

Module 2.7.2 - Summary of Clinical Pharmacology Studies

REMICADE[®] (infliximab)

Pediatric Ulcerative Colitis.

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Abbreviations and Definition of Terms

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ACT	<u>A</u> ctive <u>U</u> lcerative <u>C</u> olitis <u>T</u> rial
ATI	antibodies to infliximab
AUC _τ	area under the plasma concentration-time curve for a dose interval
AZA	azathioprine
BSV	between-subject variability
CL	total clearance of drug after intravenous administration
C _{max}	maximum observed concentration
ELISA	enzyme-linked immunosorbent assay
IBD	inflammatory bowel disease
IV	intravenous
LOQ	Limit of quantification
LLOQ	lower limit of quantification
MTX	methotrexate
PK	pharmacokinetic(s)
Q	intercompartmental clearance
q8w	every 8 weeks
q12w	every 12 weeks
REACH	A <u>R</u> andomized, <u>M</u> ulticenter, <u>O</u> pen-label Study to <u>E</u> valuate the Safety and Efficacy of <u>A</u> nti TNF α <u>C</u> himeric Monoclonal Antibody (Infliximab, REMICADE [®]) in Pediatric Subjects with Moderate to Severe Crohn's Disease
RSE	relative standard error
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
t _{1/2}	half-life
UC	ulcerative colitis
V ₁	volume of distribution in the central compartment
V ₂	volume of distribution of the peripheral compartment
V _{ss}	apparent volume of distribution at steady state after intravenous administration

1 Background and Overview

This Summary of Clinical Pharmacology (SCP) presents a summary of the pharmacokinetic (PK) and immunogenicity data for infliximab (REMICADE®) in support of the application for the use of infliximab in the treatment of pediatric ulcerative colitis (UC).

1.1 Clinical Studies and Target Indication

In addition to a summary of PK and immunogenicity data from the Phase 3 study in pediatric subjects with UC (C0168T72), this SCP compares the PK and immunogenicity results of infliximab in C0168T72 with the PK and immunogenicity of infliximab from the following studies in adult and pediatric subjects with inflammatory bowel disease (IBD):

- Two Phase 3 studies in adult subjects with active UC C0168T37 (ACT 1) and C0168T46 (ACT 2).
- One Phase 3 study C0168T47 (REACH) in pediatric subjects with active Crohn's disease.

The study designs, infliximab dosing regimens, PK and immunogenicity sampling schemes, and PK analyses in these studies are summarized in [Table 1 \(C0168T72 CSR, REACH CSR, ACT 1 54-week CSR and ACT 2 30-week CSR\)](#).

Table 1 Summary of Clinical Studies				
	C0168T72	C0168T37 (ACT 1)	C0168T46 (ACT 2)	C0168T47 (REACH)
Disease indication and subject population	Pediatric UC (moderate to severe)	Adult UC (moderate to severe)	Adult UC (moderate to severe)	Pediatric Crohn's Disease (moderate to severe)
Study design	Phase 3, randomized, open-label study	Phase 3, randomized, placebo-controlled, double-blind, 3-arm, parallel study	Phase 3, randomized, placebo-controlled, double-blind, 3-arm, parallel study	Phase 3, randomized, open-label study
Dose Groups/Regimens (No. of Subjects)	Induction: All subjects (n = 60) received an induction regimen of 5 mg/kg infliximab at Weeks 0, 2, and 6. Maintenance: Responders at Week 8 were randomized to receive 5 mg/kg infliximab every 8 weeks (Group I, n = 22) or every 12 weeks (Group II, n = 23) through Week 46 for Group I and Week 42 for Group II.	Infusions of placebo (n = 121), 5 mg/kg (n = 121) or 10 mg/kg (n = 122) infliximab at Weeks 0, 2, 6 and every 8 weeks thereafter through Week 46.	Infusions of placebo (n = 123) or infliximab at 5 mg/kg (n = 121) or 10 mg/kg (n = 120) at Weeks 0, 2, 6, 14, and 22.	Induction: All subjects (n = 112) received an induction regimen of 5 mg/kg infliximab at Weeks 0, 2, and 6. Maintenance: Responders at Week 10 were randomized to receive 5 mg/kg infliximab every 8 weeks (Group I, n = 52) or every 12 weeks (Group II, n = 51) through Week 46.
Age Median (Range)	14.5 years (6 to 17)	40.0 years (18 to 81)	38.0 years (18 to 82)	13.0 years (6 to 17)
Body Weight Median (Range)	51 kg (23 to 92)	77 kg (40 to 159)	75 kg (42 to 177)	42 kg (20 to 98)

Table 1 Summary of Clinical Studies				
	C0168T72	C0168T37 (ACT 1)	C0168T46 (ACT 2)	C0168T47 (REACH)
PK Sampling	Pre-infusion samples prior to every infusion; Post-infusion samples 1 hour after the end of infusions at Weeks 0, 2, 6 and after the last infusion (Week 46 for q8w and Week 42 for q12w); Samples at non-infusion visits of Weeks 8 and 54.	Pre-infusion samples prior to study agent infusion at Weeks 0, 2, 6, 14, 30, 38 and 46; Post-infusion samples 1 hour after the end of infusions at Week 0, 2, 6, 14 and 46; Samples at noninfusion visits of Weeks 8 and 54.	Pre-infusion samples prior to study agent infusion at Weeks 0, 2, 6, and 14; Post-infusion samples 1 hour after the end of infusions at Week 0 and 2; Samples at noninfusion visits of Weeks 8 and 30.	Pre-infusion samples prior to every infusion; Post-infusion samples 1 hour after the end of infusions at Weeks 0, 2, 6 and after the last infusion (Week 46 for q8w and Week 42 for q12w); Samples at non-infusion visits of Weeks 10 and 54.
Pharmacokinetic Modeling Approach	Population PK modeling	Individual Compartmental PK modeling (ACT 1 only) Population PK conducted using pooled data from ACT 1 and ACT 2 (Fasanmade et al, 2009)		Individual compartmental PK modeling
Sampling for Immunogenicity Assessment	Pre-infusion samples at Weeks 0, 30, 54, and 62.	Pre-infusion samples at Weeks 0, 30, 54, and 66.	Pre-infusion samples at Weeks 0, 30 and 42.	Pre-infusion samples at Weeks 0, 30, 54, and 62.
ACT = Active Ulcerative Colitis Trial; NA = not applicable; PK = pharmacokinetics; 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; UC = ulcerative colitis. Fasanmade AA, Adedokun OJ, Ford J, et al. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. <i>Eur J Clin Pharmacol.</i> 2009;65(12):1211-1228; C0168T72 CSR; REACH CSR; ACT 1, 54-week CSR; and ACT 2, 30-week CSR.				

1.2 Population Pharmacokinetic Analysis

Population PK analyses estimate the typical PK parameters of a drug entity and the between-subject and within-subject variability of this PK parameters. They also help to identify intrinsic subject characteristics or extrinsic factors that may contribute to the variability observed in the PK characteristics of the drug entity. Unlike traditional PK studies, where intensive sampling is usually required to accurately estimate PK parameters, a population PK approach offers the advantage of estimating PK parameters in a target population using sparse PK sampling methodology commonly seen in late phase clinical studies or pediatric studies.

In the C0168T72 study, a population PK modeling approach was employed to estimate infliximab PK parameters and their associated between-subject and within-subject variability. The analysis also evaluated the influence of subject demographic characteristics and other factors of interest on the disposition of infliximab in pediatric subjects with UC. The evaluable subjects in the population PK dataset included those who received at least 1 infliximab infusion and had at least 1 measurable serum infliximab concentration. The population PK analysis was performed using both confirmatory and conventional approaches. The confirmatory analysis was fully prespecified, based on the prior knowledge from the population PK model for infliximab in adult UC subjects. The confirmatory approach is considered to have potential advantages of providing unbiased results and more accurately quantifying result uncertainty (Hu and Zhou, 2008). However, a conventional population PK analysis was conducted to serve as a sensitivity analysis and was also used to assess the consistency of these 2 approaches. The results of the population PK analyses for the C0168T72 study are discussed in Section 3.3 of this SCP.

1.3 Antibodies to Infliximab

A summary of the incidence of antibodies to infliximab (ATI) and its relationship to infliximab PK is presented in Section 4.1. The relationship of ATI and clinical efficacy is summarized in the SCE, Section 2.1.6. Antibody to infliximab versus infusion reactions, possible anaphylactic reactions, or possible delayed hypersensitivity reactions is discussed in the SCS, Section 4.2. It should be noted that because only 4 subjects were positive for ATI, no conclusions could be made regarding the relationship between antibody status and clinical efficacy/safety measures.

2 Summary of Results of Individual Studies

This section presents a summary of the PK results observed in Studies C0168T72, ACT 1, ACT 2 and REACH. A summary of the study designs and clinical pharmacology results for each study is provided in Appendix A.1.

Serum concentrations of infliximab were determined using an ELISA method capable of quantifying serum concentrations of infliximab ≥ 0.1 $\mu\text{g/mL}$. Further details on methods used for data evaluation, including rules regarding inclusion/exclusion of serum infliximab concentration data are provided in the individual Clinical Study Reports (C0168T72 CSR, Section 3.11; REACH 54-Week CSR, Section 9.0; ACT 1, 54-Week CSR, Section 9; and ACT 2, 30-Week CSR, Section 9.0).

PK analyses presented in the following sections include summaries of serum infliximab concentrations over time; and the summaries of the relationship between serum infliximab concentrations by age subgroup (6 to 11 versus 12 to 17 years of age). Since PK results from previous studies suggested that infliximab PK may be influenced by concomitant immunomodulators, but not by corticosteroids and 5-aminosalicylates (5-ASA), the effect of immunomodulators and the relationship between serum infliximab

concentration and baseline immunomodulator use (monotherapy versus combination therapy) were therefore described in this SCP. Monotherapy is defined as infliximab use with no concomitant treatment with 6-mercaptopurine (6-MP)/ azathioprine (AZA), or methotrexate (MTX). Combination therapy is defined as infliximab use with concomitant treatment with baseline use of 6-MP/AZA, or MTX. These analyses were performed in subjects who received at least 1 dose of infliximab.

In addition to the above analyses, infliximab parameter estimates obtained from PK modeling are discussed where applicable. In the C0162T72 study a population PK analysis approach was used to estimate PK parameters as discussed previously (Section 1.2). In the ACT 1 and REACH studies, individual compartmental PK modeling approach using WinNonlin® (Pharsight Corporation, Mountain View, CA) was employed to estimate PK parameters such as clearance of drug after intravenous administration (CL), volume of distribution at steady state after intravenous administration (Vss) and terminal half-life (t1/2). Since PK modeling was not conducted for the ACT 2 CSR, the only PK parameter provided in this study was the maximum observed concentration (Cmax). It should be noted that due to the different approaches (compartmental analysis for individual subjects with sparse sampling versus population PK analysis) employed to derive the PK parameters, results from the comparisons of derived PK parameters across studies should be interpreted with caution.

2.1 C0168T72: Pediatric Subjects With Active Ulcerative Colitis

C0168T72 was a Phase 3, randomized, open-label, parallel-group, multicenter trial to evaluate the safety and efficacy of infliximab in pediatric subjects with moderately to severely active UC. All subjects were to receive an induction regimen of 5 mg/kg infliximab 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 every 8 weeks (q8w) through Week 46 (Group I) or every 12 weeks (q12w) through Week 42 (Group II). Subjects who were nonresponders (ie, did not achieve clinical response [Mayo score]) at Week 8 received no further infusions of infliximab. During the maintenance phase, subjects who lost clinical response would be eligible for step-up (ie., increase their infliximab dose and/or dosing frequency) only once as follows: 1) Group I: 5 mg/kg infliximab q8w → 10 mg/kg infliximab q8w; 2) Group II: 5 mg/kg infliximab q12w → 10 mg/kg infliximab q8w if loss of clinical response occurs at or before 8 weeks from the previous infliximab infusion; 3) Group II: 5 mg/kg infliximab q12w → 5 mg/kg infliximab q8w if loss of clinical response occurs after 8 weeks but before 12 weeks from the previous infliximab infusion.

Of the 60 subjects (15 subjects 6 to 11 years; 45 subjects 12 to 17 years) who received induction doses of infliximab, 45 were responders at Week 8 and subsequently randomized to receive q8w (n = 22) or q12w (n = 23) maintenance infusions (C0168T72 CSR, Attachment 2.3). Among the 45 subjects randomized to the 5 mg/kg q8w or

5 mg/kg q12w maintenance therapy, there was a total of 23 subjects who stepped-up (5 mg/kg q8 wks → 10 mg/kg q8 wks [9], 5 mg/kg q12w → 10 mg/kg q8w [8], and 5 mg/kg q12w → 5 mg/kg q8w [6]), (C0168T72 CSR, Attachment 1.3).

Pharmacokinetics were evaluated through Week 54, with blood samples obtained for measurement of serum infliximab concentrations immediately prior to every infusion; 1 hour after the end of the infusions at Weeks 0, 2, and 6; 1 hour after the last study infusion (Week 46, for subjects in the q8w maintenance treatment group and Week 42, for subjects in the q12w maintenance group); and at the noninfusion visits at Weeks 8 and 54.

2.1.1 Serum Infliximab Concentrations

Figure 1 shows the median serum infliximab concentrations through Week 54 for subjects who were randomized at Week 8; data for subjects who stepped-up their infliximab doses were excluded from the point of step-up.

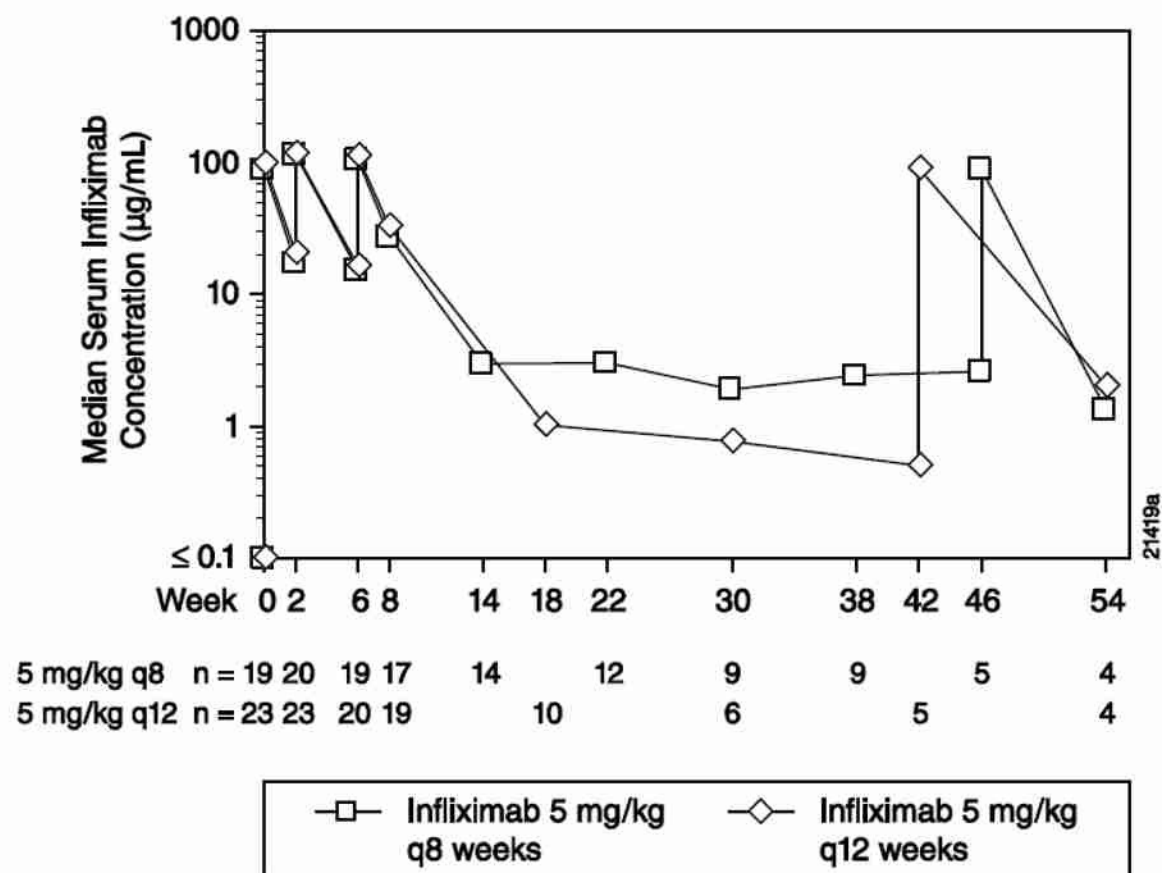


Figure 1 Median serum infliximab concentrations (micrograms/mL) through Week 54 by visit; randomized subjects by treatment received in C0168T72

During infliximab induction therapy (ie, Week 0 through 6), the median peak serum concentrations of infliximab in all treated subjects, 1 hour after the infusion of infliximab at Weeks 0, 2, and 6, were 96.1 µg/mL, 114.8 µg/mL, and 105.5 µg/mL, respectively, while the median trough (ie, preinfusion) concentrations at Weeks 2 and 6 were 19.3 µg/mL and 14.5 µg/mL, respectively. As expected, the highest median serum infliximab concentration (114.8 µg/mL) was observed in the postinfusion sample after the second infusion at Week 2 because the first 2 infusions had the shortest dosing interval and serum infliximab accumulated from the first infusion.

