatment group was in clinical remission at Week 8, and the same proportion (30.7%) was in clinical remission at Week 30 (ACT 2 Week 30 CSR, Table 8). Both of these endpoints were major secondary endpoints in ACT 2. In contrast, 5.7% and 10.6% of the subjects in the placebo treatment group were in clinical remission at Week 8 and Week 30, respectively. The comparison of the proportion of subjects in clinical remission was statistically significant at both Week 8 and Week 30 ( $p < 0.001$  for both comparisons). In addition, the proportions of subjects in clinical remission at Week 8 and Week 30 in both the 5 mg/kg and 10 mg/kg infliximab treatment groups were also significantly greater than placebo at both Week 8 and Week 30 ( $p = 0.003$ , maximum  $p$ -value among all 4 comparisons). At Week 8, the proportion of subjects in clinical remission was 33.9% and 27.5%, respectively, in the 5 mg/kg and 10 mg/kg infliximab treatment groups. At Week 30, the proportion of subjects in clinical remission was greater in the 10 mg/kg than in the 5 mg/kg infliximab treatment groups (35.8% versus 25.6%).

### 2.3.3.2 Mucosal Healing Through Week 30

At Week 8, 61.0% of subjects in the combined infliximab treatment group achieved mucosal healing, a major secondary endpoint in ACT 2, compared with 30.9% in the

placebo treatment group ( $p < 0.001$ , [ACT 2 Week 30 CSR, Attachment 3.12](#)). A similar proportion of subjects achieved mucosal healing at Week 8 in the 5 mg/kg and 10 mg/kg infliximab treatment groups (60.3% and 61.7%, respectively). At Week 30, 51.5% of subjects in the combined infliximab treatment group achieved mucosal healing compared with 30.1% in the placebo treatment group ( $p < 0.001$ ); the proportion of subjects with mucosal healing at Week 30 in the 10 mg/kg infliximab treatment group (56.7%) was higher than that in the 5 mg/kg treatment group (46.3%). In both infliximab treatment groups, a greater proportion of subjects achieved mucosal healing compared with the placebo treatment group at both Week 8 ([ACT 2 Week 30 CSR, Figure 4](#)) and Week 30 ( $p = 0.009$ , maximum p-value for all 4 comparisons).

### 2.3.3.3 Clinical Response at Week 30

The percentage of subjects in clinical response at Week 30, a major secondary endpoint in ACT 2, is shown in [ACT 2 Week 30 CSR, Table 7](#). A total of 53.5% of the subjects in the combined infliximab treatment group achieved clinical response compared with 26.0% in the placebo treatment group ( $p < 0.001$ ). In addition, the proportion of subjects in clinical response in both the 5 mg/kg and 10 mg/kg infliximab treatment groups was also significantly greater than placebo ( $p < 0.001$  for both comparisons), with a greater proportion of subjects in clinical response in the 10 mg/kg than in the 5 mg/kg infliximab treatment groups (60.0% versus 47.1%, respectively).

### 2.3.3.4 Corticosteroid Endpoints

#### 2.3.3.4.1 Corticosteroid Dose

Of subjects that were receiving corticosteroids at baseline, the median daily corticosteroid dose in the combined infliximab treatment group decreased from 20 mg/day at baseline to 6.9 mg/day at Week 30. In contrast, the median daily corticosteroid dose at Week 30 for placebo subjects (20 mg/day) was the same as the baseline median daily corticosteroid dose ([ACT 2 Week 30 CSR, Attachment 3.13](#)). The median daily corticosteroid dose at Week 30 was similar in the 5 mg/kg (7.5 mg/day) and 10 mg/kg (5.0 mg/day) infliximab treatment groups.

#### 2.3.3.4.2 Corticosteroid Use and Clinical Remission

Among subjects who were receiving corticosteroids at baseline, a greater proportion was in clinical remission and not receiving corticosteroids at Week 30 in the combined infliximab treatment group (23.0%) compared with the placebo treatment group (3.3%,  $p < 0.001$ ; [ACT 2 Week 30 CSR, Attachment 3.14](#)). In addition, the percentage of subjects in clinical remission and not receiving corticosteroids at Week 30 in both the 5 mg/kg and 10 mg/kg infliximab treatment groups was also greater than in the placebo treatment group ( $p = 0.010$  and  $p < 0.001$ , respectively, [ACT 2 Week 30 CSR, Figure 6](#)), with a greater proportion of subjects in clinical remission and not receiving



corticosteroids in the 10 mg/kg than in the 5 mg/kg infliximab treatment group (27.3% versus 18.3%, respectively).

### **2.3.3.5 Efficacy and Antibodies to Infliximab**

An evaluation of antibody to infliximab status and clinical response and clinical remission was performed to determine the influence of antibodies to infliximab on the efficacy of infliximab.

A total of 10 (83.3%) of the 12 subjects positive for antibodies to infliximab were in clinical response at Week 30, and 7 (58.3%) of these 12 subjects were also in clinical remission at Week 30. The percentage of subjects achieving clinical response and clinical remission was somewhat lower among subjects who were negative for antibodies to infliximab, 20 (58.8%) of 34 subjects and 6 (17.6%) of 34 subjects, respectively. In contrast, the percentage of subjects who were inconclusive for antibodies to infliximab (ie, antibody negative in the presence of detectable serum levels of infliximab) and in clinical response and clinical remission (ie, 116 [81.7%] of 142 and 58 [40.8%] of 142, respectively) was comparable with that observed among subjects positive for antibodies to infliximab. The presence of antibodies to infliximab was not associated with a decrease in the proportion of subjects in clinical response or clinical remission ([ACT 2 CSR, Attachment 4.61](#)).

## **3 Comparison and Analyses of Results Across Studies**

### **3.1 Study Populations**

By study inclusion criteria, the population of subjects enrolled in C0168T72, ACT 1, and ACT 2 had moderately to severely active UC as defined by Mayo scores between 6 and 12 points, inclusive, at baseline with endoscopic evidence of active colitis as indicated by an endoscopy subscore  $\geq 2$ .

Other than obvious study differences (eg, age, weight, disease duration), the baseline disease characteristics were generally similar between the pediatric and adult populations ([Table 4](#)). The demographic characteristics for the population of subjects randomized in C0168T72, ACT 1, and ACT 2 are described in [Section 2.1.1](#), [Section 2.2.1](#), and [Section 2.3.1](#) respectively. The majority of subjects in these studies were Caucasian and had a slightly greater proportion of male subjects in ACT 1 and ACT 2, but a slightly greater proportion of female subjects in C0168T72.

Subjects in each study were required to have a diagnosis of UC confirmed by biopsy. The median Mayo scores at baseline were identical in the 3 studies. However, a greater proportion of subjects had extensive disease (as opposed to disease limited to the left side

of the colon) in C0168T72 (76.7%) than in the ACT studies (45.6% and 39.9% for ACT 1 and ACT 2, respectively). The median CRP values at baseline were numerically greater in ACT 1 and ACT 2 than in C0168T72. Note, however, that the regular CRP assay was used in the ACT studies, but that the high sensitivity assay was used in C0168T72 so that the lower limit of detection was lower.

**Table 4 Summary of demographics and clinical disease characteristics at baseline; treated subjects in C0168T72, and randomized subjects in ACT 1, and ACT 2**

|                             | C0168T72 | ACT 1 | ACT 2 |
|-----------------------------|----------|-------|-------|
| Number of subjects          | 60       | 364   | 364   |
| Female                      | 53.3%    | 39.0% | 40.9% |
| Caucasian                   | 81.7%    | 93.4% | 94.5% |
| Median weight (kg)          | 50.80    | 76.5  | 75.0  |
| UC disease duration (years) |          |       |       |
| Median                      | 1.35     | 4.7   | 4.9   |
| Extent of disease           |          |       |       |
| Extensive                   | 76.7%    | 45.6% | 39.9% |
| Concomitant UC medications  |          |       |       |
| corticosteroids             | 61.7%    | 61.0% | 51.1% |
| 6-MP/AZA/MTX                | 53.3%    | 48.9% | 42.9% |
| 5-ASA compounds             | 53.3%    | 69.5% | 74.7% |
| Median Mayo score           | 8        | 8     | 8     |
| Median CRP (mg/dL)          | 0.3      | 0.8   | 0.7   |

derived from C0168T72 CSR, Section 4.2, ACT 1 Week 30 CSR, Section 8.3, ACT 2 Week 30 CSR, Section 8.3

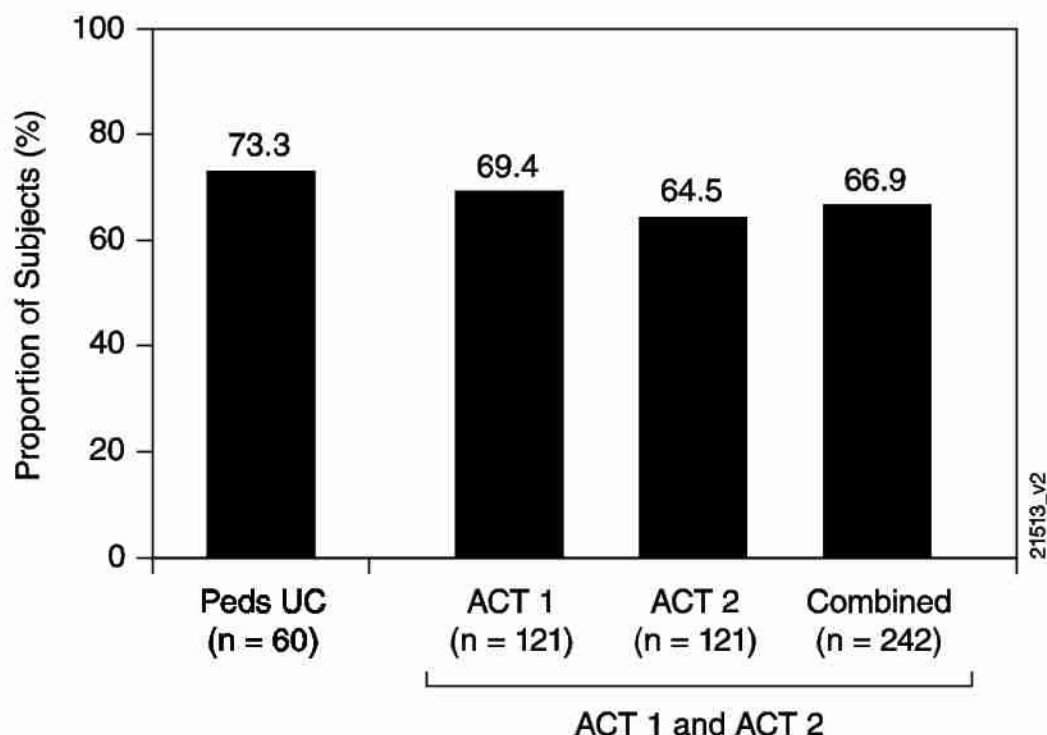
## 3.2 Comparison of Efficacy Results of All Studies

### 3.2.1 Clinical Response

The proportions of subjects in clinical response at Week 8 were similar among pediatric (C0168T72) and adult (ACT 1 and ACT 2) subjects with UC in the 5 mg/kg infliximab treatment groups ([Figure 1](#)). A total of 73.3% (95% CI 62.1% to 84.5%) of pediatric subjects and 66.9% (95% CI 61.0% to 72.9%) of adult subjects in the combined ACT studies who were in the 5 mg/kg infliximab treatment groups were in clinical response at Week 8 compared with 33.2% (95% CI 27.3% to 39.1%) of adult subjects in the combined ACT studies who were in the placebo treatment group ([Appendix 1.1](#), [Appendix 1.14](#)). The proportion of adult subjects in clinical response at Week 8 in the



ACT 1 and ACT 2 studies was similar among subjects in the 5 mg/kg treatment groups (69.4% vs 64.5%; respectively; [Appendix 1.14](#)). Although the proportion of adult subjects in clinical response at Week 8 in the placebo treatment group in ACT 1 (37.2%) was greater than that in ACT 2 (29.3%), the lower bound of the confidence interval for C0168T72 (62.1%) is still greater than the upper bound of the confidence interval for placebo in both ACT studies (45.8% and 37.3% in ACT 1 and ACT 2, respectively). The similarity in efficacy in C0168T72 and the ACT studies was present despite being able to taper corticosteroids beginning at Week 0 in C0168T72 compared with Week 8 in the ACT studies.



