
Module 2.7.3 – Summary of Clinical Efficacy

REMICADE[®] (infliximab)

Crohn's Disease in Pediatric Subjects

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ABBREVIATIONS AND DEFINITION OF TERMS

6-MP	6-mercaptopurine
ACCENT	A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen
AZA	azathioprine
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CI	confidence interval
CRP	C-reactive protein
CSR	Clinical Study Report
ESR	erythrocyte sedimentation rate
IBDQ	Inflammatory Bowel Disease Questionnaire
MTX	methotrexate
PCDAI	Pediatric Crohn's Disease Activity Index
q	every
QOL	quality of life
REACH	A Randomized, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Anti-TNFα Chimeric Monoclonal Antibody (Infliximab, REMICADE®) in Pediatric Subjects with Moderate to Severe Crohn's Disease
SCE	Summary of Clinical Efficacy
SF-36	36-item short form health survey
USA	United States of America

1 BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

Crohn's disease is a chronic inflammatory bowel disorder characterized by transmural, granulomatous inflammation, involving any part of the gastrointestinal tract in a discontinuous fashion. It is estimated that 25% of new cases of Crohn's disease occur in subjects younger than 20 years of age, with the peak frequency of new cases in the pediatric population occurring in the mid- to late teens (Motil et al, 1993; Hyams, 1996).

REMICADE (infliximab) has been shown to be effective in reducing the signs and symptoms of moderately to severely active Crohn's disease in adult patients who have had an inadequate response to conventional therapy, and for reducing the number of draining enterocutaneous fistula(e) in adult patients with fistulizing Crohn's disease. Given the effectiveness of infliximab in adults, including young adults under the age of 30 years, and the similarity in the presentation of Crohn's disease in children and young adults, it was believed that infliximab would also be effective in reducing the signs and symptoms of Crohn's disease in pediatric subjects. Moreover, at the initiation of the clinical program for infliximab for the treatment of Crohn's disease in pediatric subjects, preliminary open-label studies and case reports suggested that children with Crohn's disease also respond well to infliximab (Hyams et al, 2000; Kugathasan et al, 2000; Serrano et al, 2001). To verify these findings and to further study the safety and efficacy of infliximab in pediatric subjects with Crohn's disease, 3 studies have been conducted by Centocor (Studies C0168T47 [REACH], C0168T55, and C0168T23). An overview of study designs and results is provided in the following sections.

This Summary of Clinical Efficacy (SCE) will focus primarily on presenting the efficacy results of the REACH study, with supportive data from the study of adults with Crohn's disease (C0168T21, ACCENT I), and two Phase 1 studies in pediatric subjects with Crohn's disease (C0168T23 and C0168T55). The data reported for the REACH study are the final results following 54 weeks of study. The open label data will be reported separately upon its completion.

The overall results of the REACH study are:

- Clinical response and clinical remission were induced at Week 10 in a greater proportion of pediatric subjects with Crohn's disease than in adult subjects with Crohn's disease.
- The clinical benefit of infliximab infusions in pediatric subjects with Crohn's disease persists through Week 54.
- Improvement in secondary endpoints (such as corticosteroid dosage, height status, global assessments, quality of life) in pediatric subjects with Crohn's disease support the efficacy of infliximab.
- The q8 week maintenance regimen resulted in better clinical response in pediatric subjects with Crohn's disease than the q12 week maintenance.

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In addition, results of Study C0168T23 in pediatric subjects with Crohn's disease support the efficacy of infliximab.

1.1 Study C0168T47 (REACH)

The purpose of Study C0168T47 (REACH) was to evaluate the safety, efficacy, and pharmacokinetics of 5 mg/kg infliximab administered as a 3-dose induction regimen followed by maintenance therapy in the treatment of moderately to severely active Crohn's disease in pediatric subjects.

The study was conducted at 34 sites in North America, Western Europe, and Israel. One hundred twelve (112) subjects ranging in age from 6 to 17 years were enrolled in the study to receive 5 mg/kg infliximab induction dosing at Weeks 0, 2, and 6. At Week 10, 103 subjects were randomized to 1 of 2 maintenance treatment regimens: 52 subjects were assigned to receive 5 mg/kg every 8 weeks (q8 week maintenance group) and 51 subjects were assigned to receive 5 mg/kg every 12 weeks (q12 week maintenance group). Nine subjects, who were not responders through Week 10, did not enter the maintenance phase of the study. [REDACTED] randomized to the q12 week maintenance group received treatment as though randomized to the q8 week maintenance group. This subject was included in the pharmacokinetic and safety analyses according to treatment received.

Subjects who lost response during the maintenance phase were permitted to cross over to receive infliximab at a higher dose and/or to receive infliximab more frequently. Ten subjects had increased dose from 5 mg/kg q8 weeks to 10 mg/kg q8 weeks, 12 subjects had increased frequency from 5 mg/kg q12 weeks to 5 mg/kg q8 weeks, and 13 subjects had increased dose and frequency from 5 mg/kg q12 weeks to 10 mg/kg q8 weeks. The data reported herein are the final results following 54 weeks of the study. The study plan included an open-label extension, which is currently ongoing.

The primary endpoint of the REACH study was clinical response at Week 10. Comparisons of clinical response at Week 10 in pediatric and adult subjects with Crohn's disease after an induction regimen with 5 mg/kg infliximab were then evaluated.

Major secondary analyses were:

- The proportion of subjects in clinical response at Week 54 was summarized and compared between q8 week and q12 week maintenance groups.
- The proportion of subjects in clinical remission at Week 54 was summarized and compared between q8 week and q12 week maintenance groups.
- The change from baseline in average daily corticosteroid use at Week 54 was summarized and compared between q8 week and q12 week maintenance groups.
- The change from baseline at Week 54 in height status (as measured by age and gender-specific standardized scores) was summarized.

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Other secondary analyses performed were: clinical response at Week 30; clinical remission at Weeks 10 and 30; change from baseline in quality of life (QOL) (IMPACT III score) over time; global assessment scores over time; and global assessments of change from baseline at Week 10. Additional efficacy analyses were: corticosteroid analyses, comparison of the q8 week and q12 week maintenance treatment regimens over time, and the change from baseline in Pediatric Crohn's Disease Activity Index (PCDAI; Hyams et al, 1991) and erythrocyte sedimentation rate (ESR) over time.

For the primary endpoint, and all other efficacy endpoints evaluated at or before the Week 10 visit, the study population included all subjects who were treated in the study. The study population for efficacy endpoints evaluated after Week 10 included subjects randomized at Week 10. Subjects who were treated with the induction infusions but not randomized were not included in the efficacy analyses for endpoints evaluated after Week 10. The study population for efficacy endpoints evaluated after crossover was based on their randomized treatment group at Week 10. The subject population in the adult comparison study (ACCENT I) included the subset of all subjects who were randomized to the 5 mg/kg infliximab maintenance group.

In the REACH study, the proportions of pediatric subjects who achieved clinical response at Week 10 (88.4%) and at Week 54 (48.5%) were higher than those achieved by adults in ACCENT I (66.7% and 42.9%, respectively, at Weeks 10 and 54). Comparison of the 2 maintenance treatment regimens used in the REACH study (q8 and q12 week maintenance treatment groups) indicates that the q8 week maintenance treatment regimen results in better clinical response and remission rates while maintaining an acceptable safety profile. There was a 63.5% clinical response at Week 54 for subjects in the q8 week maintenance treatment group, and a 33.3% clinical response for those subjects in the q12 week maintenance treatment group. In addition, the majority of subjects (75%) who lost response and crossed over to a more frequent dosing interval (5 mg/kg q8 weeks) or a higher dose (10 mg/kg q8 weeks), regained response. Based on these data, the q8 week maintenance treatment regimen has a favorable benefit/risk profile relative to the q12 week maintenance treatment regimen for pediatric subjects with Crohn's disease.