Before the maintenance phase of the study, serum infliximab concentrations through Week 8 were generally similar between the 2 randomized treatment groups (5 mg/kg q8w and 5 mg/kg q12w). During the maintenance phase, however, median preinfusion serum infliximab concentrations for subjects in the q8w group were generally higher than those in the q12w maintenance treatment group. For example, at Week 30, median preinfusion serum infliximab concentrations were 1.9 µg/mL and 0.8 µg/mL in the q8w and q12w groups, respectively. Similarly, the median preinfusion serum infliximab concentration before the respective last infliximab infusions was higher in the q8w group (2.6 µg/mL at Week 46) compared with the q12w group (0.5 µg/mL at Week 42) [C0168T72 CSR, Attachment 2.3]. However, the 2 groups had comparable median serum peak infliximab concentrations in samples collected 1 hour after their respective last infliximab infusions (89.4 µg/mL at Week 46 in the q8w group and 90.6 µg/mL at Week 42 in the q12w group).

Subjects were allowed to step-up to a different infliximab dose regimen during maintenance treatment if they lost clinical response. There were 2 step-up dose regimens, 5 or 10 mg/kg infliximab q8w. Preinfusion serum infliximab concentrations for subjects who stepped up generally increased after step-up (C0168T72 CSR, Attachment 2.4 and Attachment 2.5). For subjects who stepped up from the 5 mg/kg q12w regimen to the 5 mg/kg q8w regimen, the median preinfusion serum infliximab concentration was 5.1 µg/mL, 16 weeks after step-up, versus 2.8 µg/mL before step-up. For subjects who stepped up from the 5 mg/kg q8w regimen to the 10 mg/kg q8w regimen, the median preinfusion serum infliximab level was 2.9 µg/mL, 16 weeks after step-up, versus 1.1 µg/mL before step-up. Thus, an increased dose of infliximab or a more frequent dose administration led to higher serum infliximab concentration levels.

2.1.2 Serum Infliximab Concentration by Pediatric Age Groups

A comparison of serum infliximab concentrations between 2 age groups (6 to 11 years and 12 to 17 years) through Week 8, in subjects who received infliximab in study C0168T72 is presented in Appendix B.1.

After Week 8, subjects who achieved clinical response (n = 45) were randomized into 2 maintenance groups, with 23 subjects stepping up their maintenance dose at some point during the maintenance phase of the study. The resultant small number of subjects

following randomization and dose step-up did not allow a meaningful comparison of serum concentration by the age groups of interest after Week 8.

In general, median serum infliximab concentrations at both preinfusion and postinfusion timepoints through Week 8 were not markedly different when compared between both age groups, with the exception of Week 6 where the pre-infusion serum concentration of infliximab in the 6 to 11 years age group (7.1 µg/mL) was about half of that in the 12 to 17 years age group (15.3 µg/mL). This difference at Week 6 was not observed at any other timepoint in the comparisons and may be due to the small sample sizes. Overall, these results do not suggest any substantial impact of age on serum infliximab concentrations.

In addition the effect of age on infliximab PK was assessed in the population PK analysis (Section 3.3).

2.1.3 Effect of Concomitant Immunomodulators on Serum Infliximab Concentration

Serum infliximab concentrations at Week 8 and Week 54 were summarized by baseline use of concomitant immunomodulators (ie, 6-MP/AZA or MTX). In the Week 54 analyses, data for subjects who stepped up were excluded from the point of step-up.

At Week 8, the median serum infliximab concentration in subjects who received infliximab in combination with baseline immunomodulators was 25.6 µg/mL compared with 36.5 µg/mL in subjects who received infliximab monotherapy (ie, without immunomodulators) (C0168T72 CSR, Table 6). At Week 54, the limited number of subjects precludes the assessment of the effects of concomitant immunomodulators (ie, 6-MP/AZA or MTX), on serum infliximab concentrations (C0168T72 CSR, Attachment 9). While it may be reasonable to expect that the use of concomitant immunomodulators in combination with infliximab may be associated with reduced elimination of infliximab and thus increased infliximab concentration, these foregoing results do not support this expectation. However, since the comparison was done at a single (non steady-state) time point, caution should be exercised in the interpretation of these results.

2.1.4 Pharmacokinetic Parameter Estimates

A summary of the parameters obtained from the population PK analysis in C0168T72 is presented in Section 3.3 of this SCP.

2.2 ACT 1 and ACT 2: Adult Subjects With Active Ulcerative Colitis

C0168T37 (ACT 1) and C0168T46 (ACT 2) were 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 trials in adult subjects with UC that

evaluated the safety and efficacy of treatment with 5 or 10 mg/kg of infliximab compared with placebo ([Appendix A.1](#)).

At baseline, subjects were randomized to 1 of 3 treatment groups: placebo (n = 121 for ACT 1, n = 123 for ACT 2), infliximab 5 mg/kg (n = 121 for both ACT 1 and ACT 2), or infliximab 10 mg/kg (n = 122 for ACT 1, n = 120 for ACT 2). Infusions were administered at Weeks 0, 2, and 6 and then q8w thereafter through Week 46 or Week 22 for ACT1 and ACT 2, respectively. Subjects were then followed through Week 30 or Week 54 for ACT 2 and ACT 1, respectively, before they participated in a study extension at the discretion of investigators.

In ACT 1, blood samples for determining infliximab serum concentrations were drawn just before and 1 hour after the infusion at Weeks 0, 2, 6, 14, and 46 and just before the infusion at Weeks 30 and 38. Additional blood samples for infliximab concentration determination were drawn at Weeks 8 and 54 (noninfusion visits).

In ACT 2, blood samples for determining infliximab serum concentration were drawn just before and 1 hour after the infusion at Weeks 0 and 2 and just before the infusion at Weeks 6 and 14. Additional blood samples for infliximab concentration analysis were drawn at Weeks 8 and 30 (noninfusion visits).

Since the dosing regimen of 5 mg/kg infliximab administered at Weeks 0, 2, and 6 followed by q8w maintenance dosing was common between the adult (ACT 1 and ACT 2) and pediatric (C0168T72) UC trials, only PK data from this common dosing regimen is summarized in this SCP.

2.2.1 Serum Infliximab Concentrations

Data summarizing the serum infliximab concentrations through Week 54 and Week 30 in ACT 1 and ACT 2, respectively, are presented in the individual study reports ([ACT 1 54-Week CSR, Section 9.1.1](#) and [ACT 2 30-Week CSR, Section 9.1.1.1](#)).

Following IV infusions of 5 mg/kg infliximab in ACT 1, the median serum concentrations of infliximab, 1 hour after the infusion of infliximab at Weeks 0, 2 and 6, were 110.7 µg/mL, 131.1 µg/mL, and 129.6 µg/mL, respectively, while the median trough (ie, preinfusion) concentrations at Weeks 2 and 6 were 24.8 µg/mL and 16.8 µg/mL, respectively. Following IV infusions of 5 mg/kg infliximab in ACT 2, the median serum concentrations of infliximab, 1 hour after the infusion of infliximab at Weeks 0 and 2, were 111.8 µg/mL and 132.7 µg/mL, respectively, while the median trough (ie, preinfusion) concentrations at Weeks 2 and 6 were 24.3 µg/mL and 14.9 µg/mL, respectively.

In both ACT 1 and ACT 2, the median preinfusion serum infliximab concentrations generally decreased from Week 6 to Week 30; however, in ACT 1 (where data was available beyond Week 30), the median preinfusion serum infliximab concentrations from Week 30 through Week 54 were relatively constant suggesting that steady state was

achieved. The median serum infliximab concentrations at Week 30 were 3.5 µg/mL and 1.7 µg/mL in ACT 1 and ACT 2, respectively. Given that preinfusion and/or postinfusion serum infliximab concentrations at other visits such as Weeks 0, 2, 6, 8 and 14 were similar between these 2 studies, and the subject populations in ACT 1 and ACT 2 were similar, no apparent reason could be attributed to account for the relatively large difference in median trough concentrations at Week 30 between these 2 studies.

2.2.2 Effect of Concomitant Immunomodulators on Serum Infliximab Concentration

Serum infliximab concentrations through Week 54 (ACT 1) or through Week 30 (ACT 2) were summarized by baseline use of concomitant immunomodulators (ie, 6-MP/AZA or MTX). In both studies, serum infliximab concentrations at Week 8 (primary efficacy endpoint visit) and trough concentrations at steady state were evaluated for differences in exposure between subjects on monotherapy and those treated with a combination of immunomodulators and infliximab. In both adult UC studies (ACT 1 and ACT 2), steady state was achieved by Week 30.

In ACT 1, the median serum infliximab concentration at Week 8 in subjects who received infliximab monotherapy was 35.5 µg/mL compared with 32.1 µg/mL in subjects who received infliximab in combination with immunomodulators ([Appendix B.2](#)). Furthermore in ACT 1, from Week 30 through Week 54, median steady-state trough infliximab concentrations ranged from 3.5 µg/mL to 4.8 µg/mL at different time points for subjects on monotherapy compared with a range of 2.8 µg/mL to 5.0 µg/mL in subjects on combination therapy ([Appendix B.2](#)).

In ACT 2, the median serum infliximab concentration at Week 8 in subjects who received infliximab monotherapy was 33.4 µg/mL compared with 34.8 µg/mL in subjects who received infliximab in combination with immunomodulators ([Appendix B.3](#)). In ACT 2, only 1 data point (Week 30) at steady state was available for comparison. Subjects on monotherapy had a median infliximab concentration below the LLOQ compared with a value of 5.1 µg/mL in the group that received combination therapy ([Appendix B.3](#)). The reason for this apparent discordance in the effect of concomitant immunomodulator on serum infliximab concentrations in ACT 1 compared with ACT 2 is unclear.

Overall, these assessments did not suggest any consistent difference in infliximab exposure between subjects who received infliximab monotherapy and those who received infliximab in combination with immunomodulators.

2.2.3 Derived Pharmacokinetic Parameters

In ACT 1, PK parameters were determined using individual compartmental modeling; the relatively sparse sampling scheme did not allow the use of noncompartmental estimation of the parameters. A summary of the PK parameters are presented in the ACT 1 CSR ([ACT 1 54-Week CSR, Attachment 2.2](#)). Individual compartmental modeling was not

performed for the ACT 2 CSR, but the observed C_{max} values were reported in the ACT 2 CSR (ACT 2, 30-Week CSR, Attachment 2.4). C_{max} was generally achieved at the Week 2 postinfusion sampling period for most of the subjects. The median C_{max} following the 5 mg/kg infliximab treatment regimen were 164.9 µg/mL and 147.1 µg/mL in ACT 1 and ACT 2, respectively. In ACT 1, the median infliximab CL and V_{ss} was 4.3 mL/day/kg and 69.5 mL/kg respectively. The median terminal t_{1/2} for infliximab in these subjects was 11.7 days.

2.3 REACH: Pediatric Subjects With Active Crohn's Disease

C0168T47 (REACH) was a randomized, multicenter, open-label Phase 3 study to evaluate infliximab in pediatric subjects with moderate to severe Crohn's disease. All enrolled subjects received infliximab 5 mg/kg at Weeks 0, 2, and 6. Subjects who achieved clinical response at Week 10 were randomized to treatment with 5 mg/kg infliximab q8w through Week 46 or q12w through Week 42. 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 (Appendix A.1).

In REACH, all subjects received induction doses of 5 mg/kg infliximab at Weeks 0, 2 and 6. Of the 112 subjects (25 subjects in 6 to 11 years; 87 subjects in 12 to 17 years) who received induction doses of infliximab, 103 achieved clinical response at Week 10 and were subsequently randomized to 5 mg/kg q8w (n = 52) or 5 mg/kg q12w (n = 51) maintenance infusions, and 35 of these randomized subjects crossed over to a higher dose and/or higher dosing frequency during maintenance (5 mg/kg q8 wks → 10 mg/kg q8 wks [10], 5 mg/kg q12w → 10 mg/kg q8 wks [13], and 5 mg/kg q12w → 5 mg/kg q8 wks [12]) (REACH CSR, Section 8.1.1)

Pharmacokinetics were evaluated through Week 54, with blood samples for measurement of serum infliximab concentration obtained immediately prior to every infusion; 1 hour after the end of the infusions at Weeks 0, 2, and 6; 1 hour after the last study infusion (Week 46 for subjects in the q8w maintenance treatment group and Week 42 for subjects in the q12w maintenance group); and at the noninfusion visits at Weeks 10 and 54. For subjects who discontinued the study early, a sample was obtained 16 weeks after the last study infusion.

2.3.1 Serum Infliximab Concentration

During infliximab induction therapy (ie, Week 0 through 6), the median peak serum concentrations of infliximab in all treated subjects, 1 hour after the infusion of infliximab at Weeks 0, 2, and 6, were 88.4 µg/mL, 110.4 µg/mL, and 101.6 µg/mL, respectively, while the median trough (ie, preinfusion) serum concentrations at Weeks 2 and 6 were 20.6 µg/mL and 11.6 µg/mL, respectively. As expected, the highest median serum infliximab concentration was observed in the postinfusion sample after the second infusion at Week 2 (REACH 54-Week CSR, Attachment 2.1).

Before the maintenance phase of the study, serum infliximab concentrations through Week 8 were generally similar between the 2 randomized treatment groups (5 mg/kg q8w and 5 mg/kg q12w). Data for subjects who crossed over were excluded from the point of crossover. During the maintenance phase, however, median preinfusion serum infliximab concentrations for the subjects in the q8w maintenance treatment group were generally higher than those in the q12w maintenance treatment group. For example, at Week 30, median preinfusion serum infliximab concentrations were 1.8 µg/mL and 0.2 µg/mL in the q8w and q12w groups, respectively. Similarly, the median preinfusion serum infliximab concentration before the respective last infliximab infusions was higher in the q8w group (1.8 µg/mL at Week 46) compared with the q12w group (0.3 µg/mL at Week 42) (REACH CSR, Attachment 2.3). The 2 groups had comparable median serum peak infliximab concentrations in samples collected 1 hour after their respective last infliximab infusions (94.4 µg/mL at Week 46 in the q8w group and 90.0 µg/mL at Week 42 in the q12w group). This is expected since peak infliximab concentrations are mainly determined by the dosage of infliximab (ie, 5 mg/kg for both q8w and q12w dosing regimens).

Subjects were allowed to cross over to a different infliximab dose regimen during the maintenance treatment phase if they lost clinical response. There were 2 crossover dose regimens, 5 or 10 mg/kg infliximab q8w (increased dose or dose frequency). There were no observable differences between the serum infliximab concentrations from Weeks 0 to 6 in subjects who crossed over compared with those subjects who did not cross over (REACH 54-Week CSR, Attachment 2.3 and Attachment 2.4). However, at Week 10, the median serum infliximab concentrations for subjects who crossed over from the 5 mg/kg q8w or 5 mg/kg q12w maintenance regimens to 10 mg/kg q8w (6.6 µg/mL and 6.4 µg/mL, respectively) were lower than those who remained on their randomized dosing regimens of 5 mg/kg q8w or 5 mg/kg q12w (15.3 µg/mL among subjects who remained on the 5 mg/kg q8w regimen and 12.6 µg/mL among subjects who remained on the 5 mg/kg q12w regimen, respectively). Prior to this time point (Week 10), all subjects received the same infliximab induction regimen.

After crossover (ie, dosing step-up), the median serum infliximab concentrations in affected subjects increased accordingly; the levels immediately after infusion in the subjects receiving 10 mg/kg q8w were approximately double of those in the subjects who did not cross over. The median preinfusion serum infliximab concentrations for subjects who crossed over generally increased after the change in dosing regimen (REACH 54-Week CSR, Figure 3).

For subjects who crossed over from the 5 mg/kg q12w regimen to the 5 mg/kg q8w regimen, the median preinfusion serum infliximab concentration was 3.0 µg/mL, 16 weeks after step-up, versus 0.6 µg/mL before step-up. For subjects who stepped up from the 5 mg/kg q8w regimen to the 10 mg/kg q8w regimen, the median preinfusion serum infliximab level was 4.5 µg/mL, 16 weeks after step-up, versus 1.1 µg/mL before step-up.

Thus, an increased dose of infliximab or a more frequent dosage regimen led to a higher median serum infliximab concentration in subjects who crossed over compared to their value before crossover.

2.3.2 Serum Infliximab Concentration by Pediatric Age Groups

A comparison of serum infliximab concentrations through Week 10 between 2 age groups (6 to 11 yrs and 12 to 17 years), in subjects who received infliximab in the REACH study is presented in [Appendix B.4](#).

In general, median serum infliximab concentrations at both preinfusion and postinfusion timepoints through Week 10 were similar when compared between both of the 2 age groups ([Appendix B.4](#)).