**Figure 1** Proportion of subjects in clinical response at Week 8; treated subjects in the infliximab 5 mg/kg treatment group in C0168T72 and randomized subjects in the infliximab 5 mg/kg treatment groups in ACT 1 and ACT 2

Of the pediatric subjects who had an endoscopy at Week 54, 55.6% (5 of 9) were considered to be in clinical response at Week 54. In the adult subjects, 45.5% in the 5 mg/kg infliximab treatment group and 19.8% in the placebo treatment group were in clinical response at Week 54 ([ACT 1 54 Week CSR, Section 10.1.1](#)).

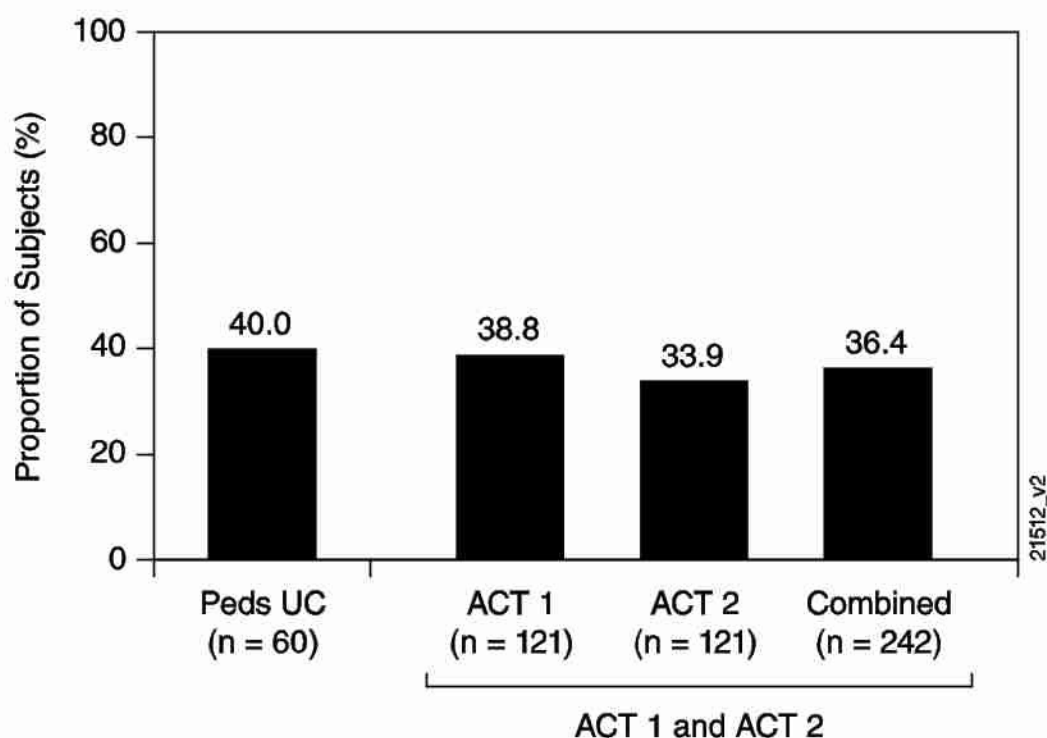
## 3.2.2 Clinical Remission

### 3.2.2.1 Clinical Remission at Week 8

The proportions of subjects in clinical remission at Week 8 were similar among pediatric (C0168T72) and adult (ACT 1 and ACT 2) subjects with UC in the 5 mg/kg infliximab treatment groups ([Figure 2](#)). When assessed using the Mayo score, 40.0% (95% CI: 27.6%, 52.4%) of pediatric subjects and 36.4% (95% CI: 30.3%, 42.4%) of adult subjects in the combined ACT studies who were in the 5 mg/kg infliximab treatment groups were in clinical remission at Week 8 compared with 10.2% (95% CI: 6.4%, 14.1%) of adult subjects in the combined ACT studies who were in the placebo treatment groups ([Appendix 1.15](#)). The proportion of pediatric subjects in remission at Week 8 when assessed using the PUCAI score was similar to that when assessed with the Mayo score (33.3% vs 40.0%, respectively).

The proportion of adult subjects in clinical remission at Week 8 was similar between subjects in ACT 1 and ACT 2 who were in the 5 mg/kg treatment group (38.8% and 33.9% in ACT 1 and ACT 2, respectively). However, for the placebo treatment group, the proportion of subjects in clinical remission at Week 8 in the ACT 1 study was greater than that in the ACT 2 study (14.9% and 5.7%, respectively, [Appendix 1.16](#)).





**Figure 2** Proportion of subjects in clinical remission at Week 8; treated subjects in the infliximab 5 mg/kg treatment group in C0168T72 and randomized subjects in the infliximab 5 mg/kg treatment groups in ACT 1 and ACT 2

### 3.2.2.2 Clinical Remission at Week 54

The proportion of pediatric subjects in the infliximab 5 mg/kg q8w maintenance treatment group in C0168T72 who were in remission at Week 54, as assessed by the PUCAI score, (8 [38.1%] of 21, 95% CI: 17.3%, 58.9%), was similar to the proportion of adult subjects in the infliximab 5 mg/kg q8w treatment group in ACT 1 who were in clinical remission at Week 54, as assessed by the Mayo score, (34.7%, 95% CI: 26.2%, 43.2%; [Appendix 1.17](#)). In the placebo treatment group in ACT 1, 16.5% (95% CI: 9.9%, 23.1%) of the adult subjects were in clinical remission at Week 54.

Because of the differences in the study designs between ACT 1 and C0168T72 (see [Section 1.1](#) and [Section 1.2](#)), different analysis populations were used in the remission analyses at Week 54 in each study. In ACT 1 the analysis population was all randomized subjects and in C0168T72 the analysis population was all subjects randomized as responders. To assess for consistency between ACT 1 and C0168T72 when similar analysis populations are used for the 2 studies, a sensitivity analysis was performed in which clinical remission for ACT 1 at Week 54 and remission for

C0168T72 at Week 54, was assessed only for subjects who were in clinical response at Week 8. This sensitivity analysis corresponds to an analysis of clinical remission at Week 54 in subjects who were responders to induction treatment. In this sensitivity analysis the proportion of pediatric subjects in the infliximab 5 mg/kg q8w maintenance treatment group who were in remission (based on the PUCAI score) at Week 54 (8 [40.0%] of 20), was similar to the proportion of adult subjects in the infliximab 5 mg/kg q8w treatment group who were in clinical remission (based on the Mayo score) at Week 54 (46.4%; [Appendix 1.18](#)).

### 3.2.3 Mucosal Healing

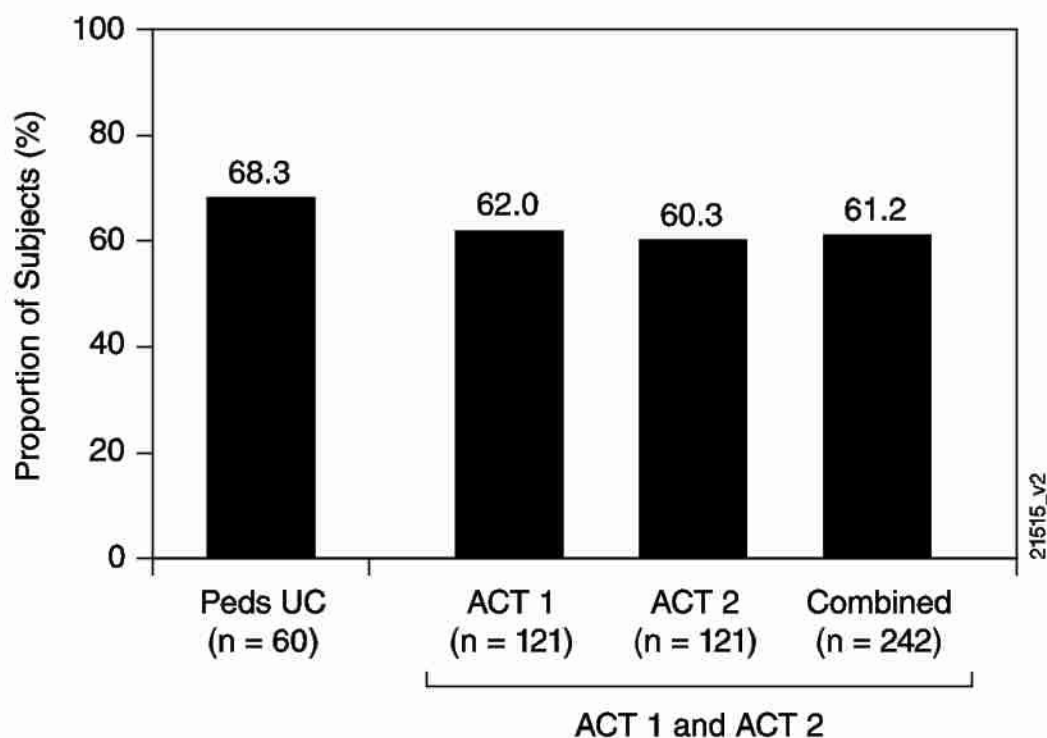
The proportions of subjects in mucosal healing at Week 8 were similar among pediatric (C0168T72) and adult (ACT 1 and ACT 2) subjects with UC in the 5 mg/kg infliximab treatment groups ([Figure 3](#)). A total of 68.3% (95% CI: 56.6%, 80.1%) of pediatric subjects and 61.2% (95% CI: 55.0%, 67.3%) of adult subjects in the combined ACT studies in the 5 mg/kg treatment groups were in mucosal healing at Week 8 compared with 32.4% (95% CI: 26.5%, 38.2%) of adult subjects in the combined ACT studies in the placebo treatment groups ([Appendix 1.19](#)).

The proportion of adult subjects in mucosal healing at Week 8 was similar between subjects in ACT 1 and ACT 2 in the 5 mg/kg infliximab treatment group (62.0% vs 60.3%; respectively) and was similar between subjects in the placebo treatment groups (33.9% vs 30.9%, respectively; [Appendix 1.20](#)).

Few subjects in C0168T72 were assessed for mucosal healing at Week 54 because a sigmoidoscopy at that timepoint was optional. Of the subjects still participating in the study at Week 54, 9 agreed to have an endoscopy at that visit. All of these subjects had achieved mucosal healing at their Week 8 visit. At the Week 54 visit, 8 (88.9%) of the 9 subjects were still in mucosal healing ([Appendix 1.5](#)).

At Week 54 in ACT 1, 45.5% of adult subjects in the 5 mg/kg infliximab treatment group were in mucosal healing compared with 18.2% of adult subjects in the placebo treatment group ([ACT 1 Week 54 CSR, Table 6](#)).





