
Module 2.7.2 – Summary of Clinical Pharmacology Studies

REMICADE[®] (infliximab)

Crohn's Disease in Pediatric Subjects

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Centocor, Inc
200 Great Valley Parkway
Malvern, PA 19355
USA

Centocor, B.V.
Einsteinweg 92
2333 CD Leiden
The Netherlands

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ABBREVIATIONS AND DEFINITION OF TERMS

ACCENT	A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen
AUC	area under the concentration versus time curve from time 0 to infinity with extrapolation of the terminal phase
AUC/dose	dose-normalized AUC
AUC _{ss}	AUC at steady state
C _{max}	maximum observed concentration
CHMP	Committee for the Medicinal Products for Human Use
CSR	Clinical Study Report
CTD	Common Technical Document
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Evaluation Agency
FDA	Food and Drug Administration
JRA	Juvenile Rheumatoid Arthritis
PCDAI	Pediatric Crohn's Disease Activity Index
q	every
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
SCP	Summary of Clinical Pharmacology
t _{1/2}	terminal elimination half-life
V _{ss}	apparent volume of distribution at steady state after intravenous administration

1 BACKGROUND AND OVERVIEW

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

REMICADE® (infliximab) has been shown to be effective in reducing the signs and symptoms of moderately to severely active Crohn's disease in adult patients who have had an inadequate response to conventional therapy, and for reducing the number of draining enterocutaneous fistula(e) in adult patients with fistulizing Crohn's disease. Given the effectiveness of infliximab in adults, including young adults under the age of 30 years, and the similarity in the presentation of Crohn's disease in children and young adults, it was believed that infliximab would also be effective in reducing the signs and symptoms of Crohn's disease in pediatric subjects. Moreover, at the initiation of the clinical program for infliximab for the treatment of Crohn's disease in pediatric subjects, preliminary open-label studies and case reports suggested that treatment response of Crohn's disease to infliximab was comparable in children and adults (Hyams et al, 2000; Kugathasan et al, 2000; Serrano et al, 2001). To verify these findings and to further study the safety and efficacy of infliximab in pediatric subjects with Crohn's disease, 3 studies have been conducted by Centocor, including one Phase 3 study (Study C0168T47 [REACH]) and two Phase 1 studies (C0168T55 and C0168T23). A brief description of these studies and an overview of the pharmacology results from the completed clinical studies of infliximab in pediatric subjects with Crohn's disease can be found in [Appendix Table 1](#) (refer also to [CTD Module 2.7.6](#)).

This summary of clinical pharmacology (SCP) focuses primarily on the pharmacology results of the REACH study, with supportive data from the two Phase 1 studies in pediatric subjects with Crohn's disease (C0168T55 and C0168T23). In addition, for comparison purposes, results are also presented for two studies in adults with Crohn's disease (C0168T11 and C0168T21 [ACCENT I]), and one study in juvenile rheumatoid arthritis (JRA, C0168T32).

Pharmacokinetic results of these studies, together with the favorable benefit/risk profile of the q8 week maintenance treatment regimen relative to the q12 week maintenance regimen, support an induction regimen with 5 mg/kg infliximab administered at Weeks 0, 2, and 6, followed by 5 mg/kg infliximab every 8 weeks thereafter for the treatment of Crohn's disease in pediatric patients.

1.1 Overview of Studies in Pediatric Subjects with Crohn's Disease

1.1.1 REACH

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

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

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

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

1.1.2 Supportive Studies in Pediatric Subjects with Crohn's Disease

As previously described, 2 additional studies have been conducted to evaluate infliximab for the treatment of Crohn's disease in pediatric subjects (C0168T55 and C0168T23). An

overview of study designs and results of these studies is provided in [Appendix Table 1](#) (refer also to [CTD Module 2.7.6](#)).

Study C0168T55 was a Phase 1 study designed to assess the pharmacokinetics and safety of a single, open-label, intravenous infusion of 5 mg/kg infliximab in younger pediatric subjects (planned age range: 6 to 11 years) with inflammatory bowel disease (Crohn's disease, ulcerative colitis, or indeterminate colitis), who were receiving maintenance treatment with 5 mg/kg commercial REMICADE. Six subjects with a primary diagnosis of Crohn's disease, ranging in age from 9 to 11 years, were enrolled and received a single infusion of 5 mg/kg infliximab at Week 0. Each of the 6 subjects had received at least 4 doses of commercial REMICADE prior to study entry. The planned follow-up period was up to 12 weeks depending on the subject's commercial REMICADE maintenance dosing interval.

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

1.2 Format and Content of this Summary of Clinical Pharmacology

[Section 2](#) of this SCP provides a review of the pharmacokinetic results observed in the pediatric Crohn's disease studies (REACH, Study C0168T55, and C0168T23). Study C0168T23 was previously submitted to the FDA and to the EMEA/CHMP.

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

- A discussion of the pharmacokinetic results observed across the 3 Crohn's disease studies in pediatric subjects (REACH, Study C0168T55, and Study C0168T23)
- A comparison of pharmacokinetic results observed in pediatric subjects relative to those observed in adult subjects with Crohn's disease (the ACCENT I study and Study C0168T11)
- A discussion of pharmacokinetic results observed in pediatric subjects with Crohn's disease relative to results observed in JRA subjects (Study C0168T32)

2 SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

This section presents a summary of the pharmacokinetic results observed in REACH, Study C0168T55, and Study C0168T23. In [Section 2.1](#), results are presented for serum infliximab concentrations over time, the proportion of subjects with undetectable preinfusion serum infliximab concentrations, and pharmacokinetic parameter estimates. [Section 2.2](#) presents a summary of efficacy relative to serum infliximab concentrations.

In REACH, pharmacokinetics were evaluated through Week 54, with blood samples to be 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 q8 week maintenance treatment group and Week 42 for subjects in the q12 maintenance group); and at the noninfusion visits at Weeks 10 and 54. For subjects who discontinued early during the study, a sample was to be obtained 16 weeks after the last study infusion. Pharmacokinetic analyses included infliximab serum concentrations over time, the proportion of subjects with undetectable preinfusion infliximab serum concentrations, pharmacokinetic parameter estimates, and an exploratory analysis of the relationship between infliximab serum concentrations and efficacy. A planned analysis of serum infliximab concentrations relative to antibody to infliximab status was not conducted because too few subjects ($n = 3$) developed antibodies to infliximab in this study. Data were also obtained in the REACH study to evaluate the pharmacological effects of infliximab on biomarkers of bone formation and resorption. The results of these pharmacodynamic analyses will be presented in a separate report ([refer to C0168T47 Addendum to 54-Week CSR](#)).

In Study C0168T55, serum concentrations of infliximab were obtained at Week 0 (immediately prior to the infliximab infusion and 2 hours after the end of the infusion), Day 3, Weeks 1, 2, and 4, and at the final visit. Note that the timing of the final visit in Study C0168T55 varied across subjects, as this visit was to occur immediately prior to each subject's next scheduled infusion of infliximab, and (as permitted by protocol) subjects could have been receiving commercial REMICADE at intervals up to every 12 weeks prior to study entry. Pharmacokinetic analyses in Study C0168T55 included serum infliximab concentrations over time and pharmacokinetic parameter estimates.

In Study C0168T23, serum infliximab concentrations were monitored during the 20-week follow-up period, with samples obtained prior to the Week 0 infusion, 1 hour after the end of the Week 0 infusion, and at Weeks 1, 2, 4, 8, 12, and 20. Pharmacokinetic analyses included serum infliximab concentrations over time and pharmacokinetic parameter estimates.

Serum concentrations of infliximab were determined in these studies using an enzyme-linked immunosorbent assay (ELISA) method capable of quantifying serum concentrations of infliximab of $\geq 0.1 \mu\text{g/mL}$. 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 ([refer to](#)

C0168T47 54-Week CSR, Section 9.0; C0168T55 CSR, Section 4.1.4 and Section 6.0; and C0168T23 20-Week CSR, Section 4.2.2 and 6.0).