2.3.3 Effect of Concomitant Immunomodulators on Serum Infliximab Concentration

The effect of concomitant immunomodulators on infliximab PK could not be assessed because per protocol all subjects in the study were to be on concomitant immunomodulators in REACH.

2.3.4 Derived Pharmacokinetic Parameters

PK parameters were determined using individual compartmental modeling as the sparse sampling scheme did not allow the use of noncompartmental estimation of the parameters. Among all treated subjects who were evaluable for PK analyses (n = 106), the median values for the C_{max}, CL, V_{ss}, and t_{1/2} were 126.7 µg/mL, 6.1 mL/day/kg, 86.4 mL/kg, and 10.7 days respectively ([REACH 54-Week CSR, Section 9.1.3; REACH 54-Week CSR, Table 7](#)).

3 Comparison and Analyses of Results Across Studies

This section presents a discussion of PK results across the relevant clinical studies included in this SCP. Section [3.1](#) provides a comparison of PK results between pediatric (C0168T72) and adult (ACT 1 and ACT 2) subjects with UC. A discussion of infliximab PK in pediatric subjects with UC relative to pediatric subjects with Crohn's disease is provided in Section [3.2](#). An overview of the population PK analyses results from the C0168T72 study is provided in Section [3.3](#).

To allow for a more meaningful interpretation of the data, only comparable treatment groups (ie similar infliximab dosage regimens) are assessed across studies. In the pediatric studies, data for subjects who stepped up or crossed over were excluded from these cross-study comparisons from the point of step-up or cross over.

Overall, infliximab PK (including peak and trough concentrations and terminal $t_{1/2}$) was generally comparable across studies in subjects with UC (C0168T72, ACT 1 and ACT 2) as well as across studies in pediatric subjects with IBD (C0168T72 and C0168T47) when consideration is given to the variability of infliximab disposition typically observed with therapeutic monoclonal antibodies.

3.1 Pharmacokinetics in Pediatric Versus Adult Subjects with Ulcerative Colitis

The results presented in this section compare infliximab PK after treatment with IV infusions of 5 mg/kg infliximab at Weeks 0, 2, and 6 followed by q8w in pediatric subjects versus adult subjects with UC in ACT 1 and ACT 2. As described in Section 2.2.1, except for a relatively large difference in median pre-infusion serum concentration at Week 30, serum infliximab concentrations were generally similar at all other common visits between ACT 1 and ACT 2. In addition, the subject populations in ACT 1 and ACT 2 were similar. Therefore, for the purpose of comparison, PK data from ACT 1 and ACT 2 were pooled through Week 30 to make use of a larger sample size and to minimize the PK variability in adult subjects from these 2 studies.

3.1.1 Serum Infliximab Concentration Through Week 54

A summary of the serum infliximab concentrations over time in pediatric and adult UC subjects is presented in [Appendix B.5](#). Median (1 hour postinfusion) serum infliximab concentrations at Week 0 were 88.6 µg/mL and 111.0 µg/mL following infusions of 5 mg/kg in pediatric and adult subjects with UC, respectively. In pediatric subjects with UC, the highest median serum infliximab concentration (115.1 µg/mL) was observed in the postinfusion sample after the second infusion at Week 2. The corresponding median serum infliximab concentration for adult subjects with UC was 131.6 µg/mL. Prior to the third induction dose at Week 6, the preinfusion concentrations were similar between pediatric and adult subjects (15.2 µg/mL versus 15.3 µg/mL, respectively).

At the visit for the primary efficacy endpoint in the pediatric and adult studies in UC (ie, the noninfusion Week 8 visit), median serum infliximab concentrations in pediatric subjects (27.5 µg/mL) was slightly lower than that of adult subjects (33.3 µg/mL). Median serum trough infliximab concentrations at the steady-state timepoints of Week 30 and Week 38 in pediatric subjects (1.9 µg/mL and 2.4 µg/mL respectively) were also lower than in adult subjects (2.5 µg/mL and 3.9 µg/mL respectively).

Overall, median serum infliximab concentrations in pediatric subjects with UC were slightly lower than those of adult subjects with UC when the dosing regimen of 5 mg/kg infliximab was given at Weeks 0, 2, and 6, followed by q8w.

3.1.2 Serum Infliximab Concentration and Concomitant Immunomodulators

A summary of serum infliximab concentration by infliximab monotherapy and combination therapy in pediatric (C0168T72) and adult subjects (ACT 1 and ACT 2) with UC is presented in [Appendix B.7](#).

At Week 8, median serum infliximab concentrations in pediatric (33.5 µg/mL) and adult subjects (33.4 µg/mL) on infliximab monotherapy were similar. At the same timepoint, pediatric subjects on combination therapy had a slightly lower median serum infliximab concentration (24.3 µg/mL) than adult subjects on combination therapy (33.2 µg/mL).

Median serum infliximab concentrations at Week 30 and Week 38 (steady-state timepoints) were 5.1 µg/mL and 3.7 µg/mL respectively in pediatric subjects on monotherapy, while the corresponding values in adult subjects on infliximab monotherapy were 1.7 µg/mL and 3.5 µg/mL, respectively. For subjects on combination therapy, median serum infliximab concentrations were 1.8 µg/mL and 2.1 µg/mL in pediatric subjects, while the corresponding values in adult subjects on combination therapy were 3.5 µg/mL and 5.0 µg/mL, respectively. Caution should be exercised in these comparisons as the number of subjects available in the pediatric UC study (C0168T72) for these comparisons, especially at steady state, was relatively small.

Overall, these data do not suggest a consistent pattern in the influence of concomitant immunomodulators on serum infliximab concentrations in either pediatric or adult subjects with UC.

3.1.3 Comparison of Infliximab Exposure at Steady State

Using the population PK models developed for infliximab in pediatric and adult subjects with UC, Monte-Carlo simulations were performed to compare infliximab concentration over time at steady state between adults and children following IV infliximab at 5 mg/kg q8w (for more details see Section 3.3). The simulations showed that there was a substantial overlap of infliximab exposure between adult and pediatric subjects with UC following a maintenance dosing regimen of infliximab 5 mg/kg q8w, even though the predicted area under the concentration versus time curve for a dose interval (AUC_τ) at steady state in pediatric subjects was approximately 20% lower than that in adult subjects. The simulation results were consistent with the observed lower serum infliximab concentrations in C0168T72 as compared to the 2 adult UC trials.

3.2 Pharmacokinetics in Pediatric Ulcerative Colitis Versus Pediatric Crohn's Disease

The results presented in this section compare infliximab PK in pediatric subjects with UC versus pediatric subjects with Crohn's disease. The study design with respect to dosing and PK sampling in C0168T72 was similar to that of REACH.

3.2.1 Serum Infliximab Concentration Through Week 54

A summary of the serum infliximab concentrations over time in pediatric subjects with UC and with Crohn's disease is presented in [Appendix B.6](#). In subjects randomized to the q8w infliximab regimen, median peak (ie., 1 hour postinfusion) serum infliximab concentrations at Week 0 were 88.6 µg/mL and 86.8 µg/mL following infusions of 5 mg/kg in pediatric UC and Crohn's disease subjects, respectively. The median peak serum infliximab concentrations (postinfusion samples after the second infusion at Week 2) were 115.1 µg/mL and 108.7 µg/mL in UC and Crohn's disease pediatric subjects, respectively. Prior to the third induction dose at Week 6, the preinfusion concentrations were similar between pediatric UC and Crohn's disease subjects (15.2 µg/mL versus 12.5 µg/mL, respectively).

Median serum infliximab concentrations at the steady-state timepoints of Week 30 and Week 38 in pediatric UC subjects in the q8w infliximab regimen (1.9 µg/mL and 2.4 µg/mL, respectively) were similar to those in pediatric Crohn's disease subjects receiving the same regimen (1.8 µg/mL and 1.8 µg/mL, respectively).

The similarities observed in the median serum infliximab concentrations between pediatric subjects with UC and pediatric subjects with Crohn's disease in the randomized q8w treatment groups were also observed with the randomized q12w treatment groups.

Overall, median peak and steady-state trough infliximab concentrations observed in pediatric UC population were similar to those observed in the pediatric Crohn's disease population.

3.2.2 Serum Infliximab Concentration and Concomitant Immunomodulators

A comparison of the effects of concomitant immunomodulators on infliximab PK in pediatric subjects with UC and pediatric subjects with Crohn's disease is not possible because, per protocol, all randomized subjects in REACH were to receive baseline immunomodulators. However, serum infliximab concentrations at steady state time points were compared in subjects randomized to q8w in REACH with subjects on combination therapy in C0168T72. The median serum infliximab concentration at Week 30 and Week 38 were 1.8 µg/mL and 1.8 µg/mL for subjects in REACH ([Appendix B.6](#)) in comparison to 1.8 µg/mL and 2.1 µg/mL respectively in subjects on combination therapy in C0168T72 ([Appendix B.7](#)). Thus it appears that the effect of immunomodulators on serum infliximab concentration was consistent between REACH and C0168T72.

3.3 Population Pharmacokinetic Analysis

Blood samples collected through Week 54 were analyzed for serum infliximab concentration. All 60 subjects in C0168T72 who received at least 1 dose of infliximab

and had at least 1 measurable PK concentration were included in the population PK data. A total of 562 concentration values from the 60 pediatric subjects were used to develop a population PK model based on a nonlinear mixed-effects analysis approach. Approximately 53% of the study population was female and the subjects were predominantly Caucasian (82%). About half of the subjects (53%) were on concomitant immunomodulators at baseline (ie 6-MP, AZA or MTX) and 4 of the 60 subjects developed ATI.

Two Phase 3 studies (ACT 1 and ACT 2) previously demonstrated the safety and efficacy of infliximab in adult subjects with UC; and a population PK model has been published from the PK data obtained from both studies ([ACT 1 54-Week CSR](#) and [ACT 2 30-Week CSR](#)). A confirmatory population PK analysis approach ([Hu and Zhou, 2008](#)) that was based on the prior knowledge from an existing population PK model in adult subjects with UC ([Fasanmade et al, 2009](#)) was used to evaluate the population PK in this pediatric population. In addition, a conventional population PK analysis served as a sensitivity analysis for assessing the consistency of these 2 approaches. Details of the methodologies of the population PK analyses can be found in the population PK technical report which is an addendum to the C0168T72 CSR ([CP 2010T-045](#)). A summary of the key results are presented in the following sections.

3.3.1 Population Pharmacokinetic Characteristics of Infliximab in Pediatric Ulcerative Colitis

The population PK of infliximab in pediatric subjects with UC was well described by a 2-compartment linear PK model. Visual predictive check showed the confirmatory model was adequate in fitting the observed data ([Appendix B.8](#)).

The primary analysis model for CL and volume of distribution in the central compartment (V_1) was described by the following equations:

$$CL(L/day) = 0.346 \times \left(\frac{Body\ Weight}{50} \right)^{0.0711} \times \left(\frac{ALB}{4} \right)^{-1.75} \times 0.84^{IMMU}$$

$$V1(L) = 3.07 \times \left(\frac{Body\ Weight}{50} \right)^{1.13}$$

where *IMMU* is 1 if immunomodulators (ie, AZA, 6-MP, MTX) were concomitantly used and 0 otherwise. *ALB* is serum albumin concentration.

The final population PK parameters from the confirmatory approach are provided in [Table 2](#).

Table 2 Summary of Infliximab Population PK Parameter Estimates of the Primary Analysis Model			
Parameters	Estimate	% RSE of estimate	BSV^a (CV%)^b
CL (L/day)	0.346	12.2	49.5
V ₁ (L)	3.07	8.8	9.6
V ₂ (L)	2.28	54.5	-
Q (L/day)	1.98	79.7	-
Correlation for BSV between CL and V ₁	-0.522		-
Body Weight Effect (on CL)	0.0711	262.2	-
Albumin Effect (on CL)	-1.75	31.6	-
Immunomodulator Effect (on CL)	-0.16	74.6	-
Weight Effect (on V ₁)	1.13	10.9	-
Proportional residual variability (%)	52.4	13.5	-
Additive residual variability (µg/mL)	0.0565	69.2	-
^a . BSV: Between subject variability, calculated as (variance) ^{1/2} *100%. ^b . CV%: Coefficient of variation expressed as percent.			
CL: Clearance (L/day); RSE: relative standard error; V ₁ : Volume of distribution of the central compartment (L); V ₂ : Volume of distribution of the peripheral compartment (L); Q: Inter-compartmental clearance (L/day)			
Source: CP 2010T-045.			

Based on the confirmatory population PK analysis approach, typical population PK parameters (%CV) for a 50 kg child with a baseline serum albumin concentration of 4 g/dL and who was not on concomitant immunomodulator therapy were CL: 0.346 L/day [12.2%], V₁: 3.07 L [8.8%], volume of distribution of the peripheral compartment (V₂): 2.28 L [54.5%] and intercompartmental clearance (Q): 1.98 L/day [79.7%]. Between subject variability (BSV, %CV) on CL and V₁ were 49.5% and 9.6%, respectively. Based on post hoc individual PK parameters, from the confirmatory approach, the median t_{1/2} of infliximab in pediatric subjects with UC was estimated to be 10.8 days (interquartile range: 8.6 to 15.4 days).

The final population PK parameters obtained using the conventional, population PK analysis approach are provided in Appendix B.9. The results of the conventional population PK analysis were generally similar to those obtained using the confirmatory approach. From the conventional population PK analysis, the median t_{1/2} estimated from the post hoc PK parameters of the final model was 11.2 days (interquartile range: 7.6 to 16 days). Thus, the median t_{1/2} in pediatric subjects with UC was comparable to the t_{1/2} which was estimated for infliximab in adult subjects UC (11.7 days in the 5 mg/kg

treatment group; refer to [ACT 1 54-Week CSR, Attachment 2.2](#)) and pediatric subjects with Crohn's disease (10.7 days; [\[REACH 54-Week CSR, Table 7\]](#)).

Overall, infliximab PK characteristics in pediatric UC subjects were generally consistent with the PK of infliximab in adult UC subjects and pediatric subjects with Crohn's disease.

3.3.2 Covariate Effects on Infliximab Pharmacokinetics

The variability in infliximab volume of distribution was primarily determined by body weight while the variability in infliximab CL was affected by serum albumin levels ([Figure 2](#)).

It is apparent from the population PK model that body size is an important determinant of infliximab exposure. The nearly proportional increase in infliximab V_1 as patient body weight increases is expected because larger body weight is associated with larger blood volume and infliximab is primarily located in the circulatory system with limited extravascular distribution. Therefore, body weight-adjusted dosing (as is approved for infliximab) is necessary to reduce the variability in infliximab exposure among children with different body weights.

While albumin was a statistically significant covariate in the model, the effect of albumin on infliximab CL is considered marginal since it appears that the CL of a majority of subjects with albumin values in the normal range was unaffected by small changes in albumin (see [Figure 2](#)). A similar finding has also been noted in the adult population with UC ([ACT 1 54-Week CSR](#) and [ACT 2 30-Week CSR](#)), where a significant impact on infliximab CL occurred only in cases where there was an abnormally low albumin concentration. However, there was not enough data in this study to draw a definitive conclusion about the impact of low albumin levels on infliximab CL and, therefore, dose adjustment according to albumin levels does not appear warranted.

Results also suggested that subjects who tested positive to ATI had a higher CL than subjects who did not test positive; however, since relatively few ($n = \blacksquare$) subjects in this PK analysis population tested positive, the impact of antibody status could not be accurately quantified.

A subject's age had no substantial impact on the PK of infliximab once body weight was accounted for in the model ([CP2010T-045](#)). This was also consistent with findings about the impact of subjects' age on serum infliximab concentrations ([Section 2.1.3](#)).

Immunomodulator use had no significant effects on infliximab PK ([Figure 3](#)). This was consistent with findings about the impact of immunomodulator use on serum infliximab concentrations ([Section 2.1.4](#)).