**Figure 3** Proportion of subjects in mucosal healing at Week 8; treated subjects in the infliximab 5 mg/kg treatment group in C0168T72 and randomized subjects in the infliximab 5 mg/kg treatment groups in ACT 1 and ACT 2

### 3.2.4 Mayo and Partial Mayo Scores

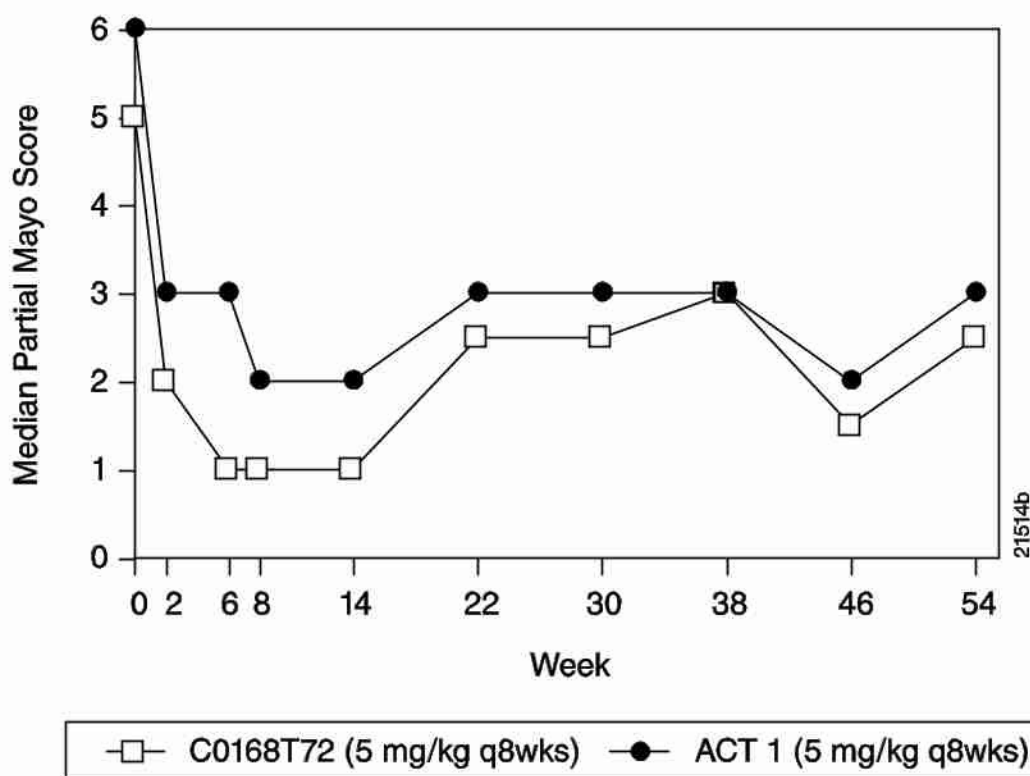
#### 3.2.4.1 Mayo Scores

The median Mayo scores were very similar between C0168T72 and the infliximab 5 mg/kg treatment group in ACT 1 at baseline (8.0 and 9.0, respectively). By Week 8, the Mayo scores had decreased such that in both studies the median Mayo score at Week 8 was 3.0 ([Appendix 1.21](#)).

#### 3.2.4.2 Partial Mayo Scores

The median partial Mayo scores for C0168T72 (5 mg/kg q8w treatment group) and ACT 1 (5 mg/kg q8w treatment group) are very similar through 54 weeks ([Figure 4](#)). In both studies, the median partial Mayo score decreased quickly during induction and remained relatively constant during maintenance treatment. The partial Mayo scores

through Week 54 for ACT 1 and C0168T72, and through Week 30 in ACT 2 are presented in [Appendix 1.22](#).



**Figure 4** Median partial Mayo score (Mayo score without endoscopy) through Week 54; randomized subjects in the 5 mg/kg q8 weeks treatment group in C0168T72 and ACT 1

### 3.2.5 Corticosteroid Reduction

Of subjects receiving corticosteroids at baseline, the proportion of subjects in remission (based on the PUCAI score) at Week 54 and not receiving corticosteroids at Week 54 was 38.5% (5 of 13 subjects) in the infliximab 5 mg/kg q8w treatment group in C0168T72. Although based on a small number of subjects, this result is consistent with the proportion of adult subjects in the infliximab 5 mg/kg q8w treatment group in ACT 1 who were receiving corticosteroids at baseline and who were in clinical remission (based on the Mayo score) and not receiving corticosteroids at Week 54 (25.7%; [ACT 1 54 Week CSR, Section 10.1.5.2](#)).

When examining corticosteroid use over time through Week 54 between C0168T72 and ACT 1, it is important to note that subjects in C0168T72 were allowed to taper corticosteroids beginning at Week 0, whereas subjects in ACT 1 were not allowed to



taper corticosteroids until Week 8. Although the specific reductions in corticosteroid use cannot be compared between C0168T72 and ACT 1 because the corticosteroid doses in C0168T72 were adjusted for body weight, substantial reductions in the corticosteroid dose were observed through Week 54 in the infliximab 5 mg/kg q8w treatment group in both of these studies. For subjects receiving corticosteroids at baseline in C0168T72, the median average daily corticosteroid dose was 0.54 mg/kg/day at baseline, and had reduced to 0.0 mg/kg/day by Week 8. The median average daily corticosteroid dose remained 0.0 mg/kg/day until Week 54 when a slight increase to 0.05 mg/kg/day was observed. For subjects receiving corticosteroids at baseline in ACT 1, the median average daily corticosteroid dose at baseline was 20 mg/day. By Week 22, the median average daily corticosteroid dose was approximately 5 mg/kg and remained at this level through Week 54. Thus, the substantial reductions in corticosteroid dose were observed in the infliximab 5 mg/kg q8w treatment groups in both C0168T72 and ACT 1.

### 3.2.6 Colectomy

In the 54 weeks after their first study administration in C0168T72, 5 (8.3%) pediatric subjects underwent a colectomy: [REDACTED] in the group that was not randomized at Week 8, 1 (4.5%) in the q8w maintenance treatment group, and [REDACTED] in the q12w maintenance treatment group (C0168T72 CSR, Attachment 4.12). Among adult subjects in the ACT studies, the proportion of subjects with a colectomy through 54 weeks was 11.6% and 14.8% for the infliximab 5 mg/kg and placebo treatment groups, respectively.

### 3.2.7 Efficacy by Immunomodulator Use

Subgroup analyses were conducted to examine the effect of the use of concomitant immunomodulators (ie, 6-MP, AZA, or MTX) on clinical response, clinical remission, and mucosal healing at Week 8 and clinical remission at Week 54 in C0168T72, ACT 1, and ACT 2 (Table 5). In these analyses, the proportion of subjects attaining an efficacy endpoint was assessed for subgroups based on subjects who received infliximab as monotherapy (ie, without a concomitant immunomodulator at baseline) or who received infliximab as combination therapy (ie, along with a concomitant immunomodulator at baseline).

Although some tendency was observed for greater efficacy in monotherapy compared with combination therapy for clinical remission and mucosal healing endpoints at Week 8 in the combined ACT studies, these endpoints showed similar results in the monotherapy and combination therapy in C0168T72. Too few subjects were in the monotherapy and combination therapy groups at Week 54 in C0168T72 to assess differences between these groups. In ACT 1 at Week 54, the proportion of subjects who maintained clinical remission was similar for the monotherapy and combination groups.

In summary, no consistent differences in efficacy were observed between the monotherapy and combination therapy groups.

**Table 5 Summary of efficacy by REMICADE monotherapy and combination therapy status; treated subjects in C0168T72 and randomized subjects in the 5 mg/kg treatment group in ACT 1, and ACT 1 and ACT 2 combined**

|                                                                       | Infliximab 5 mg/kg       |                                  |
|-----------------------------------------------------------------------|--------------------------|----------------------------------|
|                                                                       | Monotherapy <sup>a</sup> | Combination Therapy <sup>b</sup> |
| <b>Subjects treated in C0168T72</b>                                   | <b>28</b>                | <b>32</b>                        |
| Subjects in clinical response at Week 8 <sup>c,d</sup>                | 21 (75.0%)               | 23 (71.9%)                       |
| Subjects in clinical remission (Mayo score) at Week 8 <sup>c,d</sup>  | 11 (39.3%)               | 13 (40.6%)                       |
| Subjects in mucosal healing at Week 8 <sup>c,d</sup>                  | 20 (71.4%)               | 21 (65.6%)                       |
| <b>Subjects evaluable for PUCAI at Week 8<sup>e</sup></b>             | <b>27</b>                | <b>24</b>                        |
| Subjects in remission (PUCAI score) at Week 8 <sup>c,d</sup>          | 9 (33.3%)                | 8 (33.3%)                        |
| <b>Subjects evaluable for PUCAI at Week 54<sup>f</sup></b>            |                          |                                  |
| q8 wks treatment group                                                | 10                       | 11                               |
| Subjects in remission (PUCAI) at Week 54 <sup>c,d</sup>               | 3 (30.0%)                | 5 (45.5%)                        |
| q12 wks treatment group                                               | 10                       | 12                               |
| Subjects in remission (PUCAI) at Week 54 <sup>c,d</sup>               | 1 (10.0%)                | 3 (25.0%)                        |
| <b>Subjects randomized in ACT 1 and ACT 2 combined</b>                | <b>124</b>               | <b>118</b>                       |
| Subjects in clinical response at Week 8 <sup>c,d</sup>                | 87 (70.2%)               | 75 (63.6%)                       |
| Subjects in clinical remission (Mayo score) at Week 8 <sup>c,d</sup>  | 54 (43.5%)               | 34 (28.8%)                       |
| Subjects in mucosal healing at Week 8 <sup>c,d</sup>                  | 91 (73.4%)               | 57 (48.3%)                       |
| <b>Subjects randomized in ACT 1</b>                                   | <b>55</b>                | <b>66</b>                        |
| Subjects in clinical remission (Mayo score) at Week 54 <sup>c,d</sup> | 19 (34.5%)               | 23 (34.8%)                       |



**Table 5 Summary of efficacy by REMICADE monotherapy and combination therapy status; treated subjects in C0168T72 and randomized subjects in the 5 mg/kg treatment group in ACT 1, and ACT 1 and ACT 2 combined**

- <sup>a</sup> Subjects in the REMICADE monotherapy group were not receiving azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX) at baseline.
- <sup>b</sup> Subjects in the REMICADE combination therapy group were receiving concomitant treatment with AZA, 6-MP, or MTX at baseline.
- <sup>c</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in clinical response, clinical remission, remission, or in mucosal healing.
- <sup>d</sup> Subjects with insufficient data are considered to not be in clinical response, clinical remission, remission, or in mucosal healing.
- <sup>e</sup> Evaluable subjects are subjects with their first PUCAI evaluated on or prior to Week 8.
- <sup>f</sup> Evaluable subjects are subjects with their first PUCAI evaluated on or prior to Week 54.

Derived from data in Appendix 1.23, Appendix 1.24, Appendix 1.25, Appendix 1.26, Appendix 1.27, Appendix 1.28, Appendix 1.29, Appendix 1.30, Appendix 1.31

### 3.3 Summary and Discussion of Results Across Studies

C0168T72 provided clinically important evidence that infliximab was efficacious in 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.

Results of the pediatric UC study (ie, C0168T72) compared with the studies of adult subjects with UC (ie, ACT 1 and ACT 2) are notable for the similarity of efficacy during the induction and maintenance phases. All 3 studies used the standard 3-dose induction regimen of infliximab 5 mg/kg, followed by maintenance dosing. The study designs differed in that C0168T72 was an open-label study in which responders to induction dosing were randomized (at Week 8) to continue to receive infliximab 5 mg/kg in 1 of 2 dose intervals (q8w or q12w), while ACT 1 and ACT 2 were double-blind, placebo-controlled, parallel-group studies in which subjects remained on the dose to which they were randomized (at Week 0) for the duration of the study (placebo or 5 mg/kg or 10 mg/kg q8w).