2.1 Pharmacokinetic Results

2.1.1 Serum Infliximab Concentrations Over Time

2.1.1.1 REACH

In the REACH study, all subjects received a 5 mg/kg infliximab induction regimen, and therefore, the serum infliximab concentration profiles for treated subjects were similar from Week 0 through Week 10 (refer to C0168T47 54-Week CSR, Section 9.1.1.1).

Figure 1 shows the median serum infliximab concentrations through Week 54 for subjects who were randomized at Week 10 and who did not cross over to a higher dose or to a more frequent dosing regimen of infliximab. As shown in Figure 1, steady state preinfusion serum concentrations appear to have been achieved beginning at Week 22 in the q8 week maintenance treatment group and at Week 30 in the q12 week maintenance treatment group. The median preinfusion serum infliximab concentrations during steady state were generally higher for subjects in the q8 week maintenance treatment group (between 1.8 and 2.3 µg/mL) compared to those in the q12 week maintenance treatment group (between 0.2 and 0.4 µg/mL). However, the 2 groups had comparable postinfusion serum infliximab concentrations during the steady state (94.4 µg/mL at Week 46 in the q8 week maintenance treatment group and 90.0 µg/mL at Week 42 in the q12 week maintenance treatment group).

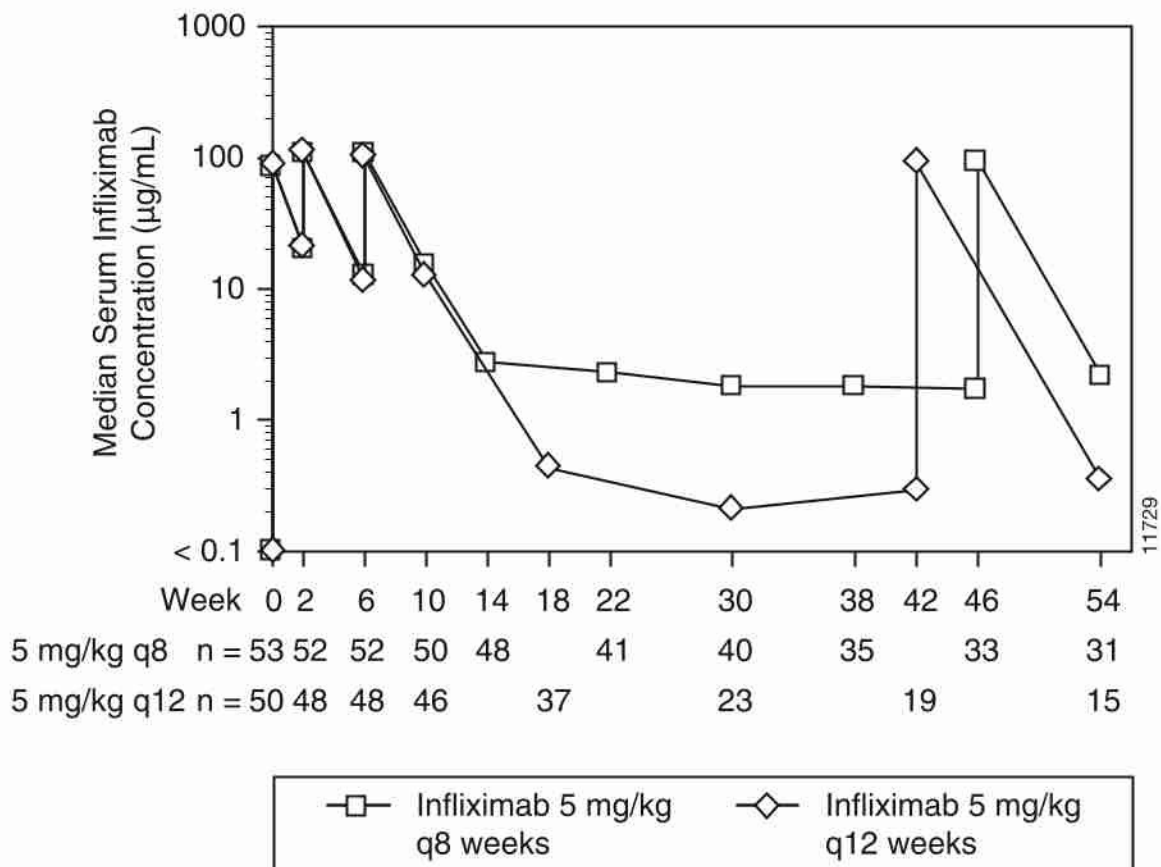
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Summary of Clinical PharmacologyCrohn's Disease in Pediatric Subjects
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Figure 1 Summary of median infliximab serum concentration (micrograms/mL) through Week 54 by visit; randomized subjects by treatment received
Data for subjects in REACH who crossed over are excluded from the point of crossover. Between Week 10 and Week 38, data presented here do not include immediate post-infusion concentrations because these samples were not taken.

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 (C0168T47 54-Week CSR, Attachment 2.3 and 2.4). However, at Week 10, the median preinfusion serum infliximab concentrations for subjects who crossed over from the 5 mg/kg q8 week or 5 mg/kg q12 week maintenance treatment groups to receive 10 mg/kg q8 weeks (6.6 µg/mL and 6.4 µg/mL, respectively) were lower than those observed among subjects who remained on the 5 mg/kg dose (15.3 µg/mL among subjects who remained on the q8 week regimen and 12.6 µg/mL among subjects who remained on the q12 week regimen). It should be noted that prior to this time point, all subjects had been on the same dosage regimen.

After crossing over, median serum infliximab concentrations increased accordingly; the levels immediately after infusion in the subjects receiving 10 mg/kg q8 weeks were

approximately double those in subjects who did not cross over. The median preinfusion serum infliximab concentrations for subjects who crossed over also showed a general increase after they crossed over, when compared to their pre-crossover values (Figure 2).

For subjects who crossed over from the 5 mg/kg q12 week regimen to the 10 mg/kg q8 week regimen, median preinfusion serum infliximab levels were 1.8 µg/mL at 16 weeks after cross over (Figure 2). In addition, for subjects who crossed over from the 5 mg/kg q8 week regimen to the 10 mg/kg q8 week regimen, median preinfusion serum infliximab levels were 4.5 µg/mL at 16 weeks after cross over. Thus, an increased dose of infliximab or a more frequent dosage regimen generally led to a higher median serum infliximab concentration in subjects who crossed over, when compared to their pre-crossover values.