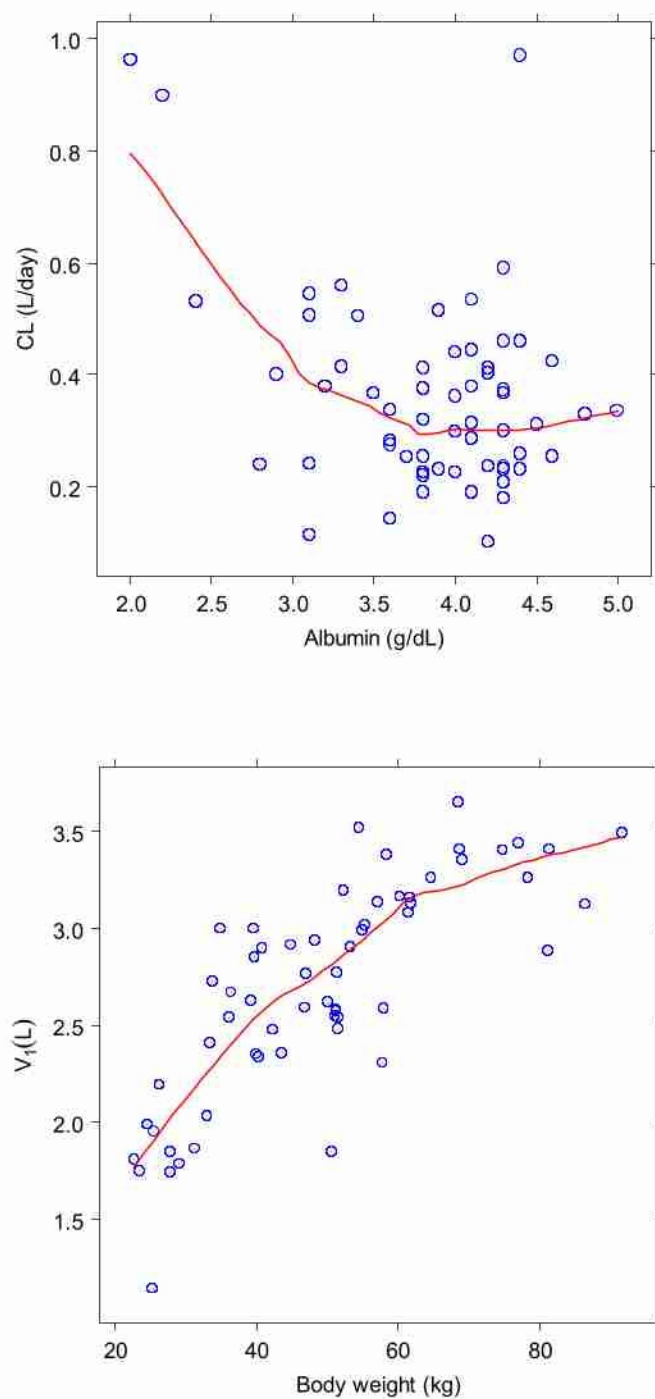


Figure 2 Relationships between *Post Hoc* Infliximab Pharmacokinetic Parameters and Significant Covariates

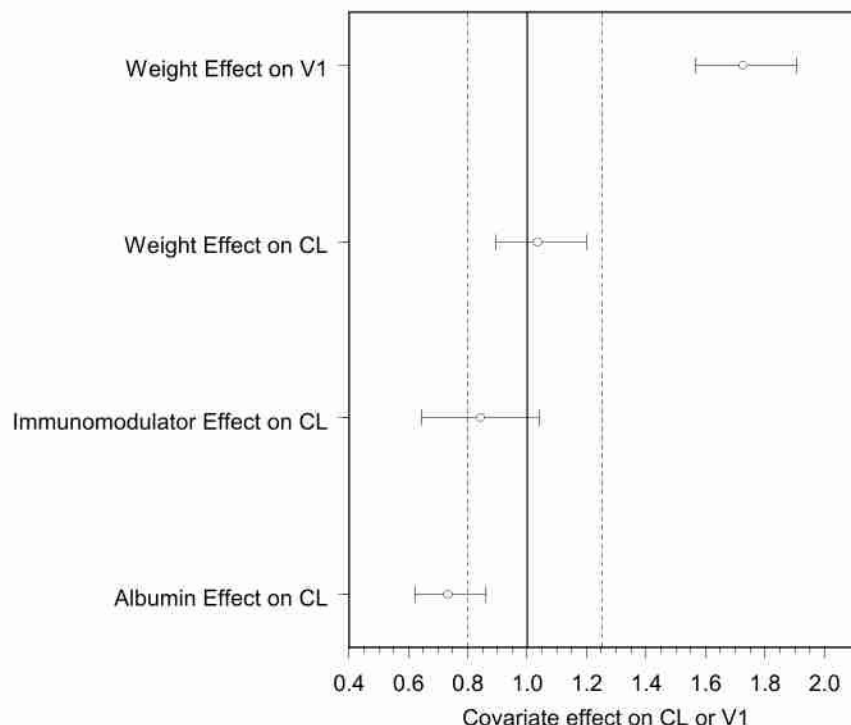


Figure 3 Covariate Effects on CL or V₁ with the Bioequivalence Interval

3.3.3 Comparison of Infliximab Exposure at Steady State between Pediatric and Adult Subjects With Ulcerative Colitis

Simulations of the 5 mg/kg q8w dosing regimen of infliximab suggest that a substantial overlap exists for infliximab exposure between adult and pediatric subjects with UC. The simulated steady-state profiles for the pediatric and adult populations over an 8-week dosing interval following maintenance dosing regimen of 5 mg/kg q8w are shown in [Figure 4](#) (left panel: Confirmatory primary analysis model; right panel: Exploratory analysis model). Simulations using the confirmatory primary analysis model and the exploratory analysis model produced similar results.

As indicated by the highlighted bands in [Figure 4](#), a substantial overlap existed for infliximab exposure between adult and pediatric subjects with UC following a maintenance dosing regimen of infliximab 5 mg/kg q8w.

Based on the typical parameter estimates of the population PK models for infliximab, median area under the plasma concentration-time curve (AUC_τ) at steady state for adults

was 946 $\mu\text{g}\cdot\text{days/mL}$ compared to 723 $\mu\text{g}\cdot\text{days/mL}$ for the confirmatory analysis and 742 $\mu\text{g}\cdot\text{days/mL}$ for the exploratory analysis in pediatric subjects. These results showed that median AUC_{τ} at steady state in pediatric subjects was approximately 20% lower than that in adult subjects. This may be expected since the clearance of monoclonal antibodies does not increase proportionally with weight. Consequently, dosing on a mg/kg basis tends to result in higher exposure in subjects with large body size and lower exposure in subjects with a small body size (Wang et al, 2009).

In adult subjects with UC, the median improvement from baseline in the Mayo score was greater in subjects whose serum infliximab concentrations was greater than 1 $\mu\text{g/mL}$ at steady state compared to subjects with lower infliximab concentrations (ACT 1 CSR, Section 10.4). PK simulations (Appendix B.10) predict that the steady-state trough concentration in a typical pediatric subject with UC receiving infliximab q12w is approximately 0.4 $\mu\text{g/mL}$. This value is much lower than the predicted steady-state concentration in the same subject receiving 5 mg/kg q8w (2.0 $\mu\text{g/mL}$). Thus, it is expected that treatment with infliximab 5 mg/kg q12w in pediatric subjects with UC would result in lower drug exposure, particularly lower trough serum infliximab concentrations. This difference in exposure may possibly account for the observation in C0168T72 that a higher proportion of subjects achieved remission during maintenance in 5 mg/kg infliximab q8w group compared with the 5 mg/kg q12w group (C0168T72 CSR, Section 6.3.1).

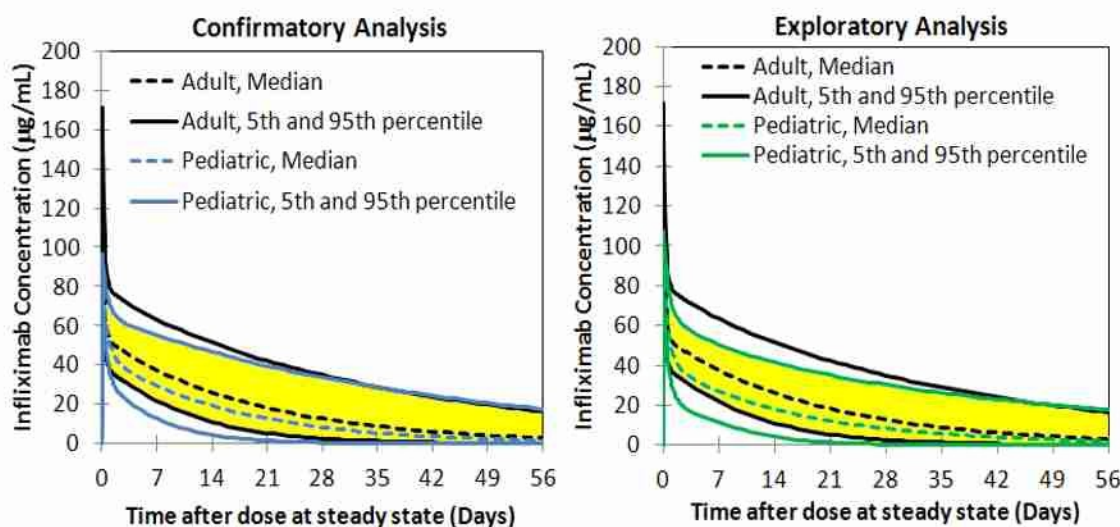


Figure 4 Simulated Steady-State Pharmacokinetic Profiles Following Maintenance Dosing Regimen of 5 mg/kg q8w between Adult and Pediatric Populations with Ulcerative Colitis

3.3.4 Overall Summary of Population Pharmacokinetics

The population PK of infliximab in pediatric subjects with UC was reasonably well described by a 2-compartment linear PK model. The $t_{1/2}$ was comparable between pediatric subjects with IBD and adult subjects with UC. Variability in infliximab clearance and volume of distribution was primarily affected by serum albumin concentration and body weight, respectively. A subject's age and immunomodulator use had no significant impact on infliximab disposition. Overall, infliximab PK characteristics in pediatric subjects with UC were largely consistent with the PK of infliximab in adult subjects with UC and pediatric subjects with Crohn's disease.

4 Special Studies

4.1 Antibodies to Infliximab

In prior studies, ATI have been observed in subjects after infliximab administration. The presence of infliximab can interfere with the detection or interpretation of an antibody response; thus, all samples evaluated for ATI were also analyzed for infliximab concentration. Any positive antibody responses were classified as positive, regardless of the presence or absence of infliximab in the sample. If infliximab was not detected in a given sample, and the antibody response was negative, then the subject was characterized as not having ATI for that sample. If the antibody to infliximab result was negative but there was a detectable concentration of infliximab present in the serum sample, then the sample was classified as inconclusive for ATI. Other studies have demonstrated that subjects with ATI generally show a more rapid elimination of infliximab from the serum. Thus, if infliximab is observed in serum more than 8 weeks after an infusion in a subject with ATI status classified as inconclusive, it is unlikely that the subject has anti-infliximab antibodies.

The incidence of ATI across the studies included in this SCP is summarized in Section 4.1.1. The effect of concomitant immunomodulator treatment on the development of ATI is also discussed in Section 4.1.1, while the relationship of ATI with serum infliximab concentrations is described in Section 4.1.2.

4.1.1 Antibodies to Infliximab Across Studies Through Week 54

The overall incidence of ATI through Week 54 (through Week 30 in ACT 2) across the studies included in this SCP is summarized in Table 3, and more detailed information can be found in the respective CSRs. Note that Table 3 includes data from both the 5 mg/kg and 10 mg/kg groups from the ACT studies. Data on immunogenicity from ACT 1 and ACT 2 were not pooled since these 2 studies had different durations for infliximab exposure. However, in order to make meaningful comparison across studies, efforts were made to have consistent sampling timepoints for immunogenicity assessment in these studies. For example, the incidence of ATI was similarly assessed after approximately

8 weeks from the last infusion of infliximab in each of these studies. In doing so, the drug interference on the detection of ATI in serum samples was minimized.

Table 3 Summary of the Incidence of Antibodies to Infliximab Following Repeated Intravenous Infusion of Infliximab In Subjects with Active Ulcerative Colitis or Crohn's Disease				
	C0168T72^a	ACT 1^a	ACT 2^b	REACH^a
Subjects treated with infliximab	60	243	241	112
Subjects with appropriate samples	52	229	188	105
Subjects positive for antibodies to infliximab		14 (6.1%)	12 (6.4%)	3 (2.9%)
^a Antibody to infliximab assessed at Week 54, (8 weeks after last infusion of infliximab)				
^b Antibody to infliximab assessed at Week 30, (8 weeks after last infusion of infliximab)				
Source: C0168T72 CSR RE278 [S_ATSA_66_A], 20Jul2010 16:07; REACH CSR RE124:[S_ATSA_66_A], 29Jun2005 16:25; ACT 1 54-week CSR RE157:[S_ATSA_71_A], 27May2005 16:55; and ACT 2 30-week CSR RE123:[S_ATSA_71_A], 19Nov2004 12:10.				

The proportion of subjects with ATI was similar across clinical trials in pediatric and adult subjects with UC. The overall incidence of ATI (8 weeks after the last infusion of infliximab in most subjects) was 7.7% in C0168T72, 6.1% in ACT 1, and 6.4% in ACT 2. In contrast, a lower incidence of 2.9% was observed in the REACH study. These data on the incidence of ATI may be explained by the differences in the use of concomitant immunomodulators that have shown to decrease the incidence of ATI. A similar proportion of subjects in C0168T72 (53.3%), ACT 1 (48.9%), and ACT 2 (42.9%) received concomitant immunomodulators while almost all (98.2%) subjects in REACH were treated with concomitant immunomodulators.

In order to have a more stringent comparison in the incidence of ATI across studies (C0168T72, ACT 1 and REACH), immunogenicity data through the same follow-up duration (ie, Week 54) from subjects who were randomized to receive the same dosing regimen (ie, 5 mg/kg infliximab infusion at Weeks 0, 2, 6 followed by q8w) were analyzed after a stratification by the use of concomitant immunomodulators (Appendix B.11). In this analysis, subjects who stepped up or crossed over in C0168T72 and REACH were excluded. This analysis showed that the incidence of ATI was lower among subjects on concomitant immunomodulators compared to infliximab monotherapy. For example, in ACT 1, 14.8% (8/54) of subjects receiving infliximab monotherapy were ATI positive, whereas only [REDACTED] of subjects receiving infliximab combination therapy, were ATI positive. However, this phenomenon was not apparent in C0168T72 probably since there was only [REDACTED] each in the 2 small subgroups with (n = 7) and without (n = 6) concomitant immunomodulators.

4.1.2 Relationship Between Antibodies to Infliximab and Infliximab Pharmacokinetics

In C0168T72, infliximab CL was higher in pediatric subjects with UC who were classified as positive for ATI (CP2010T-045). However due to the small number of subjects classified as ATI positive in C0168T72, the relationship between ATI and infliximab PK could not be accurately quantified. In adult subjects with UC (ACT 1 and ACT 2), serum infliximab concentrations were generally lower in subjects who were classified as positive for ATI (ACT 1, 54-week CSR and ACT 2, 30-week CSR). In particular, in adult UC subjects, a 47% increase in infliximab CL was estimated for subjects who developed ATI (Fasanmade et al, 2009). In pediatric subjects with Crohn's disease (REACH), there were only ATI positive subjects and a relationship between ATI and infliximab PK could not be clearly defined.

4.1.3 Overall Summary of Immunogenicity

The incidence of antibody to infliximab through Week 54 was low (7.7%) in C0168T72. Across the other Phase 3 studies (ACT 1, ACT 2, and REACH), the incidence of ATI was low and consistent after accounting for the differences in the use of concomitant immunomodulators. Subjects who were antibody-positive generally cleared infliximab faster resulting in lower serum infliximab concentrations than in antibody negative or inconclusive subjects.

5 Summary and Conclusions

The PK and immunogenicity results presented above demonstrate the following:

- PK results in pediatric UC subjects were generally consistent with those observed in adult UC subjects (ACT 1 and ACT 2) as well as in pediatric Crohn's disease subjects (REACH).
- Population PK modeling and simulation shows that substantial overlap exists for infliximab systemic exposure between adult and pediatric subjects with UC when given equivalent per kg doses. Albeit, there is a trend for lower infliximab concentration and AUC_τ in pediatric UC subjects.
- Population PK analysis shows that serum albumin concentration level was a statistically significant covariate on infliximab clearance, while the variability in infliximab V₁ was primarily determined by body weight. However, the magnitude of the effect of albumin levels on infliximab CL appears marginal and probably of little clinical relevance. There was no apparent impact of either age or concomitant immunomodulator use on the PK of infliximab.

-
- The maintenance dosing regimen of 5 mg/kg infliximab q8w resulted in higher infliximab exposure over time when compared to 5 mg/kg infliximab q12w.
 - The proportion of subjects who tested positive for ATI through Week 54 was low (7.7%) in pediatric subjects with UC, and consistent with that (6.1% in ACT 1 and 6.4% in ACT 2) in adult subjects with UC.

In conclusion, the PK analyses suggest that body weight-adjusted dosing is necessary to achieve more consistent drug exposure among subjects and to mitigate a possible body weight-related influence on infliximab exposure. The comparable infliximab exposure at the approved dosing regimen of 5 mg/kg q8w (relative to adult UC subjects and pediatric Crohn's disease subjects), together with the efficacy and safety data, support the use of 5 mg/kg infliximab administered at Weeks 0, 2, and 6, followed by a maintenance regimen of 5 mg/kg infliximab q8w thereafter for the treatment of UC in pediatric subjects.