The primary endpoint in C0168T72 and both ACT studies was clinical response at Week 8. In C0168T72, infliximab induced clinical response at Week 8 in 73.3% of pediatric subjects with UC, and met the protocol-specified criterion for determining that infliximab is effective for the treatment of UC in pediatric subjects since the lower limit of the 95% confidence interval for the proportion of subjects in clinical response at Week 8 was greater than 40% (ie, greater than the upper limit of the 95% CI for the placebo treatment group in the pooled ACT studies). The proportion of subjects in clinical response at Week 8 in C0168T72 was similar to the proportion of adult subjects

in clinical response at Week 8 in ACT 1 and ACT 2 at the same dose (66.9%; pooled data from the 5 mg/kg treatment groups; 69.4% in ACT 1 and 64.5% in ACT 2). In C0168T72, the consistency of clinical response at Week 8 was demonstrated based on subgroup analyses of demographics and baseline disease characteristics, as well as baseline concomitant UC medications.

Infliximab 5 mg/kg also induced clinical remission at Week 8 in pediatric subjects with UC in C0168T72. The proportion of pediatric subjects in clinical remission at Week 8, based on the Mayo score, was 40.0%. This result was comparable with the proportion of adult subjects with UC in clinical remission at Week 8 as measured by the Mayo score (36.4%, pooled data from the 5 mg/kg treatment groups) in ACT 1 and ACT 2. Notably, in C0168T72, the proportion of subjects in remission at Week 8 based on the PUCAI score (33.3%) was similar to the proportion of subjects in clinical remission at Week 8 based on the Mayo score.

Maintenance of remission at Week 54 was also demonstrated for pediatric subjects with UC who received infliximab 5 mg/kg q8w. The proportion of subjects in remission at Week 54 as assessed by the PUCAI score was 38.1% and was comparable with the proportion of adult subjects with UC in clinical remission at Week 54 based on the Mayo score in ACT 1 (34.7% of subjects in the 5 mg/kg treatment group).

It is noted that the assessments of remission at Week 54 in the C0168T72 and ACT 1 studies are based on a different efficacy tool (ie, the PUCAI score for C0168T72 and the Mayo score for ACT 1), and that the study designs differ during the maintenance phase. However, it was demonstrated by [Turner et al \(2007\)](#), as well as in the C0168T72 study, that the rigorously developed and validated PUCAI score is highly positively correlated with the Mayo score. Thus, assessments of remission based on these 2 tools are expected to be consistent. In the C0168T72 study, the proportion of subjects in clinical remission at Week 8 based on the Mayo score and the proportion of subjects in remission at Week 8 based on the PUCAI score are similar, demonstrating the consistency of the 2 tools. Comparisons of efficacy during the induction phase (ie, through Week 8) between C0168T72 and ACT 1 showed consistency of the Mayo scores at both baseline and Week 8, as well as consistency of the proportion of subjects in clinical remission at Week 8 based on the Mayo score. In addition, comparisons of efficacy during the maintenance phase demonstrated consistent partial Mayo scores over time through Week 54 in C0168T72 and ACT 1. Because the efficacy based on the Mayo score during both the induction and maintenance phases of the study are consistent over the 2 studies, and the PUCAI provides consistent efficacy to that of the Mayo score, it is expected that the results for clinical remission at Week 54 based on the Mayo score in C0168T72 (had the endoscopy score at Week 54 been available for all subjects) would have been consistent to those seen for remission at Week 54 based on the PUCAI score. With this result, as well as the known similarity of adult and pediatric UC disease, it is reasonable to compare remission at Week 54 based on the PUCAI score in C0168T72 with clinical remission at Week 54 based on the Mayo score in ACT 1.



In C0168T72, mucosal healing was induced at Week 8 in 41 (68.3%) of 60 subjects. This was consistent with 61.2% of adult subjects with UC in the pooled ACT studies. There is also evidence of maintenance of mucosal healing in the C0168T72 data. Although the endoscopy was optional at Week 54, 9 subjects had an endoscopy performed at Week 54. All of these subjects had achieved mucosal healing by their Week 8 visit, and at their Week 54 visit, 8 (88.9%) of the 9 subjects were still in mucosal healing. In ACT 1, maintenance of mucosal healing was demonstrated in 45.5% of subjects at Week 54. It is recognized that the results for mucosal healing at Week 54 in the C0168T72 study may have bias; however, the results for mucosal healing for the 9 subjects with data at Week 54, in addition to the strong results for mucosal healing at Week 54 in the ACT 1 study, as well as the consistency of the other efficacy endpoints between C0168T72 and ACT 1, make it reasonable to conjecture that the mucosal healing results would have been similar to that seen with adults if an endoscopy had been performed for all subjects in C0168T72.

When considering eliminating corticosteroid use, 38.5% of subjects receiving corticosteroids at baseline were in remission and off corticosteroids at Week 54 in the q8w maintenance treatment group in C0168T72. This is consistent with 25.7% of the adult subjects with UC in ACT 1 who were in clinical remission at Week 54 and not receiving corticosteroids at Week 54 (also in the 5 mg/kg q8w treatment group). In addition, a substantial reduction from baseline in the corticosteroid dose was observed at Week 54 in the 5 mg/kg q8w treatment group in C0168T72, and in ACT 1. A similar reduction in the corticosteroid dose was observed at Week 54.

In C0168T72, subgroup analyses based on age (6 to 11 and 12 to 17) showed that, although some differences were noted between the age groups in the efficacy measures examined, efficacy was observed in both age groups and no consistent pattern indicating greater efficacy in one of the age groups was apparent. The differences between the 6 to 11 and the 12 to 17 year old age groups, however, are difficult to assess because of the small sample sizes, particularly in the 6 to 11 year old age group (15 subjects).

Subgroup analyses were also conducted to examine the effect of the use of concomitant immunomodulators (ie, 6-MP, AZA, or MTX) on clinical response, clinical remission, and mucosal healing at Week 8 and clinical remission at Week 54 in C0168T72, ACT 1, and ACT 2. No consistent differences in efficacy were observed between subjects on monotherapy versus those on combination therapy.

Of subjects who lost response and stepped up their infliximab dose and/or dosing frequency during the maintenance phase of the study, most demonstrated an improvement in disease activity.

The quality of life for pediatric subjects in C0168T72 improved by a score of 15 at Week 8. In the 8 subjects who had at least a 1 year delay in bone age, an increase in height was observed as measured by age- and gender-specific z-scores. It also appears that subjects who had higher serum infliximab concentrations at Week 8 also had greater efficacy at Week 8 as measured by the Mayo and PUCAI scores.

In summary, C0168T72 provided clinically important evidence that infliximab was efficacious in 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. When the 2 maintenance treatment regimens used in C0168T72 were compared in terms of efficacy, the q8w maintenance treatment regimen resulted in better rates of remission. The results of this Phase 3 pediatric study also demonstrated similar drug effect in adult and pediatric UC populations with infliximab.

## 4 Analysis of Clinical Information Relevant to Dosing Recommendations

The posology being proposed for this indication is 5 mg/kg given as an induction regimen at Weeks 0, 2, and 6 followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter. Support for the maintenance regimen of every 8 weeks is based on the following results from the C0168T72 study:

- A greater proportion of subjects were in remission at Week 54 in the q8w maintenance group (38.1%) compared with the q12w maintenance group (18.2%).
- A greater proportion of subjects required step-up therapy in the q12w maintenance group (60.9%) compared with the q8w maintenance group (40.9%).
- A greater proportion of subjects receiving corticosteroids at baseline were in remission and off corticosteroids at Week 54 in the q8w maintenance group (38.5%) than in the q12w maintenance treatment group (0.0%).
- A greater proportion of subjects discontinued study agent in the q12w maintenance treatment group (47.8%) than in the q8w maintenance treatment group (18.2%).

In addition, pharmacokinetic results, presented in the [SCP](#), indicated that induction infusions of 5 mg/kg infliximab at Weeks 0, 2, and 6, followed by more frequent maintenance dosing (ie, infliximab 5 mg/kg q8w), resulted in higher trough infliximab concentrations when compared with less frequent dosing (ie, infliximab 5 mg/kg q12w). Among subjects who lost response, stepping up to a more frequent dosing regimen (ie, from 5 mg/kg q12w to 5 mg/kg q8w) led to higher serum infliximab concentrations. Subjects with higher trough serum concentrations of infliximab were shown to have generally greater response.



In summary, these data demonstrate that the q8w maintenance treatment regimen has the more favorable efficacy profile for pediatric subjects with UC. The recommended dose of infliximab for children with active UC is 5 mg/kg given as an induction regimen at Weeks 0, 2, and 6, followed by a maintenance regimen of 5 mg/kg q8w thereafter for the treatment of moderately to severely active UC.

## 5 Persistence of Efficacy and/or Tolerance Effects

The data reviewed in this document confirm the persistence of efficacy of infliximab in pediatric patients with UC. A comparison of the results in both C0168T72 and the ACT studies (ACT 1 up to 54 weeks and ACT 2 up to 30 weeks) suggests that persistence of efficacy over the course of a year is as high in pediatric patients as in adult patients. Persistence of efficacy in pediatric subjects with UC is supported by the following observations:

- 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). Furthermore, persistence of clinical response at Week 54 was demonstrated among the 9 pediatric subjects who underwent an endoscopy in C0168T72 at this timepoint.
- Clinical remission was induced at Week 8 in a similar proportion of pediatric subjects as in adult subjects (pooled data from the ACT 1 and ACT 2 studies).
- Maintenance of remission at Week 54 in pediatric subjects in the infliximab 5 mg/kg q8w maintenance treatment group was consistent with maintenance of clinical remission in adult subjects in the ACT 1 study.
- Maintenance through Week 54 of the reductions (obtained during the induction phase) in the partial Mayo score in the infliximab 5 mg/kg q8w group in C0168T72 was consistent with those observed in ACT 1.
- Consistent proportions of pediatric and adult subjects were in clinical remission and not receiving corticosteroids at Week 54 in C0168T72 and ACT 1 for subjects in the infliximab 5 mg/kg q8w treatment 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.
- Mucosal healing was induced at Week 8 in a similar proportion of pediatric and adult subjects (pooled data from the ACT 1 and ACT 2 studies). Furthermore, persistence of mucosal healing at Week 54 was demonstrated among the 9 pediatric subjects in the C0168T72 study who had an endoscopy at Week 54.

In summary, data from C0168T72 indicate that efficacy is maintained through Week 54 with an induction regimen of infliximab 5 mg/kg at Weeks 0, 2, and 6, followed by a maintenance regimen of infliximab 5 mg/kg q8w thereafter. The results from the C0168T72 study in pediatric subjects with UC are consistent with those observed in the ACT studies in adult subjects with UC, which demonstrated maintenance of effect through Week 54 in ACT 1.



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**Appendix 1.1 Number of subjects in clinical response at Week 8; treated subjects in C0168T72 and randomized subjects in the placebo and 5 mg/kg treatment groups in ACT 1 and ACT 2 combined**

|                                                | C0168T72<br>Infliximab 5 mg/kg | ACT 1 and ACT 2 Combined |                    |
|------------------------------------------------|--------------------------------|--------------------------|--------------------|
|                                                |                                | Placebo                  | Infliximab 5 mg/kg |
| Subjects randomized <sup>a</sup>               | 60                             | 244                      | 242                |
| Subjects in clinical response <sup>b,c,d</sup> | 44 (73.3%)                     | 81 (33.2%)               | 162 (66.9%)        |
| 95% confidence interval                        | (62.1%, 84.5%)                 | (27.3%, 39.1%)           | (61.0%, 72.9%)     |

<sup>a</sup> Subjects treated in C0168T72.

<sup>b</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in clinical response in C0168T72.

<sup>c</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical response in ACT 1 and ACT 2.

<sup>d</sup> Subjects with insufficient data are considered to not be in clinical response.