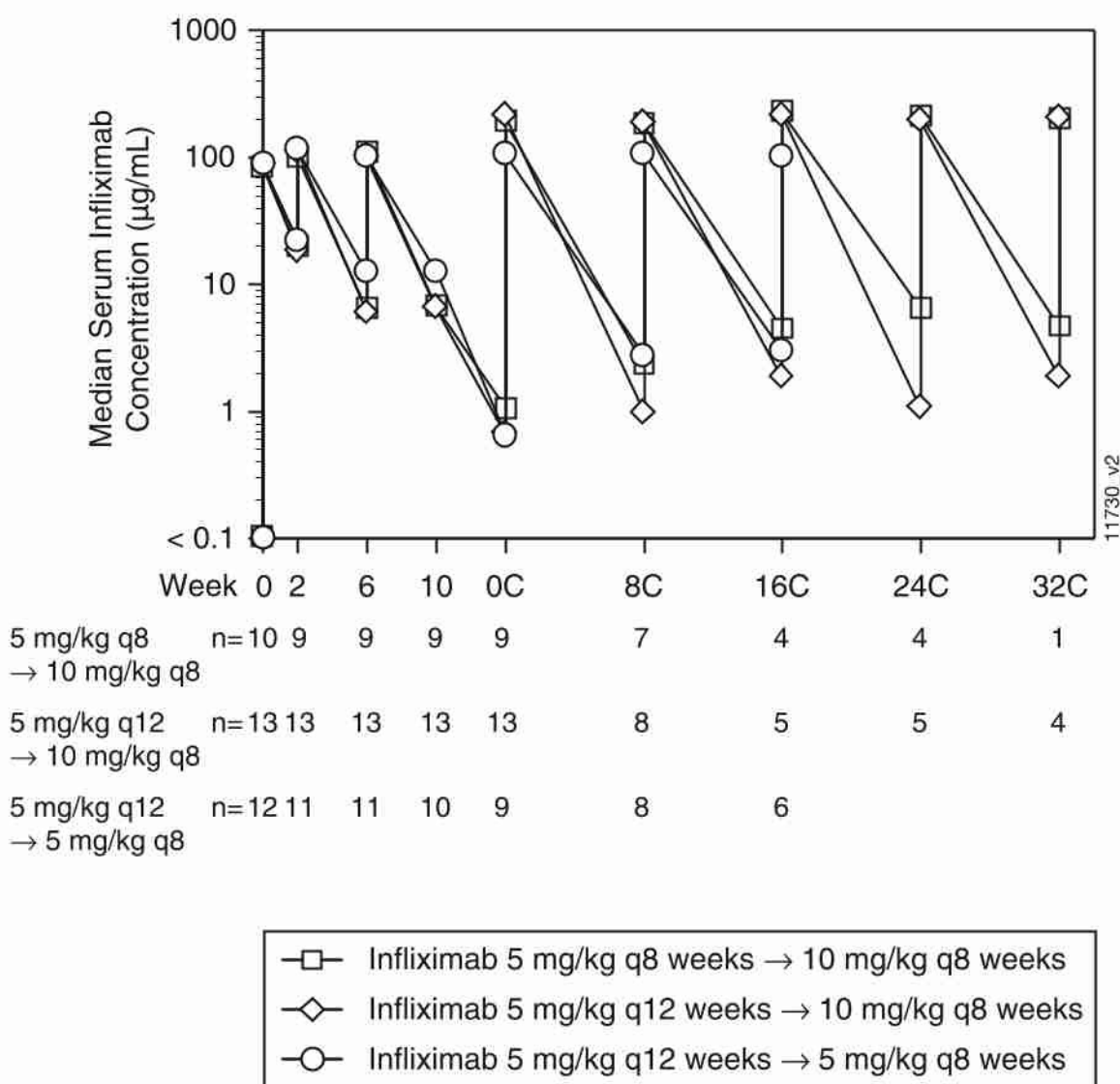
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Figure 2 Summary of median infliximab serum concentration (micrograms/mL) through Week 54 by visit; crossover subjects by treatment received
Note: In the above figure, a "C" following the Week number denotes a crossover week (eg, Week 0C = Crossover Week 0).

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

Following a single infusion of 5 mg/kg infliximab administered during maintenance treatment with REMICADE in Study C0168T55, serum infliximab concentration data indicated that all subjects maintained serum infliximab concentrations above 0.1 µg/mL immediately prior to the next infliximab infusion (Figure 3).

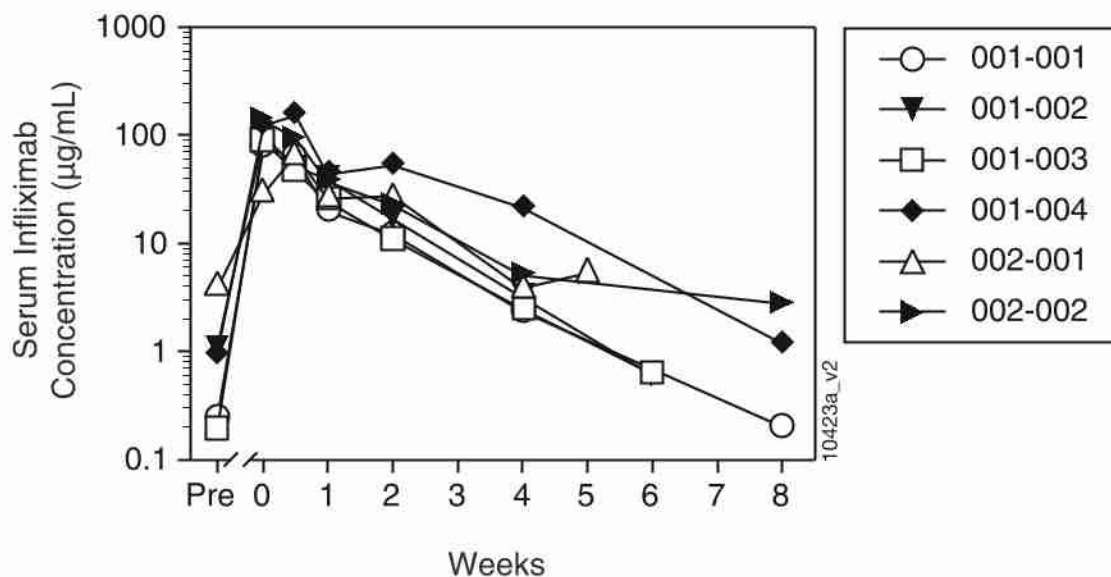


Figure 3 Infliximab concentration over time for each subject

Note: All subjects in Study C0168T55 had samples collected at Week 0 (immediately preinfusion and 2 hours postinfusion), Day 3, and Weeks 1, 2, and 4. One subject had a final visit at Week 5, 2 subjects had a final visit at Week 6, and 3 subjects had a final visit at Week 8. The box in the upper right corner of this figure shows subject identification numbers.

In Study C0168T23, the median serum concentrations of infliximab were dose-dependent (Figure 4). The median infliximab concentrations following a single infusion of 1, 5, or 10 mg/kg of infliximab in these patients fell below the measurable limits (0.1 µg/mL) at Weeks 4, 8, and 12, respectively.

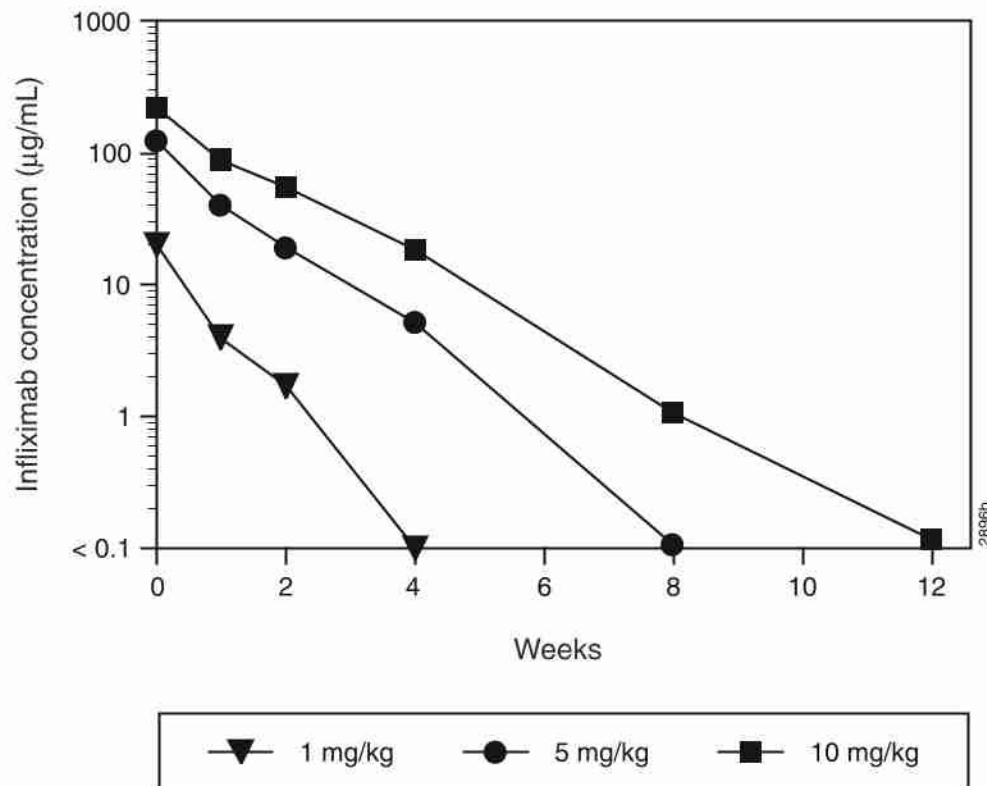


Figure 4 Median serum infliximab concentration following a single infusion
Data beyond the first time point at which median serum infliximab concentrations were < 0.1 µg/mL are not shown.

