19 January 2012

EMA/126772/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Remicade

infliximab

Procedure No.: EMEA/H/C/000240/II/0150

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Scientific discussion

1.1. Introduction

About the product

Infliximab is a tumour necrosis factor alpha (TNFα) inhibitor. It is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNFα but not to lymphotoxin α (TNFß). Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays. Infliximab prevented disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα and when administered after disease onset, it allowed eroded joints to heal. *In vivo*, infliximab rapidly forms stable complexes with human TNFα, a process that parallels the loss of TNFα bioactivity. Infliximab is currently approved for the treatment of rheumatoid arthritis (in combination with methotrexate), moderately to severely active and fistulising adult Crohn's disease, severe active paediatric Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis.

Scope of the variation

In this procedure the MAH extends the use of Remicade at the approved dosing and schedule for adult ulcerative colitis (UC) to paediatric patients aged 6 to 17 years with severely active UC who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. The approved dose of infliximab in adults is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter.

The MAH applied to extend the indication in paediatric patients aged 6 to 17 years with moderate to severely active as follows: "treatment of moderately to severely active ulcerative colitis, in paediatric patients aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies".

The incidence of paediatric UC in Europe ranges from approximately 0.1 to 13.29 per 10,000 with most countries reporting around approximately 1-2 cases of paediatric UC per 10,000 individuals. In the United States (US), the estimated prevalence of paediatric UC (children younger than 20 years) is 28 per 100,000 individuals while the estimated prevalence of adult UC is 238 per 100,000 individuals. Approximately 20% of patients with UC are detected before the age of 20 years with disease being extensive in approximately 50%–80% of the patients. The peak occurrence of UC is in late adolescence and 4% of paediatric IBD patients are diagnosed in early (age <5 years) childhood. While UC disease is quite similar in adult and paediatric patients in terms of overall disease pathology and progression, paediatric-onset UC is typically distinguished from adult-onset UC by a generally greater prevalence of moderate to severe disease.

The following variation application is made in this submission:

Clinical:

Variation requested		**Type**
C.I.6.a	Addition of a new therapeutic indication or modification of an approved one	II

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006 as amended, the application included an EMA decision P/239/2010 on the agreement of a paediatric investigation plan (PIP) with a deferral.

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

1.2. Clinical aspects

1.2.1. Introduction

The submission is based on the result from a phase III clinical trial performed in paediatric patients with ulcerative colitis (C0168T72). In addition, supportive analyses of the following studies are included:

Analyses of pharmacokinetics (PK) and immunogenicity are based upon data from C0168T72 and supported by PK data from:

- REACH (C0168T47, A Randomized, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Anti-TNFα Chimeric Monoclonal Antibody (Infliximab) in paediatric subjects with moderate to severe Crohn's Disease;
- ACT 1 and ACT 2 (C0168T37 and C0168T46, Active Ulcerative Colitis Trial 1 and 2) in adults.

Analyses of efficacy are based on data from C0168T72 and supported by efficacy data from ACT 1 and ACT 2.

The primary analyses of safety are based on data from C0168T72 and supported by safety data from the REACH, ACT 1 and ACT 2 studies. In addition, supportive safety data from other studies in paediatric populations (C0168T23, C0168T55, C0168T32 in JRA), RESULTS UC long-term safety follow-up study in paediatric and adults with UC, and post-marketing registries in paediatric and adult IBD.

In 2006, infliximab was approved in EU for the treatment of moderate to severely active UC in adult's and in 2007 it was approved for treatment of Crohn's disease in children.

1.2.2. GCP

The clinical trial submitted in support of this variation was performed in accordance with GCP as claimed by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

1.2.3. Clinical pharmacology

Data on the PK and antibodies to infliximab from 4 Phase 3 studies (C0168T72, ACT 1, ACT 2, and REACH) in paediatric and adult subjects with either active UC or Crohn's disease were included to support the application

1.2.3.1. Pharmacokinetics (Study C0168T72)

Study C0168T72 was a phase III study performed in paediatric patients with ulcerative colitis. The subjects received an induction regimen at weeks 0, 2 and 6. Responders at week 8 (as measured by the Mayo score) were then randomised to receive maintenance treatment as follows:

- Group I (infliximab 5 mg/kg q 8 wks): Doses at weeks 14, 22, 30, 38 and 46;

- Group II (infliximab 5 mg/kg q 12 wks): Doses at weeks 18, 30 and 42.

Subjects that did not respond at week 8 did not receive additional infusions of infliximab. Subjects who lost response during the maintenance phase were eligible for step-up (i.e. increase their dose and/or dosing frequency as follows: For group I: increase to 10 mg/kg every 8 weeks. For group II: lost response before week 8 could increase to 10 mg/kg every 8 weeks. Lost response after week 8, but before 12 weeks, could receive 5 mg/kg every 8 weeks).

The actual distribution of patients in these groups (original dosing or uptitrated) was as follows:

Table 1 Distribution of subjects in study groups for C0168T72

	C0168T72 (N=60)	
	N	Percent
Treatment Group		
Induction Dosing Only	15	25.0%
5 mg/kg Q8 Week Maintenance	22	36.7%
Step-up 10 mg/kg Q8 Week	(9 of 22)	(15.0%)
5 mg/kg Q12 Week Maintenance	23	38.3%
Step-up 5 mg/kg Q8 Week	(5 of 23)	(8.3%)
Step-up 10 mg/kg Q8 Week	(9 of 23)	(15.0%)

Serum infliximab concentration

Blood samples for determining serum infliximab concentrations were collected from all subjects before each infusion, 60 minutes after the infusion at Weeks 0, 2, and 6, and 60 minutes after the final infusion. Additional samples were also collected at noninfusion study visits at Weeks 8, 54, and 62. For subjects who discontinued study infusions early, blood samples for determining serum infliximab concentrations were collected 16 weeks after the last study infusion.

During infliximab induction therapy (i.e. 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 (i.e. preinfusion) concentrations at Weeks 2 and 6 were 19.3 µg/mL and 14.5 µg/mL, respectively. 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. 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) are presented in the figure below.

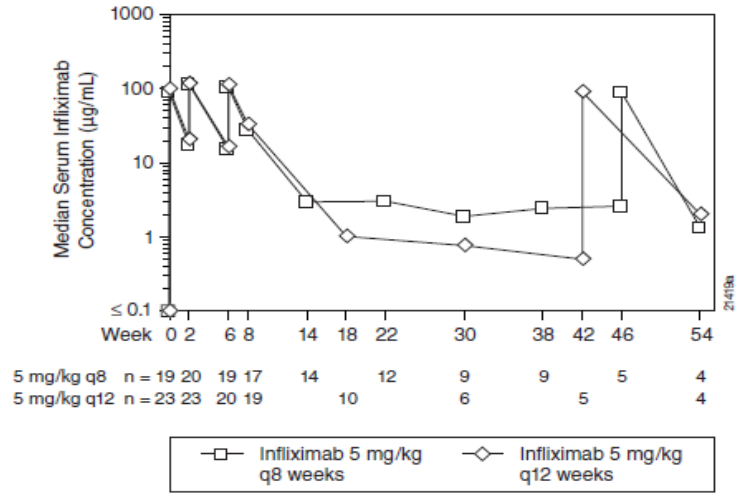

Figure 1 **Median serum infliximab concentrations (micrograms/mL) through Week 54 by visit; randomized subjects by treatment received in C0168T72**

Serum infliximab concentrations through Week 8 were generally similar between the 2 randomized treatment groups (5 mg/kg q8w and 5 mg/kg q12w). However, during the maintenance phase, median preinfusion serum infliximab concentrations for the subjects in the q8 w maintenance treatment group were generally higher than those in the q12w maintenance treatment group.

Subjects were allowed to step-up to a different infliximab dose regimen during maintenance treatment if they lost clinical response. Data showed that an increased dose of infliximab or a more frequent dose administration led to higher serum infliximab concentration levels. The serum infliximab concentrations through Week 8 were compared between the 2 age groups (6 to 11 years and 12 to 17 years). This comparison did not suggest any substantial impact of age on serum infliximab concentrations. In addition serum infliximab concentrations at Week 8 and Week 54 were summarized by baseline use of concomitant immunomodulators (i.e. 6-MP/AZA or MTX). In the Week 54 analyses, data for subjects who stepped up were excluded from the point of step-up. The data showed that the use of concomitant immunomodulators (i.e. 6-MP/AZA or MTX) did not have a significant impact on the serum concentration of infliximab.

Population PK analysis

A population PK analysis was performed based on data from the 60 paediatric subjects in this study. All 60 subjects in study 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 570 concentration values from the 60 paediatric subjects were available and 562 samples were used to develop a population PK model based on a nonlinear mixed-effects analysis approach. The first post-dose concentration below the LLOQ (42 total observations) was set to half the LLOQ, i.e. 0.05 µg/mL and was retained in the data set and used in the analysis. Any subsequent concentration result below LLOQ without intervening dose administration (4 total observations in 4 subjects) was excluded.

A confirmatory population PK analysis approach that was based on the prior knowledge from the existing population PK model in adult subjects with UC was used to evaluate the population PK in this paediatric population. In addition, a conventional population PK analysis served as a sensitivity analysis for assessing the consistency of these 2 approaches.

Modelling of population pharmacokinetic characteristics in paediatric subjects

The population PK of infliximab in paediatric subjects with UC (C0168T72) was described by a 2-compartment linear PK model.

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 t1/2 of infliximab in paediatric subjects with UC was estimated to be 10.8 days (interquartile range: 8.6 to 15.4 days).

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 t1/2 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 t1/2 in paediatric subjects with UC was comparable to the t1/2 which was estimated for infliximab in adult subjects UC (11.7 days in the 5 mg/kg treatment group) and paediatric subjects with Crohn's disease (10.7 days).

The covariate analysis demonstrated that the variability in infliximab volume of distribution was primarily determined by body weight, while the variability in infliximab CL was marginally affected by serum albumin levels. A subject's age and immunomodulator use had no significant impact on infliximab PK. In addition, subjects who tested positive for antibodies to infliximab had a higher clearance than subjects who did not test positive; however, since relatively few (n = 4) subjects in this PK analysis population tested positive, the impact of antibody status could not be accurately quantified.

Simulation of exposure at steady state comparing paediatric and adult subjects

Simulations of the 5 mg/kg q8w dosing regimen of infliximab suggest that a substantial overlap exists for infliximab exposure between adult and paediatric subjects with UC. The simulated steady-state profiles for the paediatric and adult populations over an 8-week dosing interval following maintenance dosing regimen of 5 mg/kg q8w are shown in Figure 6 (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.