1.2 Adult Crohn's Disease Study C0168T21 (ACCENT I)

Study C0168T21 (ACCENT I) was conducted to determine the efficacy and safety of maintenance treatment with infliximab versus a single infusion of infliximab in providing reductions in the signs and symptoms of Crohn's disease in 580 adult subjects with moderately to severely active disease (ie, Crohn's Disease Activity Index [CDAI] ≥ 220 to ≤ 400). All subjects received infliximab 5 mg/kg at Week 0. Blinded infusions of placebo or infliximab were given at Weeks 2 and 6, and then every 8 weeks thereafter through Week 46; the maintenance groups included treatment with either 5 or 10 mg/kg of infliximab every 8 weeks following the induction regimen. Clinical remission was defined as a CDAI score <150 points.

In the ACCENT I study, treatment with either 5 mg/kg or 10 mg/kg infliximab healed intestinal mucosa in a greater proportion of subjects, and provided a more sustained improvement in the quality of life. Treatment with infliximab increased the time to loss of response and maintained a greater proportion of subjects in remission for a longer period of time (Weeks 10 and 54: $p = 0.003$ and $p < 0.001$, respectively). With infliximab treatment, a greater proportion of subjects reduced or even discontinued corticosteroids that were administered for the treatment of Crohn's disease. A description of the analyses and results from the ACCENT study are found in [Section 2.2](#).

1.3 Supportive Pediatric Studies

Two additional completed infliximab Crohn's disease studies in pediatric subjects (C0168T23 and C0168T55) are also included in this summary. A brief description of these studies and an overview of the efficacy, safety, and pharmacology results from the completed clinical studies of infliximab in pediatric subjects with Crohn's disease can be found in [Appendix Table 1](#) and in Module 2.7.6, Synopses of Individual Studies (refer to [Module 2.7.6](#)).

Study C0168T23 was a dose-blinded, randomized, single-dose, multicenter pharmacokinetic study in 21 pediatric patients between the ages of 11 and 17 years with active Crohn's disease. The study consisted of a single infusion of infliximab administered at Week 0 with a 20-week follow-up period. Patients were randomly assigned to the following dose groups: 1 mg/kg (6 patients), 5 mg/kg (7 patients), and 10 mg/kg (8 patients) infliximab using an adaptive stratification by age (< 13 ; 13 to 17) as the stratum. As an extension of the study, patients received up to 8 infusions of 5 mg/kg of infliximab over a 48-week period after the 20 week follow-up period (8 patients).

Study C0168T55 assessed the pharmacokinetics and safety of a single, open-label, intravenous infusion of 5 mg/kg infliximab in younger pediatric subjects (planned age range: 6 to 11 years) with inflammatory bowel disease (Crohn's disease, ulcerative colitis, or indeterminate colitis), who were receiving maintenance treatment with 5 mg/kg commercial REMICADE. Six subjects with a primary diagnosis of Crohn's disease, ranging in age from 9 to 11 years, were enrolled and received a single infusion of 5 mg/kg infliximab at Week 0. Each of the 6 subjects had received at least 4 doses of commercial REMICADE prior to study entry. The planned follow-up period was up to 12 weeks depending on the subject's commercial REMICADE maintenance dosing interval.

1.4 Format and Content of this Summary of Clinical Efficacy

[Section 2](#) of this SCE provides a review of the results observed in the individual studies. The adult Crohn's disease study (Study C0168T21, ACCENT I) is provided as the control population for comparison of effect in the main study of the safety and efficacy of infliximab in pediatric subjects with Crohn's disease (Study C0168T47). The pediatric pharmacokinetic studies in Crohn's disease, Study C0168T23 and Study C0168T55 are

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provided here as additional supportive information for treatment with infliximab for Crohn's disease in pediatric subjects. No additional integrated pediatric data are included in this submission.

[Section 3](#) of this summary presents a comparison and discussion of results across studies, including the following:

- A discussion of the efficacy results observed across the Crohn's disease studies in pediatric subjects (Studies C0168T47 and C0168T23),
- A comparison of efficacy results observed in pediatric subjects relative to those observed in adult subjects with Crohn's disease (Study C0168T21)

1.5 Efficacy Conclusions

Results of the studies in pediatric subjects with Crohn's disease and comparison of these results with those for adults with Crohn's disease indicate that the efficacy profile of infliximab is generally comparable in pediatric and adult patients with Crohn's disease. Accordingly, a dosing schedule similar to that for adults is recommended for pediatric subjects, namely, an induction regimen with 5 mg/kg infliximab administered at Weeks 0, 2, and 6, and maintenance treatment with 5 mg/kg infliximab administered every 8 weeks.

2 SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

A tabular summary of the study design from the studies included in this SCE are provided in [Appendix Table 1](#). Module 2.7.6 contains synopses of the individual studies (refer to [Module 2.7.6](#)).

2.1 Study C0168T47

A description of REACH was provided in [Section 1.1](#).

2.1.1 Demographic and Baseline Disease Characteristics

The majority of the 103 randomized subjects in this study population were males (62/103, 60.2%); 85 (82.5%) overall were Caucasian, 15 (14.6%) were Black, 1 was Asian, and were of "Other" ethnicities. Overall, demographic characteristics at baseline were generally well balanced across the two maintenance treatment groups. The median age of randomized subjects was 13.0 years (range, 6 to 17 years). The distribution of REACH subjects by age is displayed in [Table 1](#).

Table 1 REACH Subjects by Age Group

Age Group, years	Number of Subjects	%
6 to 8		
9		
10	7	6.3%
11	10	8.9%
12	12	10.7%
13	20	17.9%
≥ 14	55	49.1%

The median duration of Crohn's disease for all subjects was 1.6 years (range, 0.3 to 7.0 years) with a 4-month median duration of symptoms (range, 0.3 to 42.0 months). The median PCDAI score was 40 and the median ESR was 36 mm/hr at baseline.

Subjects were receiving a stable treatment regimen with Crohn's disease medications (including corticosteroids, immunomodulatory agents, or aminosalicylates) at study entry. Thirty five percent (35.0%) of randomized subjects were receiving corticosteroids, 98.1% were receiving immunomodulatory agents, and 54.4% were receiving aminosalicylates. A total of 90.3% of subjects were receiving 6-mercaptopurine (6-MP) or azathioprine (AZA) and 8.7% were receiving MTX. No subjects were receiving treatment with mycophenolate mofetil, cyclosporine, sirolimus, or tacrolimus. Concomitant medical therapy for Crohn's disease was to remain stable through Week 54 except for corticosteroids, which could be tapered beginning at Week 2 (refer to [C0168T47 Clinical Study Report \[CSR\], Section 8.3](#)).

2.1.2 Primary Efficacy Results

The proportion of subjects achieving clinical response to infliximab at Week 10 was 88.4% (99/112) in pediatric subjects (REACH) compared with 66.7% (128/192) in adults (refer to [C0168T47 CSR, Attachment 3.1](#)). As shown in ([Figure 1](#)), the confidence intervals for the proportion of subjects in clinical response at Week 10 for the pediatric population in the REACH study lay completely above the confidence interval for the adult population in the ACCENT I study, and on this basis, the REACH study met its primary endpoint.

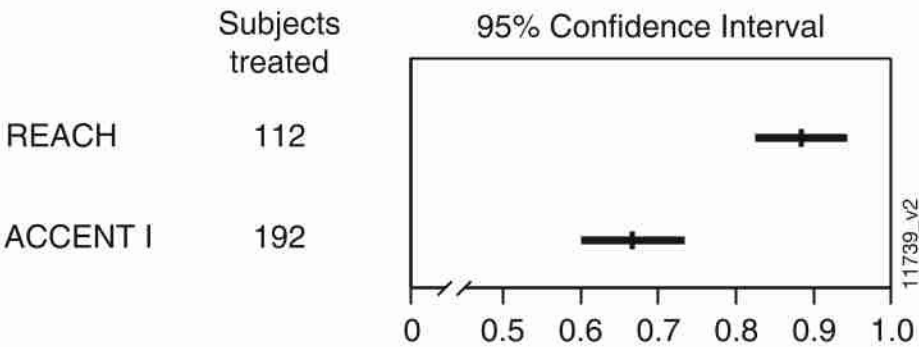


Figure 1 95% confidence intervals for the proportion of subjects in clinical response at Week 10; treated subjects

Subjects who discontinued the study, had insufficient data to assess their clinical response status, had a prohibited Crohn’s disease-related surgery, or had prohibited concomitant medication changes were considered not to be in clinical response, regardless of their PCDAI/CDAI score. For the ACCENT I study, subjects considered in clinical response at Week 10 were determined using the rules outlined in the REACH CSR (refer to [C0168T47 CSR, Section 6.3.1](#)). Subjects treated in ACCENT I were all subjects randomized at Week 2 to the infliximab 5 mg/kg maintenance treatment group.