2.1.2 Proportion of Subjects with an Undetectable Preinfusion Serum Infliximab Concentration

2.1.2.1 REACH

At preinfusion times (Weeks 0, 2, and 6), fewer than 5.0% of the subjects in the 2 maintenance treatment groups had undetectable infliximab concentrations ([C0168T47 54-Week CSR, Attachment 2.5](#)).

At all visits beyond Week 10, a consistently lower percentage of subjects in the q8 week maintenance treatment group (8.3% to 12.1%) had an undetectable preinfusion serum infliximab concentration compared to that observed among subjects in the q12 week maintenance treatment group (37.8% to 47.4%). These results indicate that, as would be expected, more frequent dosing results in a lower proportion of subjects with undetectable infliximab concentrations. Within each treatment group, the proportion of subjects with undetectable serum infliximab concentrations was consistent during maintenance treatment. These results suggest that prolonged treatment with infliximab does not result in an increasing proportion of subjects who rapidly eliminate the drug.

At Crossover Week 0, similar proportions of subjects across crossover groups (22.2% to 23.1%) had undetectable serum infliximab concentration (refer to [C0168T47 54-Week CSR, Attachment 2.6](#)). All subjects who crossed over from the 5 mg/kg q8 week maintenance treatment group to 10 mg/kg q8 weeks maintained detectable infliximab concentrations through the end of the study. In subjects who crossed over from the 5 mg/kg q12 week maintenance treatment group to 10 mg/kg q8 weeks, detectable serum infliximab concentrations were maintained from 16 weeks from the initial cross over to the end of the study. In subjects who crossed over from the 5 mg/kg q12 week maintenance treatment group to receive 5 mg/kg q8 weeks, 33.3% (2 of 6) of subjects had undetectable serum infliximab concentrations. Generally, for subjects who crossed over to receive an increased dose or more frequent dosing regimen, serum infliximab concentrations were maintained above the detectable limit (0.1 µg/mL).

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

In Study C0168T55, all 6 subjects maintained an infliximab concentration above 0.1 µg/mL immediately prior to the next infliximab infusion ([Figure 3](#)). The proportion of subjects with undetectable serum infliximab concentrations was not evaluated in Study C0168T23.

2.1.3 Pharmacokinetic Parameter Estimates

2.1.3.1 REACH

Among all treated subjects who were evaluable for pharmacokinetic parameter analyses (n = 106), the median values for the C_{max}, clearance, t_{1/2}, and V_{ss} were 126.7 µg/mL, 6.1 mL/day/kg, 10.7 days, and 86.4 mL/kg, respectively (refer to [C0168T47 54-Week CSR, Section 9.1.3](#) for data handling rules; refer to [C0168T47 54-Week CSR, Table 7](#) for a summary of pharmacokinetic parameter estimates).

For subjects who remained on their randomized doses (ie, excluding data from subjects who crossed over from the point of crossover), the median C_{max} was 126.7 and 108.6 µg/mL for the q8 week and q12 week maintenance treatment groups, respectively (refer to [C0168T47 54-Week CSR, Table 8](#)). C_{max} was generally achieved at the Week 2 postinfusion sampling period for most subjects. Median values for t_{1/2}, clearance, V_{ss}, and AUC_{ss} were similar between the q8 week maintenance treatment group and the q12 week maintenance treatment group (q8 week maintenance group: 12.5 days, 5.7 mL/day/kg, 96.9 mL/kg, and 886.6 µg•day/mL, respectively; q12 week maintenance treatment group: 10.8 days, 5.8 mL/day/kg, 91.9 mL/kg, and 868.5 µg•day/mL, respectively).

As would be expected, subjects who crossed over to a higher infliximab dose from the q12 week maintenance treatment group (5 mg/kg q12 weeks to 10 mg/kg q8 weeks) had a higher C_{max} (251.9 µg/mL) than those who remained on the 5 mg/kg q12 week treatment regimen (108.6 µg/mL; refer to [C0168T47 54-Week CSR, Attachment 2.7](#)). It

also appeared that these 10 mg/kg crossover subjects had a higher median clearance (7.8 mL/kg/day) than the subjects remaining on the 5 mg/kg q12 week treatment regimen (5.8 mL/kg/day). This resulted in a shorter $t_{1/2}$ in the subjects who crossed over to the 10 mg/kg regimen (6.4 days) versus subjects who remained on the 5 mg/kg q12 week treatment regimen (10.8 days). A similar trend was observed for subjects who crossed over from the 5 mg/kg q8 week regimen to the 10 mg/kg q8 week regimen. Thus, it appears that subjects who crossed over to a higher dose had an intrinsically higher clearance of infliximab than those who maintained their original treatment regimen. The reason for the difference in clearance is not obvious. Factors that are known to affect infliximab clearance such as the incidence of antibody to infliximab or concomitant medications do not appear to be different between subjects who require a dose increase and those who do not.

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

In Study C0168T55, the median C_{max} was 93.2 $\mu\text{g/mL}$ (refer to [C0168T55 CSR, Table 5](#)). C_{max} values were generally obtained at sample time closest to the end of the infliximab infusion, as would be expected. The median V_{ss} of infliximab observed in this study (66.9 mL/kg) is similar to the expected vascular volume and suggests that infliximab is predominantly distributed within the vascular space. The median infliximab $t_{1/2}$ in subjects in this study was 6.0 days, with a range of 4.7 to 10.8 days. The median AUC_{ss} was 613.5 $\mu\text{g}\cdot\text{day/mL}$.

In Study C0168T23, the C_{max} and AUC increased, as expected, with escalating dose (refer to [C0168T23 20-Week CSR, Table 7](#)). The AUC/dose , clearance, V_{ss} , mean residence time, and $t_{1/2}$ showed smaller changes with increased dose than that observed for C_{max} and AUC . These data show that infliximab in pediatric patients has a median half-life that ranges from 5.9 days to 8.1 days for the dose range of 1 mg/kg to 10 mg/kg, respectively, and the V_{ss} data suggests that infliximab is predominantly distributed within the vascular space.

2.2 Efficacy and Serum Infliximab Concentrations

The REACH study included an analysis to examine the relationship between infliximab serum concentrations and efficacy. Studies C0168T23 and C0168T55 did not include an analysis of efficacy relative to serum infliximab concentrations.

In REACH, to relate the median change from baseline in Pediatric Crohn's Disease Activity Index (PCDAI) score to infliximab exposure, the serum infliximab concentrations at Week 54 were categorized into 4 ranges: $< 0.1 \mu\text{g/mL}$, 0.1 to $< 1 \mu\text{g/mL}$, 1 to $< 10 \mu\text{g/mL}$, and $\geq 10 \mu\text{g/mL}$. As shown in [Figure 5](#), subjects with higher preinfusion serum infliximab concentrations had generally higher responses as measured by the improvement in PCDAI score than subjects with lower preinfusion serum infliximab concentrations. However, these results should be interpreted with caution given the small number of subjects available for this analysis.