6 Appendix

Appendix A Table of Studies

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Appendix A.1 Summary of results of studies included in Summary of Clinical Pharmacology

Study ID	No. of Study Centers	Study Start Enrollment Status, Date	Design & Control Type	Study & Control Drugs	Study Objective(s)	No. of Subjects by Arm	Duration of Treatment	Gender Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)	Clinical Pharmacology Results
C0168T72 CSR Module 5.3:5	23 US Canada Netherlands Belgium	25 Aug 2006 - 24 Jun 2010 60 enrolled Completed through Week 62 follow-up	Phase 3, randomized, multicenter, open-label	Infliximab 5 mg/kg infusion at Weeks 0, 2, and 6. At Week 8, responders randomly assigned 1:1 to maintenance treatment with either • 5 mg/kg infliximab q8w through Week 46 • 5 mg/kg infliximab administered q12w through Week 42	Efficacy of a 3-dose induction regimen of infliximab in inducing clinical response and to evaluate the safety profile of infliximab during induction and maintenance treatment.	Induction at Weeks 0,2,6: 60 subjects Maintenance: At Week 8, 45/60 responders q8w: 22 q12w: 23	Treated through Week 46 with follow-up through Week 50	M: 28 F: 32 Median age: 14.5 (range 6-17)	Pediatric UC Age 6 to 16 or 17 years with moderately to severely active UC (defined as a baseline Mayo score of 6 to 12) confirmed by biopsy and a Mayo endoscopy subscore ≥ 2 at a screening sigmoidoscopy, and receiving adequate treatment with, have failed to respond to 5-ASAs, immunomodulators (6-MP or AZA), or oral or IV corticosteroids.	Clinical response at Week 8, defined as a decrease from baseline in the Mayo score by $\geq 30\%$ and ≥ 3 points, with a decrease in the rectal bleeding subscore ≥ 1 or a rectal bleeding subscore of 0 or 1.	• Median serum infliximab concentration was maintained above detectable levels after 5 mg/kg infliximab q8w or q12w doses in this study. • Median preinfusion serum infliximab concentrations during maintenance treatment in subjects who received 5 mg/kg infliximab q8w were generally higher than those in subjects receiving 5 mg/kg infliximab q12w. • An increase in infliximab dose or dose frequency resulted in higher serum infliximab concentration levels in subjects who stepped up their dose regimen.

Appendix A.1 Summary of results of studies included in Summary of Clinical Pharmacology

Study ID	No. of Study Centers	Study Start	Design & Control Type	Study & Control Drugs	Study Objective(s)	No. of Subjects by Arm	Duration of Treatment	Gender	Diagnosis	Primary Endpoint(s)	Clinical Pharmacology Results
		Enrollment Status, Date									
Study Report Type & Location Within the Submission	Location(s)	Total Enrollment/ Enrollment Goal Study Status		Dose, Route, & Regimen(s)		Entered/ Completed		Median Age (Range)	Inclusion Criteria		
											- Among 52 infliximab-treated subjects with appropriate samples for the assessment of antibodies to infliximab, 4 (7.7%) subjects were positive for antibodies to infliximab through Week 54, all with low antibody titers (1:10 to 1:40). - The development of antibodies to infliximab did not appear to be the major determinant of either clinical response during induction treatment or loss of clinical response during maintenance therapy, although the number of subjects who were antibody-positive was small. Infliximab treatment decreased proinflammatory marker IL-8 and increased IL-12.

Appendix A.1 Summary of results of studies included in Summary of Clinical Pharmacology

Study ID	No. of Study Centers	Study Start Enrollment Status, Date	Design & Control Type	Study & Control Drugs Dose, Route, & Regimen(s)	Study Objective(s)	No. of Subjects by Arm Entered/Completed	Duration of Treatment	Gender Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)	Clinical Pharmacology Results
C0168T47 REACH Efficacy, Safety, PK Module 5.3.5	34 North America [US and CA], Western Europe [UK, Belgium, Denmark, Netherlands], and Israel.	Feb 03 Completed as of Apr 05. 112/110 Main portion of trial completed as of Apr 05. OLE ongoing.	Phase 3, randomized, multicenter, open-label study to evaluate the safety and efficacy of infliximab in pediatric subjects with moderate to severe Crohn's disease.	<u>Induction:</u> All subjects (112) received 5 mg/kg infliximab at Wks 0, 2, and 6. <u>Maintenance:</u> Responders at Wk 10 were randomized to receive 5 mg/kg infliximab every 8 wks (Group I) or every 12 wks (Group II) through Wk 46. <u>Nonresponders/Loss of Response:</u> Nonresponders to induction dosing at Wk 10 were discontinued from the study. <u>Group I</u> nonresponders were eligible to receive 10 mg/kg infliximab every 8 wks.	<u>Primary:</u> To evaluate the efficacy of a 3-dose induction regimen of infliximab in reducing signs and symptoms in pediatric subjects with moderately to severely active Crohn's disease. <u>Secondary:</u> To evaluate the efficacy of 2 infliximab maintenance dosing regimens (q8 versus q12 wks) in maintaining clinical response and inducing clinical remission in pediatric subjects with moderately to	At Wk 10, 103 subjects were randomized to 1 of 2 maintenance regimens: Group I: 52/46 Group II: 51/42	46 wks. Subjects completing treatment through Wk 46 could enter an OLE starting at Wk 54 for a maximum of 3 yrs.	M: 66 F: 46 13.0 yrs (6.0, 17.0)	Moderate to severe Crohn's disease Pediatric subjects (6 through 17 yrs old) with a diagnosis of moderate to severe Crohn's disease (PCDAI > 30) at baseline, despite adequate current treatment with an immunomodulator. Infliximab naïve.	Clinical response at Wk 10 (compared with historical clinical response observed in adults), clinical response at Wk 54, clinical remission at Wk 54, change from baseline in average daily corticosteroid use at Wk 54, and change from baseline in height status at Wk 54.	The median infliximab serum level was maintained above detection limits and the median terminal half-life was 10.7 days in this study. The C _{max} was 126.7 µg/mL, CL was 6.1 mL/day/kg, V _{ss} was 86.4 mL/kg, and AUC _{ss} was 833.8 µg.day/mL. More frequent dosing resulted in a lower proportion of subjects with undetectable infliximab concentration. An increased dose of infliximab or a more frequent dosage regimen led to a sustained presence of infliximab in the serum of subjects who crossed over. Subjects who crossed over to 10 mg/kg had intrinsically higher infliximab clearance than subjects who remained on their original 5 mg/kg dose.

Appendix A.1 Summary of results of studies included in Summary of Clinical Pharmacology

Study ID	No. of Study Centers	Study Start Enrollment Status, Date	Design & Control Type	Study & Control Drugs	No. of Subjects by Arm	Duration of Treatment	Gender Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)	Clinical Pharmacology Results
Study Report Type & Location Within the Submission	Location(s)	Total Enrollment/ Enrollment Goal Study Status	Dose, Route, & Regimen(s)	Study Objective(s)	Entered/ Completed					
				<u>Group II</u> subjects who lost response ≤ 8 wks after the previous infliximab infusion were eligible to receive 10 mg/kg infliximab every 8 wks. <u>Group II</u> subjects who lost response > 8 wks but ≤ 12 wks after the previous infliximab infusion were eligible to receive 5 mg/kg infliximab every 8 wks. <u>Open-label Extension</u> : Subjects completing treatment through Wk 46 could enter an open-label extension beginning at Wk 54 for a maximum of 3 yrs.	severely active Crohn's disease, to determine the PK profile in pediatric subjects following induction and maintenance dosing with 5 mg/kg infliximab, to determine the effect of dosing with infliximab on the use of corticosteroids, and to determine the effect of maintenance dosing with infliximab on growth over the course of 1 yr.					

Appendix A.1 Summary of results of studies included in Summary of Clinical Pharmacology

Study ID	No. of Study Centers	Study Start Enrollment Status, Date	Design & Control Type	Study & Control Drugs	Study Objective(s)	No. of Subjects by Arm	Duration of Treatment	Gender Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)	Clinical Pharmacology Results
C0168T37 ACT I Safety and Efficacy Module 5.3.5	62 sites 31 North America 17 European Union 9 Australia 4 New Zealand 1 Argentina	19 Mar 2002 Enrollment complete in main study, 23 Feb 2004 364 enrolled/ 360 planned Extension active	Randomized, double-blind, placebo-controlled, parallel-group in subjects with active UC	Infliximab (5 mg/kg or 10 mg/kg)/ placebo IV infusion at Weeks 0, 2, 6, 14, 22, and 30 and every 8 weeks thereafter through Week 46	Primary Objective: To evaluate the safety and efficacy of infliximab in subjects with active UC	Placebo: 121/46 (through main portion of study) 5 mg/kg Infliximab: 121/76 10 mg/kg Infliximab: 122/72	Main study: 46 weeks, plus 8 weeks safety follow-up Extension: up to 3 years	M: 222 F: 142 40 yrs (18 - 81 yrs)	Active UC Endoscopic evidence of active colitis as indicated by endoscopy subscore of ≥ 2 ; Failed to respond to or failed to tolerate oral corticosteroids, 6-MP (mercaptopurine) or AZA (azathioprine)	The proportion of patients with clinical response, defined as a decrease in the Mayo score by $\geq 30\%$ and ≥ 3 points, with a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1, at Week 8.	Pharmacokinetic analyses in subjects with ulcerative colitis demonstrated a dose proportional maximum observed concentration (C _{max}) following multiple infusions of 5 mg/kg or 10 mg/kg infliximab. In general, the majority of subjects in both the 5 mg/kg and 10 mg/kg infliximab treatment groups maintained detectable serum infliximab concentrations through Week 30. The postinfusion serum concentrations indicated that infliximab is distributed primarily into the vascular space.

Appendix A.1 Summary of results of studies included in Summary of Clinical Pharmacology

Study ID	No. of Study Centers	Study Start Enrollment Status, Date	Design & Control Type	Study & Control Drugs	Study Objective(s)	No. of Subjects by Arm	Duration of Treatment	Gender Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)	Clinical Pharmacology Results
C0168T46 ACT 2 Safety and Efficacy Module 5.3.5	55 sites 30 North America 21 European Union 4 Israel	04 Jun 2002 Enrollment complete, 10 Feb 2004 364 enrolled/ 360 planned Extension active	Randomized, double-blind, placebo-controlled, parallel-group in subjects with active UC	5 mg/kg or 10 mg/kg Infliximab or placebo IV infusion at Weeks 0, 2, 6, 14, and 22	Primary Objective: To evaluate the safety and efficacy of infliximab in subjects with active UC Secondary Objective: To determine the proportion of subjects: (1) in clinical remission at Week 8, (2) with mucosal healing at Week 8, (3) in clinical response at Week 30, and (4) in clinical remission at Week 30	Placebo: 123/55 (through main portion of study) 5 mg/kg Infliximab: 121/87 10 mg/kg Infliximab: 120/84	Main study: 22 weeks, plus 8 weeks safety follow-up Extension: up to 3 years	M: 215 F: 149 38 yrs (18 – 82 yrs)	Active UC Endoscopic evidence of active colitis as indicated by an endoscopy subscore of ≥ 2	Clinical response at Week 8, which was defined as a decrease from baseline in the Mayo score by $\geq 30\%$ and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1, at Week 8.	Pharmacokinetic analyses in subjects with ulcerative colitis demonstrated a dose proportional C _{max} following multiple infusions of 5 mg/kg or 10 mg/kg infliximab. In general, the majority of subjects in both the 5 mg/kg and 10 mg/kg infliximab treatment groups maintained detectable serum infliximab concentrations from infusion to infusion.

Appendix A.1 Summary of results of studies included in Summary of Clinical Pharmacology

Study ID	Study Report Type & Location Within the Submission	No. of Study Centers	Location(s)	Study Start Enrollment Status, Date	Total Enrollment/ Enrollment Goal	Study Status	Design & Control Type	Study & Control Drugs	Dose, Route, & Regimen(s)	Study Objective(s)	No. of Subjects by Arm	Entered/ Completed	Duration of Treatment	Gender	Median Age (Range)	Diagnosis	Inclusion Criteria	Primary Endpoint(s)	Clinical Pharmacology Results		
C0168T23	Efficacy, Safety, PK	CSR	Module 5.3.3	20-Wk Period: 7	48-Wk Retreatment Extension: 4	US, The Netherlands, Switzerland	Jul 98 (20-Wk Period); Apr 99 (48-Wk Retreatment Extension).	Phase 1/2, randomized, single-dose, multicenter study of anti-TNF chimeric monoclonal antibody (infliximab) in the treatment of pediatric subjects with active Crohn's disease.	20-Wk Period: Single IV infusion of 1 mg/kg, 5 mg/kg, or 10 mg/kg infliximab (dose-blinded).	48-Wk Retreatment Extension (open-label): Subjects received up to 8 IV infusions of 5 mg/kg infliximab over a 48-wk period.	20-Wk Period: 1 mg/kg - 6 5 mg/kg - 7 10 mg/kg - 8	48-Wk Retreatment Extension: 8	21/21	Single IV infusion of infliximab at Wk 0 with a 20-wk follow-up period.	Seven subjects received additional commercial infliximab infusions through Wk 20 (protocol deviations). One of these 7 subjects also received an additional blinded dose (1 mg/kg) of the study	M: 15 F: 6	15.0 yrs (11.0, 17.0)	Crohn's disease	Subjects ≥ 8 and ≤ 17 yrs of age with a modified CDAI of ≥ 200 (with pediatric-adjusted hematocrit and standard body weight), or PCDAI of ≥ 30. Subjects must have had Crohn's disease of at least 6 months' duration, with colitis, ileitis, or ileocolitis confirmed by radiography or endoscopy. Also, subjects must have had active disease despite the use of oral corticosteroid therapy; azathioprine or 6-MP; IM, SC, or oral MTX; or must have failed to	PK profile of infliximab given as a single infusion of 1, 5, or 10 mg/kg in pediatric subjects; safety and efficacy.	Exposure of pediatric patients to infliximab as measured by AUC increased with increasing dose. The median AUC values were 122, 908, and 2308 µg/mL x day for the doses of 1, 5, and 10 mg/kg, respectively. The median CI, Vdss, MRT and half-life of infliximab in the pediatric patients in the 5 mg/kg treatment group were 5.5 mL/day/kg, 47 mL/kg, 7.5 days and 7.6 days, respectively. The median values of the PK parameters of infliximab in the 5 mg/kg treatment group in the pediatric patients in this study were similar to those of adult patients in the same treatment group in an earlier single dose study (Centocor study C0168T11). In adult patients, the median AUC, CI, Vdss, MRT,

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Study ID	Study Report Type & Location Within the Submission	No. of Study Centers	Location(s)	Study Start Enrollment Status, Date	Total Enrollment/ Enrollment Goal	Study Status	Design & Control Type	Study & Control Drugs	Dose, Route, & Regimen(s)	Study Objective(s)	No. of Subjects by Arm	Entered/ Completed	Duration of Treatment	Gender	Median Age (Range)	Diagnosis	Inclusion Criteria	Primary Endpoint(s)	Clinical Pharmacology Results
													agent with the permission of the Sponsor.			respond to cyclosporine or tacrolimus (FK506).			and half-life in the patients in the 5 mg/kg treatment group were 788 µg/mL x day, 6.3 mL/day/kg, 80 mL/kg, 11.9 days, and 7.8 days, respectively. Overall, at the 5 mg/kg and 10 mg/kg doses, all of the median derived PK parameters for the pediatric patients were within the 80% to 125% interval of the logarithmic transform of the median adult values.

Appendix A.1 Summary of results of studies included in Summary of Clinical Pharmacology

Study ID	No. of Study Centers	Study Start Enrollment Status, Date	Design & Control Type	Study & Control Drugs	No. of Subjects by Arm	Duration of Treatment	Gender Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)	Clinical Pharmacology Results
C0168T55 Safety and PK Module 5.3.3	2 US	May 03 Completed as of Sep 04. 6/8-20 Completed.	Phase 1, open-label study to evaluate the safety and PK of a single infusion of infliximab in pediatric Crohn's disease subjects receiving maintenance treatment with infliximab.	Single IV infusion of 5 mg/kg infliximab.	6/6	Single dose.	M: 2 F: 4 9.0 yrs (9.0, 11.0)	IBD Subjects between the ages of 6 and 11 yrs with IBD of at least 3 months' duration. IBD included those subjects with a primary diagnosis of Crohn's disease, ulcerative colitis, or indeterminate colitis.	PK and short-term safety.	The pharmacokinetics of infliximab at steady state in pediatric subjects with Crohn's disease (age range 9 to 11 years), demonstrated a continuous exposure of the subjects to infliximab when subjects were administered 5 mg/kg infliximab at intervals of 5, 6, or 8 weeks as judged by their prior response to treatment. The median values of CL, Vss, AUCss, and t1/2 for infliximab in these subjects were 8.2 mL/day/kg, 66.9 mL/kg, 613.5 µg·day/mL, and 6.0 days, respectively.