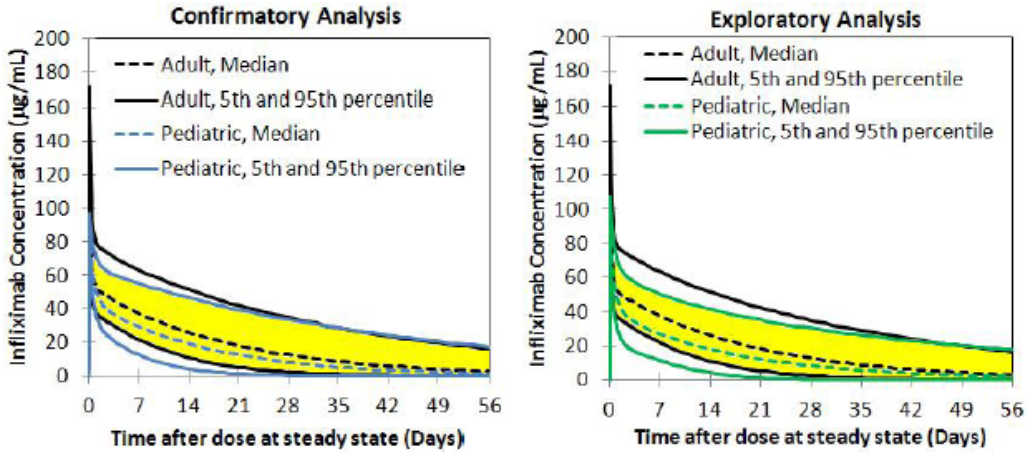

Figure 5 Simulated Steady State PK Profiles Following Maintenance Dosing Regimen of 5 mg/kg Q8 Weeks between Adult and Paediatric Populations with Ulcerative Colitis

Based on the typical parameter estimates of the population PK models for infliximab, median AUCT for adults was 946 µg·days/mL compared to 723 µg·days/mL for the confirmatory analysis and 742 µg·days/mL for the exploratory analysis in paediatric subjects. These results showed that median AUCT in paediatric subjects was approximately 20% lower than that in adult subjects.

Furthermore, PK simulations predict that the steady-state trough concentration in a typical paediatric subject with UC receiving infliximab q12w is approximately 0.4 µg/mL. This value is much lower than the predicted steady-state concentration in the same subject receiving 5 mg/kg q8w (2.0 µg/mL). Thus, it is expected that treatment with infliximab 5 mg/kg q12w in paediatric subjects with UC would result in lower drug exposure, particularly lower trough serum infliximab concentration.

1.2.3.2. Comparisons of Pharmacokinetics of Infliximab Across Studies

The PK of infliximab in paediatric subjects with active UC (C0168T72) was compared with the PK in adult subjects with active UC (ACT 1 and ACT 2) and paediatric subjects with active Crohn's disease (REACH), respectively A summary of PK parameters in the C0168T72, REACH, and ACT studies is provided in Table 5.

Table 5 Summary of infliximab 5 mg/kg PK in the C0168T72, REACH, and ACT studies

	C0168T72	REACH	ACT studies
Median peak serum concentration during induction (µg/mL)[a]	115.1 [b]	108.7[b]	131.6[b]
Median trough serum concentration during maintenance at Week 30 (µg/mL)[a]	1.9	1.8	2.5
Median t1/2 (days)	10.8[c]	10.7	11.7[d]

a) Data is presented for the 5 mg/kg q8w treatment group, b) At Week 2, c) Obtained from the confirmatory population PK analysis, d) Derived from data only in ACT 1

Pharmacokinetics in paediatric versus adult subjects with ulcerative colitis

Pharmacokinetic data in paediatric subjects with ulcerative colitis at weeks 0, 2 and 6 were compared with the pharmacokinetics in adult subjects from studies ACT1 and ACT2. Data from ACT1 and 2 were pooled from week 30 and onwards (a difference in the pre-infusion concentrations were observed at week 30). 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 paediatrics and adult subjects with UC, respectively. In paediatrics 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 paediatric and adult subjects (15.2 µg/mL versus 15.3 µg/mL, respectively). Median serum trough infliximab concentrations at the steady-state timepoints of Week 30 and Week 38 in paediatric 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). The overall median serum infliximab concentrations in paediatric 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. There was no significant change in the pharmacokinetics upon concomitant administration of immunomodulators. At steady state, the predicted exposure as obtained from the population pharmacokinetic analysis was 20 % lower in paediatric subjects compared to adults.

Pharmacokinetics in paediatric ulcerative colitis versus paediatric Crohn's disease
The two studies with similar design, one in paediatric subjects with ulcerative colitis (C0168T72) and one in Crohn's Disease (REACH), were compared.

In subjects randomized to the q8w infliximab regimen, median peak (i.e., 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 paediatric 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 paediatric subjects, respectively. Prior to the third induction dose at Week 6, the preinfusion concentrations were similar between paediatric 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 paediatric UC subjects in the q8w infliximab regimen (1.9 µg/mL and 2.4 µg/mL, respectively) were similar to those in paediatric 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 paediatric subjects with UC and paediatric subjects with Crohn's disease in the randomized q8w treatment groups were also observed with the randomized q12w treatment groups.

1.2.3.3. Immunogenicity (Study C0168T72)

Analyses for the detection of antibodies to infliximab were performed using a bridging immunoassay in which infliximab was used to capture and detect induced immune responses to infliximab. The presence of antibodies to infliximab was evaluated in blood drawn from subjects at Weeks 0, 30, 54, 0S (if applicable - Week 0S, i.e. the visit at which the infliximab dose and/or dosing frequency is increased due to loss of clinical response), and Week 62. For those subjects who discontinued the study, blood samples for detecting antibodies to infliximab was collected 16 weeks after the last study infusion.

Twenty-nine of 35 patients, who did not have the treatment stepped up, had appropriate samples available for analysis (i.e. had antibodies to infliximab at some time point after their first study agent administration or had 1 or more samples obtained after their last study agent administration). Three patients were positive for antibodies to infliximab (titers 1:20, 1:10 and 1:10 respectively). Two of the patients were in the q8w group. The remaining subjects were either negative (n=6) or had inconclusive results (n=2) (through week 62).

Of subjects who had their treatment stepped up and appropriate samples (n=23), one patient was positive for antibodies to infliximab (stepped up from 5 mg/kg q8w to 10 mg/kg q8w, titer 1:40). Of the remaining patients, 5 were determined to be negative for antibodies and 17 had inconclusive results through week 62.

Overall of the 60 subjects in C0168T72, 52 subjects had an appropriate sample for analysis of antibodies to infliximab, and of these 52 subjects, 4 subjects (7.7%) were positive for antibodies to infliximab at any time during the study. Due to the limited number of subjects who were positive for antibodies to infliximab, these results should be interpreted with caution. All infusion reactions were of mild or moderate intensity. No serious infusion reactions, possible delayed hypersensitivity-type reactions, or anaphylactic reactions were observed during the study.

Discussion:

Serum concentrations of infliximab were determined by using an enzyme-linked immunosorbent assay. The lower limit of quantification (LLOQ) for infliximab in serum was 0.1 µg/mL. The performance of the

enzyme-linked immunosorbent assay (ELISA) standards and controls, assay failures and any deviations in assay procedures that occurred during bio analysis were documented and found acceptable by the CHMP.

For the population PK analysis, eight data points (8/570) were excluded due to measureable levels pre-dose (n=2), incongruous data points (n=2) and being below LLOQ (n=4). The method used for taking into account samples below the LLOQ data points is not the preferable method and may lead to biased estimates. However, the number of samples accounts for less than 10% of the total data points and the approach is therefore acceptable.

The most marked effect was the expected effect of body weight on volume of distribution. There was also an effect of albumin on clearance, but in the normal range of albumin levels, the effect was not pronounced. Therefore, no dose adjustment is necessary based on albumin levels. With respect to the effect on volume of distribution, the dosing based on body weight is supported.

Following a request from the CHMP, the MAH provided further individual estimates of AUC following the recommended dose versus body weight and versus age, respectively, for all paediatric patients in this study, in order to judge if the dosing is adequate. Although there was notable variability in infliximab exposure when body weight-normalized doses were administered to paediatric subjects with UC, the exposure achieved by the proposed 5 mg/kg dose regimen was generally sufficient to induce response in a majority of paediatric subjects with ulcerative colitis. Additionally, a subject's age did not appear to have a substantial impact on infliximab exposure or clinical response when subjects received the recommended body weight-normalized dose regimen of 5 mg/kg.

The MAH also provided information on individual exposure versus weight and age separated on those patients that received induction treatment only, and for those patients that had their dose increased from 5 mg/kg to 10 mg/kg (present their exposure before dose increase) compared to the patients that remained on the recommended dose of 5 mg/kg q 8 weeks. There is a clearly lower exposure in subjects who only received induction treatment. No clear relationship to body weight was identified to explain this as subjects with low body weight were also present in the group that remained on their randomised dose or who stepped up. Low weight subjects were also not more frequent in the group that needed a dose increase. The MAH explored – as requested by the CHMP - whether there is sufficient support for a more flexible dose regimen for use in paediatric UC. It was pointed out that there are no data from adults in UC with a flexible dose regimen, and thus there are no efficacy or safety data to support such approach for the paediatric population. The available PK data showed a lower exposure of children than of adults. However, these data are not considered sufficient enough to propose a more flexible dose recommendation in paediatric patients. This position was endorsed by the CHMP and the proposal to maintain the initially proposed posology; an induction regimen at week 0, 2 and 6 of 5 mg/kg, followed by 8 weekly infusions of 5 mg/kg is agreed.

Further comparison in term of the variability of the PK data between paediatric and adult subjects with UC and between paediatric subjects with UC and paediatric subjects with CD were provided by the MAH. Overall, median peak and steady-state trough serum infliximab concentrations observed in the paediatric UC population were similar to those observed in the paediatric CD population. The variability is comparable at week 2 and 30. Data at week 54 is limited for UC patients (n=4), therefore comparisons of variability at this time-point should be made with caution. Median serum infliximab concentrations in paediatric subjects with UC were generally slightly lower than those of adult subjects with UC when a dosing regimen of 5 mg/kg infliximab was administered at Weeks 0, 2, and 6, followed by q8w. Data at week 54 is limited therefore comparisons of variability at this time-point should also be made with caution.

Very few subjects had a positive antibody status, but out of those subjects who were positive, they were not unevenly distributed to the group that received induction treatment only, although the results should be interpreted with caution, given the limited number of subjects being antibody positive. The age ranges were similar for the three groups, induction phase only, patients who remained on their maintenance dose and those who increased their maintenance dose.

Conclusion

Overall, infliximab PK (including peak and trough concentrations, and terminal t1/2) were generally comparable across studies in paediatrics and adult subjects with UC (C0168T72 compared with ACT 1 and ACT 2), as well as across studies in paediatrics subjects with UC or Crohn's disease (C0168T72 compared with REACH), although infliximab concentrations in the paediatrics studies (C0168T72 and REACH) were slightly lower than in adult subjects with UC. However, this difference in infliximab serum concentration is small considering the variability in PK observed with infliximab and other therapeutic monoclonal antibodies.

Based on the safety, efficacy, and PK results from ACT 1 and ACT 2 in adult subjects with UC, which demonstrated similar infliximab efficacy and safety at both 5 mg/kg and 10 mg/kg, and on the PK results from the paediatric Crohn's disease trials, the infliximab dose chosen for the paediatric subjects in C0168T72 was 5 mg/kg as an induction regimen at Weeks 0, 2, and 6, followed by a maintenance treatment regimen of 5 mg/kg either q8w or q12w. This was considered appropriate by the CHMP.

1.2.4. Clinical efficacy

1.2.4.1. Main study

The clinical development programme for infliximab for the treatment of paediatric UC consist of one phase III clinical trial. Study C0168T72: A randomised, open-label, dose-comparison parallel-group, and multicentre trial of infliximab in paediatric patients from 6 to less than 18 years old with moderately to severely active ulcerative colitis.

Methods

Study participants

Paediatric patients 6 to 17 with moderately to severely active UC (defined as a baseline Mayo score of 6 to 12) that was diagnosed or referred for diagnosis at least 2 weeks before screening and confirmed by biopsy and a Mayo endoscopy subscore ≥ 2 at a screening sigmoidoscopy.