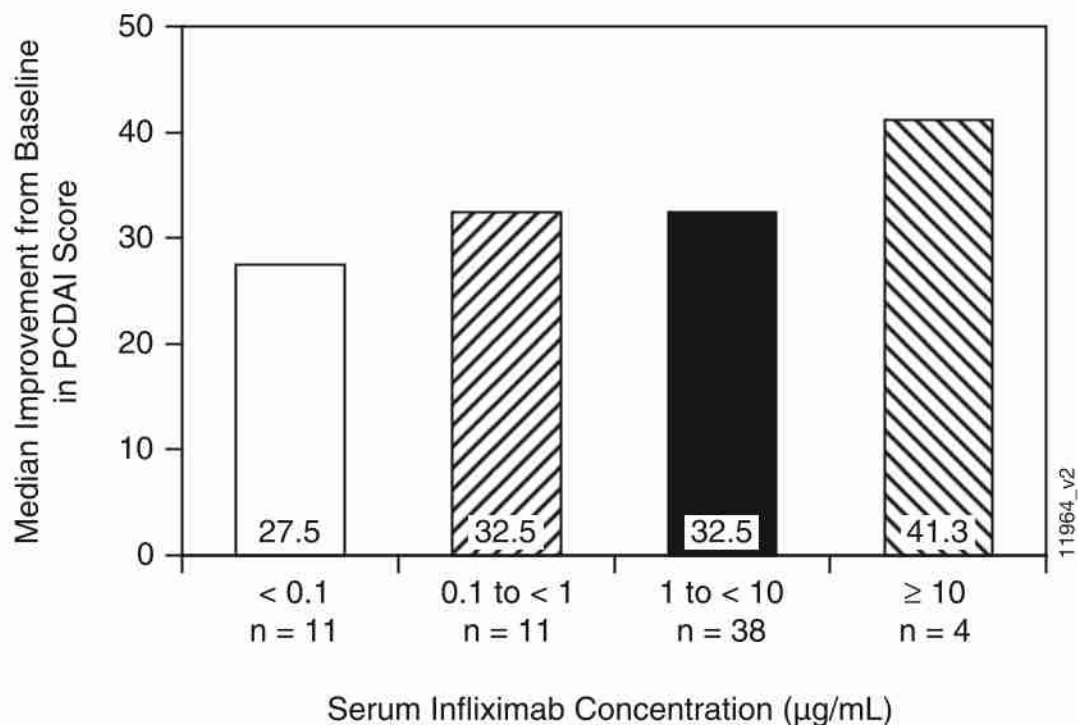


Figure 5 Median improvement from baseline in the PCDAI score by serum infliximab concentration (micrograms/mL) at Week 54; treated subjects

Subjects in REACH who discontinued the study or had insufficient data had their last nonmissing PCDAI score carried forward. Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes had their last nonmissing PCDAI score prior to the event carried forward to all subsequent visits.

3 COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

As previously described, this section presents a discussion of results across studies. [Section 3.1](#) provides an overview of results across the 3 Crohn's disease studies in pediatric subjects, including a pooled analysis of pharmacokinetic parameter estimates from these 3 studies and an analysis of pharmacokinetic parameter estimates by age subgroups within this population. A discussion of the infliximab pharmacokinetics in pediatric subjects with Crohn's disease relative to adult subjects with Crohn's disease is provided in [Section 3.2](#). [Section 3.3](#) includes a discussion of infliximab pharmacokinetics in pediatric subjects with Crohn's disease versus those in JRA.

3.1 Pediatric Subjects with Crohn's Disease

3.1.1 Results Across Studies

[Table 1](#) shows a summary of pharmacokinetic parameter estimates from the 3 studies in pediatric subjects with Crohn's disease. For the REACH study, data were included for 77 subjects who did not cross over from their original regimen (ie, 42 subjects in the q8 week maintenance group, 26 subjects in the q12 week maintenance group, and the 9 subjects not randomized at Week 10). For Study C0168T23, data were included for all subjects who received a single infusion of 5 mg/kg infliximab (n = 7). For Study C0168T55, data are shown for all subjects who received a single infusion of 5 mg/kg infliximab during maintenance treatment with commercial REMICADE (n = 6).

The median C_{max} was similar across the 3 studies (from 93.2 to 123.8 µg/mL). The median AUC_{ss} and clearance were also similar in the REACH study and Study C0168T23 (AUC_{ss}: 868.5 and 907.7 µg•day/mL, respectively; clearance: 5.87 and 5.51 mL/day/kg, respectively). There appeared to be small differences, however, in the median values for infliximab clearance, t_{1/2}, and AUC_{ss} between the REACH study and Study C0168T55, and the median infliximab V_{ss} across all 3 studies ([Table 1](#)).

These differences may have resulted from the small number of subjects in Studies C0168T23 and C0168T55, and the different study designs across the 3 Crohn's disease studies in pediatric subjects. Study C0168T23 evaluated a single dose of 5 mg/kg infliximab in 7 subjects. Study C0168T55 evaluated a single dose of 5 mg/kg infliximab administered at steady state to 6 subjects, and REACH evaluated induction and maintenance dosing with 5 mg/kg infliximab in up to 106 subjects. Despite these differences in median values, the ranges of the various pharmacokinetic parameter estimates extensively overlapped across the 3 studies.

In addition, the differences noted between the REACH study and Study C0168T55 may be explained by the fact that the few subjects (n = 6) in Study C0168T55 had, on average, a higher infliximab clearance. Some of these subjects had an increased infliximab dosing frequency prior to enrolling in the study (allowed per protocol) in order to maintain efficacy (██████ had a q5 week dosing interval, ██████ had a q6 week dosing interval, and ██████ had a q8 week dosing interval). In REACH, it was also shown that subjects who increased dose or required more frequent administration of infliximab in order to maintain efficacy were subsequently found to have a higher infliximab clearance. Notably, the median infliximab t_{1/2} among subjects in REACH who crossed over from 5 mg/kg q12 weeks to 10 mg/kg q8 weeks was 6.4 days (refer to [C0168T47 54-Week CSR, Attachment 2.7](#)), which is similar to the median infliximab t_{1/2} (6 days) obtained in Study C0168T55 ([Table 1](#)). The median infliximab t_{1/2} in Study C0168T23 fell between the median values observed in REACH and in Study C0168T55.

Overall, in the combined population, median values for C_{max}, clearance, V_{ss}, t_{1/2}, and AUC_{ss} following 5 mg/kg dosing were 116.8 µg/mL, 5.9 mL/day/kg, 87.6 mL/kg, 10.9 days, and 860.1 µg•day/mL, respectively.