The primary endpoint analysis was robust to changes in analysis rules regarding missing data and treatment failures. In sensitivity analyses in which the treatment failure rules were suspended and the last value carried forward was used (for subjects who discontinued the study or had insufficient data), the proportion of subjects in clinical response at Week 10 was greater for REACH (92.9%) than for adults in ACCENT I (70.7 %). The 95% confidence intervals (CIs) for REACH were above those for ACCENT I (refer to [C0168T47 CSR, Attachment 3.2](#)). Results from a sensitivity analysis based on only those subjects who were receiving concomitant immunomodulators (AZA, 6-MP, or methotrexate [MTX]) at baseline provided a similar conclusion. In this analysis the proportion of subjects in clinical response was 89.1% (98/110) in REACH and 64.7% (33/51) in ACCENT I studies, with the CI for REACH above the CI for ACCENT I (refer to [C0168T47 CSR, Attachment 3.3](#)).

2.1.3 Secondary Efficacy Results

Results of the secondary endpoint analyses support the efficacy of infliximab infusions q8 weeks in the treatment of pediatric subjects with Crohn’s disease. These results are summarized below and in the REACH CSR (refer to [C0168T47 CSR, Section 10.2](#)).

2.1.3.1 Clinical Response Analyses through Week 54

The proportion of subjects in clinical response at Week 54 was significantly greater for subjects randomized to the q8 week maintenance treatment group (63.5%, 33/52) than for subjects randomized to the q12 week maintenance treatment group (33.3%, 17/51; $p = 0.002$). A significant difference between the maintenance treatment groups was also seen at Week 30; a greater proportion of subjects in the q8 week maintenance treatment group achieved clinical response (73.1%, 38/52) than the proportion of subjects randomized to the q12 week maintenance treatment group (47.1%, 24/51; $p = 0.007$; Figure 2).

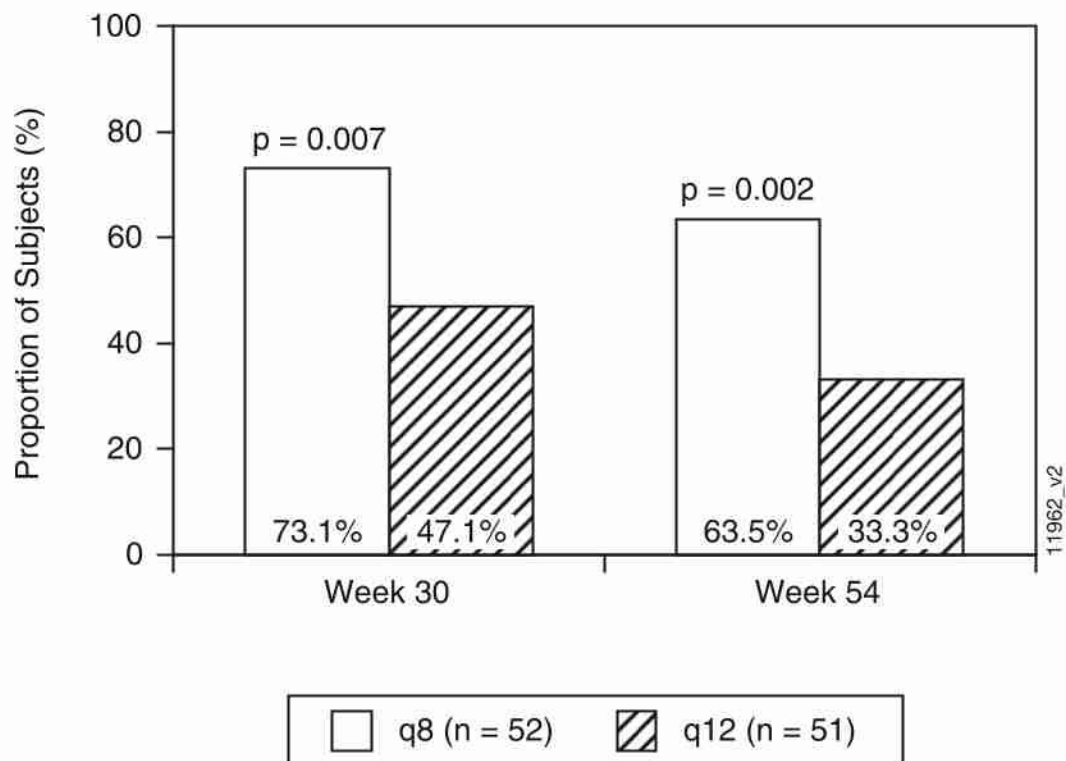


Figure 2 Summary of proportion of subjects in clinical response through Week 54; randomized subjects

Subjects who discontinued the study, had insufficient data to assess their clinical response status, had a prohibited Crohn's disease-related surgery, had prohibited concomitant medication changes, or crossed over were considered to not be in clinical response at the timepoint of interest and at any timepoint thereafter, regardless of their PCDAI score.

The analyses of clinical response at Week 30 and Week 54 were robust to changes in the analysis rules regarding treatment failures, insufficient data, and whether subjects crossed over. Subjects who discontinued the study, had insufficient data to assess their clinical response status, or crossed over had their last PCDAI score carried forward to the

timepoint of interest. The proportion of subjects in clinical response in the q8 week maintenance treatment group was significantly greater than the proportion of subjects in the q12 week maintenance treatment group at Weeks 30 ($p = 0.028$) and 54 ($p = 0.012$) (refer to C0168T47 CSR, Attachments 3.6 and 3.7).

2.1.3.2 Clinical Remission Analyses

The clinical remission results were better for the q8 week maintenance treatment regimen at both Weeks 54 and 30. At Week 54, a significantly greater proportion of subjects randomized to the q8 week maintenance treatment group (55.8% [29/52]) were in clinical remission compared with the proportion of subjects randomized to the q12 week maintenance treatment group (23.5% [12/51]; $p < 0.001$). At Week 30, a significantly greater proportion of subjects randomized to the q8 week maintenance treatment group (59.6% [31/52]) were in clinical remission compared with the proportion of subjects randomized to the q12 week maintenance treatment group (35.3% [18/51]; $p = 0.013$; Figure 3).