The patients had active disease either despite adequate treatment with 6-MP, AZA, corticosteroids, and/or 5-aminosalicylate (5-ASA) compounds, or had previously been unsuccessfully treated with 6-MP, AZA, corticosteroids and/or 5-ASA compounds.

Further major inclusion criteria were:

- subjects had to meet criteria for concomitant medication stability, screening laboratory test results, and tuberculosis (TB) history and testing results
- have a well documented history of chicken pox or a positive varicella antibody titre
- has had a colonoscopy to assess the presence of dysplasia if at increased risk for colon cancer

- have agreed to use adequate birth control measures if sexually active

Major exclusion criteria were:

- severe extensive colitis or UC limited to the rectum
- receiving or experience of within specified interval before screening Bacille Calmette-Guérin vaccination or live viral or bacterial vaccination, non-tuberculous mycobacterial infection, opportunistic or other serious infection
- prior treatment with drugs considered to be investigational for UC (e.g. infliximab or other TNF antagonists)
- requirement of frequent antimotility agents or receiving high-dose corticosteroids
- latent or active granulomatous infection, predisposition to infections or of increased potential for malignancy

Treatments

Based on the available clinical data and pharmacokinetic considerations, the chosen dose for paediatric UC patients was 5 mg/kg (see section "Pharmacokinetics"). Initially the patients received an induction regimen at Weeks 0, 2, and 6. Subjects in clinical response at week 8 were randomized in a 1:1 ratio to receive a maintenance treatment regimen of 5 mg/kg either every 8 weeks (q8w) through week 46 or 12 weeks (q12w) through week 42. The 2 maintenance treatment regimens were chosen to determine if the maintenance dose administration interval for paediatric subjects with UC can be longer than the approved interval for adults with UC.

Non-responders at week 8 received no further injections.

Concomitant medical therapy for UC was to be stable for specified periods before screening. With the exception of corticosteroids and the immunomodulatory agents 6-MP, AZA, and MTX, UC–specific medical therapies were to be maintained at a stable dose until the Week 54 visit or until the infliximab treatment regimen has been increased due to loss of clinical response. The dose of corticosteroids could be tapered if clinically indicated and immunomodulators could be discontinued at any time during the study period.

Patients that lost response, as measured by the partial Mayo score, were eligible to have their infliximab dose and/or dosing frequency increased during the maintenance treatment phase, see Figure 7.

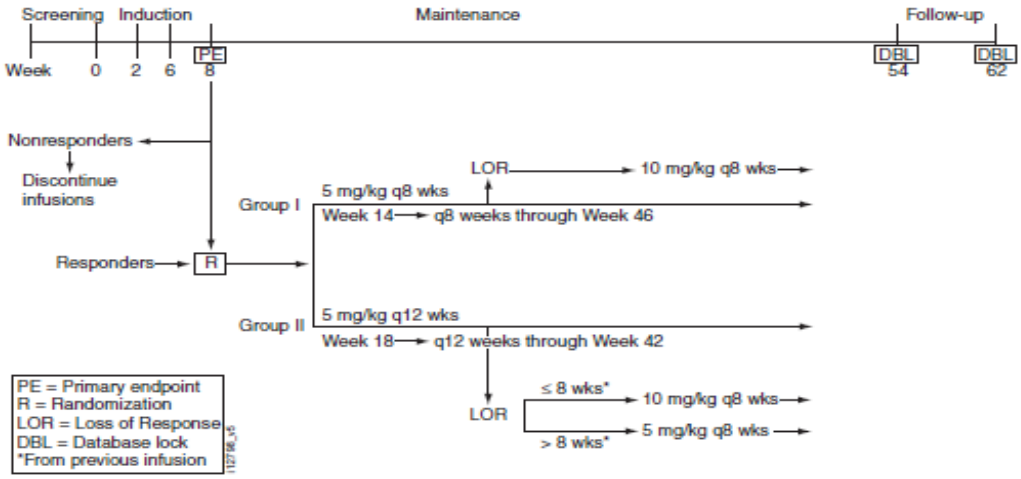

Figure 7 Treatment schedule of study C0168T72

Objectives

The primary objective of the study was to evaluate the efficacy of a 3-dose induction regimen of infliximab in inducing clinical response, as measured by the Mayo score, in paediatric patients with moderately to severely active UC and to evaluate the safety profile of infliximab during induction and maintenance treatment.

The major secondary objectives were to:

- evaluate the efficacy of 2 infliximab maintenance dosing regimens (every 8 weeks (q8w) or every 12 weeks (q12w)) in maintaining remission, as measured by the Paediatric Ulcerative Colitis Activity Index (PUCAI) score
- evaluate the efficacy of a 3-dose induction regimen of infliximab in inducing clinical remission, as measured by the Mayo score
- evaluate the efficacy of a 3-dose induction regimen of infliximab in inducing remission, as measured by the PUCAI score
- evaluate the efficacy of a 3-dose induction regimen of infliximab in inducing mucosal healing

Outcomes/endpoints

Clinical response was defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

Loss of clinical response was defined as meeting one of the following criteria:

- an increase in the partial Mayo score of ≥2 points from the reference (Week 8) partial Mayo score at 2 consecutive visits at least 7 days apart.
- an increase in the partial Mayo score of ≥3 points from the reference (Week 8) partial Mayo score at any scheduled or unscheduled visit.

Clinical remission (as measured by the Mayo score) was defined as a Mayo score ≤2 points, with no individual subscore >1.

Remission (as measured by the PUCAI score) was defined as a PUCAI score <10.

Mucosal healing was determined from the endoscopy subscore of the Mayo score and was defined as an endoscopy subscore of 0 or 1.

Safety endpoints were based on the following variables:

- adverse events (AEs)

- clinical laboratory parameters

- vital sign measurements

- physical examinations

- tuberculosis testing

- antinuclear antibodies/anti-double strande DNA antibodies

Sample size

A sample size of 60 subjects was planned to ensure <12% precision in estimating the true proportion of paediatric subjects in clinical response at Week 8 using a 95 % confidence interval (CI). This sample size calculation assumes a clinical response rate of 67% at Week 8 and was based on the clinical response rate of all randomized adult subjects receiving 5 mg/kg infliximab in the ACT 1 and ACT 2 trials. The study was not powered to show a difference between maintenance treatment regimens.

With 67% of subjects in clinical response at Week 8, about 40 subjects (20 in each group) would be expected to enter the maintenance phase of the study. The table below provides the statistical power for comparing the q8w and q12w maintenance regimens assuming various proportions of subjects in remission at Week 54, as measured by the PUCAI score. The power to detect a 50% decrease in the proportion of subjects in remission (as measured by the PUCAI score) in the q12w regimen compared with the proportion in the q8w regimen ranges from 20% to 28%.

Power calculation for the various q8w and q12w remission rates		
q8w	q12w	Power
44%	22%	0.2020
48%	24%	0.2400
52%	26%	0.2845

Randomisation/blinding

The study was an open-label study. During the induction phase of the study, all subjects were to receive a 5 mg/kg infusion of infliximab at Weeks 0, 2, and 6. At Week 8, each subject was determined to be a responder or non-responder based on his or her Week 8 complete Mayo score data that was entered into an interactive voice response system (IVRS). No infusion was given at Week 8.

Subjects who were non-responders at Week 8 were to return for safety evaluations but receive no further infusions. Subjects who were responders were randomly assigned (in a 1:1 ratio) to 1 of 2 maintenance treatment groups:

• 5 mg/kg infliximab administered q8w through Week 46 (Group I) or

• 5 mg/kg infliximab administered q12w through Week 42 (Group II).

A centralized randomization list was produced from which subjects were allocated into the 2 treatment groups using block randomization, with a block size of 4. The randomization was stratified by subjects'

use of corticosteroids at baseline. The treatment assignment was not blinded for investigative sites, site monitors, or subjects participating in the study.

Statistical methods

Categorical data were compared between the two maintenance groups by Chi-square test analyses. Continuous variables were summarized by using descriptive statistics. The statistical testing were performed at the α=0.05 (2-sided) level using SAS version 9.1.

The lower limit of the 95% CI for the proportion of paediatric patients in clinical response at week 8 was to be used to determine the efficacy of infliximab (primary efficacy endpoint). The criterion was based on pooled data from the ACT 1 and ACT 2 studies. The upper limit of the 95% CI for the proportion of placebo patients in clinical response at week 8 was 39% and therefore the cut-off for this study was set at >40%.

Results

Participant flow

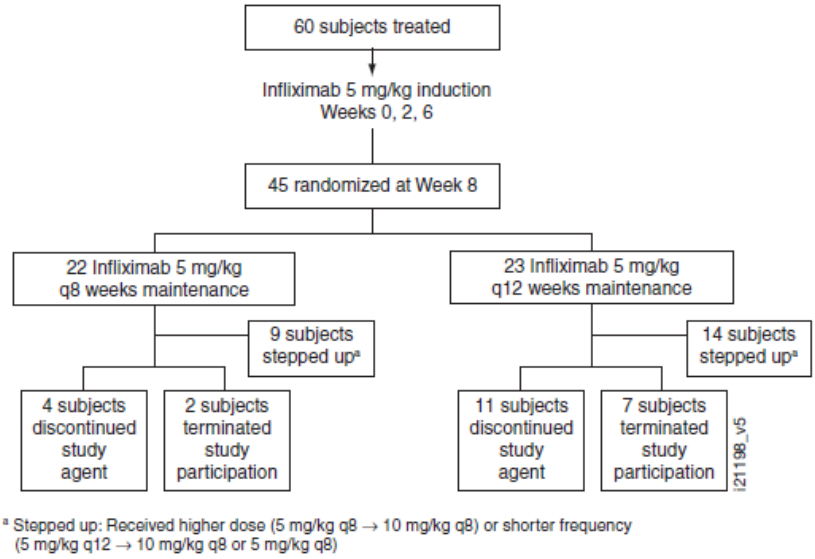

Figure 8 Participant flow

Sixty patients were enrolled at 23 sites in the United States (32 subjects), Canada (20 subjects), the Netherlands (5 subjects) and Belgium (3 subjects).

At Week 8, 45 of the 60 enrolled subjects were randomized as responders (22 and 23 in the q8w and q12w maintenance treatment groups, respectively); the 15 subjects who were not randomized were discontinued from study agent administration at Week 8.

For 23 of the 45 randomized patients the dose or dosing frequency was stepped up. There were more subjects that had their treatment stepped up in the q12w group than in the q8w group (61 vs 41%). Of 14 patients in the q12w group who stepped up, 8 received 10 mg/kg q8w and 6 received 5mg/kg q8w. Nine patients in the q8w group had their treatment stepped-up (10 mg/kg q8w). Overall, 30 subjects (50.0% of all subjects in the study) permanently discontinued infliximab treatment (Table 6): 15 subjects each in the groups that were and were not randomized to maintenance treatment at Week 8. Of the 15 subjects who were not randomized, 12 discontinued because of their disease status (ie,

unsatisfactory therapeutic effect, reported AEs of worsening disease, or not meeting criteria for response at Week 8), 2 because they had not met inclusion criteria, and 1 because of an AE (neutropenia). Reasons for discontinuation were similar among the 15 subjects who were randomized: 12 discontinued because of their disease status (ie, unsatisfactory therapeutic effect or AEs of worsening disease), 2 because of other AEs, and 1 withdrew consent.