Module 2.7.2
Summary of Clinical PharmacologyCrohn's Disease in Pediatric Subjects
REMICADE® (infliximab)**Table 1** Summary of pharmacokinetic parameter estimates through final visit; treated subjects

	Infliximab 5 mg/kg			
	C0168T23	C0168T55	C0168T47	Combined
Subjects treated	7	6	77	90
Cmax (µg/mL)				
N	7	6	71	84
Mean ± SD	114.0 ± 23.3	102.9 ± 34.2	129.1 ± 34.2	126.0 ± 34.0
Median	123.80	93.15	116.82	116.79
IQ range	(93.97, 132.91)	(77.08, 137.04)	(104.95, 146.26)	(103.19, 144.13)
Range	(72.6, 135.7)	(65.3, 151.7)	(78.9, 230.2)	(65.3, 230.2)
Clearance (mL/day/kg)				
N	7	6	71	84
Mean ± SD	5.8 ± 2.3	7.5 ± 2.7	6.5 ± 3.1	6.5 ± 3.0
Median	5.51	8.17	5.87	5.88
IQ range	(3.64, 7.72)	(5.28, 9.29)	(4.51, 7.87)	(4.64, 7.87)
Range	(3.0, 9.6)	(3.2, 10.6)	(2.4, 19.4)	(2.4, 19.4)
Vss (mL/kg)				
N	7	6	71	84
Mean ± SD	49.0 ± 13.4	72.3 ± 34.3	102.2 ± 47.0	95.7 ± 47.0
Median	47.39	66.93	92.15	87.55
IQ range	(38.81, 60.37)	(41.51, 83.83)	(66.30, 129.02)	(61.82, 120.99)
Range	(31.1, 69.7)	(41.2, 133.6)	(40.2, 322.2)	(31.1, 322.2)
t1/2 (day)				
N	7	6	71	84
Mean ± SD	8.7 ± 4.1	7.0 ± 2.3	13.1 ± 6.2	12.3 ± 6.1
Median	7.63	6.00	12.12	10.88
IQ range	(5.42, 14.31)	(5.49, 8.82)	(8.48, 16.28)	(7.71, 15.30)
Range	(5.4, 14.8)	(4.7, 10.8)	(2.6, 29.2)	(2.6, 29.2)
AUCss (µg day/mL)				
N	7	6	71	84
Mean ± SD	989.8 ± 400.0	790.4 ± 402.5	921.1 ± 388.2	917.5 ± 387.4
Median	907.72	613.48	868.54	860.07

Table 1 Summary of pharmacokinetic parameter estimates through final visit; treated subjects

	Infliximab 5 mg/kg			
	C0168T23	C0168T55	C0168T47	Combined
IQ range	(647.69, 1372.88)	(553.41, 946.87)	(638.58, 1108.03)	(637.11, 1078.34)
Range	(520.8, 1642.2)	(473.5, 1541.9)	(258.3, 2084.5)	(258.3, 2084.5)

Note: For the REACH study, data were included for 77 subjects who did not cross over from their original regimen (ie, 42 subjects in the q8 week maintenance group, 26 subjects in the q12 week maintenance group, and the 9 subjects not randomized at Week 10). For Study C0168T23, data were included for all subjects who received a single infusion of 5 mg/kg infliximab (n = 7). For Study C0168T55, data are shown for all subjects who received a single infusion of 5 mg/kg infliximab during maintenance treatment with commercial REMICADE (n = 6).

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3.1.2 Results by Pediatric Age Subgroups

A summary of pharmacokinetic parameter estimates by pediatric age subgroups (≤ 11 years and > 11 years) is shown in Table 2. For the REACH study, data were included for 77 subjects: those who did not cross over in the q8 week maintenance group (n = 42), those who did not cross over in the q12 week maintenance group (n = 26), and those not randomized at Week 10 (n = 9). In the combined population, data were included for the 77 subjects in REACH, for the 7 subjects who received a single infusion of 5 mg/kg infliximab in Study C0168T23, and for the 6 subjects who received a single infusion of 5 mg/kg infliximab during maintenance treatment in Study C0168T55.

In REACH, the Vss was slightly lower among younger pediatric subjects with Crohn's disease compared to that observed in older pediatric subjects with Crohn's disease (75.4 versus 97.4 mL/kg). However, no meaningful differences were observed in the remaining pharmacokinetic parameter estimates between these age groups. Furthermore, this conclusion remained the same when data from the pediatric Crohn's disease studies were combined and analyzed by age subgroups. Thus, it does not appear that age would affect the pharmacokinetics of infliximab in this population.

Module 2.7.2
Summary of Clinical PharmacologyCrohn's Disease in Pediatric Subjects
REMICADE® (infliximab)**Table 2** Summary of pharmacokinetic parameter estimates through final visit by age group; treated subjects

	Infliximab 5 mg/kg			
	C0168T47		C0168T23, C0168T55, C0168T47	
	Age ≤ 11 yrs	Age > 11 yrs	Age ≤ 11 yrs	Age > 11 yrs
Subjects treated	18	59	24	66
C _{max} (µg/mL)				
n	18	53	24	60
Mean ± SD	118.9 ± 27.0	132.6 ± 35.9	114.9 ± 29.0	130.4 ± 35.1
Median	108.47	118.86	107.17	121.33
IQ range	(101.62, 138.10)	(107.12, 149.08)	(94.38, 137.57)	(106.74, 145.74)
Range	(86.6, 169.6)	(78.9, 230.2)	(65.3, 169.6)	(72.6, 230.2)
Clearance (mL/day/kg)				
n	18	53	24	60
Mean ± SD	7.1 ± 4.1	6.3 ± 2.7	7.2 ± 3.7	6.3 ± 2.6
Median	5.73	5.87	6.28	5.81
IQ range	(4.94, 7.87)	(4.51, 7.69)	(5.01, 8.44)	(4.51, 7.70)
Range	(2.4, 19.4)	(2.5, 17.2)	(2.4, 19.4)	(2.5, 17.2)
V _{ss} (mL/kg)				
n	18	53	24	60
Mean ± SD	103.5 ± 67.8	101.8 ± 38.4	95.7 ± 62.0	95.6 ± 40.1
Median	75.35	97.36	73.53	92.05
IQ range	(68.18, 106.31)	(66.30, 129.02)	(63.81, 100.95)	(59.54, 124.33)
Range	(40.2, 322.2)	(44.7, 190.8)	(40.2, 322.2)	(31.1, 190.8)
t _{1/2} (day)				
n	18	53	24	60
Mean ± SD	11.9 ± 5.3	13.6 ± 6.5	10.7 ± 5.2	13.0 ± 6.4
Median	10.15	12.14	9.12	11.91
IQ range	(8.27, 15.86)	(9.78, 16.28)	(6.42, 14.96)	(8.04, 15.65)
Range	(3.1, 22.0)	(2.6, 29.2)	(3.1, 22.0)	(2.6, 29.2)
AUC _{ss} (µg.day/mL)				
n	18	53	24	60
Mean ± SD	890.9 ± 422.3	931.3 ± 379.7	865.8 ± 411.1	938.1 ± 379.1
Median	875.49	868.54	797.18	869.11

Table 2 Summary of pharmacokinetic parameter estimates through final visit by age group; treated subjects

	Infliximab 5 mg/kg			
	C0168T47		C0168T23, C0168T55, C0168T47	
	Age ≤ 11 yrs	Age > 11 yrs	Age ≤ 11 yrs	Age > 11 yrs
	(635.64, 1011.30)	(648.85, 1108.03)	(592.62, 1006.88)	(648.27, 1116.41)
IQ range				
Range	(258.3, 2084.5)	(290.8, 2040.2)	(258.3, 2084.5)	(290.8, 2040.2)

Note: For the REACH study, data are included for 77 subjects: those who did not cross over in the q8 week maintenance group (n = 42), those who did not cross over in the q12 week maintenance group (n = 26), and those not randomized at Week 10 (n = 9). In the combined population, data are presented for the 77 subjects in REACH, for all 7 subjects who received a single infusion of 5 mg/kg infliximab in Study C0168T23, and for all 6 subjects who received a single infusion of 5 mg/kg infliximab during maintenance treatment in Study C0168T55.

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3.2 Pediatric Subjects with Crohn's Disease and Adult Subjects with Crohn's Disease

The pharmacokinetic results from 2 studies in adult subjects with Crohn's disease (C0168T11 and ACCENT I) were utilized to compare to results observed in pediatric subjects with Crohn's disease.

Study C0168T11 was a Phase 2, multicenter, open-label, single-dose, dose-escalation study conducted to identify the lowest effective dose of infliximab and the largest infliximab dose that could be safely administered to adult subjects with Crohn's disease (CSR in EMEA/H/C/240). Twenty subjects between the ages of 20 and 51 years were enrolled, treated, and included in pharmacokinetic analyses in this study, with 5 subjects assigned to each of the following treatment groups: 1 mg/kg infliximab, 5 mg/kg infliximab, 10 mg/kg infliximab, and 20 mg/kg infliximab.