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**Appendix 1.2 Summary of remission status as measured by the PUCAI score and corticosteroid use at Week 54 by corticosteroid use at baseline; randomized subjects in C0168T72**

|                                                                                       | Infliximab 5 mg/kg |           |            |
|---------------------------------------------------------------------------------------|--------------------|-----------|------------|
|                                                                                       | q8 wks             | q12 wks   | Combined   |
| Subjects randomized                                                                   | 22                 | 23        | 45         |
| Subjects on corticosteroids at baseline <sup>a</sup>                                  | 14                 | 14        | 28         |
| Subjects evaluable for PUCAI at Week 54 <sup>b</sup>                                  | 13                 | 13        | 26         |
| Subjects in remission and not receiving corticosteroids at Week 54 <sup>c,d</sup>     | 5 (38.5%)          | 0 (0.0%)  | 5 (19.2%)  |
| Subjects in remission and receiving corticosteroids at Week 54 <sup>c,d</sup>         | 0 (0.0%)           | 0 (0.0%)  | 0 (0.0%)   |
| Subjects not in remission and not receiving corticosteroids at Week 54 <sup>c,d</sup> | 6 (46.2%)          | 6 (46.2%) | 12 (46.2%) |
| Subjects not in remission and receiving corticosteroids at Week 54 <sup>c,d</sup>     |                    | 7 (53.8%) | 9 (34.6%)  |
| Subjects not receiving corticosteroids at baseline <sup>a</sup>                       | 8                  | 9         | 17         |
| Subjects evaluable for PUCAI at Week 54 <sup>b</sup>                                  | 8                  | 9         | 17         |
| Subjects in remission and not receiving corticosteroids at Week 54 <sup>c,d</sup>     |                    | 4 (44.4%) | 7 (41.2%)  |
| Subjects in remission and receiving corticosteroids at Week 54 <sup>c,d</sup>         | 0 (0.0%)           | 0 (0.0%)  | 0 (0.0%)   |

**Appendix 1.2 Summary of remission status as measured by the PUCAI score and corticosteroid use at Week 54 by corticosteroid use at baseline; randomized subjects in C0168T72**

|                                                                                       | Infliximab 5 mg/kg |         |           |
|---------------------------------------------------------------------------------------|--------------------|---------|-----------|
|                                                                                       | q8 wks             | q12 wks | Combined  |
| Subjects not in remission and not receiving corticosteroids at Week 54 <sup>c,d</sup> | 5 (62.5%)          |         | 7 (41.2%) |
| Subjects not in remission and receiving corticosteroids at Week 54 <sup>c,d</sup>     | 0 (0.0%)           |         |           |

<sup>a</sup> Oral or parenteral corticosteroids includes budesonide.

<sup>b</sup> Evaluable subjects are subjects with their first PUCAI evaluated on or prior to Week 54.

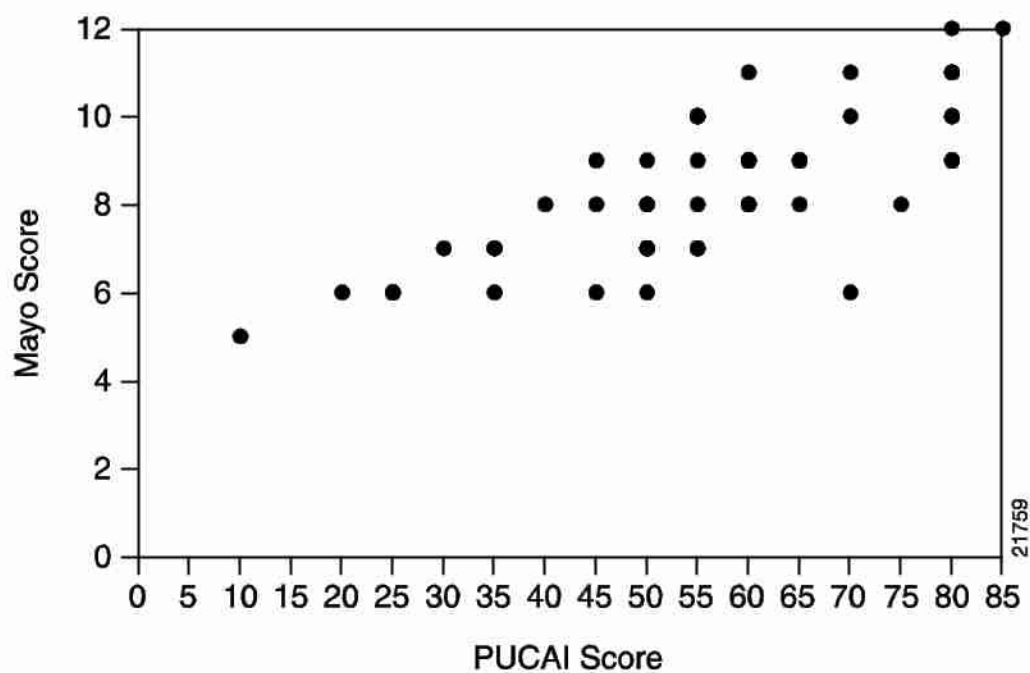
<sup>c</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, stepped up, discontinued study agent due to unsatisfactory therapeutic effect, or had insufficient data are considered to not be in remission.

<sup>d</sup> Subjects who had discontinued the study will have their last known corticosteroid information carried forward to Week 54.

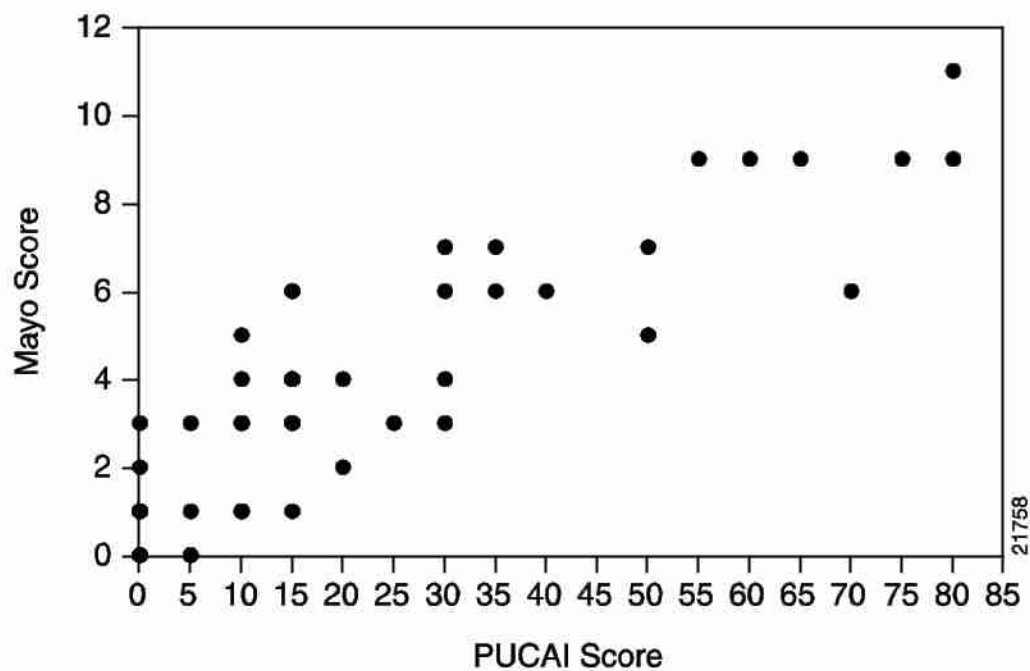
RE500:[E CREM 39 A], 23SEP2010 9:38



**Appendix 1.3 Scatter plot of Mayo score vs PUCAI score at baseline; treated subjects in C0168T72**



**Appendix 1.4 Scatter plot of Mayo score vs PUCAI score at Week 8; treated subjects in C0168T72**



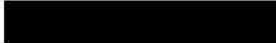
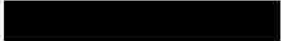
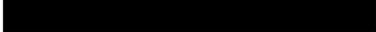
### Appendix 1.5 List of subjects with an endoscopy at Week 54; randomized subjects in C0168T72

| Treatment Group                                             | Subject ID | Baseline<br>Endoscopy Score | Week 8<br>Endoscopy Score | Week 54<br>Endoscopy Score |
|-------------------------------------------------------------|------------|-----------------------------|---------------------------|----------------------------|
| 5 mg/kg Infliximab q8 wks                                   |            | 2                           | 1                         | 0                          |
|                                                             |            | 2                           | 0                         | 0                          |
|                                                             |            | 2                           | 0                         | 0                          |
| 5 mg/kg Infliximab q12 wks                                  |            | 3                           | 1                         | 1                          |
|                                                             |            | 2                           | 1                         | 0                          |
|                                                             |            | 3                           | 0                         | 0                          |
| 5 mg/kg Infliximab q8 wks<br>--> 10 mg/kg infliximab q8 wks |            | 2                           | 1                         | 2                          |
|                                                             |            |                             |                           |                            |
| 5 mg/kg Infliximab q12 wks --> 10 mg/kg infliximab q8 wks   |            | 2                           | 0                         | 0                          |
|                                                             |            | 3                           | 1                         | 1                          |

RE500: [L E MAYO 1 A], 16SEP2010 11:44



**Appendix 1.6 Number of subjects who showed improvement after the point of step-up as measured by the partial Mayo score (Mayo score without endoscopy); step-up subjects by randomized treatment in C0168T72**

|                                                                          |            | Infliximab                                                                            |                                                                                     |
|--------------------------------------------------------------------------|------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
|                                                                          |            | 5 mg/kg q12 weeks →                                                                   |                                                                                     |
|                                                                          |            | 5 mg/kg q8 wks →<br>10 mg/kg q8 wks                                                   | 10 mg/kg q8 wks    5 mg/kg q8 wks                                                   |
| Step-up subjects by randomized treatment                                 | 9          | 8                                                                                     | 6                                                                                   |
| Subjects with Week 0S visit                                              | 9          | 8                                                                                     | 6                                                                                   |
| Subjects with Week 8S visit                                              | 7          | 5                                                                                     |  |
| Subjects who showed improvement based on partial Mayo score <sup>a</sup> | 6 (85.7%)  |    |                                                                                     |
| Subjects with Week 16S visit                                             | 6          |    |                                                                                     |
| Subjects who showed improvement based on partial Mayo score <sup>a</sup> | 6 (100.0%) |    |                                                                                     |
| Subjects with Week 24S visit                                             | 5          |  |                                                                                     |
| Subjects who showed improvement based on partial Mayo score <sup>a</sup> | 5 (100.0%) |  |                                                                                     |
| Subjects with Week 32S visit                                             | 1          |  |                                                                                     |
| Subjects who showed improvement based on partial Mayo score <sup>a</sup> | 1 (100.0%) |  |                                                                                     |
| Subjects with Week 54 visit                                              | 5          |  |                                                                                     |
| Subjects who showed improvement based on partial Mayo score <sup>a</sup> | 4 (80.0%)  |  |                                                                                     |

<sup>a</sup> Decrease in the partial Mayo score of ≥ 2 points from Week 0S visit.