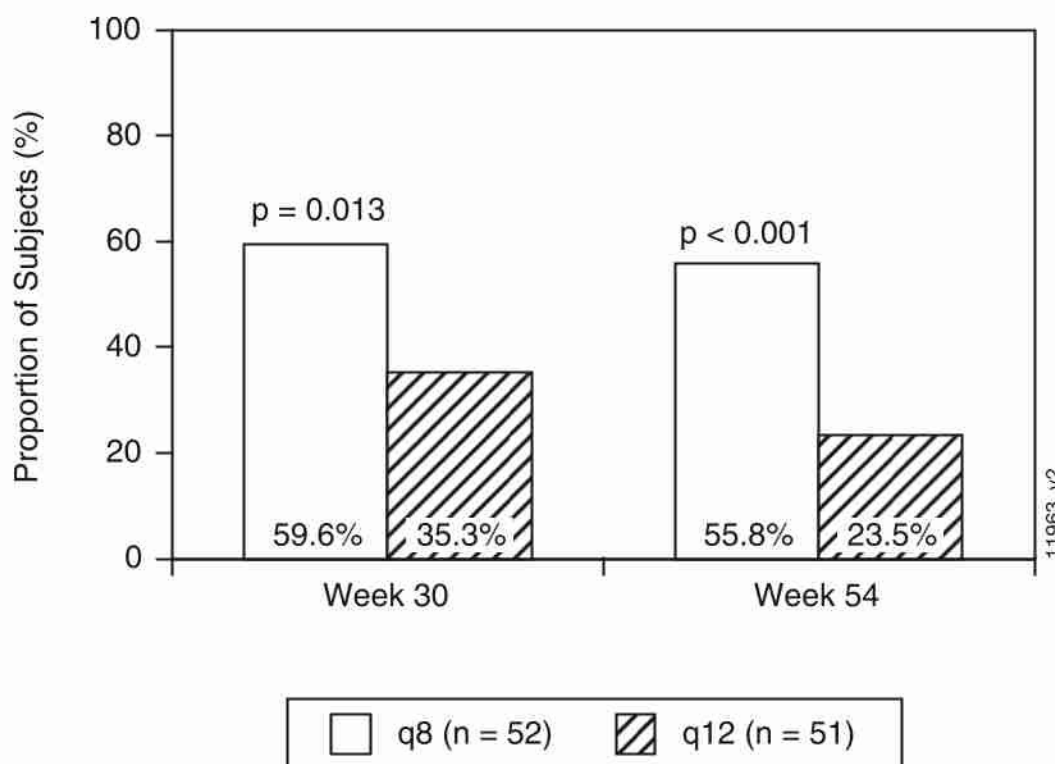


Figure 3 Summary of proportion of subjects in clinical remission through Week 54; randomized subjects

Subjects who discontinued the study, had insufficient data to assess their clinical remission status, had a prohibited Crohn's disease-related surgery, had prohibited concomitant medication changes, or crossed over are considered to not be in clinical remission at the timepoint of interest and at any timepoint thereafter, regardless of their PCDAI score.

Sensitivity analyses demonstrated that this secondary efficacy analysis was robust to changes in analysis rules regarding treatment failures. Subjects who discontinued the study, had insufficient data to assess their clinical response status, or crossed over had their last PCDAI score carried forward to the timepoint of interest. The proportion of subjects in clinical remission in the q8 week maintenance treatment group was significantly greater than the proportion of subjects in the q12 week maintenance treatment group at Week 30 ($p = 0.023$) and Week 54 ($p < 0.001$) (refer to [C0168T47 CSR](#), [Attachments 3.10](#) and [3.11](#)).

Clinical remission results from REACH at Week 10 were compared with the clinical remission results from ACCENT I at Week 10. In REACH, 58.9% (66/112) of the subjects were in clinical remission at Week 10 compared with 39.1% (75/192) of the subjects in ACCENT I. A similar result was observed in the associated sensitivity analyses. Subjects who discontinued the study or had insufficient data for assessment of their clinical remission status had their last PCDAI/CDAI score carried forward, irrespective of Crohn's disease-related surgery and prohibited concomitant medication changes (refer to [C0168T47 CSR](#), [Section 10.2.2](#)).

2.1.3.3 Corticosteroid Dosage Analyses

The number of subjects on corticosteroids and the median average daily corticosteroid dose were notably different at baseline between the q8 week and q12 week maintenance treatment groups (refer to [C0168T47 CSR](#), [Section 10.2.3](#)). At baseline, in those subjects receiving corticosteroids, the median average daily corticosteroid dose in the q8 week maintenance treatment group was 0.3 mg/kg/day, while the median average daily corticosteroid dose was 0.6 mg/kg/day in the q12 week maintenance treatment group. A substantial reduction in median corticosteroid use had occurred by Week 10 in both groups and was maintained through Week 54. In both treatment groups, by the first maintenance visit (Week 14 and Week 18, respectively) at least 50% of the subjects in each group had discontinued corticosteroids, as indicated by the median dose of 0 observed in [Figure 4](#). No significant difference in the change from baseline in corticosteroid dose was noted between the q8 week and q12 week maintenance treatment groups through Week 54.

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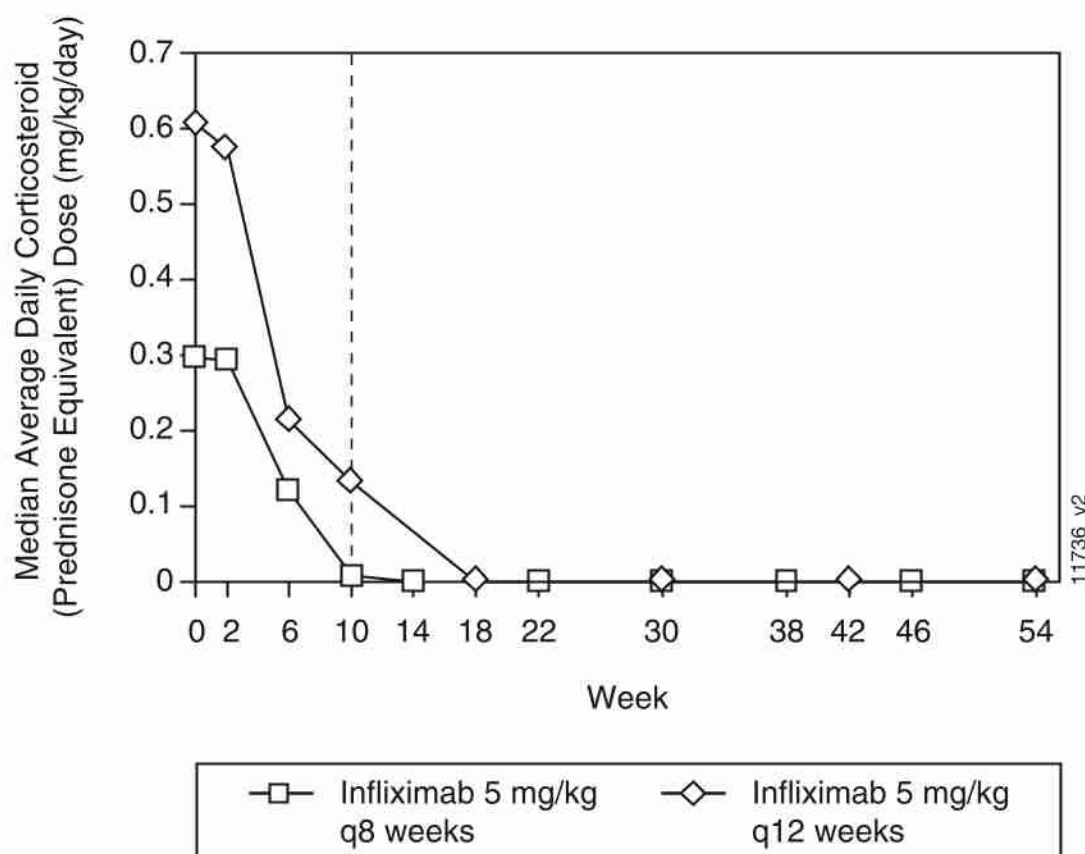


Figure 4 Summary of median average daily corticosteroid (prednisone equivalent) dose (mg/kg/day) through Week 54; randomized subjects taking corticosteroids at baseline

Subjects who crossed over had their average daily corticosteroid value for the 6 days prior to crossover carried forward for all subsequent timepoints.

When the q8 week and q12 week maintenance treatment groups were combined, the change from baseline in average daily corticosteroid use was significant at Weeks 10, 30, and 54 ($p < 0.001$ for all comparisons; refer to C0168T47 CSR, Attachment 3.13). A consistently greater proportion of subjects on corticosteroids at baseline were in clinical remission and off corticosteroids from Week 30 through Week 54 in the q8 week than in the q12 week maintenance treatment group (refer to C0168T47 CSR, Section 10.2.3). A consistently greater proportion of subjects on corticosteroids at baseline were able to discontinue corticosteroids from Week 30 through Week 54 in the q8 week maintenance treatment group compared with the q12 week maintenance treatment group (refer to C0168T47 CSR, Attachment 3.14).