The ACCENT I study was a Phase 3, randomized, double-blind, placebo-controlled study conducted to evaluate long-term treatment with infliximab in adult subjects with moderately to severely active Crohn's disease (54wkCSR in EMEA/H/C/240/II/25). Five hundred seventy-three (573) subjects in this study were randomly assigned to receive placebo (n = 188), 5 mg/kg infliximab q8 weeks (n = 192), or 10 mg/kg infliximab q8 weeks (n = 193). Sparse samples for serum concentrations of infliximab were obtained up to Week 54.

A summary of pharmacokinetic parameter estimates in pediatric and adult subjects is presented in [Appendix Table 2](#). Note that data are shown for the combined pediatric population from REACH, Study C0168T55, and C0168T23 (n = 90) and for adults in Study C0168T11 who received a single dose of 5 mg/kg infliximab (n = 5). When the

Module 2.7.2
Summary of Clinical PharmacologyCrohn's Disease in Pediatric Subjects
REMICADE® (infliximab)

adult pharmacokinetic parameter estimates in Study C0168T11 were compared to those of the combined pediatric population with Crohn's disease, there were no marked differences in the median results for clearance, V_{ss} , and AUC_{ss} between pediatric subjects (5.9 mL/day/kg, 87.6 mL/kg and 860.1 $\mu\text{g}\cdot\text{day/mL}$ respectively) and adult subjects (6.3 mL/day/kg, 80.0 mL/kg, and 788.0 $\mu\text{g}\cdot\text{day/mL}$ respectively).

It appeared that the pediatric population, in general, had a higher median infliximab C_{max} than the adult population (116.8 $\mu\text{g/mL}$ versus 74.9 $\mu\text{g/mL}$). The $t_{1/2}$ also appeared to be longer in the pediatric population (10.9 days) compared to that observed in adults (7.8 days). However, these results need to be interpreted with caution considering that Study C0168T11 was a single-dose study with only 5 subjects in the 5 mg/kg group. Differences in study designs could also explain the apparent differences noted in these pharmacokinetic parameters. A more appropriate study that can be directly compared to Study C0168T11 is Study C0168T23, as both were single-dose studies with a small number of subjects. In these 2 studies, the median values for clearance and $t_{1/2}$ were similar in pediatric (5.5 mL/day/kg and 7.6 days, respectively) and adult (6.3 mL/day/kg and 7.8 days, respectively) subjects with Crohn's disease following a single infusion of 5 mg/kg infliximab. These results suggest that there is no notable difference between the clearance and $t_{1/2}$ of infliximab in pediatric and adult subjects with Crohn's disease.

The most appropriate studies to compare infliximab pharmacokinetics during maintenance treatment in pediatric and adult subjects with Crohn's disease are REACH and ACCENT 1. ACCENT 1 was a large study that included a maintenance dosing regimen of 5 mg/kg infliximab q8 weeks. Pharmacokinetic parameter estimates were not calculated in ACCENT 1; however, there were several corresponding time points when infliximab serum concentrations were determined in both studies. At each corresponding time point in the 2 studies, median serum infliximab concentrations were similar (Table 3). Notably, median postinfusion concentrations of infliximab in the pediatric and adult studies were comparable at Week 0 (86.8 $\mu\text{g/mL}$ and 92.8 $\mu\text{g/mL}$, respectively) and at Week 46 (94.4 $\mu\text{g/mL}$ and 99.7 $\mu\text{g/mL}$, respectively) for the 5 mg/kg q8 weeks regimen. Results were similar for median preinfusion concentrations of infliximab in pediatric and adult subjects at equivalent doses. These data confirm that, when dosed similarly, exposure to infliximab is comparable among pediatric and adult subjects with Crohn's disease.

Module 2.7.2
Summary of Clinical PharmacologyCrohn's Disease in Pediatric Subjects
REMICADE® (infliximab)**Table 3 Median serum concentrations of 5 mg/kg infliximab over time in pediatric and adult subjects with Crohn's disease**

		Study C0168T47 Subjects randomized as responders at Week 10		Study C0168T21 Subjects randomized as responders at Week 2
		5 mg/kg q8 wks	5 mg/kg q12 wks	5 mg/kg q8 wks
Pts randomized		53	50	113
Week 0 preinfusion,	n	53	50	111
	Median	<0.1	<0.1	<0.1
Week 0 postinfusion,	n	51	48	108
	Median	86.8	88.4	92.8
Week 2 preinfusion,	n	52	48	110
	Median	20.5	20.8	18.9
Week 6 preinfusion,	n	52	47	106
	Median	12.5	11.6	8.8
Week 14 preinfusion,	n	48	0	100
	Median	2.8	NA	2.6
Week 22 preinfusion,	n	41	0	84
	Median	2.3	NA	1.8
Week 30 preinfusion,	n	40	23	72
	Median	1.8	0.2	1.4
Week 38 preinfusion,	n	35	0	61
	Median	1.8	NA	1.2
Week 42 preinfusion,	n	0	19	0
	Median	NA	0.3	NA
Week 46 preinfusion,	n	33	0	50
	Median	1.8	NA	1.4
Week 46 postinfusion,	n	31	0	28
	Median	94.4	NA	99.7
Week 54 preinfusion,	n	31	15	47
	Median	2.2	0.4	2.4

Note: In both studies, data for subjects who had a dose or regimen escalation were excluded from the point of crossover.

NA = Not applicable. A sample was not obtained at that time point.

Source: CSR C0168T47, Attachment 2.3 and CSR C0168T21, Table 9.2.3

3.3 Pediatric Subjects with Crohn's Disease and Juvenile Rheumatoid Arthritis

One study evaluated infliximab for the treatment of JRA. Study C0168T32 was a Phase 3, multicenter, randomized, placebo-controlled, double-blind study for 14 weeks, followed by a double-blind, all-active treatment extension. Subjects in this study received maintenance treatment with either 3 mg/kg infliximab every 8 weeks or 6 mg/kg infliximab every 8 weeks in the presence of concomitant methotrexate. A summary of pharmacokinetic parameter estimates for subjects with JRA is presented in Table 20 of the CSR for Study C0168T32 (refer to C0168T32 64-Week CSR, Table 20). In Study C0168T32, the pharmacokinetic parameters for the 3 mg/kg infliximab regimen were found to be different from the 6 mg/kg infliximab regimen.

When the pharmacokinetic parameters for the 3 mg/kg infliximab regimen in JRA subjects were compared with those for the combined pediatric population with Crohn's disease who received 5 mg/kg infliximab, there were marked differences in the median results for V_{ss} and $t_{1/2}$ (pediatric subjects with Crohn's disease: 87.6 mL/kg and 10.9 days respectively; JRA subjects who received 3 mg/kg infliximab q8 weeks: 58.5 mL/kg and 6.9 days respectively). However, clearance was similar in both populations (pediatric subjects with Crohn's disease: 5.9 mL/day/kg; JRA subjects who received 3 mg/kg infliximab q8 weeks: 5.8 mL/day/kg).

However, when the pharmacokinetic parameters for the 6 mg/kg infliximab regimen in the JRA study were compared to those for the combined pediatric population with Crohn's disease, no differences were noted in the median results for the $t_{1/2}$ (pediatric subjects with Crohn's disease: 10.9 days; JRA subjects who received 6 mg/kg infliximab q8 weeks: 9.5 days). Both the V_{ss} and clearance were lower for JRA subjects who received 6 mg/kg infliximab (63.6 mL/kg and 4.9 mL/day/kg) than for pediatric subjects with Crohn's disease (87.6 mL/kg and 5.9 mL/day/kg). This relationship between the V_{ss} and the clearance resulted in similar $t_{1/2}$ for infliximab for the 6 mg/kg dose in the JRA population and the 5 mg/kg infliximab dose in the Crohn's disease population.