RE500;[E MAYO 35 A], 14SEP2010 13:38

**Appendix 1.7 Number of subjects who showed improvement after the point of step-up as measured by the PUCAI score; step-up subjects by randomized treatment in C0168T72**

|                                                                   | Infliximab                          |                                                            |   |
|-------------------------------------------------------------------|-------------------------------------|------------------------------------------------------------|---|
|                                                                   | 5 mg/kg q8 wks →<br>10 mg/kg q8 wks | 5 mg/kg q12 weeks →<br>10 mg/kg q8 wks      5 mg/kg q8 wks |   |
| Step-up subjects by randomized treatment                          | 9                                   | 8                                                          | 6 |
| Subjects with Week 0S visit <sup>a</sup>                          | 7                                   | 7                                                          | 6 |
| Subjects with Week 8S visit                                       | 5                                   |                                                            |   |
| Subjects who showed improvement based on PUCAI score <sup>b</sup> |                                     |                                                            |   |
| Subjects with Week 16S visit                                      |                                     |                                                            |   |
| Subjects who showed improvement based on PUCAI score <sup>b</sup> | 5 (100.0%)                          |                                                            |   |
| Subjects with Week 24S visit                                      |                                     |                                                            |   |
| Subjects who showed improvement based on PUCAI score <sup>b</sup> |                                     |                                                            |   |
| Subjects with Week 32S visit                                      |                                     |                                                            |   |
| Subjects who showed improvement based on PUCAI score <sup>b</sup> |                                     |                                                            |   |
| Subjects with Week 54 visit                                       |                                     |                                                            |   |
| Subjects who showed improvement based on PUCAI score <sup>b</sup> |                                     |                                                            |   |

<sup>a</sup> Subjects with their first PUCAI score evaluated at time of step up.

<sup>b</sup> Decrease in the PUCAI score of ≥ 20 points from Week 0S visit.

RE500:[E PUCAI 6 A], 09SEP2010 16:14

## Appendix 1.8 Summary of the Mayo score at baseline and at Week 8 by age group; treated subjects in C0168T72

|                       | Infliximab 5 mg/kg |            |
|-----------------------|--------------------|------------|
|                       | Ages 6-11          | Ages 12-17 |
| Subjects treated      | 15                 | 45         |
| Baseline              |                    |            |
| n                     | 15                 | 45         |
| Mean ± SD             | 8.0 ± 1.60         | 8.2 ± 1.75 |
| Median                | 8.0                | 8.0        |
| IQ range              | (7.0, 9.0)         | (7.0, 9.0) |
| Range                 | (5, 10)            | (6, 12)    |
| Week 8 <sup>a,b</sup> |                    |            |
| n                     | 15                 | 45         |
| Mean ± SD             | 3.9 ± 3.70         | 3.4 ± 2.64 |
| Median                | 3.0                | 3.0        |
| IQ range              | (0.0, 9.0)         | (1.0, 6.0) |
| Range                 | (0, 9)             | (0, 11)    |

<sup>a</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect had their baseline value carried forward.

<sup>b</sup> Subjects with insufficient data had their last value carried forward.

RE500;[E MAYO 34 A], 26JUL2010 15:27



## Appendix 1.9 Number of subjects in clinical response at Week 8 by age group; treated subjects in C0168T72

|                                              | Infliximab 5 mg/kg |            |
|----------------------------------------------|--------------------|------------|
|                                              | Ages 6-11          | Ages 12-17 |
| Subjects treated                             | 15                 | 45         |
| Subjects in clinical response <sup>a,b</sup> | 9 (60.0%)          | 35 (77.8%) |

<sup>a</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in clinical response.

<sup>b</sup> Subjects with insufficient data are considered to not be in clinical response.

RE500;E CRES 26 C1, 26JUL2010 15:27

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**Appendix 1.10 Number of subjects in clinical remission as measured by the Mayo score at Week 8 by age group; treated subjects in C0168T72**

|                                               | Infliximab 5 mg/kg |            |
|-----------------------------------------------|--------------------|------------|
|                                               | Ages 6-11          | Ages 12-17 |
| Subjects treated                              | 15                 | 45         |
| Subjects in clinical remission <sup>a,b</sup> | 7 (46.7%)          | 17 (37.8%) |

<sup>a</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in clinical remission.

<sup>b</sup> Subjects with insufficient data are considered to not be in clinical remission.

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RE500;[E CREM 4 C], 27AUG2010 8:32

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**Appendix 1.11 Number of subjects in mucosal healing at Week 8 by age group; treated subjects in C0168T72**

|                                            | Infliximab 5 mg/kg |            |
|--------------------------------------------|--------------------|------------|
|                                            | Ages 6-11          | Ages 12-17 |
| Subjects treated                           | 15                 | 45         |
| Subjects in mucosal healing <sup>a,b</sup> | 8 (53.3%)          | 33 (73.3%) |

- <sup>a</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in mucosal healing.
- <sup>b</sup> Subjects with insufficient data are considered to not be in mucosal healing.

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RE500;JE MUCO 17 C1, 27AUG2010 8:33



**Appendix 1.12 Number of subjects in remission as measured by the PUCAI score at Week 8 by age group; treated subjects in C0168T72**

|                                      | Infliximab 5 mg/kg |            |
|--------------------------------------|--------------------|------------|
|                                      | Ages 6-11          | Ages 12-17 |
| Subjects treated                     | 15                 | 45         |
| Subjects evaluable <sup>a</sup>      | 12                 | 39         |
| Subjects in remission <sup>b,c</sup> |                    | 13 (33.3%) |

<sup>a</sup> Evaluable subjects are subjects with their first PUCAI evaluated on or prior to Week 8.

<sup>b</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in remission.

<sup>c</sup> Subjects with insufficient data are considered to not be in remission.

RE500;[E CREM 36 B], 27AUG2010 8:31

**Appendix 1.13 Number of subjects in remission as measured by the PUCAI score at Week 54 by age group; randomized subjects in C0168T72**

|                                      | Infliximab 5 mg/kg |          |          |            |         |           |
|--------------------------------------|--------------------|----------|----------|------------|---------|-----------|
|                                      | Ages 6-11          |          |          | Ages 12-17 |         |           |
|                                      | q8 wks             | q12 wks  | Combined | q8 wks     | q12 wks | Combined  |
| Subjects randomized                  | 5                  |          | 9        | 17         | 19      | 36        |
| Subjects evaluable <sup>a</sup>      | 5                  |          | 9        | 16         | 18      | 34        |
| Subjects in remission <sup>b,c</sup> |                    | 0 (0.0%) |          | 5 (31.3%)  |         | 9 (26.5%) |

<sup>a</sup> Evaluable subjects are subjects with their first PUCAI evaluated on or prior to Week 54.

<sup>b</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, stepped up, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in remission.

<sup>c</sup> Subjects with insufficient data are considered to not be in remission.

RES00;[E CREM 36 C], 27AUG2010 8:32

**Appendix 1.14 Number of subjects in clinical response at Week 8; randomized subjects in the placebo and 5 mg/kg treatment groups in ACT 1 and ACT 2**

|                                              | ACT 1          |                       | ACT 2          |                       |
|----------------------------------------------|----------------|-----------------------|----------------|-----------------------|
|                                              | Placebo        | Infliximab<br>5 mg/kg | Placebo        | Infliximab<br>5 mg/kg |
| Subjects randomized                          | 121            | 121                   | 123            | 121                   |
| Subjects in clinical response <sup>a,b</sup> | 45 (37.2%)     | 84 (69.4%)            | 36 (29.3%)     | 78 (64.5%)            |
| 95% confidence interval                      | (28.6%, 45.8%) | (61.2%, 77.6%)        | (21.2%, 37.3%) | (55.9%, 73.0%)        |

<sup>a</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical response.

<sup>b</sup> Subjects with insufficient data are considered to not be in clinical response.

RE500;E CRES 17 B1, 27AUG2010 8:33



**Appendix 1.15 Number of subjects in clinical remission as measured by the Mayo score and remission as measured by the PUCAI score at Week 8; treated subjects in C0168T72 and randomized subjects in the placebo and 5 mg/kg treatment groups in ACT 1 and ACT 2 combined**

|                                                    | C0168T72                                                                     |                                                                                      | ACT 1 and ACT 2 Combined                              |                       |
|----------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------------------|-----------------------|
|                                                    | Remission<br>(As Measured by<br>the PUCAI<br>Score)<br>Infliximab<br>5 mg/kg | Clinical<br>Remission<br>(As Measured by<br>the Mayo Score)<br>Infliximab<br>5 mg/kg | Clinical Remission<br>(As Measured by the Mayo Score) |                       |
|                                                    |                                                                              |                                                                                      | Placebo                                               | Infliximab<br>5 mg/kg |
| Subjects randomized <sup>a</sup>                   | 60                                                                           | 60                                                                                   | 244                                                   | 242                   |
| Subjects evaluable <sup>b</sup>                    | 51                                                                           | 60                                                                                   | 244                                                   | 242                   |
| Subjects in (clinical)<br>remission <sup>c,d</sup> | 17 (33.3%)                                                                   | 24 (40.0%)                                                                           | 25 (10.2%)                                            | 88 (36.4%)            |
| 95% confidence interval                            | (20.4%, 46.3%)                                                               | (27.6%, 52.4%)                                                                       | (6.4%, 14.1%)                                         | (30.3%, 42.4%)        |

<sup>a</sup> Subjects treated in C0168T72.

<sup>b</sup> Evaluable subjects in C0168T72 for remission are subjects with their first PUCAI evaluated on or prior to Week 8. Evaluable subjects in C0168T72 for clinical remission are subjects who are treated. Evaluable subjects in ACT 1 and ACT 2 combined are subjects who are randomized.

<sup>c</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in (clinical) remission. Subjects with insufficient data are considered to not be in (clinical) remission in C0168T72.

<sup>d</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical remission as measured by the Mayo score. Subjects with insufficient data are considered to not be in clinical remission as measured by the Mayo score in ACT 1 and ACT 2.

RE500;E CREM 37 A; 30AUG2010 13:34

**Appendix 1.16 Number of subjects in clinical remission as measured by the Mayo score at Week 8; randomized subjects in the placebo and 5 mg/kg treatment groups in ACT 1 and ACT 2**

|                                               | ACT 1         |                       | ACT 2        |                       |
|-----------------------------------------------|---------------|-----------------------|--------------|-----------------------|
|                                               | Placebo       | Infliximab<br>5 mg/kg | Placebo      | Infliximab<br>5 mg/kg |
| Subjects randomized                           | 121           | 121                   | 123          | 121                   |
| Subjects in clinical remission <sup>a,b</sup> | 18 (14.9%)    | 47 (38.8%)            | 7 (5.7%)     | 41 (33.9%)            |
| 95% confidence interval                       | (8.5%, 21.2%) | (30.2%, 47.5%)        | (1.6%, 9.8%) | (25.5%, 42.3%)        |

<sup>a</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical remission.

<sup>b</sup> Subjects with insufficient data are considered to not be in clinical remission.

RE500:JE CREM 9 A1, 27AUG2010 8:32

**Appendix 1.17 Number of subjects in clinical remission as measured by the Mayo score and remission as measured by the PUCAI score at Week 54; randomized subjects in the 5 mg/kg q8 weeks treatment group in C0168T72 and randomized subjects in the placebo and 5 mg/kg treatment groups in ACT 1**

|                                                 | C0168T72           | ACT 1         |                    |
|-------------------------------------------------|--------------------|---------------|--------------------|
|                                                 | Infliximab 5 mg/kg | Placebo       | Infliximab 5 mg/kg |
| Subjects randomized                             | 22                 | 121           | 121                |
| Subjects evaluable <sup>a</sup>                 | 21                 | 121           | 121                |
| Subjects in (clinical) remission <sup>b,c</sup> | 8 (38.1%)          | 20 (16.5%)    | 42 (34.7%)         |
| 95% confidence interval                         | (17.3%, 58.9%)     | (9.9%, 23.1%) | (26.2%, 43.2%)     |

<sup>a</sup> Evaluable subjects in C0168T72 are subjects with their first PUCAI evaluated on or prior to Week 54. Evaluable subjects in ACT 1 are subjects who are randomized.

<sup>b</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, stepped up, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in remission as measured by the PUCAI score. Subjects who had insufficient data are considered to not be in remission as measured by the PUCAI score in C0168T72.

<sup>c</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical remission as measured by the Mayo score. Subjects with insufficient data are considered to not be in clinical remission as measured by the Mayo score in ACT 1.