A higher proportion of subjects discontinued study agent in the 5 mg/kg q12w maintenance treatment group (47.8%) than in the 5 mg/kg q8w maintenance treatment group (18.2%). A greater proportion of subjects in the q12w group compared with the q8w group discontinued study agent due to AEs (26.1% in the q12w group [all due to worsening of UC] compared with 13.6% in the q8w group [only 1 (of 3) due to worsening of UC]) or to unsatisfactory therapeutic effect (17.4% in the q12w group compared with 4.5% in the q8w group).

Table 6 Summary of study participation status through Week 54; treated subjects by randomized treatment

	Subjects Not Randomized at Week 8	Subjects Randomized at Week 8			Total
		Infliximab 5 mg/kg q8 wks	Infliximab 5 mg/kg q12 wks	Combined	
Subjects treated	15	22	23	45	60
Subjects who did not end study participation	0 (0.0%)	18 (81.8%)	11 (47.8%)	29 (64.4%)	29 (48.3%)
Subjects who ended study participation	15 (100.0%)	4 (18.2%)	12 (52.2%)	16 (35.6%)	31 (51.7%)
Subjects who discontinued study agent and completed safety follow-up	6 (40.0%)	2 (9.1%)	5 (21.7%)	7 (15.6%)	13 (21.7%)
Subjects who terminated study participation	9 (60.0%)	2 (9.1%)	7 (30.4%)	9 (20.0%)	18 (30.0%)
Withdrawal of consent	0 (0.0%)	1 (4.5%)	2 (8.7%)	3 (6.7%)	3 (5.0%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	9 (60.0%)	1 (4.5%)	5 (21.7%)	6 (13.3%)	15 (25.0%)

Overall, 31 subjects (51.7% of all subjects in the study) ended their study participation before Week 54. Of those, 13 subjects (21.7%) discontinued study agent and completed safety follow-up. The remaining 18 subjects (30.0%) terminated their study participation due to withdrawal of consent or other reasons ("other" included not meeting criteria for response at Week 8, not meeting inclusion criteria, surgery, and AEs). One subject received all scheduled study agent administrations but withdrew from the study early. More subjects who were originally randomized to the q12w maintenance treatment group than to the q8w maintenance treatment group terminated their study participation (7 subjects vs. 2 subjects). Of the subjects who stepped up, 11 (47.8%) ended their study participation through Week 54; most (9 subjects) were originally randomized to the q12w maintenance treatment group. Eight subjects terminated their study participation after they stepped up; 3 subjects discontinued study agent but completed safety follow-up.

Conduct of the study

There were four amendments to the protocol, none of which had a major impact on the assessment of the study results.

Baseline data

Baseline demographic characteristics were similar between patients in the randomized treatment groups while patients not randomized were younger and weighed less at week 8 (median age 12 vs

14.5 years and median weight 41 vs 51 kg, respectively). There were 32 female and 28 male paediatric patients enrolled, 82% were Caucasian. The median age was 14.5 years (range 6-17 years).

Table 7 Summary of demographics at baseline

	Subjects Not Randomized at Week 8	Subjects Randomized at Week 8			
		Infliximab 5 mg/kg q8 wks	Infliximab 5 mg/kg q12 wks	Combined	Total
Subjects treated	15	22	23	45	60
Sex					
n	15	22	23	45	60
Male	8 (53.3%)	10 (45.5%)	10 (43.5%)	20 (44.4%)	28 (46.7%)
Female	7 (46.7%)	12 (54.5%)	13 (56.5%)	25 (55.6%)	32 (53.3%)
Race					
n	15	22	23	45	60
Caucasian	10 (66.7%)	20 (90.9%)	19 (82.6%)	39 (86.7%)	49 (81.7%)
Black	3 (20.0%)	1 (4.5%)	1 (4.3%)	2 (4.4%)	5 (8.3%)
Asian	1 (6.7%)	1 (4.5%)	1 (4.3%)	2 (4.4%)	3 (5.0%)
Other	1 (6.7%)	0 (0.0%)	2 (8.7%)	2 (4.4%)	3 (5.0%)
Age (yrs)					
n	15	22	23	45	60
Mean ± SD	11.9 ± 2.64	13.7 ± 3.20	14.2 ± 3.03	14.0 ± 3.09	13.4 ± 3.10
Median	12.0	15.0	15.0	15.0	14.5
IQ range	(10.0, 14.0)	(12.0, 16.0)	(12.0, 16.0)	(12.0, 16.0)	(11.5, 16.0)
Range	(7, 16)	(7, 17)	(6, 17)	(6, 17)	(6, 17)
Weight (kg)					
n	15	22	23	45	60
Mean ± SD	42.19 ± 13.870	51.54 ± 18.294	52.80 ± 16.855	52.18 ± 17.384	49.69 ± 17.030
Median	40.80	50.40	52.30	51.20	50.80
IQ range	(29.10, 55.30)	(36.10, 61.50)	(40.30, 68.60)	(39.50, 61.70)	(36.25, 59.35)
Range	(22.7, 64.7)	(26.2, 91.6)	(24.5, 86.4)	(24.5, 91.6)	(22.7, 91.6)
Height (cm)					
n	15	22	23	45	60
Mean ± SD	151.23 ± 17.774	156.52 ± 13.752	160.08 ± 19.088	158.34 ± 16.603	156.56 ± 17.034
Median	154.20	156.45	163.50	161.00	159.65
IQ range	(134.00, 165.00)	(151.80, 165.70)	(157.00, 173.60)	(154.50, 167.00)	(149.60, 166.50)
Range	(119.0, 177.0)	(123.5, 178.3)	(108.0, 193.0)	(108.0, 193.0)	(108.0, 193.0)

Figure 9 provides the age-distribution (per year) of the children included in study. Of the 60 subjects enrolled in the study, 15 subjects are <12 years of age and 45 subjects are ≥12 years of age.

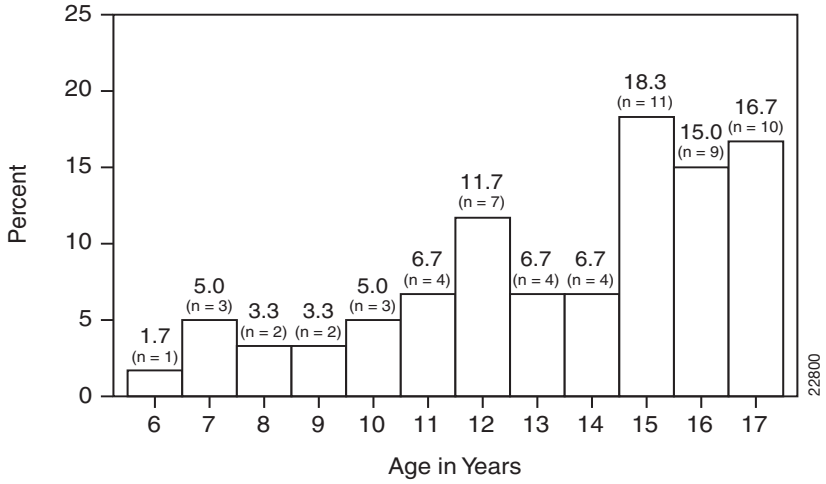

Figure 9 Age-distribution at baseline (per year) in the C0168T72 study; treated subjects

Baseline disease characteristics are seen in Table 8.

Table 8 Baseline disease characteristics

	Subjects Not Randomized at Week 8	Subjects Randomized at Week 8: Infliximab 5 mg/kg q8 wks	Subjects Randomized at Week 8: Infliximab 5 mg/kg q12 wks	Subjects Randomized at Week 8: Combined	Total
Subjects treated	15	22	23	45	60
UC disease duration (yrs)					
n	15	22	23	45	60
Mean ± SD	1.97 ± 1.970	2.08 ± 1.756	1.68 ± 1.844	1.88 ± 1.793	1.90 ± 1.822
Median	1.20	1.80	1.10	1.40	1.35
IQ range	(0.70, 3.00)	(0.60, 2.40)	(0.60, 1.90)	(0.60, 2.30)	(0.65, 2.35)
Range	(0.0, 6.6)	(0.0, 6.6)	(0.1, 8.2)	(0.0, 8.2)	(0.0, 8.2)
UC symptoms duration prior to diagnosis (months)					
n	15	22	23	45	60
Mean ± SD	9.1 ± 17.63	7.5 ± 6.93	7.4 ± 13.52	7.4 ± 10.69	7.9 ± 12.63
Median	3.0	5.5	2.0	3.0	3.0
IQ range	(1.0, 11.0)	(1.0, 12.0)	(1.0, 7.0)	(1.0, 9.0)	(1.0, 10.0)
Range	(1, 71)	(1, 27)	(0, 60)	(0, 60)	(0, 71)
Extent of disease					
n	15	22	23	45	60
Limited to left side of colon	4 (26.7%)	6 (27.3%)	4 (17.4%)	10 (22.2%)	14 (23.3%)
Extensive	11 (73.3%)	16 (72.7%)	19 (82.6%)	35 (77.8%)	46 (76.7%)
CRP (mg/dL)					
n	15	21	23	44	59
Mean ± SD	0.99 ± 1.139	1.23 ± 1.812	1.43 ± 2.056	1.33 ± 1.924	1.25 ± 1.755
Median	0.50	0.30	0.30	0.30	0.30
IQ range	(0.30, 1.00)	(0.30, 1.50)	(0.30, 2.20)	(0.30, 1.70)	(0.30, 1.50)
Range	(0.3, 4.2)	(0.3, 7.2)	(0.3, 7.2)	(0.3, 7.2)	(0.3, 7.2)

Forty-six patients were considered having extensive disease based on endoscopy. The median Mayo score was 8.0 and the median PUCAI score 55.0.

Baseline disease characteristics were similar in the groups that were and were not randomized at Week 8. However, a higher proportion of subjects in the group that was not randomized (73.3%) reported obvious blood with stool most of the time for the Mayo rectal bleeding subscore, compared with 46.7% in the group that was randomized. Baseline disease characteristics were also generally similar between the maintenance treatment groups. However, the median duration of UC disease was longer in the q8w maintenance treatment group (1.8 years) than in the q12w maintenance treatment group (1.1 years). In addition, more subjects in the q12w than the q8w group reported 5 or more stools more than normal (13 and 7 subjects, respectively) on the Mayo stool frequency subscore; more subjects in the q8w group than the q12w group reported obvious blood with stool most of the time (13 and 8 subjects, respectively) for the Mayo rectal bleeding subscore.

Concomitant medications

All 60 patients were receiving concomitant treatment medications for UC at baseline. The use of concomitant medications at baseline was generally similar between the groups that were and were not randomized at Week 8. In the group that was not randomized at Week 8, 66.7% of subjects were receiving aminosalicylates at baseline, versus 48.9% in the randomized group. The use of concomitant medications for UC at baseline was similar between the maintenance treatment groups. Of the randomized patients at week 8, 28 were on corticosteroids at baseline and 24 were on immunomodulators, see Table 9.