3.4 Conclusions

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

Infliximab pharmacokinetic results observed in the supportive Phase 1 studies (C0168T55 and C0168T23) were generally comparable to those observed in REACH. There were no apparent differences in the pharmacokinetics of infliximab when examined by pediatric age subgroups. In addition, review of results observed in the adult

studies of Crohn's disease (Study C0168T11 and ACCENT I) indicates that the pharmacokinetic profile of infliximab is similar in pediatric and adult patients with Crohn's disease.

These results, together with the favorable benefit/risk profile of the q8 week maintenance treatment regimen relative to the q12 week maintenance regimen, support an induction regimen with 5 mg/kg infliximab administered at Weeks 0, 2, and 6, followed by 5 mg/kg infliximab every 8 weeks thereafter for the treatment of Crohn's disease in pediatric patients.

4 SPECIAL STUDIES [NOT APPLICABLE]

5 APPENDIX

Appendix Table 1	Crohn’s disease studies in pediatric subjects	29
Appendix Table 2	Pharmacokinetic parameter estimates in pediatric and adult subjects with Crohn’s disease	32

Module 2.7.2
Summary of Clinical Pharmacology

Crohn's Disease in Pediatric Subjects
REMICADE® (infliximab)

Appendix Table 1 Crohn's disease studies in pediatric subjects

Protocol No. (Acronym) No. of Sites No. of Subjects	Study Start to End Dates	Age (range) Gender and Race (N)	Study Design	Dose Regimen	Clinical Pharmacology Results
C0168T23 (No acronym) 7 sites 21 subjects enrolled and treated	14 Jul 1998 to 06 May 1999 ^a	11 – 17 yr M: [REDACTED] F: [REDACTED] C: [REDACTED] B: [REDACTED] A: 0 O: 0	Phase 1/2, randomized (with an adaptive stratified design with age [< 13 ; 13- 17] as the stratum) dose- blinded, parallel-group, single-dose, dose-ranging efficacy, safety, and pharmacokinetic study with a 20-week follow-up period.	Single dose by IV infusion: 1 mg/kg (n = 6) 5 mg/kg (n = 7) 10 mg/kg (n = 8)	- The overall exposure of pediatric subjects to infliximab in this study, as measured by AUC, is similar to that of adult subjects with Crohn's disease in the same dose groups. - The median maximum serum concentrations of infliximab in pediatric subjects were dose-dependent, and these values are comparable with those obtained in adult subjects with Crohn's disease in an earlier single-dose study (C0168T11).
C0168T55 (No acronym) 2 sites 6 subjects	05 May 2003 to 10 Sep 2004	9 - 11 yr M: [REDACTED] F: [REDACTED] C: [REDACTED] B: [REDACTED] A: [REDACTED] O: [REDACTED]	Phase 1, open-label, single- dose, safety, and pharmacokinetic study. Subjects in this study had received at least 4 doses of commercial REMICADE prior to study entry.	Single dose by IV infusion: 5 mg/kg (n = 6)	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 clearance, V_{ss}, AUC_{ss}, and t_{1/2} 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.

Module 2.7.2
Summary of Clinical Pharmacology

Crohn's Disease in Pediatric Subjects
REMICADE® (infliximab)

Appendix Table 1 Crohn's disease studies in pediatric subjects

Protocol No. (Acronym) No. of Sites No. of Subjects	Study Start to End Dates	Age (range) Gender and Race (N)	Study Design	Dose Regimen	Clinical Pharmacology Results
C0168T47 (REACH) 34 sites 112 subjects enrolled and treated	11 Feb 2003 to 13 Apr 2005	6 – 17 yr M: [REDACTED] F: [REDACTED] C: [REDACTED] B: [REDACTED] A: [REDACTED] O: [REDACTED]	Phase 3, randomized, open-label study to evaluate the efficacy, safety, and pharmacokinetics of infliximab in pediatric subjects with moderately to severely active Crohn's disease.	Infliximab was administered by IV infusion: Induction (n = 112): 5 mg/kg at Weeks 0, 2, and 6 Maintenance Treatment: Responders at Week 10 were to be randomized to 1 of 2 groups: • 5 mg/kg q8 wks • 5 mg/kg q12 wks If a subject lost clinical response during the Maintenance Phase, they were permitted a dose and/or regimen escalation as follows: • 5 mg/kg q8 wks → 10 mg/kg q8 wks • 5 mg/kg q12 wks → 5 mg/kg q8 wks (if response lost at > 8 to ≤ 12 weeks from previous infusion) • 5 mg/kg q12 wks → 10 mg/kg q8 wks (if response lost at ≤ 8 weeks from previous infusion)	• 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, clearance 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.

Module 2.7.2
Summary of Clinical PharmacologyCrohn's Disease in Pediatric Subjects
REMICADE® (infliximab)**Appendix Table 1 Crohn's disease studies in pediatric subjects**

Protocol No. (Acronym) No. of Sites No. of Subjects	Study Start to End Dates	Age (range) Gender and Race (N)	Study Design	Dose Regimen	Clinical Pharmacology Results
^a 20-Week start and stop dates. This study had a 48-week extension. Pharmacology was evaluated through Week 20.					
Abbreviations:					
A	Asian				
AUC	area under the concentration versus time curve from time 0 to infinity with extrapolation of the terminal phase				
AUC _{ss}	AUC at steady state				
B	Black				
C	Caucasian				
C _{max}	maximum observed concentration				
F	female				
IV	intravenous				
M	male				
n	number of subjects				
No.	number				
O	Other				
q8 wks	every 8 weeks				
q12 wks	every 12 weeks				
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				
t _{1/2}	terminal elimination half-life				
V _{ss}	apparent volume of distribution at steady state after intravenous administration				
yr	year				

Module 2.7.2
Summary of Clinical PharmacologyCrohn's Disease in Pediatric Subjects
REMICADE® (infliximab)**Appendix Table 2 Pharmacokinetic parameter estimates in pediatric and adult subjects with Crohn's disease**

	Infliximab 5 mg/kg	
	Pediatric Subjects with Crohn's Disease	Adult Subjects with Crohn's Disease
	(Studies C0168T23, C0168T55, and C0168T47 Pooled)	(Study C0168T11)
Subjects treated	90	5
C _{max} (µg/mL)		
n	84	5
Mean ± SD	126.0 ± 34.0	84.5 ± 19.4
Median	116.79	74.9
IQ range	(103.19, 144.13)	(74.7, 102.0)
Range	(65.3, 230.2)	(63.0, 108.0)
Clearance (mL/day/kg)		
n	84	5
Mean ± SD	6.5 ± 3.0	7.5 ± 2.7
Median	5.88	6.3
IQ range	(4.64, 7.87)	(5.9, 7.7)
Range	(2.4, 19.4)	(5.6, 12.1)
V _{ss} (mL/kg)		
n	84	5
Mean ± SD	95.7 ± 47.0	76 ± 17
Median	87.55	80
IQ range	(61.82, 120.99)	(67, 80)
Range	(31.1, 322.2)	(53, 100)
t _{1/2} (day)		
n	84	5
Mean ± SD	12.3 ± 6.1	6.4 ± 2.5
Median	10.88	7.8
IQ range	(7.71, 15.30)	(5.2, 8.3)
Range	(2.6, 29.2)	(2.6, 8.3)
AUC _{ss} (µg.day/mL)		
n	84	5
Mean ± SD	917.5 ± 387.4	715 ± 190
Median	860.07	788
IQ range	(637.11, 1078.34)	(648, 833)
Range	(258.3, 2084.5)	(415, 891)

Source: Table 1 of this SCP and CSR C0168T23, Table 8