2.1.3.4 Height Status Analyses

The height z-score is a measure of the deviation of the subject's height from the expected height for a population of the same age and gender. In the population studied, the z-scores significantly improved from baseline at both Week 30 ($p < 0.001$) and Week 54 ($p < 0.001$) (refer to [C0168T47 CSR, Attachment 3.15](#)).

2.1.4 Other Efficacy Endpoints

These results for other secondary efficacy endpoints are summarized below and in the REACH CSR (refer to [C0168T47 CSR, Section 10.3](#)).

2.1.4.1 Global Assessments Analyses

Global assessments by subject, parent/guardian, and the investigator were performed at each visit. A 5-point scale was used to assess the subject's general well being from the perspective of the subject and the parent/guardian. The investigator provided a subjective rating of the subject's condition using a 4-point scale.

Of 103 subjects randomized at Week 10, the median subject's, physician's, and parent/guardian's global assessment scores were all 3.0 at baseline. At Week 10, all global assessment scores had improved (decreased). The improvement (decrease) in the global assessment scores continued through Week 54, at which time the median of the subject's and the physician's global assessment scores were both 1.0, and the parent/guardian's global assessment score was 2.0 (refer to [C0168T47 CSR, Attachment 3.18](#)).

2.1.4.2 Quality of Life Analyses

IMPACT III is a pediatric QOL questionnaire specifically developed to assess the QOL in patients with inflammatory bowel disease. The mean change from baseline of the IMPACT III score at Week 10 (-22.9) was significant ($p < 0.001$, all treated subjects) (refer to [C0168T47 CSR, Attachment 3.19](#)). The IMPACT III score also showed a significant mean improvement at Weeks 30 (-21.1) and 54 (-24.3; $p < 0.001$ for both timepoints, randomized subjects) (refer to [C0168T47 CSR, Attachment 3.20](#)).

2.1.4.3 Pediatric Crohn's Disease Activity Index

At Weeks 2, 6, and 10, the median PCDAI reduction from baseline was -22.5, -27.5, and -30, respectively. The improvement of PCDAI score was seen as early as 2 weeks after the first study agent administration. The median PCDAI decreased from 40 at baseline to a median of 10 at Week 10. When PCDAI was examined for the combined q8 week and q12 week populations, the mean change from baseline in PCDAI score was significant at Weeks 30 and 54 ($p < 0.001$ for the combined groups at both timepoints) (refer to [C0168T47 CSR, Attachment 3.22](#)).

2.1.4.4 ESR

When the q8 week and q12 week maintenance treatment groups were combined, the change from baseline in ESR was significant at Weeks 10, 30, and 54 ($p < 0.001$ for all comparisons) (refer to [C0168T47 CSR, Attachment 3.23](#)).

2.1.4.5 Clinical Response Following Crossover

Of the 103 subjects randomized, 35 (34.0%) subjects crossed over between Week 10 and Week 54. Nearly half (25/51) of the subjects in the q12 week maintenance treatment group lost response and crossed over compared to less than 20.0% (10/52) in the q8 week maintenance treatment group.

Of the 35 subjects who crossed over, 32 subjects satisfied the criteria for being evaluable in the analysis of regained response. Evaluable subjects were in clinical response at Week 10 as well as at some point during their maintenance phase, and subsequently lost response prior to crossover. Of the 32 subjects evaluated, 24 (75.0%) subjects regained response after crossing over. Clinical response was regained after crossing over in 55.6% (5/9) of subjects from the q8 week maintenance treatment group and in 82.6% (19/23) of subjects from the q12 week maintenance treatment group. For the q12 week maintenance treatment group, 92.3% (12/13) of subjects regained response after crossing over from q12 week maintenance treatment group to the 10 mg/kg q8 week regimen; 70.0% (7/10) of subjects regained response after crossing over from the q12 week maintenance treatment group to the 5 mg/kg q8 week regimen (refer to [C0168T47 CSR, Section 10.3.5](#)).

2.1.4.6 Subgroup Analyses

The primary efficacy endpoint, clinical response at Week 10, was examined by demographic and baseline disease characteristic subgroups (sex, race, age [≤ 13 years old, > 13 years old], weight [≤ 42 kg, > 42 kg], and severity [$\text{PCDAI} \leq 40$, $\text{PCDAI} > 40$] and duration of disease [≤ 1 year, > 1 year]). A summary table for clinical response, at Week 10 by demographic and baseline disease characteristics, is located in [Appendix Table 2](#). The relationship between baseline corticosteroid use and efficacy is discussed below in [Section 2.1.4.6.1](#).

The proportions of REACH subjects in clinical response at Week 10 were consistently high and similar to what was observed in overall subjects across the various demographic subgroups examined. The overall proportion of subjects in REACH achieving clinical response to infliximab at Week 10 was 88.4% (99/112). The proportion of female subjects achieving clinical response to infliximab at Week 10 was 89.1% (41/46), compared with 87.9% (58/66) of male subjects. With respect to race, the proportion of Black subjects achieving clinical response to infliximab at Week 10 was 93.3% (14/15), compared with 87.2% (82/94), response observed in Caucasian subjects. The proportion of subjects who weighed ≤ 42 kg at baseline that were in clinical response at Week 10 was 91.2% (52/57), compared with 85.5% (47/55) of subjects who weighed > 42 kg. The

proportion of subjects ≤ 13 years old achieving clinical response to infliximab at Week 10 was 91.2% (52/57), compared with 85.5% (47/55) in subjects > 13 years old. The distribution of REACH subjects by age is located in [Table 1](#).

Clinical response at Week 10 was slightly higher in subjects with more severe disease at baseline, but was the same with respect to disease duration (≤ 1 year, > 1 year). The proportion of subjects in clinical response at Week 10, with a baseline PCDAI > 40 , was 93.8% (45/48), compared with 84.4% (54/64) in subjects with a baseline PCDAI ≤ 40 . The proportion of subjects in clinical response at Week 10 with disease duration ≤ 1 year was 88.9% (32/36), compared with 88.2% (67/76) in subjects with disease duration > 1 year.

2.1.4.6.1 Relationship of Corticosteroid Use and Efficacy

As previously described in [Section 2.1.3.3](#), the number of subjects on corticosteroids and the median average daily corticosteroid dose were notably different at baseline between the q8 week and q12 week maintenance treatment groups (refer to [C0168T47 CSR](#), [Section 10.2.3](#)). At baseline, in those subjects receiving corticosteroids, the median average daily corticosteroid dose in the q8 week maintenance treatment group was 0.3 mg/kg/day, while the median average daily corticosteroid dose was 0.6 mg/kg/day in the q12 week maintenance treatment group.

In the q12 week maintenance treatment group, subjects on corticosteroids at baseline and subjects not on corticosteroids at baseline had generally similar proportions in clinical response and remission (refer to [C0168T47 CSR](#), [Attachments 3.25](#) and [3.26](#)). In the q8 week maintenance treatment group, subjects not on corticosteroids at baseline had a greater proportion in clinical response and remission than subjects on corticosteroids at baseline.

2.2 Adult Crohn's Disease Study C0168T21 (ACCENT I)

A description of ACCENT I was provided in [Section 1.2](#).

2.2.1 Demographic and Baseline Disease Characteristics

In the ACCENT I study, no significant differences were observed among treatment groups in categories of sex, race, age, or height (CSR, Table 11; in EMEA/H/C/240/II/25). A difference in weight, however, was observed among the treatment groups ($p = 0.017$). Within each treatment group 61.2% were female. A majority (94.0%) of the patients were Caucasian and the median age of patients was 35 years.

Among all patients randomized as responders, the median duration of Crohn's disease was 7.5 years. The baseline median CDAI for all treatment groups was 299.

2.2.2 Efficacy Results

These results are summarized below and in the ACCENT I CSR (refer to C0168T21 CSR, Section 7; in EMEA/H/C/240/II/25).