Appendix A.1 Summary of results of studies included in Summary of Clinical Pharmacology

Study ID	No. of Study Centers	Study Start Enrollment Status, Date	Design & Control Type	Study & Control Drugs	Study Objective(s)	No. of Subjects by Arm	Duration of Treatment	Gender Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)	Clinical Pharmacology Results
C0168T62 RESULTS UC Safety Module 5.3.5	96 sites 47 North America 9 Australia 4 New Zealand 1 Argentina 4 Israel 31 European Union	04 Oct 2004 Enrollment Active 284 subjects analyzed	Observational, long-term, multicenter, safety study	No study agent administered	To evaluate long-term safety information on subjects who have participated in infliximab clinical studies in ulcerative colitis that require long-term safety follow-up.	Randomized treatment in ACT 1 or ACT 2: Placebo: 117/ NA Infliximab: 167/ NA	5 years of safety follow-up	M: 163 F: 121 38.5 yrs (18 – 75 yrs)	Ulcerative Colitis Received at least 1 dose of study agent in ACT 1 or ACT 2	The number of subjects with each of the following safety events: serious infection, new malignancies, new autoimmune diseases, death, delayed hypersensitivity reactions, or dysplasia of the colon.	No pharmacology assessments were performed in this study.

Appendix A.1 Summary of results of studies included in Summary of Clinical Pharmacology

Study ID	No. of Study Centers	Study Start Enrollment Status, Date		Study & Control Drugs	No. of Subjects by Arm		Gender	Diagnosis			
Study Report Type & Location Within the Submission	Location(s)	Total Enrollment/ Enrollment Goal Study Status	Design & Control Type	Dose, Route, & Regimen(s)	Study Objective(s)	Entered/ Completed	Duration of Treatment	Median Age (Range)	Inclusion Criteria	Primary Endpoint(s)	Clinical Pharmacology Results
C0168T32 (JRA) Efficacy, Safety, Pharmacokinetics Module 5.3.5	34 centers. US: 7 Canada: 2 Argentina: 3 Europe: 22	19 Oct 2001 to 01 Apr 2004 OLE at Week 52 Completed	Multicenter randomized, placebo-controlled, double-blind, study	Subjects in Group I: placebo at Weeks 0, 2, and 6; 6 mg/kg of infliximab at Weeks 14, 16, and 20, and then every 8 weeks through Week 44. Subjects in Group II: infliximab 3 mg/kg at Weeks 0, 2, 6, 14, and placebo at Week 16; then 3 mg/kg of infliximab at Week 20 and every 8 weeks through Week 44.	<u>Primary:</u> Evaluate safety of infliximab in subjects with active JRA who were receiving concomitant MTX therapy, either with or without NSAIDs and/or low-dose corticosteroids. <u>Secondary:</u> The secondary objective of this study was to evaluate the PK profile of infliximab in subjects with JRA with active disease despite background therapy.	120 subjects planned, 122 randomized; 2 subjects were randomized and not treated. Group I; n = 60 placebo/6 mg/kg infliximab plus MTX therapy (Group II; n = 60). Subjects initially randomized to placebo were subsequently permitted to receive (after Week 14) 6 mg/kg infliximab plus MTX therapy. 120 subjects analyzed for safety, 117 subjects analyzed for PK 121 subjects	44 weeks OLE at Week 52 – Week 216 Subjects who did not enter the OLE at Week 52 continued in the study through Week 64	M: 102 F: 20 Median age: 12.0 (range: 4-17)	Active JRA aged 4 to < 18 years, treated with oral, intramuscular, or subcutaneous methotrexate (MTX) for 3 months prior to study entry with a sub-optimal response and no serious MTX-related toxicity.	The proportion of subjects with ACR-pedi 30 at Week 14.	Pharmacokinetic analyses demonstrated dose-proportional postinfusion serum concentrations following multiple infusions of 3 or 6 mg/kg infliximab. The 3 mg/kg dose of infliximab was associated with slightly higher clearance and shorter half-life of infliximab compared with the 6 mg/kg dose. In general, by the end of the Week 36 and Week 44 treatments, more than half of the subjects in the 3 mg/kg group did not maintain detectable infliximab in their blood through the 8 weeks up to the next scheduled assessment. The results from the PD marker analyses indicate that treatment with 3 mg/kg of infliximab produced a greater median percent decrease from baseline in IL-6,

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Study ID	No. of Study Centers	Study Start Enrollment Status, Date	Design & Control Type	Study & Control Drugs	Study Objective(s)	No. of Subjects by Arm	Duration of Treatment	Gender Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)	Clinical Pharmacology Results
Study Report Type & Location Within the Submission	Location(s)	Total Enrollment/ Enrollment Goal Study Status		Dose, Route, & Regimen(s)		Entered/ Completed					
						analyzed for efficacy. 78 subjects entered the OLE					MMP-3, VEGF, and ICAM-1 compared with placebo up to Week 14. A dose response effect was shown after Week 14 in the 6 mg/kg group, with larger reductions from baseline in markers IL-6, MMP-3 and VEGF at most timepoints, compared with the 3 mg/kg group.

6-MP = 6-mercaptopurine, CDAI = Crohn's Disease Activity Index, F = female, IBD = inflammatory bowel disease, IM = intramuscular, IV = intravenous, M = male, MTX = methotrexate, OLE = open-label extension, PCDAI = Pediatric Crohn's Disease Activity Index, PK = pharmacokinetic(s), REACH = A Randomized, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Anti-TNF α Chimeric Monoclonal Antibody (Infliximab, REMICADE®) in Pediatric Subjects with Moderate to Severe Crohn's Disease, SC = subcutaneous, TNF = tumor necrosis factor, US = United States, wk(s) = week(s), yr(s) = years

Appendix B Supportive Data

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Appendix B.1 **Summary of serum infliximab concentrations (micrograms/mL) through Week 8 by age group; treated subjects**

	Infliximab 5 mg/kg	
	Ages 6-11	Ages 12-17
Subjects treated	15	45
Week 0, preinfusion		
n	13	44
Mean ± SD	0.00 ± 0.000	4.44 ± 20.659
Median	0.00	0.00
Range	(0.0, 0.0)	(0.0, 105.9)
Week 0, 1 hour postinfusion		
n	14	41
Mean ± SD	99.78 ± 29.508	90.07 ± 25.896
Median	98.52	96.13
Range	(58.5, 166.3)	(0.0, 143.1)
Week 2, preinfusion		
n	14	44
Mean ± SD	22.37 ± 21.299	20.12 ± 8.939
Median	18.21	19.30
Range	(2.6, 91.8)	(1.2, 43.0)
Week 2, 1 hour postinfusion		
n	14	37
Mean ± SD	98.79 ± 29.653	117.02 ± 23.515
Median	97.76	118.51
Range	(26.2, 149.0)	(69.4, 174.3)
Week 6, preinfusion		
n	13	36
Mean ± SD	8.73 ± 8.511	15.26 ± 11.279
Median	7.08	15.29
Range	(0.0, 26.1)	(0.0, 43.5)
Week 6, 1 hour postinfusion		
n	10	30
Mean ± SD	121.01 ± 51.265	106.49 ± 27.843
Median	98.56	107.00
Range	(84.6, 249.3)	(20.0, 175.8)

Appendix B.1 **Summary of serum infliximab concentrations (micrograms/mL) through Week 8 by age group; treated subjects**

		Infliximab 5 mg/kg	
		Ages 6-11	Ages 12-17
Week 8			
n		11	33
Mean ± SD		25.85 ± 12.402	30.85 ± 14.550
Median		22.89	29.57
Range		(11.0, 46.1)	(0.0, 79.4)

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Appendix B.2 Summary of serum infliximab concentrations (micrograms/mL) over time by infliximab antibody status for REMICADE monotherapy vs REMICADE combination therapy; treated subjects who received 5 mg/kg infliximab in ACT 1 (C0168T37)

	REMICADE Monotherapy ^a			REMICADE Combination Therapy ^b			Overall
	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	
Treated subjects with appropriate samples ^e	8	45	53		58	59	112
Week 0 preinfusion							
n	8	45	53		57	58	111
Mean ± SD	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± NA	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.1
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IQ range	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)
Range	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)
Week 0 postinfusion							
n	7	45	52		57	58	110
Mean ± SD	97.8 ± 25.0	119.4 ± 42.9	116.5 ± 41.5	312.1 ± NA	115.4 ± 44.6	118.8 ± 51.2	117.7 ± 46.6
Median	110.3	115.4	113.9	312.1	109.8	110.0	110.5
IQ range	(72.1, 119.3)	(89.6, 136.3)	(88.3, 130.5)	(312.1, 312.1)	(89.9, 121.2)	(89.9, 124.6)	(88.8, 128.6)
Range	(66.1, 125.7)	(0.0, 214.5)	(0.0, 214.5)	(312.1, 312.1)	(56.3, 306.2)	(56.3, 312.1)	(0.0, 312.1)
Week 2 preinfusion							
n	8	45	53		57	58	111
Mean ± SD	46.0 ± 80.7	34.6 ± 28.0	36.3 ± 39.5	0.0 ± NA	27.4 ± 30.3	26.9 ± 30.3	31.4 ± 35.1
Median	21.1	30.8	30.5	0.0	24.2	23.6	24.9

Appendix B.2 Summary of serum infliximab concentrations (micrograms/mL) over time by infliximab antibody status for REMICADE monotherapy vs REMICADE combination therapy; treated subjects who received 5 mg/kg infliximab in ACT 1 (C0168T37)

	REMICADE Monotherapy ^a			REMICADE Combination Therapy ^b			Overall
	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	
IQ range	(14.6, 23.0)	(20.9, 38.6)	(20.7, 38.3)	(0.0, 0.0)	(14.6, 29.7)	(14.4, 29.7)	(16.8, 34.4)
Range	(5.7, 245.1)	(0.0, 185.3)	(0.0, 245.1)	(0.0, 0.0)	(2.9, 222.8)	(0.0, 222.8)	(0.0, 245.1)
Week 2 postinfusion							
n	8	45	53	■	56	57	110
Mean ± SD	106.7 ± 34.4	159.8 ± 66.4	151.8 ± 65.3	90.3 ± NA	140.5 ± 54.9	139.6 ± 54.8	145.5 ± 60.1
Median	111.2	146.1	137.4	90.3	125.7	125.0	131.0
IQ range	(103.9, 128.9)	(121.8, 187.0)	(113.1, 180.1)	(90.3, 90.3)	(108.0, 150.6)	(107.9, 150.4)	(109.4, 157.0)
Range	(28.0, 137.4)	(0.0, 354.9)	(0.0, 354.9)	(90.3, 90.3)	(75.2, 364.5)	(75.2, 364.5)	(0.0, 364.5)
Week 6 preinfusion							
n	8	44	52	■	54	55	107
Mean ± SD	9.7 ± 5.5	22.5 ± 14.5	20.5 ± 14.2	0.0 ± NA	19.4 ± 19.3	19.1 ± 19.3	19.8 ± 17.0
Median	10.7	22.5	19.2	0.0	16.5	16.1	16.9
IQ range	(6.0, 13.8)	(12.8, 32.5)	(11.3, 30.9)	(0.0, 0.0)	(7.4, 27.5)	(6.3, 27.5)	(7.4, 28.5)
Range	(0.0, 16.8)	(0.0, 60.5)	(0.0, 60.5)	(0.0, 0.0)	(0.0, 110.4)	(0.0, 110.4)	(0.0, 110.4)
Week 6 postinfusion							
n	8	45	53	■	50	51	104
Mean ± SD	113.7 ± 17.9	141.5 ± 51.7	137.3 ± 49.1	53.9 ± NA	136.3 ± 52.8	134.6 ± 53.6	136.0 ± 51.1
Median	115.5	134.7	129.9	53.9	129.6	129.4	129.6
IQ range	(102.1, 128.3)	(102.3, 180.0)	(102.3, 176.0)	(53.9, 53.9)	(101.4, 153.6)	(100.7, 153.6)	(101.1, 158.5)
Range	(83.8, 134.1)	(0.0, 238.5)	(0.0, 238.5)	(53.9, 53.9)	(61.0, 371.3)	(53.9, 371.3)	(0.0, 371.3)

Appendix B.2 **Summary of serum infliximab concentrations (micrograms/mL) over time by infliximab antibody status for REMICADE monotherapy vs REMICADE combination therapy; treated subjects who received 5 mg/kg infliximab in ACT 1 (C0168T37)**

	REMICADE Monotherapy ^a			REMICADE Combination Therapy ^b			Overall
	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	
Week 8							
n	8	44	52	■	52	53	105
Mean ± SD	23.2 ± 12.6	46.4 ± 34.2	42.9 ± 32.8	0.0 ± NA	39.6 ± 37.9	38.8 ± 37.9	40.8 ± 35.4
Median	25.3	40.9	35.5	0.0	32.3	32.1	33.8
IQ range	(16.7, 31.3)	(29.7, 55.8)	(25.3, 53.6)	(0.0, 0.0)	(19.7, 48.3)	(19.4, 48.1)	(22.4, 51.0)
Range	(0.0, 39.4)	(0.0, 205.4)	(0.0, 205.4)	(0.0, 0.0)	(2.9, 253.2)	(0.0, 253.2)	(0.0, 253.2)
Week 14 preinfusion							
n	7	37	44	■	47	48	92
Mean ± SD	3.3 ± 3.3	9.8 ± 11.8	8.8 ± 11.1	0.0 ± NA	8.3 ± 19.2	8.1 ± 19.0	8.4 ± 15.7
Median	1.6	7.2	6.1	0.0	3.4	3.4	4.7
IQ range	(1.3, 6.3)	(3.0, 12.6)	(2.6, 11.7)	(0.0, 0.0)	(1.7, 7.8)	(1.5, 7.1)	(2.0, 9.4)
Range	(0.0, 9.2)	(0.0, 68.6)	(0.0, 68.6)	(0.0, 0.0)	(0.0, 128.3)	(0.0, 128.3)	(0.0, 128.3)
Week 14 postinfusion							
n	7	36	43	■	43	44	87
Mean ± SD	110.2 ± 55.5	161.6 ± 77.9	153.3 ± 76.6	79.7 ± NA	140.8 ± 57.0	139.4 ± 57.1	146.2 ± 67.4
Median	120.1	150.4	144.9	79.7	133.5	132.8	134.6
IQ range	(93.5, 124.8)	(109.0, 187.5)	(106.7, 184.3)	(79.7, 79.7)	(100.6, 182.6)	(99.3, 180.8)	(104.8, 182.6)
Range	(5.3, 192.1)	(0.0, 365.5)	(0.0, 365.5)	(79.7, 79.7)	(64.9, 357.8)	(64.9, 357.8)	(0.0, 365.5)

Appendix B.2 Summary of serum infliximab concentrations (micrograms/mL) over time by infliximab antibody status for REMICADE monotherapy vs REMICADE combination therapy; treated subjects who received 5 mg/kg infliximab in ACT 1 (C0168T37)

	REMICADE Monotherapy ^a			REMICADE Combination Therapy ^b			Overall
	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	
Week 30 preinfusion							
n	7	33	40		40	41	81
Mean ± SD	0.4 ± 0.7	36.5 ± 82.3	30.2 ± 75.9	0.0 ± NA	12.0 ± 31.5	11.7 ± 31.2	20.8 ± 58.1
Median	0.0	6.0	4.8	0.0	3.0	2.8	3.5
IQ range	(0.0, 0.7)	(2.8, 11.2)	(1.0, 10.6)	(0.0, 0.0)	(1.2, 6.0)	(1.2, 6.0)	(1.2, 8.0)
Range	(0.0, 1.8)	(0.0, 356.5)	(0.0, 356.5)	(0.0, 0.0)	(0.0, 182.0)	(0.0, 182.0)	(0.0, 356.5)
Week 38 preinfusion							
n	6	29	35		39	40	75
Mean ± SD	0.1 ± 0.2	7.3 ± 6.4	6.1 ± 6.5	0.0 ± NA	7.1 ± 6.6	6.9 ± 6.6	6.5 ± 6.5
Median	0.0	5.0	3.5	0.0	5.3	5.0	3.9
IQ range	(0.0, 0.0)	(2.4, 12.9)	(1.2, 11.4)	(0.0, 0.0)	(2.3, 14.1)	(2.0, 13.4)	(1.5, 12.8)
Range	(0.0, 0.4)	(0.0, 24.4)	(0.0, 24.4)	(0.0, 0.0)	(0.0, 23.1)	(0.0, 23.1)	(0.0, 24.4)
Week 46 preinfusion							
n	4	29	33		38	39	72
Mean ± SD	40.9 ± 81.8	7.1 ± 6.4	11.2 ± 28.1	0.0 ± NA	7.3 ± 6.5	7.2 ± 6.5	9.0 ± 19.5
Median	0.0	5.3	3.7	0.0	4.8	4.4	4.3
IQ range	(0.0, 81.8)	(2.5, 10.6)	(1.6, 10.6)	(0.0, 0.0)	(2.5, 11.1)	(2.5, 11.1)	(2.3, 10.9)
Range	(0.0, 163.6)	(0.0, 23.3)	(0.0, 163.6)	(0.0, 0.0)	(0.0, 23.8)	(0.0, 23.8)	(0.0, 163.6)

Appendix B.2 Summary of serum infliximab concentrations (micrograms/mL) over time by infliximab antibody status for REMICADE monotherapy vs REMICADE combination therapy; treated subjects who received 5 mg/kg infliximab in ACT 1 (C0168T37)

	REMICADE Monotherapy ^a			REMICADE Combination Therapy ^b			Overall
	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	
Week 46 postinfusion							
n	3	30	33	■	34	35	68
Mean ± SD	92.5 ± 80.1	141.6 ± 50.4	137.1 ± 53.9	149.7 ± NA	139.3 ± 35.8	139.5 ± 35.4	138.4 ± 45.0
Median	136.3	132.3	133.0	149.7	132.6	135.0	134.0
IQ range	(0.0, 141.2)	(115.8, 153.0)	(115.8, 152.2)	(149.7, 149.7)	(114.4, 165.8)	(114.4, 165.8)	(114.8, 155.5)
Range	(0.0, 141.2)	(81.0, 348.5)	(0.0, 348.5)	(149.7, 149.7)	(78.0, 224.2)	(78.0, 224.2)	(0.0, 348.5)
Week 54							
n	3	30	33	■	38	39	72
Mean ± SD	0.0 ± 0.0	11.7 ± 27.6	10.6 ± 26.5	0.0 ± NA	9.3 ± 24.6	9.0 ± 24.4	9.8 ± 25.2
Median	0.0	5.0	4.8	0.0	3.6	3.6	3.7
IQ range	(0.0, 0.0)	(2.6, 11.0)	(1.7, 9.8)	(0.0, 0.0)	(1.6, 6.5)	(1.6, 6.5)	(1.7, 8.7)
Range	(0.0, 0.0)	(0.0, 154.2)	(0.0, 154.2)	(0.0, 0.0)	(0.1, 153.6)	(0.0, 153.6)	(0.0, 154.2)

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

^b Subjects in the REMICADE combination therapy group were receiving concomitant treatment with azathioprine (AZA), 6-mercaptopurine (6-MP), or MTX at baseline.