Table 9 Summary of concomitant medication for UC at baseline

	Subjects Not Randomized at Week 8	Subjects Randomized at Week 8			Total
		Infliximab 5 mg/kg q8 wks	Infliximab 5 mg/kg q12 wks	Combined	
Subjects treated	15	22	23	45	60
Subjects with 1 or more concomitant medications	15 (100.0%)	22 (100.0%)	23 (100.0%)	45 (100.0%)	60 (100.0%)
Corticosteroids (parenteral or oral)[a]	9 (60.0%)	14 (63.6%)	14 (60.9%)	28 (62.2%)	37 (61.7%)
Subjects with baseline ≤ 1 mg/kg P.Eq	8 (53.3%)	10 (45.5%)	10 (43.5%)	20 (44.4%)	28 (46.7%)
Subjects with baseline > 1 mg/kg P.Eq	1 (6.7%)	4 (18.2%)	4 (17.4%)	8 (17.8%)	9 (15.0%)
Corticosteroids (budesonide)[b]	1 (6.7%)	1 (4.5%)	0 (0.0%)	1 (2.2%)	2 (3.3%)
Corticosteroids (rectal)[a]	1 (6.7%)	2 (9.1%)	1 (4.3%)	3 (6.7%)	4 (6.7%)
Immunomodulatory agents	8 (53.3%)	11 (50.0%)	13 (56.5%)	24 (53.3%)	32 (53.3%)
6-mercaptopurine/ azathioprine	8 (53.3%)	10 (45.5%)	11 (47.8%)	21 (46.7%)	29 (48.3%)
Methotrexate	0 (0.0%)	1 (4.5%)	2 (8.7%)	3 (6.7%)	3 (5.0%)
Aminosalicylates	10 (66.7%)	10 (45.5%)	12 (52.2%)	22 (48.9%)	32 (53.3%)
Antibiotics	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)

[a] Excluding budesonide
[b] Including oral or rectal

Historic use of corticosteroids, immunosuppressive and aminosalicylate therapy is summarised in Table 10. All patients had previously been treated with corticosteroids, the majority for ≤1 year. Approximately 23% and 50% of the patients had used 6-MP or AZA, respectively.

Table 10 Summary of UC medication history of corticosteroids, immunomodulatory and aminosalicylate therapy

	Subjects Not Randomized at Week 8	Subjects Randomized at Week 8			Total
		Infliximab 5 mg/kg q8 wks	Infliximab 5 mg/kg q12 wks	Combined	
Subjects treated	15	22	23	45	60
Any UC medication					
n	15	22	23	45	60
Subjects with any UC medication	15 (100.0%)	22 (100.0%)	23 (100.0%)	45 (100.0%)	60 (100.0%)
Corticosteroids					
n	15	22	23	45	60
Subjects with corticosteroids	15 (100.0%)	22 (100.0%)	23 (100.0%)	45 (100.0%)	60 (100.0%)
Never used	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Used ≤ 1 year	10 (66.7%)	14 (63.6%)	14 (60.9%)	28 (62.2%)	38 (63.3%)
Used > 1 to ≤ 2 years	2 (13.3%)	6 (27.3%)	6 (26.1%)	12 (26.7%)	14 (23.3%)
Used > 2 years	3 (20.0%)	2 (9.1%)	3 (13.0%)	5 (11.1%)	8 (13.3%)
Immunomodulatory agent					
n	15	22	23	45	60
Subjects with any immunomodulatory agent	11 (73.3%)	17 (77.3%)	14 (60.9%)	31 (68.9%)	42 (70.0%)
6-mercaptopurine					
n	15	22	23	45	60
Never used	12 (80.0%)	17 (77.3%)	17 (73.9%)	34 (75.6%)	46 (76.7%)
Used ≤ 1 year	2 (13.3%)	4 (18.2%)	4 (17.4%)	8 (17.8%)	10 (16.7%)
Used > 1 to ≤ 2 years	0 (0.0%)	1 (4.5%)	2 (8.7%)	3 (6.7%)	3 (5.0%)
Used > 2 years	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
Azathioprine					
n	15	22	23	45	60
Never used	6 (40.0%)	10 (45.5%)	14 (60.9%)	24 (53.3%)	30 (50.0%)
Used ≤ 1 year	3 (20.0%)	6 (27.3%)	5 (21.7%)	11 (24.4%)	14 (23.3%)
Used > 1 to ≤ 2 years	5 (33.3%)	4 (18.2%)	2 (8.7%)	6 (13.3%)	11 (18.3%)
Used > 2 years	1 (6.7%)	2 (9.1%)	2 (8.7%)	4 (8.9%)	5 (8.3%)
Methotrexate					
n	15	22	23	45	60
Never used	15 (100.0%)	21 (95.5%)	22 (95.7%)	43 (95.6%)	58 (96.7%)
Used ≤ 1 year	0 (0.0%)	1 (4.5%)	0 (0.0%)	1 (2.2%)	1 (1.7%)
Used > 1 to ≤ 2 years	0 (0.0%)	0 (0.0%)	1 (4.3%)	1 (2.2%)	1 (1.7%)
Used > 2 years	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any aminosalicylates					
n	15	22	23	45	60
Subjects with any aminosalicylates	13 (86.7%)	19 (86.4%)	22 (95.7%)	41 (91.1%)	54 (90.0%)
Sulfasalazine					
n	15	22	23	45	60
Never used	11 (73.3%)	16 (72.7%)	16 (69.6%)	32 (71.1%)	43 (71.7%)
Used ≤ 1 year	2 (13.3%)	3 (13.6%)	4 (17.4%)	7 (15.6%)	9 (15.0%)
Used > 1 to ≤ 2 years	1 (6.7%)	3 (13.6%)	1 (4.3%)	4 (8.9%)	5 (8.3%)
Used > 2 years	1 (6.7%)	0 (0.0%)	2 (8.7%)	2 (4.4%)	3 (5.0%)
Mesalamine					
n	15	22	23	45	60
Never used	6 (40.0%)	6 (27.3%)	6 (26.1%)	12 (26.7%)	18 (30.0%)
Used ≤ 1 year	6 (40.0%)	11 (50.0%)	12 (52.2%)	23 (51.1%)	29 (48.3%)
Used > 1 to ≤ 2 years	2 (13.3%)	3 (13.6%)	3 (13.0%)	6 (13.3%)	8 (13.3%)
Used > 2 years	1 (6.7%)	2 (9.1%)	2 (8.7%)	4 (8.9%)	5 (8.3%)

Outcomes

Efficacy endpoints evaluated at or before week 8 are based on all treated patients. Efficacy endpoints evaluated after week 8 are based on all randomized patients.

Primary efficacy endpoint

Forty-four of the 60 treated patients (73%) at week 8 were in clinical response (95 % CI, 62.1% and 84.5%) defined as decrease in Mayo score ≥30% and ≥3 points, with a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1. The lower limit of the 95% CI for the proportion of patients in clinical response at week 8 was 62% and the set criterion for efficacy of 40% was considered met.

In patients on immunomodulators at baseline, 72% (23 of 32) were in clinical response at week 8 and in patients with no immunomodulating treatment at baseline the corresponding figure was 75% (21 of 28).

Major secondary efficacy endpoints

PUCAI score

The PUCAI score was used to evaluate the maintenance of remission. However, PUCAI score was added in Amendment 1 and there are several subjects with missing values. Patients were therefore considered evaluable from the first visit when PUCAI was obtained.

Table 11 Number of subjects in remission measured by PUCAI score at week 30 and 54 (randomized patients)

	Infliximab 5 mg/kg		
	q8 wks	q12 wks	Combined
Subjects randomized	22	23	45
Subject evaluable for PUCAI at Week 30[a]	20	21	41
Subjects in remission at Week 30[b,c]	8 (40.0%)	4 (19.0%)	12 (29.3%)
p-value[d]		0.141	
Subjects evaluable for PUCAI at Week 54[a]	21	22	43
Subjects in remission at Week 54[b,c]	8 (38.1%)	4 (18.2%)	12 (27.9%)
p-value[d]		0.146	

[a] Evaluable subjects are subjects with their first PUCAI evaluated on or prior to the visit of interest.
[b] Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, stepped up, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in clinical remission.
[c] Subjects with insufficient data are considered to not be in remission.
[d] p-values for treatment group difference are based on chi-square test.

The proportion of subjects in remission at Week 54 was higher in the q8w maintenance treatment group (38.1% [8 of 21 subjects]) than in the q12w maintenance treatment group (18.2% [4 of 22 subjects]). The proportion of subjects in remission at Week 30 was also higher in the q8w maintenance treatment group (40.0% [8 of 20 subjects]) than in the q12w maintenance treatment group (19.0% [4 of 21 subjects]).

Clinical remission at week 8 (Mayo score) and remission at week 8 (PUCAI score)

At week 8, 24 of 60 patients (40 %) were in clinical remission according to Mayo score. Of 51 patients evaluated for PUCAI score at week 8, 17 (33 %) were in remission.

Mucosal healing at week 8

Of the 60 patients treated, 41 (68.3%) had healed mucosa at week 8 with 20 (33.3 %) having endoscopy subscore indicating normal or inactive disease.

Clinical response at week 54

Only 9 of 45 randomized patients had endoscopy subscore for the Mayo score (endoscopy was optional at week 54). Five patients were considered to be in clinical response (3 of 4 in q8W group and 3 of 4 in q12w group).

Corticosteroids

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

Table 12 Summary of baseline and change from baseline in average daily corticosteroid (P.Eg) dose through week 54 by regimen

	Infliximab 5 mg/kg		
	q8 wks	q12 wks	Combined
Subjects randomized	22	23	45
Randomized subjects taking corticosteroids at baseline[c]	14	14	28
Baseline			
n	14	14	28
Mean ± SD	0.64 ± 0.409	0.63 ± 0.434	0.64 ± 0.414
Median	0.54	0.49	0.51
IQ range	(0.40, 1.10)	(0.33, 1.02)	(0.36, 1.05)
Range	(0.1, 1.3)	(0.1, 1.5)	(0.1, 1.5)
Change from baseline[a,b]			
Week 8			
n	14	14	28
Mean ± SD	-0.54 ± 0.398	-0.37 ± 0.334	-0.46 ± 0.370
Median	-0.46	-0.41	-0.43
IQ range	(-0.83, -0.25)	(-0.57, -0.01)	(-0.64, -0.11)
Range	(-1.3, 0.1)	(-1.1, 0.0)	(-1.3, 0.1)
Week 30			
n	14	14	28
Mean ± SD	-0.39 ± 0.485	-0.01 ± 0.017	-0.20 ± 0.391
Median	-0.11	0.00	0.00
IQ range	(-0.73, 0.00)	(0.00, 0.00)	(-0.11, 0.00)
Range	(-1.3, 0.0)	(-0.1, 0.0)	(-1.3, 0.0)
Week 54			
n	14	14	28
Mean ± SD	-0.39 ± 0.491	0.01 ± 0.041	-0.19 ± 0.398
Median	-0.06	0.00	0.00
IQ range	(-0.73, 0.00)	(0.00, 0.00)	(-0.06, 0.00)
Range	(-1.3, 0.0)	(0.0, 0.2)	(-1.3, 0.2)

[a] Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, stepped up, or discontinued study agent due to unsatisfactory therapeutic effect will have their baseline value carried forward for all subsequent visits from the time the treatment failure or step-up occurs.
[b] Subjects with insufficient data will have their last value carried forward from the previous visit.
[c] Subjects taking oral or parenteral corticosteroids including budesonide.

Global assessment

At week 8, 82% of all patients assessed their health status as good or fair. In contrast, at baseline none of the patients assessed their health as good and 42% assessed their health as fair.