2.2.2.1 Evaluation of Efficacy

The CDAI was the primary tool for assessing clinical response to infliximab therapy in this study. Observations during endoscopic examinations were used to determine mucosal healing, and the Crohn's Disease Endoscopic Index of Severity (CDEIS) was the tool used to evaluate endoscopic findings. Two quality of life assessments, the Inflammatory Bowel Disease Questionnaire (IBDQ), which is a disease-specific quality of life assessment, and the SF-36, which is a nondisease-specific quality-of-life assessment, were performed periodically during the study. C-reactive protein (CRP) was used to assess systemic inflammatory activity.

2.2.2.2 Primary Endpoint

For patients receiving infliximab maintenance treatment, the median time to loss of response through Week 54 was greater than for patients receiving placebo maintenance. The median time to loss of response through Week 54 (ie, the primary endpoint) was 38 weeks and greater than 54 weeks for the 5 mg/kg and 10 mg/kg infliximab maintenance groups, respectively, versus 19 weeks for the placebo maintenance group ($p = 0.002$ and $p < 0.001$ in pairwise comparisons, respectively). Sensitivity analyses confirmed that these results were robust.

2.2.2.3 Secondary Endpoints

At Weeks 10, 30, and 54, a significantly greater proportion of patients in the combined infliximab maintenance groups were in clinical response than patients in the placebo maintenance group ($p = 0.008$, $p < 0.001$, and $p < 0.001$, respectively). At Week 54, almost 3 times as many patients were in clinical response in the combined infliximab maintenance groups compared with the placebo maintenance group (42.9% versus 15.5%, respectively).

At Weeks 10 and 54, a significantly greater proportion of patients in the combined infliximab maintenance groups ($p = 0.003$ and $p < 0.001$, respectively) were in clinical remission than were patients in the placebo maintenance group. At Week 54, approximately 2.5 times as many patients were in clinical remission in the combined infliximab maintenance groups compared with the placebo maintenance group (33.3% versus 13.6%, respectively). Approximately 3 times as many patients in the combined infliximab maintenance groups were in sustained clinical remission than in the placebo maintenance group. From Week 14 to Week 54, 21% of patients in the combined infliximab maintenance group were in remission versus 7% in the placebo maintenance group.

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Changes in CDAI showed rapid and significant improvement in patients receiving infliximab maintenance therapy compared with placebo maintenance. Median CDAI scores were at or near the remission levels (defined as a CDAI score < 150 points) for all treatment groups at Week 2. Through Week 54, median CDAI scores worsened for patients in the placebo maintenance group, but stayed at or near remission levels for the infliximab maintenance groups.

Initial improvement in IBDQ scores was observed for all treatment groups. By Week 10, the change from baseline was lower in the placebo maintenance group than the combined infliximab maintenance group. This difference was maintained through Week 54.

Both the physical and mental components of the SF-36 improved from baseline. The change from baseline in the SF-36 physical component summary scores at Weeks 10, 30, and 54 were significantly greater for the combined infliximab maintenance groups than for the placebo maintenance group ($p < 0.001$ for all comparisons). Additionally, significant differences in the changes from baseline SF-36 in the mental component summary scores were observed between placebo and infliximab maintenance groups, in favor of infliximab at Week 54 ($p = 0.023$).

A greater number of patients, randomized as responders, in the combined infliximab maintenance group achieved mucosal healing at Weeks 10 and 54 than in the placebo maintenance group (at Week 10, 31.1% versus 0.0% and at Week 54, 63.2% versus 0.0%).

Among patients randomized as responders who were receiving corticosteroids at baseline, a significantly greater proportion of patients in both infliximab maintenance treatment groups received ≤ 10 mg/day (prednisone equivalent) for ≥ 3 months than patients in the placebo maintenance group; approximately 45.5% of the combined infliximab maintenance treatment group versus approximately 17% of the placebo maintenance group were receiving this dose. The median number of weeks that ≤ 10 mg/day (prednisone equivalent) was received for patients in the placebo maintenance group was 5.5 weeks versus 35.5 and 41.0 weeks for patients in the 5 and 10 mg/kg infliximab maintenance groups, respectively.

Among patients randomized as responders who were receiving corticosteroids at baseline, approximately 3 times as many patients in the combined infliximab maintenance group had discontinued all corticosteroids and were in clinical remission at Week 54 than in the placebo maintenance group (28.1% versus 8.9%, respectively, $p = 0.004$). For the 5 and 10 mg/kg infliximab maintenance groups, these values were 24.1% and 32.1%, respectively ($p = 0.029$, and $p = 0.002$ for pairwise comparisons with the placebo maintenance group).

2.2.2.4 Subgroup Analyses

Consistency in the 54-week primary endpoint outcome across various subgroups was assessed by looking at treatment comparisons within each subgroup, using odds ratios

and 95% confidence intervals. Consistent treatment benefit for infliximab maintenance treatment versus placebo maintenance treatment was observed across all subgroups defined by demographic characteristics, geographic location, baseline disease characteristics, and concomitant medication.

2.3 Supportive Crohn's Disease Studies in Pediatric Subjects (C0168T23 and C0168T55)

Descriptions of Study C0168T23 and Study C0168T55 were provided in [Section 1.3](#).

2.3.1 Demographic and Baseline Disease Characteristics

In the C0168T23 Crohn's disease study, given the small sample size, the distribution of patients across treatment groups was well balanced. Among all patients, the median age at enrollment was 15.0 years (range 11 to 17 years). Among all patients, 90.5% were Caucasian and 71.4% were male (refer to [C0168T23 CSR, Section 5.3.1, Table 4](#)). Among all 21 treated patients, the median disease duration was 3.8 years, with a range of 1.0 to 9.0 years, and the median PCDAI at baseline was 43 with a range of 30 to 73.

In the C0168T55 Crohn's disease study all 6 subjects enrolled and treated were Caucasian: [REDACTED] were male and [REDACTED] were female (refer to [C0168T55 CSR, Table 3](#)). Age ranged from 9 to 11 years (median: 9.0 years). The duration of Crohn's disease ranged from 0.6 to 4.4 years.

In general, the demographic and baseline disease characteristics were balanced across all of the studies of Crohn's disease in pediatric subjects.

2.3.2 Efficacy Results

The results from the 20-week portion of C0168T23 showed that infliximab was effective in the treatment of Crohn's disease, as measured by the positive correlation between the change from baseline at Week 4 for the endoscopist's lesion severity score, and the modified CDAI and PCDAI. Notably, all subjects achieved clinical response (defined as a ≥ 70 -point reduction in the modified CDAI score or a ≥ 10 -point reduction in the PCDAI) at some point during the 20 week period. Clinical remission (defined as a reduction in the modified CDAI score to < 150 points or a reduction in the PCDAI to < 10 points) was achieved by 47.6% of the evaluated subjects during the first 20 weeks and was greatest in the 5 mg/kg and 10 mg/kg treatment groups. Results from the 48-week retreatment extension of C0168T23 showed that, in general, most subjects generally demonstrated improvement following retreatment with infliximab. Limited information on the magnitude of benefit was available and duration of benefit was varied. Detailed results of the C0168T23 study can be found in the C0168T23 CSR (refer to [C0168T23 48-Week CSR](#)). In addition, an addendum to the C0168T23 study report for biopsy results, that were initially planned to be discussed in the 48-week retreatment extension supplemental report, is found in CTD Module 1 (refer to [C0168T23 Biopsy](#)

[Addendum to the 20-Week CSR](#)). Efficacy was not formally evaluated in Study C0168T55.

3 COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

A summary of the results of REACH, ACCENT I, and Study C0168T23 is located in Module 2.7.6 (refer to [Module 2.7.6](#)). No pooled efficacy analyses are presented.

3.1 Demographics and Baseline Disease Characteristics

The demographic data and baseline disease characteristics for REACH were presented in [Section 2.1.1](#). The demographic data and baseline disease characteristics for ACCENT I were presented in [Section 2.2.1](#). The demographic data and baseline disease characteristics for Study C0168T23 were presented in [Section 2.3.1](#).

Based on differences in study design and the populations studied, meaningful comparisons of demographic and other baseline characteristics between the pediatric studies with the adult study are limited to race, sex, disease duration, and baseline disease severity. The majority of subjects in the REACH and ACCENT I studies were Caucasian females; the majority of subjects in the C0168T23 study were Caucasian males.