^c Includes all subjects who had at least 1 positive sample at any time.

^d Excludes subjects who were positive at any time and includes subjects whose samples may contain infliximab.

^e Subjects with appropriate samples either had antibodies to infliximab at some timepoint following their first infusion or had 1 or more samples obtained after their last infusion.

RE157;[K CONC 49 D 157], 21JUL2009 14:03

Appendix B.3 Summary of serum infliximab concentrations (micrograms/mL) over time by infliximab antibody status for REMICADE monotherapy vs REMICADE combination therapy; treated subjects who received 5 mg/kg infliximab in ACT 2 (C0168T46)

	REMICADE Monotherapy ^a			REMICADE Combination Therapy ^b			Overall
	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	
Treated subjects with appropriate samples ^e	12	41	53		42	43	96
Week 0 preinfusion							
n	12	40	52		41	42	94
Mean ± SD	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± NA	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0
IQ range	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)
Range	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)
Week 0 postinfusion							
n	12	39	51		38	39	90
Mean ± SD	129.9 ± 77.5	123.4 ± 52.3	124.9 ± 58.4	111.0 ± NA	132.0 ± 70.5	131.5 ± 69.7	127.7 ± 63.2
Median	105.9	113.6	112.8	111.0	116.4	112.0	112.5
IQ range	(76.8, 156.1)	(92.9, 141.0)	(88.7, 141.0)	(111.0, 111.0)	(92.6, 146.9)	(92.6, 146.9)	(89.4, 141.6)
Range	(66.7, 331.5)	(38.7, 335.6)	(38.7, 335.6)	(111.0, 111.0)	(13.9, 357.8)	(13.9, 357.8)	(13.9, 357.8)

Appendix B.3 **Summary of serum infliximab concentrations (micrograms/mL) over time by infliximab antibody status for REMICADE monotherapy vs REMICADE combination therapy; treated subjects who received 5 mg/kg infliximab in ACT 2 (C0168T46)**

	REMICADE Monotherapy ^a			REMICADE Combination Therapy ^b			Overall
	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	
Week 2 preinfusion							
n	12	41	53	■	42	43	96
Mean ± SD	24.7 ± 12.0	29.4 ± 14.0	28.4 ± 13.6	14.8 ± NA	29.4 ± 30.7	29.1 ± 30.4	28.7 ± 22.6
Median	22.4	26.5	26.1	14.8	24.5	24.0	25.6
IQ range	(18.5, 31.2)	(21.4, 34.0)	(21.2, 31.6)	(14.8, 14.8)	(15.4, 32.4)	(14.8, 32.4)	(18.6, 32.4)
Range	(3.7, 46.9)	(7.7, 74.6)	(3.7, 74.6)	(14.8, 14.8)	(2.1, 203.7)	(2.1, 203.7)	(2.1, 203.7)
Week 2 postinfusion							
n	12	39	51	■	40	41	92
Mean ± SD	127.8 ± 40.2	159.6 ± 66.2	152.1 ± 62.2	142.0 ± NA	146.7 ± 57.8	146.5 ± 57.1	149.6 ± 59.7
Median	129.8	137.9	132.9	142.0	134.9	136.0	134.9
IQ range	(114.8, 158.2)	(115.5, 203.3)	(115.5, 188.1)	(142.0, 142.0)	(113.7, 169.6)	(114.3, 169.1)	(114.9, 170.2)
Range	(35.6, 183.8)	(50.4, 312.2)	(35.6, 312.2)	(142.0, 142.0)	(17.6, 314.8)	(17.6, 314.8)	(17.6, 314.8)
Week 6 preinfusion							
n	12	39	51	■	42	43	94
Mean ± SD	15.6 ± 15.1	24.0 ± 51.2	22.0 ± 45.3	3.4 ± NA	23.4 ± 28.1	23.0 ± 27.9	22.5 ± 38.2
Median	13.0	16.4	15.9	3.4	15.7	15.3	15.6
IQ range	(3.5, 25.9)	(6.6, 23.7)	(6.1, 23.7)	(3.4, 3.4)	(10.6, 30.5)	(9.1, 30.5)	(8.1, 24.5)
Range	(0.1, 49.3)	(2.5, 330.9)	(0.1, 330.9)	(3.4, 3.4)	(0.0, 167.8)	(0.0, 167.8)	(0.0, 330.9)

Appendix B.3 **Summary of serum infliximab concentrations (micrograms/mL) over time by infliximab antibody status for REMICADE monotherapy vs REMICADE combination therapy; treated subjects who received 5 mg/kg infliximab in ACT 2 (C0168T46)**

	REMICADE Monotherapy ^a			REMICADE Combination Therapy ^b			Overall
	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	Antibody Positive ^c	Antibody Negative or Antibody Inconclusive ^d	Combined	
Week 8							
n	12	40	52	■	41	42	94
Mean ± SD	167.1 ± 497.5	40.6 ± 29.2	69.8 ± 238.6	17.9 ± NA	51.6 ± 58.0	50.8 ± 57.5	61.3 ± 181.0
Median	25.6	35.8	33.4	17.9	36.0	34.8	33.6
IQ range	(16.3, 38.4)	(24.8, 46.4)	(21.2, 45.5)	(17.9, 17.9)	(26.1, 50.1)	(25.9, 50.1)	(23.1, 47.5)
Range	(0.0, 1746.2)	(4.0, 161.1)	(0.0, 1746.2)	(17.9, 17.9)	(5.1, 337.2)	(5.1, 337.2)	(0.0, 1746.2)
Week 14 preinfusion							
n	12	40	52	■	42	43	95
Mean ± SD	5.1 ± 11.9	16.9 ± 80.2	14.2 ± 70.5	0.0 ± NA	25.6 ± 106.8	25.0 ± 105.6	19.1 ± 87.8
Median	0.8	2.9	2.8	0.0	6.1	5.8	3.3
IQ range	(0.0, 4.8)	(1.4, 5.4)	(1.0, 5.4)	(0.0, 0.0)	(2.3, 11.0)	(2.1, 11.0)	(1.4, 8.1)
Range	(0.0, 42.0)	(0.0, 510.4)	(0.0, 510.4)	(0.0, 0.0)	(0.0, 697.9)	(0.0, 697.9)	(0.0, 697.9)

Appendix B.3 **Summary of serum infliximab concentrations (micrograms/mL) over time by infliximab antibody status for REMICADE monotherapy vs REMICADE combination therapy; treated subjects who received 5 mg/kg infliximab in ACT 2 (C0168T46)**

	REMICADE Monotherapy ^a			REMICADE Combination Therapy ^b			Overall
	Antibody Positive ^c	Antibody Negative or Inconclusive ^d	Combined	Antibody Positive ^c	Antibody Negative or Inconclusive ^d	Combined	
Week 30							
n	9	37	46	0	40	41	87
Mean ± SD	0.7 ± 2.2	2.6 ± 4.6	2.2 ± 4.3	0.0 ± NA	28.5 ± 138.6	27.8 ± 137.0	14.3 ± 94.3
Median	0.0	0.2	0.0	0.0	5.3	5.1	1.7
IQ range	(0.0, 0.0)	(0.0, 2.4)	(0.0, 2.3)	(0.0, 0.0)	(1.7, 7.0)	(1.6, 6.9)	(0.0, 6.5)
Range	(0.0, 6.7)	(0.0, 17.7)	(0.0, 17.7)	(0.0, 0.0)	(0.0, 881.7)	(0.0, 881.7)	(0.0, 881.7)

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

^b Subjects in the REMICADE combination therapy group were receiving concomitant treatment with azathioprine (AZA), 6-mercaptopurine (6-MP), or MTX at baseline.

^c Includes all subjects who had at least 1 positive sample at any time.

^d Excludes subjects who were positive at any time and includes subjects whose samples may contain infliximab.

^e Subjects with appropriate samples either had antibodies to infliximab at some timepoint following their first infusion or had 1 or more samples obtained after their last infusion.

RE123;[K CONC 49 D 123], 21JUL2009 14:04

Appendix B.4 **Summary of serum infliximab concentrations (micrograms/mL) through Week 10 by age group; treated subjects in REACH**

		Infliximab 5 mg/kg	
		Ages 6-11	Ages 12-17
Subjects treated		25	87
Week 0, preinfusion			
n		25	87
Mean ± SD		0.00 ± 0.000	0.02 ± 0.149
Median		0.00	0.00
Range		(0.0, 0.0)	(0.0, 1.4)
Week 0, 1 hour postinfusion			
n		25	81
Mean ± SD		95.62 ± 43.513	95.61 ± 29.802
Median		85.95	88.93
Range		(62.1, 279.1)	(59.8, 230.2)
Week 2, preinfusion			
n		25	81
Mean ± SD		19.41 ± 8.778	20.16 ± 8.143
Median		20.80	20.47
Range		(3.5, 40.3)	(2.4, 44.1)
Week 2, 1 hour postinfusion			
n		24	78
Mean ± SD		121.76 ± 53.062	114.48 ± 31.644
Median		109.60	110.63
Range		(80.0, 343.7)	(57.1, 217.4)
Week 6, preinfusion			
n		25	78
Mean ± SD		12.04 ± 10.311	12.50 ± 9.064
Median		12.08	11.09
Range		(0.0, 45.9)	(0.0, 41.3)
Week 6, 1 hour postinfusion			
n		24	73
Mean ± SD		101.66 ± 28.462	108.04 ± 25.064
Median		101.91	99.81
Range		(39.4, 169.6)	(66.1, 184.1)

Appendix B.4 **Summary of serum infliximab concentrations (micrograms/mL) through Week 10 by age group; treated subjects in REACH**

		Infliximab 5 mg/kg	
		Ages 6-11	Ages 12-17
Week 10			
n		25	74
Mean ± SD		19.42 ± 25.598	14.60 ± 10.103
Median		13.37	14.04
Range		(0.0, 131.4)	(0.0, 45.1)

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Appendix B.5 **Summary of serum infliximab concentration (micrograms/mL) through Week 54 by visit; randomized subjects in the 5 mg/kg q8 weeks treatment group in C0168T72 and ACT 1 and ACT 2 combined by treatment received**

	Infliximab 5 mg/kg	
	C0168T72	ACT 1 and ACT 2 Combined
Randomized subjects by treatment received ^a	22	242
Week 0, preinfusion		
n	19	237
Mean ± SD	0.00 ± 0.000	0.0 ± 0.1
Median	0.00	0.00
Range	(0.0, 0.0)	(0.0, 0.9)
Week 0, 1 hour postinfusion		
n	19	230
Mean ± SD	85.97 ± 36.527	121.0 ± 53.6
Median	88.61	111.0
Range	(0.0, 144.0)	(0.0, 357.8)
Week 2, preinfusion		
n	20	239
Mean ± SD	20.31 ± 9.900	30.0 ± 32.6
Median	17.31	24.6
Range	(1.8, 43.0)	(0.0, 278.0)
Week 2, 1 hour postinfusion		
n	19	233
Mean ± SD	110.23 ± 31.905	146.6 ± 59.0
Median	115.06	131.6
Range	(26.2, 174.3)	(0.0, 364.5)
Week 6, preinfusion		
n	19	227
Mean ± SD	16.18 ± 13.136	20.3 ± 28.0
Median	15.21	15.3
Range	(0.0, 43.5)	(0.0, 330.9)
Week 6, 1 hour postinfusion ^b		
n	16	110
Mean ± SD	114.40 ± 44.277	137.5 ± 54.5
Median	105.00	129.6
Range	(66.1, 249.3)	(0.0, 371.3)

Appendix B.5 **Summary of serum infliximab concentration (micrograms/mL) through Week 54 by visit; randomized subjects in the 5 mg/kg q8 weeks treatment group in C0168T72 and ACT 1 and ACT 2 combined by treatment received**

	Infliximab 5 mg/kg	
	C0168T72	ACT 1 and ACT 2 Combined
Week 8		
n	17	224
Mean ± SD	31.19 ± 18.797	49.3 ± 121.1
Median	27.51	33.3
Range	(0.0, 79.4)	(0.0, 1746.2)
Week 14, preinfusion		
n	14	200
Mean ± SD	5.18 ± 6.804	13.1 ± 61.6
Median	2.97	3.6
Range	(0.0, 26.5)	(0.0, 697.9)
Week 30, preinfusion		
n	9	170
Mean ± SD	3.82 ± 5.623	18.0 ± 78.8
Median	1.90	2.5
Range	(0.0, 18.0)	(0.0, 881.7)
Week 38, preinfusion ^b		
n	9	77
Mean ± SD	3.41 ± 4.521	6.6 ± 6.6
Median	2.43	3.9
Range	(0.0, 14.9)	(0.0, 24.4)
Week 46, preinfusion ^b		
n	5	74
Mean ± SD	4.49 ± 5.888	8.8 ± 19.3
Median	2.61	4.1
Range	(0.0, 14.2)	(0.0, 163.6)
Week 46, 1 hour postinfusion ^b		
n	■	70
Mean ± SD	89.56 ± 3.114	138.2 ± 44.3
Median	89.44	134.0
Range	(85.9, 93.5)	(0.0, 348.5)

Appendix B.5 **Summary of serum infliximab concentration (micrograms/mL) through Week 54 by visit; randomized subjects in the 5 mg/kg q8 weeks treatment group in C0168T72 and ACT 1 and ACT 2 combined by treatment received**

	Infliximab 5 mg/kg	
	C0168T72	ACT 1 and ACT 2 Combined
Week 54 ^b		
n	71	71
Mean ± SD	4.90 ± 8.115	9.9 ± 25.4
Median	1.33	3.8
Range	(0.0, 16.9)	(0.0, 154.2)

^a Data for subjects who stepped are excluded from the point of step-up in C0168T72.

^b Data not evaluated for subjects in ACT 2.

Source: RE207:[K CONC 49 A], 24FEB2005 12:47) in addition to Attachment 2.1 in the T37 (ACT 1) Week 54 CSR; and Attachment 2.3 in the T72 CSR.