Summary of efficacy depending on age

Of the 60 subjects enrolled in the study, 15 subjects are <12 years of age and 45 subjects are ≥12 years of age. At Week 30, 4 of the 9 randomized subjects were in remission for subjects whose ages are <12 years and 8 of the 32 randomized subjects were in remission for subjects whose ages are ≥12 years. At Week 54, 3 of the 9 randomized subjects were in remission for subjects whose ages are <12 years and 9 of the 34 randomized subjects were in remission for subjects whose ages are ≥ 12 years. Although the sample size is small, it should be noted that none of the subjects <12 years of age who were in the 5 mg/kg q12 treatment group were in remission at either Week 30 (0/4) or Week 54 (0/4). In comparison, in this group of subjects <12 years of age, 4 of 5 subjects at Week 30 and 3 of 5 subjects at Week 54 were in remission in the 5 mg/kg q8w treatment group. In subjects who were ≥12 years of age, the numbers of subjects who were in remission in the 5 mg/kg q8w and q12w treatment groups were similar. A summary of the results is shown in Table 13. Table 14 and 15 provide the number of randomized subjects who were evaluable for PUCAI and were in remission at Week 30 and at Week 54, respectively, by baseline age.

Table 13 Summary of efficacy by age group; all treated patients

	Infliximab 5 mg/kg	
	Ages 6-11	Ages 12-17
Subjects treated	15	45
Baseline Mayo score		
Median	8.0	8.0
Week 8 Mayo score[a,b]		
Median	3.0	3.0
Subjects in clinical response at Week 8[c, d]	9 (60.0%)	35 (77.8%)
Subjects in clinical remission at Week 8[c, d]	7 (46.7%)	17 (37.8%)
Subjects in mucosal healing at Week 8[c, d]	8 (53.3%)	33 (73.3%)
Subjects with evaluable PUCAI scores at Week 8[e]	12	39
Subjects in remission at Week 8[c, d]	4 (33.3%)	13 (33.3%)
Subjects with evaluable PUCAI scores at Week 54[f]		
q8wk treatment group	5	16
Subjects in remission at Week 54[c, d]	3 (60.0%)	5 (31.3%)
q12wk treatment group	4	18
Subjects in remission at Week 54[c, d]	0 (0.0%)	4 (22.2%)

[a] Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect had their baseline value carried forward.
[b] Subjects with insufficient data had their last value carried forward.
[c] Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in clinical response, or in clinical remission (based on Mayo score), or in remission (based on PUCAI score), or in mucosal healing.
[d] Subjects with insufficient data are considered to not be in clinical response or in clinical remission (based on Mayo score), or in remission (based on PUCAI score) , or in mucosal healing.
[e] Evaluable subjects are subjects with their first PUCAI evaluated on or prior to Week 8.
[f] Evaluable subjects are subjects with their first PUCAI evaluated on or prior to Week 54.

Table 14 Number of subjects in remission as measured by the PUCAI score at Week 30 by baseline age; randomized subjects

	Infliximab 5 mg/kg		
	q8 wks	q12 wks	Combined
Subjects randomized	22	23	45
Subjects evaluable[a]	20	21	41
Age[b,c]			

	Infliximab 5 mg/kg		
	q8 wks	q12 wks	Combined
6 yrs	NA (0/0)	0.0% (0/1)	0.0% (0/1)
7 yrs	100.0% (2/2)	NA (0/0)	100.0% (2/2)
8 yrs	NA (0/0)	0.0% (0/1)	0.0% (0/1)
9 yrs	100.0% (1/1)	NA (0/0)	100.0% (1/1)
10 yrs	0.0% (0/1)	0.0% (0/1)	0.0% (0/2)
11 yrs	100.0% (1/1)	0.0% (0/1)	50.0% (1/2)
12 yrs	0.0% (0/1)	0.0% (0/1)	0.0% (0/2)
13 yrs	50.0% (2/4)	NA (0/0)	50.0% (2/4)
14 yrs	NA (0/0)	0.0% (0/2)	0.0% (0/2)
15 yrs	33.3% (1/3)	75.0% (3/4)	57.1% (4/7)
16 yrs	0.0% (0/3)	20.0% (1/5)	12.5% (1/8)
17 yrs	25.0% (1/4)	0.0% (0/5)	11.1% (1/9)

[a] Evaluable subjects are subjects with their first PUCAI evaluated on or prior to Week 30.
[b] Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, stepped up, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in remission.
[c] Subjects with insufficient data are considered to not be in remission.

Table 15 Number of subjects in remission as measured by the PUCAI score at Week 54 by baseline age; randomized subjects

	Infliximab 5 mg/kg		
	q8 wks	q12 wks	Combined
Subjects randomized	22	23	45
Subjects evaluable[a]	21	22	43
Age[b,c]			
6 yrs	NA (0/0)	0.0% (0/1)	0.0% (0/1)
7 yrs	50.0% (1/2)	NA (0/0)	50.0% (1/2)
8 yrs	NA (0/0)	0.0% (0/1)	0.0% (0/1)
9 yrs	100.0% (1/1)	NA (0/0)	100.0% (1/1)
10 yrs	0.0% (0/1)	0.0% (0/1)	0.0% (0/2)
11 yrs	100.0% (1/1)	0.0% (0/1)	50.0% (1/2)
12 yrs	0.0% (0/1)	0.0% (0/2)	0.0% (0/3)
13 yrs	75.0% (3/4)	NA (0/0)	75.0% (3/4)
14 yrs	NA (0/0)	0.0% (0/2)	0.0% (0/2)
15 yrs	25.0% (1/4)	50.0% (2/4)	37.5% (3/8)
16 yrs	0.0% (0/3)	20.0% (1/5)	12.5% (1/8)
17 yrs	25.0% (1/4)	20.0% (1/5)	22.2% (2/9)

[a] Evaluable subjects are subjects with their first PUCAI evaluated on or prior to Week 54.
[b] Subjects who had a prohibited change in concomitant medication, had an ostomy or colectomy, stepped up, or discontinued study agent due to unsatisfactory therapeutic effect are considered to not be in remission.
[c] Subjects with insufficient data are considered to not be in remission.

Overall, from the age-distribution and remission data at week 30 and 54, the number of children, in particular in the youngest group 6-11 years, is limited.

Supporting studies - Efficacy data from ACT 1 and ACT 2 (EMEA/H/C/240/II/65)

In procedure EMEA/H/C/240/II/65 the CHMP concluded that efficacy has been shown with infliximab 5 mg/kg and 10 mg/kg during 30 weeks in patients with moderate to severe ulcerative colitis, not responding to or having side-effects from steroids/Aza/6MP or who have been in remission but with

relapse when tapering of corticosteroids. In ACT2, also non-responders to 5-ASA (>2.4g) were included. Overall, the results are in favour of infliximab treatment in a population of patients with ulcerative colitis with a considerable social impairment, where other treatment options are restricted to surgery. In many cases surgery is followed by social limitations and other complications from surgery. The corticosteroid sparing effect with infliximab is clinically relevant. There is a slight tendency towards tapering of effects for some endpoints, but taking all endpoints into account, efficacy is sufficiently demonstrated up to 30 weeks. The CHMP considered that data from the 54 weeks continuation study were of importance to prove long-term sustained efficacy. Following a request for supplementary information, the MAH submitted the requested data. The proportion of patients in clinical response at week 54 were significantly greater than placebo for both infliximab treated groups (46% for the 5 mg/kg group and 44% for the 10 mg/kg group versus 20% for placebo, $p<0.001$). As symptom-free intervals often occur, intermittent therapy or retreatment could be an option.

In this procedure the comparison between the effect of infliximab in paediatric and adult patients using the same primary efficacy endpoint, clinical response based on Mayo scores, shows that response was induced to a similar extent in both populations at week 8. Results of secondary endpoints further support this conclusion. The observed adult efficacy data can therefore be regarded as supportive of the efficacy data shown in the paediatric population in study C0168T72.

Discussion on Efficacy:

C0168T72 is an open-label study that included 60 paediatric subjects with moderately to severe UC, who received a 5 mg/kg infliximab induction regimen through Week 8, followed by randomization of responders to infliximab 5 mg/kg maintenance therapy with every 8 weeks (q8w) or every 12 weeks (q12w) infusions in an unblinded fashion. The open-label design of the study was selected to address feasibility issues and ethical concerns with randomised placebo-controlled studies in this patient population. The sample size of 60 subjects was chosen to ensure acceptable precision in estimating the true proportion of paediatric subjects in clinical response at Week 8, and limiting subjects' exposure to infliximab in the event that treatment with infliximab proved less effective than in adults with UC. The open-label non-placebo controlled design of the study has its limitation nevertheless the methodological and ethical challenges of undertaking a placebo-controlled study in this population are acknowledged by the CHMP hence this design was accepted.

Concerns were raised that inclusion of patients who had failed only to a 5-ASA treatment is not in accordance with the intended patient population which should be patients with moderately to severely active UC who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies. The MAH clarified that 4 of the 60 subjects enrolled in C0168T72 study met the UC medication criteria for study entry based solely on failure of 5-ASAs. Three of these subjects were currently failing 5-ASAs at entry into the study (i.e. receiving adequate treatment) and the fourth subject had failed 5-ASAs within the past 18 months. When the 4 subjects who had only failed 5-ASAs were excluded from the analysis of the primary endpoint, 73.2% of subjects (41/56) were in clinical response at Week 8 (95% CI: [61.6%, 84.8%], which is consistent with the results observed for all subjects (73.3%, 44/60, [62.1%, 84.5%]). Thus, the inclusion of subjects who had only met the criteria for 5-ASA failure did not affect the conclusions of the primary endpoint analysis.

Study C0168T72 is conducted in paediatric patients with moderately to severely active UC (defined as a baseline Mayo score of 6 to 12) who were diagnosed or referred for diagnosis at least 2 weeks before screening and whose diagnosis was confirmed by biopsy and a Mayo endoscopy subscore ≥2 at a screening sigmoidoscopy. The patients had active disease either despite adequate treatment with 6-MP, AZA, corticosteroids, and/or 5-ASA compounds, or had previously been unsuccessfully treated with

6-MP, AZA, corticosteroids and/or 5-ASA compounds. The study objectives and the chosen endpoints are adequate and relevant for determining the efficacy of infliximab in paediatric patients with UC. The primary efficacy endpoint, evaluated at week 8, was met by showing that the 3-dose induction regimen induced a clinical response, measured by the Mayo score, in 73% (95% CI [62.1%-84.5%]) of the patients.

At week 8, 45 of 60 patients who were in clinical response were randomized to receive 5 mg/kg every 8 weeks (q8w) or every 12 weeks (q12w). The proportion of randomized subjects in remission (PUCAI score) at Week 54 was 27.9% (12/43). A notably greater proportion of subjects was in remission at Week 54 in the q8w maintenance treatment group (38.1% [8/21]) than in the q12w maintenance treatment group (18.2% [4/22] p = 0.146). It is therefore recognised that there is a dose related effect i.e. the more frequent dose interval (q8w) results in a higher degree of clinical response or remission. The proportion of subjects in remission at Week 30 was also higher in the q8w maintenance treatment group (40.0% [8/20]) than in the q12w maintenance treatment group (19.0% [4/21]). Of the 60 subjects treated with infliximab, 24 (40.0%) were in clinical remission as measured by the Mayo score at Week 8. Of the 51 subjects evaluable for PUCAI at Week 8, 17 (33.3%) were in remission as measured by the PUCAI at Week 8. Of the 60 subjects treated with infliximab, 41 (68.3%) were in mucosal healing at Week 8. Twenty subjects (33.3%) had an endoscopy subscore of 0 (indicating normal or inactive disease) at Week 8.