RE500;E CREM 37 B; 30AUG2010 13:34



**Appendix 1.18 Number of subjects in clinical remission as measured by the Mayo score and remission as measured by the PUCAI score at Week 54; randomized subjects in the 5 mg/kg q8 weeks treatment group in C0168T72 and randomized subjects in the placebo and 5 mg/kg treatment groups in ACT 1 (sensitivity analysis)**

|                                                          | C0168T72           | ACT 1          |                    |
|----------------------------------------------------------|--------------------|----------------|--------------------|
|                                                          | Infliximab 5 mg/kg | Placebo        | Infliximab 5 mg/kg |
| Subjects randomized                                      | 22                 | 121            | 121                |
| Subjects evaluable <sup>a</sup>                          | 21                 | 121            | 121                |
| Subjects in clinical response at Week 8 <sup>b,c,d</sup> | 20                 | 45             | 84                 |
| Subjects in (clinical) remission <sup>e,f</sup>          | 8 (40.0%)          | 16 (35.6%)     | 39 (46.4%)         |
| 95% confidence interval                                  | (18.5%, 61.5%)     | (21.6%, 49.5%) | (35.8%, 57.1%)     |

<sup>a</sup> Evaluable subjects in C0168T72 are subjects with their first PUCAI evaluated on or prior to Week 54.

Evaluable subjects in ACT 1 are subjects who are randomized.

<sup>b</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in clinical response as measured by the Mayo score in C0168T72.

<sup>c</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical response as measured by the Mayo score in ACT 1.

<sup>d</sup> Subjects with insufficient data are considered to not be in clinical response.

<sup>e</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, stepped up, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in remission as measured by the PUCAI score. Subjects with insufficient data are considered to not be in remission as measured by the PUCAI score in C0168T72.

<sup>f</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study infusion due to lack of efficacy are considered to not be in clinical remission as measured by the Mayo score. Subjects who had insufficient data are considered to not be in clinical remission as measured by the Mayo score in ACT 1.

RE500:[E CREM 38 A], 30AUG2010 13:35

**Appendix 1.19 Number of subjects in mucosal healing at Week 8; treated subjects in C0168T72 and randomized subjects in the placebo and 5 mg/kg treatment groups in ACT 1 and ACT 2 combined**

|                                              | C0168T72<br>Infliximab 5 mg/kg | ACT 1 and ACT 2 Combined |                    |
|----------------------------------------------|--------------------------------|--------------------------|--------------------|
|                                              |                                | Placebo                  | Infliximab 5 mg/kg |
| Subjects randomized <sup>a</sup>             | 60                             | 244                      | 242                |
| Subjects in mucosal healing <sup>b,c,d</sup> | 41 (68.3%)                     | 79 (32.4%)               | 148 (61.2%)        |
| 95% confidence interval                      | (56.6%, 80.1%)                 | (26.5%, 38.2%)           | (55.0%, 67.3%)     |

<sup>a</sup> Subjects treated in C0168T72.

<sup>b</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in mucosal healing in C0168T72.

<sup>c</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in mucosal healing in ACT 1 and ACT 2.

<sup>d</sup> Subjects with insufficient data are considered to not be in mucosal healing.

RE500;JE MUCO 25 A; 30AUG2010 13:33

**Appendix 1.20 Number of subjects in mucosal healing at Week 8; randomized subjects in the placebo and 5 mg/kg treatment groups in ACT 1 and ACT 2**

|                                            | ACT 1          |                       | ACT 2          |                       |
|--------------------------------------------|----------------|-----------------------|----------------|-----------------------|
|                                            | Placebo        | Infliximab<br>5 mg/kg | Placebo        | Infliximab<br>5 mg/kg |
| Subjects randomized                        | 121            | 121                   | 123            | 121                   |
| Subjects in mucosal healing <sup>a,b</sup> | 41 (33.9%)     | 75 (62.0%)            | 38 (30.9%)     | 73 (60.3%)            |
| 95% confidence interval                    | (25.5%, 42.3%) | (53.3%, 70.6%)        | (22.7%, 39.1%) | (51.6%, 69.0%)        |

<sup>a</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in mucosal healing.

<sup>b</sup> Subjects with insufficient data are considered to not be in mucosal healing.

RE500;E MUCO 25 B1, 27AUG2010 8:34



**Appendix 1.21 Summary of the Mayo score at baseline and at Week 8; treated subjects in C0168T72 and randomized subjects in the 5 mg/kg treatment group in ACT 1**

|                                  | Infliximab 5 mg/kg |             |
|----------------------------------|--------------------|-------------|
|                                  | C0168T72           | ACT 1       |
| Subjects randomized <sup>a</sup> | 60                 | 121         |
| Baseline                         |                    |             |
| n                                | 60                 | 121         |
| Mean ± SD                        | 8.1 ± 1.70         | 8.5 ± 1.72  |
| Median                           | 8.0                | 9.0         |
| IQ range                         | (7.0, 9.0)         | (7.0, 10.0) |
| Range                            | (5, 12)            | (4, 12)     |
| Week 8 <sup>b,c,d</sup>          |                    |             |
| n                                | 60                 | 121         |
| Mean ± SD                        | 3.5 ± 2.91         | 4.1 ± 3.25  |
| Median                           | 3.0                | 3.0         |
| IQ range                         | (1.0, 6.0)         | (1.0, 6.0)  |
| Range                            | (0, 11)            | (0, 12)     |

<sup>a</sup> Subjects treated in C0168T72.

<sup>b</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect had their baseline value carried forward in C0168T72.

<sup>c</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward in ACT 1.

<sup>d</sup> Subjects with insufficient data had their last value carried forward.

RE500:[E MAYO 1 A], 07SEP2010 12:17

**Appendix 1.22 Summary of the partial Mayo score (Mayo score without endoscopy) through Week 54; randomized subjects in the 5 mg/kg q8 weeks treatment group in C0168T72, ACT 1, and ACT 2**

|                     | Infliximab 5 mg/kg      |                      |                      |                                         |
|---------------------|-------------------------|----------------------|----------------------|-----------------------------------------|
|                     | C0168T72 <sup>a,c</sup> | ACT 1 <sup>b,c</sup> | ACT 2 <sup>b,c</sup> | ACT 1 and ACT 2 Combined <sup>b,c</sup> |
| Subjects randomized | 22                      | 121                  | 121                  | 242                                     |
| Baseline            |                         |                      |                      |                                         |
| n                   | 22                      | 121                  | 121                  | 242                                     |
| Mean ± SD           | 5.5 ± 1.26              | 6.1 ± 1.48           | 5.9 ± 1.29           | 6.0 ± 1.39                              |
| Median              | 5.0                     | 6.0                  | 6.0                  | 6.0                                     |
| IQ range            | (5.0, 6.0)              | (5.0, 7.0)           | (5.0, 7.0)           | (5.0, 7.0)                              |
| Range               | (4, 8)                  | (2, 9)               | (3, 9)               | (2, 9)                                  |
| Week 2              |                         |                      |                      |                                         |
| n                   | 22                      | 121                  | 121                  | 242                                     |
| Mean ± SD           | 2.2 ± 1.34              | 3.7 ± 2.11           | 3.8 ± 1.90           | 3.8 ± 2.00                              |
| Median              | 2.0                     | 3.0                  | 4.0                  | 4.0                                     |
| IQ range            | (2.0, 3.0)              | (2.0, 5.0)           | (2.0, 5.0)           | (2.0, 5.0)                              |
| Range               | (0, 4)                  | (0, 8)               | (0, 7)               | (0, 8)                                  |
| Week 6              |                         |                      |                      |                                         |
| n                   | 22                      | 121                  | 121                  | 242                                     |
| Mean ± SD           | 1.8 ± 1.92              | 3.3 ± 2.32           | 3.4 ± 2.47           | 3.3 ± 2.39                              |
| Median              | 1.0                     | 3.0                  | 3.0                  | 3.0                                     |
| IQ range            | (0.0, 4.0)              | (2.0, 5.0)           | (1.0, 5.0)           | (1.0, 5.0)                              |
| Range               | (0, 6)                  | (0, 9)               | (0, 9)               | (0, 9)                                  |
| Week 8              |                         |                      |                      |                                         |
| n                   | 22                      | 121                  | 121                  | 242                                     |
| Mean ± SD           | 1.3 ± 1.42              | 2.8 ± 2.55           | 3.0 ± 2.31           | 2.9 ± 2.43                              |
| Median              | 1.0                     | 2.0                  | 2.0                  | 2.0                                     |
| IQ range            | (0.0, 2.0)              | (1.0, 4.0)           | (1.0, 4.0)           | (1.0, 4.0)                              |
| Range               | (0, 4)                  | (0, 9)               | (0, 8)               | (0, 9)                                  |
| Week 14             |                         |                      |                      |                                         |
| n                   | 22                      | 121                  | 121                  | 242                                     |
| Mean ± SD           | 2.0 ± 2.15              | 3.2 ± 2.74           | 3.4 ± 2.56           | 3.3 ± 2.65                              |
| Median              | 1.0                     | 2.0                  | 3.0                  | 3.0                                     |
| IQ range            | (0.0, 3.0)              | (1.0, 6.0)           | (1.0, 6.0)           | (1.0, 6.0)                              |
| Range               | (0, 7)                  | (0, 9)               | (0, 8)               | (0, 9)                                  |

**Appendix 1.22 Summary of the partial Mayo score (Mayo score without endoscopy) through Week 54; randomized subjects in the 5 mg/kg q8 weeks treatment group in C0168T72, ACT 1, and ACT 2**

|                | Infliximab 5 mg/kg      |                      |                      |                                         |
|----------------|-------------------------|----------------------|----------------------|-----------------------------------------|
|                | C0168T72 <sup>a,c</sup> | ACT 1 <sup>b,c</sup> | ACT 2 <sup>b,c</sup> | ACT 1 and ACT 2 Combined <sup>b,c</sup> |
| <b>Week 22</b> |                         |                      |                      |                                         |
| n              | 22                      | 121                  | 121                  | 242                                     |
| Mean ± SD      | 2.7 ± 2.19              | 3.4 ± 2.65           | 3.6 ± 2.51           | 3.5 ± 2.58                              |
| Median         | 2.5                     | 3.0                  | 3.0                  | 3.0                                     |
| IQ range       | (1.0, 4.0)              | (1.0, 6.0)           | (2.0, 6.0)           | (1.0, 6.0)                              |
| Range          | (0, 7)                  | (0, 9)               | (0, 8)               | (0, 9)                                  |
| <b>Week 30</b> |                         |                      |                      |                                         |
| n              | 22                      | 121                  | 121                  | 242                                     |
| Mean ± SD      | 2.6 ± 2.34              | 3.5 ± 2.84           | 3.7 ± 2.55           | 3.6 ± 2.69                              |
| Median         | 2.5                     | 3.0                  | 4.0                  | 3.0                                     |
| IQ range       | (0.0, 4.0)              | (1.0, 6.0)           | (1.0, 6.0)           | (1.0, 6.0)                              |
| Range          | (0, 7)                  | (0, 9)               | (0, 9)               | (0, 9)                                  |
| <b>Week 38</b> |                         |                      |                      |                                         |
| n              | 22                      | 121                  | 0                    | 121                                     |
| Mean ± SD      | 2.6 ± 2.40              | 3.4 ± 2.81           | NA ± NA              | 3.4 ± 2.81                              |
| Median         | 3.0                     | 3.0                  | NA                   | 3.0                                     |
| IQ range       | (0.0, 4.0)              | (1.0, 6.0)           | (NA, NA)             | (1.0, 6.0)                              |
| Range          | (0, 7)                  | (0, 9)               | (NA, NA)             | (0, 9)                                  |
| <b>Week 46</b> |                         |                      |                      |                                         |
| n              | 22                      | 121                  | 0                    | 121                                     |
| Mean ± SD      | 2.5 ± 2.44              | 3.3 ± 2.85           | NA ± NA              | 3.3 ± 2.85                              |
| Median         | 1.5                     | 2.0                  | NA                   | 2.0                                     |
| IQ range       | (0.0, 4.0)              | (1.0, 6.0)           | (NA, NA)             | (1.0, 6.0)                              |
| Range          | (0, 7)                  | (0, 9)               | (NA, NA)             | (0, 9)                                  |