Appendix B.6 **Summary of serum infliximab concentrations (micrograms/mL) by visit; randomized subjects in the 5 mg/kg treatment group in C0168T72 and REACH by treatment received**

	Infliximab 5 mg/kg			
	C0168T72		REACH	
	q8 wks	q12 wks	q8 wks	q12 wks
Randomized subjects by treatment received ^a	22	23	53	50
Week 0, preinfusion				
n	19	23	53	50
Mean ± SD	0.00 ± 0.000	4.60 ± 22.073	0.00 ± 0.000	0.03 ± 0.197
Median	0.00	0.00	0.00	0.00
Range	(0.0, 0.0)	(0.0, 105.9)	(0.0, 0.0)	(0.0, 1.4)
Week 0, 1 hour postinfusion				
n	19	22	51	48
Mean ± SD	85.97 ± 36.527	99.17 ± 20.025	97.79 ± 41.270	90.35 ± 17.082
Median	88.61	98.88	86.76	88.42
Range	(0.0, 144.0)	(70.5, 166.3)	(61.1, 279.1)	(59.8, 133.9)
Week 2, preinfusion				
n	20	23	52	48
Mean ± SD	20.31 ± 9.900	21.56 ± 7.257	19.97 ± 9.037	20.31 ± 7.363
Median	17.31	20.59	20.49	20.78
Range	(1.8, 43.0)	(3.2, 34.8)	(3.5, 44.1)	(5.1, 39.0)
Week 2, 1 hour postinfusion				
n	19	20	51	47
Mean ± SD	110.23 ± 31.905	119.93 ± 18.786	123.45 ± 46.929	106.46 ± 22.102
Median	115.06	116.93	108.73	108.74
Range	(26.2, 174.3)	(91.9, 163.5)	(78.0, 343.7)	(57.1, 153.3)
Week 6, preinfusion				
n	19	20	52	47
Mean ± SD	16.18 ± 13.136	15.40 ± 8.663	13.13 ± 10.192	12.22 ± 8.457
Median	15.21	16.43	12.52	11.56
Range	(0.0, 43.5)	(0.0, 33.7)	(0.0, 45.9)	(0.0, 32.2)
Week 6, 1 hour postinfusion				
n	16	18	48	46
Mean ± SD	114.40 ± 44.277	109.98 ± 31.366	111.91 ± 26.844	100.74 ± 23.993
Median	105.00	112.38	107.49	98.57
Range	(66.1, 249.3)	(20.0, 151.8)	(57.3, 184.1)	(39.4, 170.2)

Appendix B.6 **Summary of serum infliximab concentrations (micrograms/mL) by visit; randomized subjects in the 5 mg/kg treatment group in C0168T72 and REACH by treatment received**

	Infliximab 5 mg/kg			
	C0168T72		REACH	
	q8 wks	q12 wks	q8 wks	q12 wks
Week 14, preinfusion				
n	14	0	48	0
Mean ± SD	5.18 ± 6.804	NA ± NA	4.71 ± 5.967	NA ± NA
Median	2.97	NA	2.79	NA
Range	(0.0, 26.5)	(NA, NA)	(0.0, 25.7)	(NA, NA)
Week 18, preinfusion				
n	0	10	0	37
Mean ± SD	NA ± NA	2.12 ± 2.877	NA ± NA	3.29 ± 14.173
Median	NA	1.02	NA	0.43
Range	(NA, NA)	(0.0, 9.9)	(NA, NA)	(0.0, 86.7)
Week 22, preinfusion				
n	12	0	41	0
Mean ± SD	3.93 ± 5.030	NA ± NA	4.39 ± 6.369	NA ± NA
Median	3.04	NA	2.31	NA
Range	(0.0, 18.4)	(NA, NA)	(0.0, 26.9)	(NA, NA)
Week 30, preinfusion				
n	9	6	40	23
Mean ± SD	3.82 ± 5.623	1.60 ± 2.263	3.32 ± 4.807	6.72 ± 22.782
Median	1.90	0.77	1.81	0.21
Range	(0.0, 18.0)	(0.3, 6.2)	(0.0, 23.9)	(0.0, 105.6)
Week 38, preinfusion				
n	9	0	35	0
Mean ± SD	3.41 ± 4.521	NA ± NA	3.81 ± 5.249	NA ± NA
Median	2.43	NA	1.83	NA
Range	(0.0, 14.9)	(NA, NA)	(0.0, 19.8)	(NA, NA)
Week 42, preinfusion				
n	0	5	0	19
Mean ± SD	NA ± NA	0.89 ± 1.139	NA ± NA	0.68 ± 0.959
Median	NA	0.50	NA	0.29
Range	(NA, NA)	(0.1, 2.9)	(NA, NA)	(0.0, 3.4)

Appendix B.6 **Summary of serum infliximab concentrations (micrograms/mL) by visit; randomized subjects in the 5 mg/kg treatment group in C0168T72 and REACH by treatment received**

	Infliximab 5 mg/kg			
	C0168T72		REACH	
	q8 wks	q12 wks	q8 wks	q12 wks
Week 42, 1 hour postinfusion				
n	0	3	0	18
Mean ± SD	NA ± NA	87.50 ± 5.482	NA ± NA	93.70 ± 15.194
Median	NA	90.56	NA	89.99
Range	(NA, NA)	(81.2, 90.8)	(NA, NA)	(68.9, 125.7)
Week 46, preinfusion				
n	5	0	33	0
Mean ± SD	4.49 ± 5.888	NA ± NA	3.75 ± 5.489	NA ± NA
Median	2.61	NA	1.75	NA
Range	(0.0, 14.2)	(NA, NA)	(0.0, 22.8)	(NA, NA)
Week 46, 1 hour postinfusion				
n	4	0	31	0
Mean ± SD	89.56 ± 3.114	NA ± NA	103.75 ± 35.012	NA ± NA
Median	89.44	NA	94.39	NA
Range	(85.9, 93.5)	(NA, NA)	(59.6, 202.0)	(NA, NA)
Week 54				
n	■	■	31	15
Mean ± SD	4.90 ± 8.115	14.80 ± 26.740	4.30 ± 6.331	0.90 ± 1.254
Median	1.33	2.02	2.20	0.35
Range	(0.0, 16.9)	(0.3, 54.9)	(0.0, 32.8)	(0.0, 4.0)

^a Data for subjects who stepped up are excluded from the point of step-up.

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Appendix B.7 **Summary of serum infliximab concentration (micrograms/mL) through Week 54 by REMICADE monotherapy and combination therapy status and visit; randomized subjects in the 5 mg/kg q8 weeks treatment group in C0168T72 and ACT 1 and ACT 2 combined**

	Infliximab 5 mg/kg			
	C0168T72		ACT 1 and ACT 2 Combined	
	Monotherapy ^a	Combination Therapy ^b	Monotherapy ^a	Combination Therapy ^b
Randomized subjects by treatment received ^c	11	11	124	118
Week 0, preinfusion				
n	11	8	121	116
Mean ± SD	0.00 ± 0.000	0.00 ± 0.000	0.00 ± 0.000	0.01 ± 0.086
Median	0.00	0.00	0.00	0.00
Range	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.9)
Week 0, 1 hour postinfusion				
n	9	10	118	112
Mean ± SD	82.44 ± 38.232	89.16 ± 36.680	119.04 ± 51.272	123.04 ± 56.181
Median	88.55	90.89	111.85	110.82
Range	(0.0, 143.1)	(0.0, 144.0)	(0.0, 335.6)	(13.9, 357.8)
Week 2, preinfusion				
n	10	10	123	116
Mean ± SD	19.14 ± 10.133	21.47 ± 10.060	30.82 ± 28.128	29.12 ± 36.785
Median	18.24	17.08	26.18	23.09
Range	(1.8, 36.4)	(9.0, 43.0)	(0.0, 245.1)	(0.0, 278.0)
Week 2, 1 hour postinfusion				
n	8	11	120	113
Mean ± SD	109.29 ± 25.615	110.92 ± 37.038	148.56 ± 61.195	144.44 ± 56.764
Median	113.69	117.19	133.13	131.13
Range	(73.8, 144.3)	(26.2, 174.3)	(0.0, 354.9)	(17.6, 364.5)
Week 6, preinfusion				
n	8	11	117	110
Mean ± SD	16.04 ± 14.958	16.27 ± 12.409	20.02 ± 31.750	20.68 ± 23.386
Median	15.42	15.21	15.28	15.34
Range	(0.0, 43.1)	(1.1, 43.5)	(0.0, 330.9)	(0.0, 167.8)

Appendix B.7 **Summary of serum infliximab concentration (micrograms/mL) through Week 54 by REMICADE monotherapy and combination therapy status and visit; randomized subjects in the 5 mg/kg q8 weeks treatment group in C0168T72 and ACT 1 and ACT 2 combined**

	Infliximab 5 mg/kg			
	C0168T72		ACT 1 and ACT 2 Combined	
	Monotherapy ^a	Combination Therapy ^b	Monotherapy ^a	Combination Therapy ^b
Week 6, 1 hour postinfusion ^d				
n	8	8	54	56
Mean ± SD	108.75 ± 33.590	120.06 ± 54.769	137.03 ± 48.643	137.89 ± 60.045
Median	107.48	101.26	129.50	129.58
Range	(66.1, 175.8)	(77.3, 249.3)	(0.0, 238.5)	(53.9, 371.3)
Week 8				
n	8	9	118	106
Mean ± SD	33.41 ± 24.921	29.22 ± 12.407	53.82 ± 160.537	44.41 ± 48.543
Median	33.54	24.26	33.37	33.16
Range	(0.0, 79.4)	(11.0, 44.9)	(0.0, 1746.2)	(0.0, 337.2)
Week 14, preinfusion				
n	6	8	103	97
Mean ± SD	7.14 ± 10.193	3.71 ± 2.452	11.00 ± 50.506	15.35 ± 71.664
Median	2.80	3.23	3.29	4.59
Range	(0.0, 26.5)	(1.0, 7.6)	(0.0, 510.4)	(0.0, 697.9)
Week 30, preinfusion				
n	■	6	87	83
Mean ± SD	7.70 ± 9.277	1.88 ± 1.627	16.56 ± 54.478	19.54 ± 98.460
Median	5.09	1.82	1.73	3.47
Range	(0.0, 18.0)	(0.0, 3.8)	(0.0, 356.5)	(0.0, 881.7)
Week 38, preinfusion ^d				
n	■	6	35	42
Mean ± SD	6.20 ± 7.737	2.02 ± 1.328	6.05 ± 6.458	7.09 ± 6.767
Median	3.72	2.09	3.52	5.02
Range	(0.0, 14.9)	(0.0, 3.7)	(0.0, 24.4)	(0.0, 23.1)
Week 46, preinfusion ^d				
n	■	■	34	40
Mean ± SD	6.62 ± 7.120	1.31 ± 1.846	10.86 ± 27.725	6.98 ± 6.482
Median	5.71	1.31	3.65	4.29
Range	(0.0, 14.2)	(0.0, 2.6)	(0.0, 163.6)	(0.0, 23.8)

Appendix B.7 **Summary of serum infliximab concentration (micrograms/mL) through Week 54 by REMICADE monotherapy and combination therapy status and visit; randomized subjects in the 5 mg/kg q8 weeks treatment group in C0168T72 and ACT 1 and ACT 2 combined**

	Infliximab 5 mg/kg			
	C0168T72		ACT 1 and ACT 2 Combined	
	Monotherapy ^a	Combination Therapy ^b	Monotherapy ^a	Combination Therapy ^b
Week 46, 1 hour postinfusion ^d				
n	■	■	34	36
Mean ± SD	89.67 ± 5.356	89.44 ± 0.592	137.21 ± 53.077	139.17 ± 34.920
Median	89.67	89.44	134.65	132.62
Range	(85.9, 93.5)	(89.0, 89.9)	(0.0, 348.5)	(78.0, 224.2)
Week 54 ^d				
n	■	■	33	38
Mean ± SD	8.46 ± 11.966	1.33 ± 1.884	10.61 ± 26.535	9.26 ± 24.645
Median	8.46	1.33	4.82	3.63
Range	(0.0, 16.9)	(0.0, 2.7)	(0.0, 154.2)	(0.0, 153.6)

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

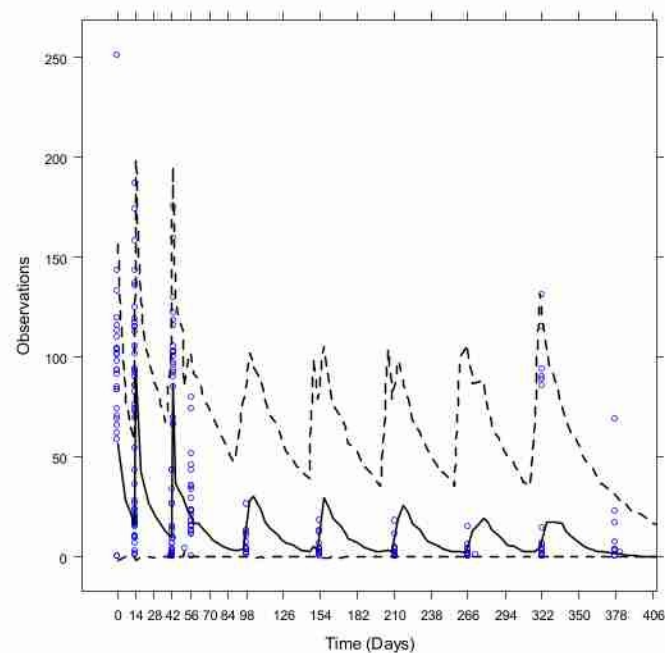
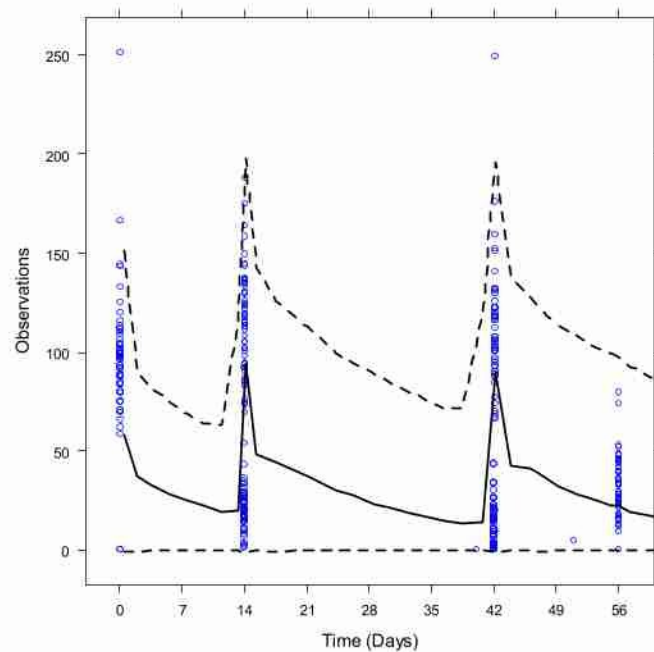
^b Subjects in the REMICADE combination therapy group were receiving concomitant treatment with AZA, 6-MP, or MTX at baseline.

^c Data for subjects who stepped up are excluded from the point of step-up in C0168T72.

^d Data not evaluated for subjects in ACT 2.

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Appendix B.8 Visual Predictive Check (VPC) of the Primary Analysis Model



Appendix B.9 Summary of Infliximab Population Pharmacokinetic Parameter Estimates of the Final Exploratory Model

Parameters	Estimate	% RSE of estimate	BSV ^a (CV%) ^b
CL (L/day)	0.337	4.8	42.9
V ₁ (L)	2.77	6.1	0 (FIXED)
V ₂ (L)	3.22	11.5	70.1
Q (L/day)	2.64	22.3	-
Albumin Effect on CL	-1.56	40.9	-
Weight Effect on V ₁	0.913	28.2	-
Weight Effect on V ₂	1.2	28.2	-
Proportional residual variability (%)	48.0	7.1	-
Additive residual variability (µg/mL)	0.0577	7.6	-

^a BSV: Between subject variability, calculated as (variance)^{1/2}*100%.

^b CV%: Coefficient of variation expressed as percent.

Source: CP 2010T-045.

Appendix B.10 Population PK Model-Predicted Infliximab Concentrations at Steady State by Dosing Frequency in C0168T72		
	Dosing Frequency	
	q8w	q12w
Steady state Infliximab concentration ^a (µg/mL)	2.0	0.4
^a Concentrations for a typical subject using population PK parameters from the conventional analysis Source: Appendix B.9		

Appendix B.11 Summary of antibody to infliximab status through Week 54 by REMICADE monotherapy and combination therapy status; randomized subjects in the 5 mg/kg q8 weeks treatment group in C0168T72, REACH, and ACT 1 by treatment received

	Infliximab 5 mg/kg q8 wks					
	C0168T72 ^c		REACH ^c		ACT 1	
	Monotherapy ^a	Combination Therapy ^b	Monotherapy ^a	Combination Therapy ^b	Monotherapy ^a	Combination Therapy ^b
Randomized subjects by treatment received	6	7	0	42	55	66
Subjects with appropriate samples ^d	6	7	0	40	54	62
Subjects positive for antibodies to infliximab at any time ^{e,f}	1 (16.7%)	1 (14.3%)	0 (NA)		8 (14.8%)	
Titers						
1:10		0	0			0
1:20	0		0	0		0
1:80	0	0	0	0		0
1:160	0	0	0	0		0
1:320	0	0	0	0	0	
Subjects negative for antibodies to infliximab ^{e,g}			0 (NA)		7 (13.0%)	9 (14.5%)
Subjects inconclusive for antibodies to infliximab ^{e,h}		5 (71.4%)	0 (NA)	36 (90.0%)	39 (72.2%)	52 (83.9%)

**Appendix B.11 Summary of antibody to infliximab status through Week 54 by REMICADE monotherapy and combination therapy status;
randomized subjects in the 5 mg/kg q8 weeks treatment group in C0168T72, REACH, and ACT 1 by treatment received**

- ^a Subjects in the REMICADE monotherapy group were not receiving azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX) at baseline.
- ^b Subjects in the REMICADE combination therapy group were receiving concomitant treatment with AZA, 6-MP, or MTX at baseline.
- ^c Subjects who stepped up are not included in the analysis.
- ^d Subjects with appropriate samples had antibodies to infliximab at some timepoint following their first study agent administration, or had 1 or more samples obtained after their last study agent administration.
- ^e Denominator is subjects with appropriate samples.
- ^f Includes all subjects who had at least 1 positive sample at any time.
- ^g Includes all subjects who had at least 1 negative sample after their last study agent administration and excludes subjects who were positive.
- ^h Includes subjects whose samples after their last study agent administration were all inconclusive and excludes subjects who were positive.

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