In the q8w group, 40.9% experienced a lack of efficacy (defined as discontinuation due to worsening of UC, or discontinuation due to unsatisfactory effect, or stepping up the dose/dose interval) compared with subjects randomized to the q12w group (69.6%). The % of subjects discontinuing due to adverse events (mainly worsening of UC) was 40% in the lower age group and 15.6% in the higher age range. In summary, of subjects who discontinued their study participation, a greater proportion in the younger age group discontinued by Week 8 compared with the older age group. However, a similar proportion of subjects who were randomized to maintenance treatment discontinued their study participation in each of the age groups. The majority of subjects who discontinued their study participation did so due to a worsening of the disease under study.

A corticosteroid-sparing effect over time was observed in both maintenance treatment groups.Both groups had similar values at baseline. For the q8w group, the values had decreased after 8 weeks, and remained very low until Week 54 when a slight increase was observed. For the q12w group the reduction at week 8 was not as large as the reduction observed in the q8w treatment group, but was further reduced before the first maintenance treatment visit at Week 18. However, by Week 54, the values had returned to baseline levels in the q12w treatment group.

In study C0168T72, 48% of subjects were on concomitant AZA /6-MP at baseline and 5% on MTX. At week 8, among the 32 subjects who were on immunomodulators at baseline, 23 (71.9%) were in clinical response at Week 8 and among the 28 subjects who were not on immunomodulators at baseline, 21 (75.0%) were in clinical response. Overall the totality of the efficacy data analysed in the paediatric UC study (C0168T72), the paediatric CD studies, or adult IBD studies indicated no consistent differences in efficacy in maintenance results between subgroups receiving infliximab monotherapy or concomitant AZA/6-MP. However, it is recognised that the development of antibodies against infliximab increases without use of immunomodulators and in some individuals combination therapy is likely needed to retain efficacy.

The numbers of patients in the study was limited, particularly at the week 54 time point. Overall 31 patients ended their study participation before week 54, leaving only 29 patients, 18 in the q8w group and 11 in the q12w group for further evaluation. With respect to ages ranges, there were in total 15 children aged 6-11 years (1 six, 3 seven, 2 eight, 2 nine, 3 ten, and 4 eleven years old); and there were 9 with evaluable PUCAI scores at week 54. From the age-distribution and remission data at week

30 and 54, the number of children, in particular in the youngest group 6-11 years, is limited. It is also noted that 6/15 of the 6-11 years age group did not continue after 8 weeks induction, compared with 9/45 in the higher age range. Overall, the numbers of patients evaluable is limited, especially in the youngest ages.

Overall concerns regarding the efficacy of infliximab in the treatment of paediatric UC were in particular due to the design of study C0168T72 (open label) and limited number of evaluable patients bringing a lower degree of evidence for the demonstration of efficacy than anticipated. The number of patients discontinuing study agent or stepping up in dose was relatively high, particularly for the q12w maintenance group. On the other hand, these data show a dose response relationship, with higher response rate, and fewer discontinuations or dose escalations with the proposed q8w dose regimen compared with the q12w regimen, thereby supporting a treatment effect.

In addition, study C0168T72 was not planned as a stand-alone study, but was designed to establish efficacy by making a comparison with the larger datasets from the ACT 1 and ACT 2 studies, which supported the approval of infliximab in the treatment of adult UC patients. The primary endpoint was a pre-specified comparison to the combined placebo groups in ACT 1 and ACT 2. This approach was taken since the paediatric C0168T72 study was challenging to design and enrol. The primary endpoint was positive in the C0168T72 study demonstrating that the proportion of subjects in clinical response at Week 8 for subjects receiving 5 mg/kg infliximab was greater than the upper bound of the 95% confidence interval for clinical response at Week 8 in subjects from the placebo groups in ACT 1 and ACT 2 combined. Additionally, it was demonstrated that the results from the primary and major secondary endpoints in the C0168T72 study were comparable with the results from the infliximab 5 mg/kg group in the ACT 1 and ACT 2 studies. The etiology and clinical manifestation of UC in adult and paediatric patients above 6 years as well as the treatment management of the condition are considered to be similar. The clinical efficacy results observed in adults with UC can therefore be translated to children above 6 years with UC providing additional support to the efficacy observed in study CT0168T72.

In order to further support an indication in paediatric UC, the MAH presented the main efficacy data in adults UC from the ACT 1 and ACT 2 studies, with data separated by subgroups with moderate and severe disease respectively. Data showed that infliximab induced clinical response and maintained clinical remission in adult subjects with UC, irrespective of their baseline disease severity. Patients with severe disease were clearly a minority in the studies, 11%. Looking at the week 8, 30 and 52 data for clinical remission, there is no obvious difference in the subgroups who had severe or moderate disease at baseline. In the long-term extension, data on Physician's Global Assessment (PGA) only were collected. There were 25 patients in the combined ACT 1 and ACT 2 extension data set, who had had severe disease at baseline. Among those, a PGA score of 0 or 1 was achieved of at least 76%. These data should be interpreted with caution as, possibly, patients who did not respond adequately left the study. Overall, the controlled data do not indicate any obvious difference in the clinical remission rate among subjects who had moderate or severe disease at baseline.

Finally, comparable PK exposure was established between children and adults with UC. Pharmacokinetic data showed a slightly lower median serum infliximab concentrations in paediatric UC patients than dosing of adult UC subjects following dosing with 5 mg/kg infliximab Weeks 0, 2, and 6, followed by q8w (20-30%), although the data from paediatric subjects are limited due to the low number of subjects. The MAH has discussed the proposed posology, and whether there is sufficient support for a more flexible dose regimen for use in paediatric UC. It was pointed out that there are no data from adults in UC with a flexible dose regimen, and thus there are no efficacy or safety data to support such approach for the paediatric population. The available PK data (including population analyses) showed an approximate 25% lower exposure of children than of adults. However, these data

are not considered sufficient enough to propose a more flexible dose recommendation in paediatric patients. This position was endorsed by the CHMP and the proposal to maintain the initially proposed posology; an induction regimen at week 0, 2 and 6 of 5 mg/kg, followed by 8 weekly infusions of 5 mg/kg is agreed.

Conclusion on efficacy

Study C0168T72 showed that the proportion of patients in clinical response at week 8 was 73.3% (44/60). Clinical response at week 8 was similar between those with or without concomitant immunomodulator use at baseline. Clinical remission at week 8 was 33.3% (17/51) as measured by the Paediatric Ulcerative Colitis Activity Index (PUCAI) score. At week 54, the proportion of patients in clinical remission as measured by the PUCAI score was 38% (8/21) in the q8 week maintenance group and 18% (4/22) in the q12 week maintenance treatment group. For patients receiving corticosteroids at baseline, the proportion of patients in remission and not receiving corticosteroids at week 54 was 38.5% (5/13) for the q8 week and 0% (0/13) for the q12 week maintenance treatment group. In this study, there were more patients in the 12 to 17 year age group than in the 6 to 11 year age group (45/60 vs.15/60). While the numbers of patients in each subgroup are too small to draw definitive conclusions about the effect of age, there was a higher number of patients in the younger age group who stepped up in dose or discontinued treatment due to inadequate efficacy.

The study design, the relatively high number of subjects who discontinued or dose escalated and the overall limited remaining number of patients evaluable limit the clinical relevance of the observed effects. However, it was showed that the 3-dose induction regimen induced a clinical response and the observed differences in effect between the two treatment groups indicate that there is a clinical effect of infliximab treatment. In addition, data translated from studies in adult's patients with UC (ACT 1 and ACT 2) provide a support to the observed treatment effect in paediatric patients.

Overall the paediatric efficacy data from study C0168T72 taken together with the efficacy data in adults UC patients from study ACT 1 and ACT 2 constitute enough efficacy data to support the treatment in paediatric UC patients 6 to 17 years.

1.2.5. Clinical safety

Study C0168T72

Patient exposure

All enrolled patients received infliximab infusion at week 0. Of the 15 subjects that were not randomized, 14 (93%) and 11 (73%) received the week 2 and 6 administrations, respectively. All subjects that were randomized received three infusions during the induction part of the study. The group that was randomized at week 8 received an average number of 7 infliximab administrations and a median total dose of 39.2 mg/kg, through week 54. Subjects in q8w group received an average of 8 administrations and a mean total dose of 40 mg/kg. Corresponding figures in the q12w group were 6 administrations and 30 mg/kg. The average duration of follow-up was 50.4 and 44.6 weeks, respectively.

The following treatment changes were made during the maintenance phase

- 5 mg/kg infliximab q8w -->10 mg/kg q8w (n = 9)
- 5 mg/kg infliximab q12w -->10 mg/kg q8w (n = 8)
- 5 mg/kg infliximab q12w -->5 mg/kg q8w (n = 6)

The average duration of follow-up and the average exposure were slightly shorter for all treated subjects ages 6 to 11 years than for those ages 12 to 17 years. The average duration of follow-up was 32.1 weeks for all treated subjects ages 6 to 11 years and 40.0 weeks for those ages 12 to 17 years. The average exposure was 25.6 weeks for all treated subjects ages 6 to 11 years and 30.7 weeks for those ages 12 to 17 years. Of the 15 subjects in the 6 to 11 years age group, 6 subjects were not randomized at Week 8, 5 subjects were randomized as responders to the q8 treatment group, and 4 subjects were randomized as responders to the q12 treatment group. Of the 45 subjects in the 12 to 18 years age group, 9 subjects were not randomized at Week 8, 17 subjects were randomized as responders to the q8 treatment group, and 19 subjects were randomized as responders to the q12 treatment group. At Week 54, 32 subjects were evaluable for safety: 18 in the q8w group and 14 in the q12w group (Table 16).

Table 16 Number of subjects evaluable for safety at each visit through Week 54; treated subjects in C0168T72

	Subjects Not Randomized at Week 8	Subjects Randomized at Week 8	
		Infliximab 5 mg/kg q8 wks	Infliximab 5 mg/kg q12 wks
Treated subjects in C0168T72[a,b]	15	22	23
Visits			
Baseline	15 (100.0%)	22 (100.0%)	23 (100.0%)
Week 2	14 (93.3%)	22 (100.0%)	23 (100.0%)
Week 6	14 (93.3%)	22 (100.0%)	23 (100.0%)
Week 8	12 (80.0%)	22 (100.0%)	23 (100.0%)
Week 14[c]	5 (33.3%)	22 (100.0%)	NA
Week 18	0 (0.0%)	NA	23 (100.0%)
Week 22	0 (0.0%)	22 (100.0%)	NA
Week 30	0 (0.0%)	18 (81.8%)	22 (95.7%)
Week 38	0 (0.0%)	18 (81.8%)	NA
Week 42	0 (0.0%)	NA	16 (69.6%)
Week 46	0 (0.0%)	19 (86.4%)	NA
Week 54	0 (0.0%)	18 (81.8%)	14 (60.9%)

[a] Data for subjects who stepped up are included according to the regimen received prior to step-up.
[b] Subjects are included until they terminate study participation or complete the study (including completion of safety follow-up after discontinuation of study agent).
[c] Includes subjects who are non-responders at Week 8.

Adverse events

Summaries of AEs were completed through week 54 on the safety population (n=60). Subjects who had their medication stepped up are included in the presentations according to the treatment before step-up. There are no comparisons available for AEs connected with other therapies for paediatric patients with UC in this open-label study. The average duration of follow-up was 9.8 weeks in patients that were not randomized at week 8 and 47.5 weeks in randomized patients.

Through week 8, 42 of 60 patients (70 %) had one or more treatment-related AE. The majority of AEs were in the system organ class Respiratory system disorders (n=17) (upper respiratory tract infections (7), pharyngitis (5) and coughing (3)) and Gastro-intestinal system disorders (n=15) (ulcerative colitis (7), vomiting (4) and abdominal pain and nausea (2 each)).