**Appendix 1.22 Summary of the partial Mayo score (Mayo score without endoscopy) through Week 54; randomized subjects in the 5 mg/kg q8 weeks treatment group in C0168T72, ACT 1, and ACT 2**

|           | Infliximab 5 mg/kg      |                      |                      |                                         |
|-----------|-------------------------|----------------------|----------------------|-----------------------------------------|
|           | C0168T72 <sup>a,c</sup> | ACT 1 <sup>b,c</sup> | ACT 2 <sup>b,c</sup> | ACT 1 and ACT 2 Combined <sup>b,c</sup> |
| Week 54   |                         |                      |                      |                                         |
| n         | 22                      | 121                  | 0                    | 121                                     |
| Mean ± SD | 2.7 ± 2.40              | 3.6 ± 2.92           | NA ± NA              | 3.6 ± 2.92                              |
| Median    | 2.5                     | 3.0                  | NA                   | 3.0                                     |
| IQ range  | (0.0, 5.0)              | (1.0, 6.0)           | (NA, NA)             | (1.0, 6.0)                              |
| Range     | (0, 7)                  | (0, 9)               | (NA, NA)             | (0, 9)                                  |

<sup>a</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, stepped up, or discontinued study agent due to unsatisfactory therapeutic effect had their baseline value carried forward for all subsequent visits from the time the treatment failure or step-up occurs in C0168T72.

<sup>b</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy had their baseline value carried forward from the time of the event onward in ACT 1 and ACT 2.

<sup>c</sup> Subjects with insufficient data had their last value carried forward.

RE500:[E MAYO 2 A], 07SEP2010 12:24

**Appendix 1.23 Number of subjects in clinical response at Week 8 by REMICADE monotherapy and combination therapy status; treated subjects in C0168T72**

|                                              | Infliximab 5 mg/kg       |                                  |
|----------------------------------------------|--------------------------|----------------------------------|
|                                              | Monotherapy <sup>a</sup> | Combination Therapy <sup>b</sup> |
| Subjects treated                             | 28                       | 32                               |
| Subjects in clinical response <sup>c,d</sup> | 21 (75.0%)               | 23 (71.9%)                       |

<sup>a</sup> Subjects in the REMICADE monotherapy group were not receiving azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX) at baseline.

<sup>b</sup> Subjects in the REMICADE combination therapy group were receiving concomitant treatment with AZA, 6-MP, or MTX at baseline.

<sup>c</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in clinical response.

<sup>d</sup> Subjects with insufficient data are considered to not be in clinical response.

RE500:[E CRES 26 A], 26JUL2010 15:23

**Appendix 1.24 Number of subjects in clinical response at Week 8 by REMICADE monotherapy and combination therapy status; randomized subjects in the 5 mg/kg treatment group in ACT 1 and ACT 2 combined**

|                                              | Infliximab 5 mg/kg       |                                  |
|----------------------------------------------|--------------------------|----------------------------------|
|                                              | Monotherapy <sup>a</sup> | Combination Therapy <sup>b</sup> |
| Subjects randomized                          | 124                      | 118                              |
| Subjects in clinical response <sup>c,d</sup> | 87 (70.2%)               | 75 (63.6%)                       |

<sup>a</sup> Subjects in the REMICADE monotherapy group were not receiving azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX) at baseline.

<sup>b</sup> Subjects in the REMICADE combination therapy group were receiving concomitant treatment with AZA, 6-MP, or MTX at baseline.

<sup>c</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical response.

<sup>d</sup> Subjects with insufficient data are considered to not be in clinical response.

RE500;E CRES 26 B1, 26JUL2010 15:24



**Appendix 1.25 Number of subjects in clinical remission as measured by the Mayo score at Week 8 by REMICADE monotherapy and combination therapy status; treated subjects in C0168T72**

|                                               | Infliximab 5 mg/kg       |                                  |
|-----------------------------------------------|--------------------------|----------------------------------|
|                                               | Monotherapy <sup>a</sup> | Combination Therapy <sup>b</sup> |
| Subjects treated                              | 28                       | 32                               |
| Subjects in clinical remission <sup>c,d</sup> | 11 (39.3%)               | 13 (40.6%)                       |

<sup>a</sup> Subjects in the REMICADE monotherapy group were not receiving azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX) at baseline.

<sup>b</sup> Subjects in the REMICADE combination therapy group were receiving concomitant treatment with AZA, 6-MP, or MTX at baseline.

<sup>c</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in clinical remission.

<sup>d</sup> Subjects with insufficient data are considered to not be in clinical remission.

RE500:[E CREM 4 A], 26JUL2010 15:23

**Appendix 1.26 Number of subjects in remission as measured by the PUCAI score at Week 8 by REMICADE monotherapy and combination therapy status; treated subjects in C0168T72**

|                                      | Infliximab 5 mg/kg       |                                  |
|--------------------------------------|--------------------------|----------------------------------|
|                                      | Monotherapy <sup>a</sup> | Combination Therapy <sup>b</sup> |
| Subjects treated                     | 28                       | 32                               |
| Subjects evaluable <sup>c</sup>      | 27                       | 24                               |
| Subjects in remission <sup>d,e</sup> | 9 (33.3%)                | 8 (33.3%)                        |

<sup>a</sup> Subjects in the REMICADE monotherapy group were not receiving azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX) at baseline.

<sup>b</sup> Subjects in the REMICADE combination therapy group were receiving concomitant treatment with AZA, 6-MP, or MTX at baseline.

<sup>c</sup> Evaluable subjects are subjects with their first PUCAI evaluated on or prior to Week 8.

<sup>d</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in remission.

<sup>e</sup> Subjects with insufficient data are considered to not be in remission.

RE500;[E, CREM\_36\_A], 26JUL2010 15:27

**Appendix 1.27 Number of subjects in clinical remission as measured by the Mayo score at Week 8 by REMICADE monotherapy and combination therapy status; randomized subjects in the 5 mg/kg treatment group in ACT 1 and ACT 2 combined**

|                                               | Infliximab 5 mg/kg       |                                  |
|-----------------------------------------------|--------------------------|----------------------------------|
|                                               | Monotherapy <sup>a</sup> | Combination Therapy <sup>b</sup> |
| Subjects randomized                           | 124                      | 118                              |
| Subjects in clinical remission <sup>c,d</sup> | 54 (43.5%)               | 34 (28.8%)                       |

<sup>a</sup> Subjects in the REMICADE monotherapy group were not receiving azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX) at baseline.

<sup>b</sup> Subjects in the REMICADE combination therapy group were receiving concomitant treatment with AZA, 6-MP, or MTX at baseline.

<sup>c</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical remission.

<sup>d</sup> Subjects with insufficient data are considered to not be in clinical remission.

RE500[E CREM 4 B], 26JUL2010 15:24



**Appendix 1.28 Number of subjects in remission as measured by the PUCAI score at Week 54 by REMICADE monotherapy and combination therapy status; randomized subjects in C0168T72**

|                                      | Infliximab 5 mg/kg       |         |          |                                  |         |           |
|--------------------------------------|--------------------------|---------|----------|----------------------------------|---------|-----------|
|                                      | Monotherapy <sup>a</sup> |         |          | Combination Therapy <sup>b</sup> |         |           |
|                                      | q8 wks                   | q12 wks | Combined | q8 wks                           | q12 wks | Combined  |
| Subjects randomized                  | 11                       | 10      | 21       | 11                               | 13      | 24        |
| Subjects evaluable <sup>c</sup>      | 10                       | 10      | 20       | 11                               | 12      | 23        |
| Subjects in remission <sup>d,e</sup> |                          |         |          |                                  |         | 8 (34.8%) |

<sup>a</sup> Subjects in the REMICADE monotherapy group were not receiving azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX) at baseline.

<sup>b</sup> Subjects in the REMICADE combination therapy group were receiving concomitant treatment with AZA, 6-MP, or MTX at baseline.

<sup>c</sup> Evaluable subjects are subjects with their first PUCAI evaluated on or prior to Week 54.

<sup>d</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, stepped up, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in remission.

<sup>e</sup> Subjects with insufficient data are considered to not be in remission.

RE500;[E CREM 32 A], 26JUL2010 15:24

**Appendix 1.29 Number of subjects in clinical remission as measured by the Mayo score at Week 54 by REMICADE monotherapy and combination therapy status; randomized subjects in the 5 mg/kg treatment group in ACT 1**

|                                               | Infliximab 5 mg/kg       |                                  |
|-----------------------------------------------|--------------------------|----------------------------------|
|                                               | Monotherapy <sup>a</sup> | Combination Therapy <sup>b</sup> |
| Subjects randomized                           | 55                       | 66                               |
| Subjects in clinical remission <sup>c,d</sup> | 19 (34.5%)               | 23 (34.8%)                       |

<sup>a</sup> Subjects in the REMICADE monotherapy group were not receiving azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX) at baseline.

<sup>b</sup> Subjects in the REMICADE combination therapy group were receiving concomitant treatment with AZA, 6-MP, or MTX at baseline.

<sup>c</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical remission.

<sup>d</sup> Subjects with insufficient data are considered to not be in clinical remission.

RE500;[E: CREM 4 F], 26JUL2010 15:26

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**Appendix 1.30 Number of subjects in mucosal healing at Week 8 by REMICADE monotherapy and combination therapy status; treated subjects in C0168T72**

|                                            | Infliximab 5 mg/kg       |                                  |
|--------------------------------------------|--------------------------|----------------------------------|
|                                            | Monotherapy <sup>a</sup> | Combination Therapy <sup>b</sup> |
| Subjects treated                           | 28                       | 32                               |
| Subjects in mucosal healing <sup>c,d</sup> | 20 (71.4%)               | 21 (65.6%)                       |

<sup>a</sup> Subjects in the REMICADE monotherapy group were not receiving azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX) at baseline.

<sup>b</sup> Subjects in the REMICADE combination therapy group were receiving concomitant treatment with AZA, 6-MP, or MTX at baseline.

<sup>c</sup> Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in mucosal healing.

<sup>d</sup> Subjects with insufficient data are considered to not be in mucosal healing.

RE500[E MUCO 17. A], 26JUL2010 15:23

**Appendix 1.31 Number of subjects in mucosal healing at Week 8 by REMICADE monotherapy and combination therapy status; randomized subjects in the 5 mg/kg treatment group in ACT 1 and ACT 2 combined**

|                                            | Infliximab 5 mg/kg       |                                  |
|--------------------------------------------|--------------------------|----------------------------------|
|                                            | Monotherapy <sup>a</sup> | Combination Therapy <sup>b</sup> |
| Subjects randomized                        | 124                      | 118                              |
| Subjects in mucosal healing <sup>c,d</sup> | 91 (73.4%)               | 57 (48.3%)                       |

<sup>a</sup> Subjects in the REMICADE monotherapy group were not receiving azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX) at baseline.

<sup>b</sup> Subjects in the REMICADE combination therapy group were receiving concomitant treatment with AZA, 6-MP, or MTX at baseline.

<sup>c</sup> Subjects who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in mucosal healing.

<sup>d</sup> Subjects with insufficient data are considered to not be in mucosal healing.

RE500:FE MUCO-17 B1, 26JUL2010 15:25