At baseline the median duration of Crohn's disease in REACH was 1.6 years compared with 3.8 years in Study C0168T23, and 7.5 years in ACCENT I. The median PCDAI score in REACH was 40. In Study C0168T23, the range in the PCDAI at baseline was 30 to 73, and the range in the modified CDAI at baseline was 175 to 566. The baseline median CDAI in ACCENT I was 299.

3.2 Comparison of Efficacy Results of All Studies

Formal comparisons with the ACCENT I adult study population were performed as part of the planned efficacy analyses for REACH. Comparisons with REACH for clinical response and remission at Week 10 were presented in [Sections 2.1.2](#) and [2.1.3.2](#), respectively.

In REACH, 58.9% of subjects were in clinical remission at Week 10 compared with 39.1% of subjects in ACCENT I. In REACH, 59.6% of subjects were in clinical remission at Week 30 compared with 38.9% of subjects in ACCENT I. At Week 54, 55.8% of subjects in the REACH study compared with 28.3% of subjects in the ACCENT I study were in clinical remission (the 30- and 54-week comparisons include the 5 mg/kg q8 week infliximab groups from both the REACH and ACCENT I studies).

In addition to clinical response and clinical remission, other benefits of the use of infliximab that were seen in ACCENT I were also seen in REACH. Pediatric subjects in the REACH study had a substantial reduction in median corticosteroid dose by Week 10 that was maintained through Week 54. Furthermore, at least half of these pediatric subjects had discontinued corticosteroid use by the time of their first maintenance

treatment visit. In addition, a greater proportion of subjects on corticosteroids at baseline were in remission and off corticosteroids at Week 54 in the q8 week maintenance treatment group (45.8%) than in the q12 week maintenance treatment group (16.7%). This proportion of subjects in remission and off corticosteroids at Week 54 in the q8 week maintenance treatment group in the REACH trial was similar to that seen in the ACCENT I 5 mg/kg q8 week maintenance group (24.1%). Given the well recognized toxicity of long term corticosteroid use, particularly in children (Hyams and Markowitz, 2005), this steroid sparing effect of infliximab therapy may have important long term health benefits to children with Crohn's disease.

The limited efficacy data from Study C0168T23 also supports the efficacy of infliximab in the treatment of Crohn's disease in pediatric subjects. Although the number of subjects in Study C0168T23 was small (21 subjects), efficacy results, as demonstrated by clinical remission, were comparable to those in the REACH study. In C0168T23, clinical remission was achieved by 47.6% of the evaluated subjects during the first 20 weeks compared with 55.8% in clinical remission in the q8 week maintenance treatment group and 23.5% in the q12 week maintenance treatment group at Week 54 in the REACH study. Results from the 48-week retreatment extension of C0168T23 showed that most subjects generally demonstrated improvement following retreatment with infliximab.

3.3 Comparison of Results in Subpopulations

Due to the small numbers of subjects in subgroups and to differences in study designs, no formal comparisons of results were made between subpopulations of the respective studies. A discussion of results in subpopulations in the REACH study was presented in [Section 2.1.4.6](#).

4 ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

The REACH study has provided clinically important evidence that infliximab is efficacious in pediatric subjects with Crohn's disease, with similar efficacy as seen in adults. The q8 week maintenance treatment regimen was better than the q12 week maintenance treatment regimen in maintaining clinical response and remission at both Week 30 and Week 54.

Pharmacokinetic results, presented in Module 2.7.2, the Summary of Clinical Pharmacology (refer to [Module 2.7.2](#)), indicated that induction infusions of 5 mg/kg infliximab at Weeks 0, 2, and 6, followed by more frequent maintenance dosing (ie, 5 mg/kg infliximab every 8 weeks), resulted in a lower proportion of subjects with undetectable trough infliximab concentration when compared to less frequent dosing (ie, 5 mg/kg infliximab every 12 weeks). Among subjects who lost response, crossing over to an increased dose of infliximab or a more frequent dosing regimen led to a sustained presence of infliximab in the serum. Subjects with higher preinfusion serum concentrations of infliximab were shown to have generally greater response.

These data demonstrate that the q8 week maintenance treatment regimen has the more favorable efficacy profile for pediatric subjects with Crohn's disease. The recommended dose of infliximab for children with active Crohn's disease 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 for the treatment of moderately to severely active Crohn's disease.

4.1 Dose Response

At Week 30, the REACH q8 week maintenance treatment group showed significant improvement over the q12 week maintenance treatment group with respect to both clinical remission (59.6% versus 35.3%, respectively; $p = 0.013$) and clinical response (73.1% versus 47.1%, respectively; $p = 0.007$). This level of clinical improvement continued through Week 54, when a significantly higher proportion of subjects in the q8 week maintenance treatment group compared with the q12 week maintenance treatment group achieved clinical remission (55.8% versus 23.5%, respectively; $p < 0.001$) and clinical response (63.5% versus 33.3%, respectively; $p = 0.002$). The superior efficacy seen in the q8 week compared with the q12 week maintenance treatment group is likely related to the higher infliximab trough levels seen in the q8 week maintenance treatment group.

4.2 Relationship of Pharmacokinetics and/or Pharmacodynamics and Efficacy

To relate the median change from baseline in PCDAI score to infliximab exposure, the serum infliximab concentrations at Week 54 were categorized into 4 ranges: $< 0.1 \mu\text{g/mL}$, 0.1 to $< 1 \mu\text{g/mL}$, 1 to $< 10 \mu\text{g/mL}$, and $\geq 10 \mu\text{g/mL}$. At Week 54, the improvement in the PCDAI score from baseline was greatest (41.3) in subjects with median infliximab concentrations $\geq 10 \mu\text{g/mL}$ (refer to C0168T47 CSR, Figure 10).

The improvement from baseline in the PCDAI score was greater (32.5) in subjects with infliximab concentrations of 1 to $< 10 \mu\text{g/mL}$ and 0.1 to $< 1 \mu\text{g/mL}$, respectively compared with an improvement of 27.5 in subjects with serum infliximab concentrations of $< 0.1 \mu\text{g/mL}$. Thus, subjects with higher preinfusion serum infliximab concentrations had generally higher responses as measured by the PCDAI score than subjects with lower preinfusion serum infliximab concentrations.

4.3 Antibodies to Infliximab and Clinical Response

An evaluation of antibody to infliximab status and clinical response and remission was performed to determine the influence of antibodies to infliximab on the efficacy of infliximab in pediatric subjects with Crohn's disease in the REACH study. These data did not suggest an effect of antibodies to infliximab on clinical response (refer to C0168T47 CSR, Attachment 3.24). However, it should be noted that there were a limited number of subjects in several of the subgroups in this analysis; hence, the data should be interpreted with caution. For a complete summary of the incidence of antibodies to infliximab, see the REACH CSR (refer to C0168T47 CSR, Section 11.5.3).

5 PERSISTENCE OF EFFICACY EFFECTS

In the REACH study, benefit from infliximab therapy was greater than that reported for the adult Crohn's disease study population at Week 10, and was also consistently maintained through Week 30 and Week 54. Additional supporting evidence for the efficacy of infliximab in pediatric Crohn's disease includes the following:

- Clinical response and clinical remission were induced at Week 10 in a greater proportion of pediatric Crohn's disease subjects than in the adult Crohn's disease subjects (ACCENT I study).
- The q8 week maintenance treatment regimen was more effective than the q12 week maintenance treatment regimen in maintaining clinical response and remission at Week 30 and Week 54 (see [Figure 2](#) and [Figure 3](#)).
- Subjects with active Crohn's disease who were on corticosteroids at baseline were able to reduce corticosteroid use. A substantial reduction in median corticosteroid use was observed by Week 10. A consistently greater proportion of subjects on corticosteroids at baseline were able to discontinue corticosteroids from Week 30 through Week 54 in the q8 week maintenance treatment group compared with the q12 week maintenance treatment group. Both maintenance treatment groups maintained reduced corticosteroid use through Week 54. No significant difference in the change from baseline in corticosteroid dose was noted between the q8 week and q12 week maintenance treatment groups through Week 54.
- The height status (measured as z-score) for pediatric subjects with Crohn's disease was significantly improved at both Weeks 30 and 54.
- Subject, physician, and parent/guardian global assessment scores were numerically improved after treatment with infliximab when compared with baseline.
- The QOL for pediatric subjects with Crohn's disease was significantly improved at Weeks 10, 30, and 54 in the subgroup evaluated.
- The improvement of PCDAI score was seen as early as 2 weeks after the first study agent administration and continued through Week 10. When the q8 week and q12 week maintenance treatment groups were combined, the significant improvement from baseline in PCDAI score observed at Week 10 was maintained at both Week 30 and Week 54.
- The improvement in ESR was evident when first examined at Week 10 and continued improvement was observed through Week 54.

In addition to clinical response and clinical remission, some other benefits of the use of infliximab that were seen in ACCENT I were also seen in REACH. Pediatric subjects in the REACH study had a substantial reduction in median corticosteroid dose by Week 10 that was maintained through Week 54. Furthermore, at least half of these pediatric

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subjects had discontinued corticosteroid use by the time of their first maintenance treatment visit.

In summary, comparison of the 2 maintenance treatment regimens used in the REACH study indicates that the q8 week maintenance treatment regimen results in better clinical response and remission rates while maintaining an acceptable safety profile. There was a 63.5% clinical response at Week 54 for subjects in the q8 week maintenance treatment group, and a 33.3% clinical response for those subjects in the q12 week maintenance treatment group. Based on these data, the q8 week maintenance treatment regimen has a favorable efficacy profile relative to the q12 week maintenance treatment regimen for pediatric subjects with Crohn's disease.

6 **APPENDIX**

Appendix Table 1	Completed and ongoing Crohn’s disease clinical trials in pediatric subjects and supportive adult Crohn’s disease study...30
Appendix Table 2	Number of subjects in clinical response at Week 10 by demographics and baseline disease characteristics; treated subjects.....32

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Appendix Table 1 Completed and ongoing Crohn's disease clinical trials in pediatric subjects and supportive adult Crohn's disease study			
Protocol No. (No. of Sites)	Study Start – End Dates	Study Design	Dose Groups/Regimens (No. of Subjects)
C0168T23 (7; 20-Week Portion) (4; 48-Week Retreatment Extension)	Jul 98 – May 99 (20-week portion) Apr 99 – Jan 01 (48-week retreatment extension)	Phase 1/2, randomized, single-dose, study of anti-tumor necrosis factor (TNF) chimeric monoclonal antibody (infliximab) in the treatment of pediatric subjects with active Crohn's disease. <u>48-Week Retreatment Extension:</u> Open-label	<u>20-Week Portion:</u> Single infusion of 1 mg/kg (6), 5 mg/kg (7) or 10 mg/kg (8), infliximab. <u>48-Week Retreatment Extension:</u> Subjects received up to 8 infusions of 5 mg/kg infliximab over a 48-week period (8).
C0168T47 REACH (34)	Feb 2003 – Apr 2005	Phase 3, randomized, open-label study to evaluate the safety and efficacy of infliximab in pediatric subjects with moderate to severe Crohn's disease.	Induction: All subjects (112) will receive an induction regimen of 5 mg/kg infliximab at Weeks 0, 2, and 6. Maintenance: Responders at Week 10 will be randomized to receive 5 mg/kg infliximab every 8 weeks (Group I) or every 12 weeks (Group II) through Week 46. Nonresponders/Loss of Response: Nonresponders to induction dosing at Week 10 will be discontinued from the study. Group I nonresponders will be eligible to receive 10 mg/kg infliximab every 8 weeks. Group II subjects who lose response at or before 8 weeks after the previous infliximab infusion will be eligible to receive 10 mg/kg infliximab every 8 weeks. Group II subjects who lose response $\geq$ 8 weeks but $\leq$ 12 weeks after the previous infliximab infusion will be eligible to receive 5 mg/kg infliximab every 8 weeks. Subjects completing treatment through Week 46 may enter an open-label extension beginning at Week 54 for a period of up to 1 year.

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Appendix Table 1 Completed and ongoing Crohn's disease clinical trials in pediatric subjects and supportive adult Crohn's disease study			
Protocol No. (No. of Sites)	Study Start – End Dates	Study Design	Dose Groups/Regimens (No. of Subjects)
C0168T55 (2)	May 2003 – Sep 2004	Phase 1, open-label study to evaluate the safety and pharmacokinetics of a single infusion of infliximab in pediatric Crohn's disease subjects receiving maintenance treatment with infliximab.	Single 250 mL infusion of 5 mg/kg infliximab (6).
C0168T21 ACCENT 1 (55)	Feb 99 – Mar 01	Phase 3, randomized, double-blind, placebo-controlled trial of maintenance infliximab dosing in subjects with moderately to severely active Crohn's disease.	Induction therapy: 5 mg/kg infliximab at Week 0; maintenance therapy (Week 2): Placebo at Weeks 2 and 6, then q 8 weeks (188), 5 mg/kg at Weeks 2 and 6, then q 8 weeks (192), or 5 mg/kg at Weeks 2 and 6, then 10 mg/kg q 8 weeks (193). Subjects who responded to treatment and subsequently lost their clinical benefit were eligible to crossover to episodic retreatment (5 mg/kg infliximab). Placebo to 5 mg/kg (92), 5 mg/kg to 10 mg/kg infliximab (58), or 10 mg/kg to 15 mg/kg (51) infliximab.

Appendix Table 2 Number of subjects in clinical response at Week 10 by demographics and baseline disease characteristics; treated subjects

	Infliximab 5 mg/kg
Subjects treated	112
Sex	
Male	
n	66
Subjects in clinical response ^a	58 (87.9%)
95% confidence interval	(80.0%, 95.8%)
Female	
n	46
Subjects in clinical response	41 (89.1%)
95% confidence interval	(80.1%, 98.1%)
Race	
Caucasian	
n	94
Subjects in clinical response ^a	82 (87.2%)
95% confidence interval	(80.5%, 94.0%)
Black	
n	15
Subjects in clinical response ^a	14 (93.3%)
95% confidence interval	(80.7%, 100%)
Asian	
n	
Subjects in clinical response ^a	
95% confidence interval	
Other	
n	
Subjects in clinical response ^a	
95% confidence interval	
Age	
≤ 13 years	
n	57
Subjects in clinical response ^a	52 (91.2%)
95% confidence interval	(83.9%, 98.6%)

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Appendix Table 2 Number of subjects in clinical response at Week 10 by demographics and baseline disease characteristics; treated subjects

	Infliximab 5 mg/kg
> 13 years	
n	55
Subjects in clinical response ^a	47 (85.5%)
95% confidence interval	(76.1%, 94.8%)
Severity of disease	
PCDAI ≤ 40	
n	64
Subjects in clinical response ^a	54 (84.4%)
95% confidence interval	(75.5%, 93.3%)
PCDAI > 40	
n	48
Subjects in clinical response ^a	45 (93.8%)
95% confidence interval	(86.9%, 100%)
Duration of disease	
≤ 1 year	
n	36
Subjects in clinical response ^a	32 (88.9%)
95% confidence interval	(78.6%, 99.2%)
> 1 year	
n	76
Subjects in clinical response ^a	67 (88.2%)
95% confidence interval	(80.9%, 95.4%)
Weight	
≤ 42 kg	
n	57
Subjects in clinical response ^a	52 (91.2%)
95% confidence interval	(83.9%, 98.6%)
> 42 kg	
n	55
Subjects in clinical response ^a	47 (85.5%)
95% confidence interval	(76.1%, 94.8%)

^a Subjects who discontinued the study, had insufficient data to assess their clinical response status, had a prohibited Crohn's disease-related surgery, or had prohibited concomitant medication changes are considered to not be in clinical response, regardless of their PCDAI score.

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