Patients that were not randomized at week 8 were to be followed up for 8 weeks after their last study drug administration. Twelve patients had one or more AE with the highest incidence of AEs being gastrointestinal system disorders (n=8). Adverse events reported in two or more patients were ulcerative colitis (n=4), abdominal pain (n=3), pharyngitis (n=3) and headache (n=2).

All randomized patients reported one or more AEs through week 54. The system-organ class with the highest incidence of AEs was gastrointestinal system disorders (n=28) (worsening of UC (n=23, q8W

n=8, q12w n=15), abdominal pain (n=5), vomiting and nausea (n=3), and diarrhoea and ulcerative stomatitis (n=2 each).

Among all treated patients the numbers of AEs with severe intensity were 23. The predominant event was worsening of UC (n=11), followed by abdominal pain (n=3) and one event each of pharyngitis, sinusitis, pancreatitis, viral infection, malnutrition, pneumonia, neutropenia and headache.

There were 8 patients who had at least one infusion reaction (defined as any AE occurring during or within 1 hour after infliximab infusion). The reactions were reported as being mild or moderate in intensity.

The proportion of subjects with 1 or more AEs in the 6 to 11 year old age group was similar to the proportion of subjects with 1 or more AEs in the 12 to 17 year old age group. There were comparable proportions of subjects across the infliximab treatment groups (q8w compared with q12w) with 1 or more AEs in the 6 to 11 year old age and 12 to 17 age groups.

The types and frequencies of AEs were generally consistent between the 2 age groups (6 to 11 years old and 12 to 17 years old) and were not notable given the disease under study (UC) and the age of the study population.

In both age groups, ulcerative colitis-related AEs were the most frequently reported with GI system disorders being the system-organ class with the highest incidence of AEs (10 subjects [66.7%] in the 6 to 11 age group and 26 subjects [57.8%] in the 12 to 17 age group.

The next most frequently reported AEs occurred in the respiratory system disorders class (10 subjects [66.7%] in the 6 to 11 age group and 18 subjects [40.0%] in the 12 to 17 age group). Most of these AEs were respiratory tract infections and were mild to moderate in severity

Serious adverse events and deaths

No individual SAE was reported in more than one patient except for worsening of UC. There were no deaths during the study period. Five patients underwent a colectomy through week 54, two in the group that was not randomized at week 8 and one and two patients respectively in the q8w and q12w groups.

An SAE of lupus erythematosus syndrome (lupus-like reaction) associated with positive ANA was reported after week 54 in a patient in the q8w maintenance group.

The numbers of SAEs are shown in Table 17.

Table 17 Number of patients with serious treatment-emergent AEs through week 54 (safety population)

	Subjects Not Randomized at Week 8	Subjects Randomized at Week 8			Total
		Infliximab 5 mg/kg q8 wks	Infliximab 5 mg/kg q12 wks	Combined	
Subjects treated[a]	15	22	23	45	60
Avg duration of follow-up (weeks)	9.8	50.4	44.6	47.5	38.0
Avg exposure (weeks)	5.1	41.0	34.3	37.6	29.4
Subjects with 1 or more serious adverse events	5 (33.3%)	4 (18.2%)	5 (21.7%)	9 (20.0%)	14 (23.3%)
System-organ class/preferred term					
Gastro-intestinal system disorders	4 (26.7%)	2 (9.1%)	3 (13.0%)	5 (11.1%)	9 (15.0%)
Colitis ulcerative	4 (26.7%)	2 (9.1%)	3 (13.0%)	5 (11.1%)	9 (15.0%)
Pancreatitis	0 (0.0%)	1 (4.5%)	0 (0.0%)	1 (2.2%)	1 (1.7%)
Resistance mechanism disorders	0 (0.0%)	3 (13.6%)	0 (0.0%)	3 (6.7%)	3 (5.0%)
Cellulitis	0 (0.0%)	1 (4.5%)	0 (0.0%)	1 (2.2%)	1 (1.7%)
Infection	0 (0.0%)	1 (4.5%)	0 (0.0%)	1 (2.2%)	1 (1.7%)
Infection viral	0 (0.0%)	1 (4.5%)	0 (0.0%)	1 (2.2%)	1 (1.7%)
Respiratory system disorders	1 (6.7%)	0 (0.0%)	1 (4.3%)	1 (2.2%)	2 (3.3%)
Pharyngitis	0 (0.0%)	0 (0.0%)	1 (4.3%)	1 (2.2%)	1 (1.7%)
Pneumonia lobar	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
Red blood cell disorders	0 (0.0%)	1 (4.5%)	0 (0.0%)	1 (2.2%)	1 (1.7%)
Anemia	0 (0.0%)	1 (4.5%)	0 (0.0%)	1 (2.2%)	1 (1.7%)
Urinary system disorders	0 (0.0%)	0 (0.0%)	1 (4.3%)	1 (2.2%)	1 (1.7%)
Urinary tract infection	0 (0.0%)	0 (0.0%)	1 (4.3%)	1 (2.2%)	1 (1.7%)
White cell and res disorders	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
Neutropenia	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)

[a] Data for subjects who stepped up are included according to the regimen received prior to step-up.

The proportion of treated subjects in C0168T72 who had 1 or more SAEs was higher in the 6 to 11 years age group (6/15 [40.0%]) than in the 12 to 17 years age group (8/45 [17.8%]), driven primarily by the subjects in the 6 to 11 years age group who were not randomized at Week 8 experiencing worsening ulcerative colitis. Table 18 summarizes SAEs through Week 54 in the 2 age categories grouped by type of SAE.

Table 18 Summary of serious adverse events through Week 54 in subjects by paediatric age group; treated subjects in C0168T72

Type of SAE	Age	SAE (Preferred term)	SAE (Verbatim term)	Relation to study agent
Ages 6-11 years				
UC-related	11	Colitis ulcerative	Exacerbation of ulcerative colitis	Not related
	10	Colitis ulcerative	Ulcerative colitis flare	Possible
	9	Colitis ulcerative	Worsening ulcerative colitis	Unlikely
	11	Colitis ulcerative	Worsening ulcerative colitis	Unlikely
Infection-related		Pneumonia lobar	Left lower lobe pneumonia	Unlikely
	11	Pharyngitis	Strep pharyngitis	Not related
Other	7	Neutropenia	Neutropenia	Possible
Ages 12-17 years				
UC-related	12	Colitis ulcerative	Worsening ulcerative colitis	Unlikely
	16	Colitis ulcerative	Ulcerative colitis flare-up	Not related
		Colitis ulcerative	Worsening ulcerative colitis	Not related
	16	Colitis ulcerative	Worsening of ulcerative colitis	Not related
	14	Colitis ulcerative	UC flare	Unlikely

		Colitis ulcerative	Ulcerative colitis flare	Unlikely
	13	Colitis ulcerative	Worsening of ulcerative colitis	Not related
		Pancreatitis	Pancreatitis	Unlikely
Infection-related		Infection viral	Viral infection	Unlikely
	17	Urinary tract infection	Urinary tract infection	Possible
	13	Infection	Infection unknown origin	Possible
	16	Cellulitis	Facial cellulitis	Possible
Other		Anemia	Anemia	Possible

Gastrointestinal (GI) system disorders was the system-organ class with the highest incidence of SAEs in both age groups (4/15 [26.7%] in the 6 to 11 age group and 5/45 [11.1%] in the 12 to 17 age group), with worsening ulcerative colitis being the only SAE reported in more than 1 subject.

SAEs that were not GI system disorders reported in subjects aged 6 to 11 years included pneumonia and neutropenia in subjects not randomized at Week 8, and pharyngitis in 1 subject in the q12w maintenance treatment group. Of note, only 2 of the 7 (28.5%) SAEs in this younger age group were considered possibly related to study agent (an ulcerative colitis exacerbation and neutropenia).

SAEs that were not GI system disorders reported in subjects aged 12 to 17 years included cellulitis, infection, viral infection, and anemia in subjects in the q8w maintenance treatment group, and urinary tract infection in 1 subject in the q12w maintenance treatment group. Of note, only 4 of the 13 (30.7%) SAEs were considered possibly related to study agent (urinary tract infection, viral infection, cellulitis, and anemia). All other SAEs were either not related or unlikely related.

AEs leading to discontinuation of study drug

There were 3 of 22 (14%) patients in the q8w group and 6 of 23 (26%) in q12w that discontinued because of AEs. In the 12qw group all discontinuation were due to worsening UC. In the q8w group discontinuations were due to worsening of UC (n=1), cyanosis and dyspnoea (n=1) and alopecia (n=1). In the group of patients not being randomized at week 8, there were 4 discontinuations (worsening UC (n=3), and neutropenia (n=1).

The proportion of subjects in C0168T72 who discontinued study agent because of 1 or more AEs was higher in the 6 to 11 years age group (6/15 [40.0%]) than in the 12 to 17 year age group (7/45 [15.6%]).

The majority of subjects in both age groups discontinued study agent because of worsening ulcerative colitis (4 of 6 [66.7%] subjects and 6 of 7 [85.7%] subjects in the 6 to 11 and 12 to 17 years age groups, respectively). These data are consistent with the efficacy data in C0168T72 in which efficacy was observed in both age groups and no consistent pattern indicating greater efficacy in one of the age groups was apparent.

Other AEs leading to discontinuation of study agent in the 6 to 11 years age group were neutropenia in 1 subject not randomized at Week 8 (discussed in Serious Adverse Events section above), and cyanosis and dyspnea in 1 subject in the q8w maintenance group. One subject receiving q8w maintenance treatment in the 12 to 17 years age group discontinued study agent because of alopecia.

Table 19 Permanent discontinuation from study agent due to AE

Reason for discontinuation	Age	Approximate time point for discontinuation after start of infliximab
Worsening UC	6	214
Neutropenia	7	After 1 dose
Dyspnea, Cyanosis	7	272 days
Worsening UC	11	After 2 doses
Pneumonia lobar (Left lower lobe pneumonia)	11	112 days
Worsening UC	11	154 days
Worsening UC	12	50 days
Worsening UC	13	185 days
Worsening UC	14	181 days
Alopecia (mild)	15	Approx 120
Worsening UC	16	320 days
Worsening UC	16	235 days
Worsening UC	17	218 days

Infections

Through Week 54, 31 (51.7%) treated subjects had an infection. Upper respiratory infection (11.7%) and pharyngitis (8.3%) were the most common respiratory infection. The proportion of infections was similar in the q8w (13 [59.1%]) and q12w (14 [60.9%]) maintenance treatment groups. Twenty-two (36.7%) treated subjects had an infection that required oral or parenteral treatment.

Among patients randomized at week 8, the overall incidence of infections was 60% in both groups and among non-randomized patients the corresponding figure was 27%. Infections occurring in more than 1 patient in a treatment group in need for antimicrobial treatment were pharyngitis (2 patients in each maintenance groups), bronchitis (2 patients in the q8w group) and urinary tract infection (one patient in the q8w group and 3 in the q12w group).

There were 7 AEs classified as serious; pneumonia (n=1, non-randomized patient), infection of unknown origin, viral infection, and facial cellulitis (1 patient each in the q8w group), pharyngitis, worsening UC and urinary tract infection (1 patient each in the q12w group during the induction phase). There were no cases of TB or opportunistic infections.

The proportion of treated subjects in C0168T72 who reported 1 or more treatment-emergent infections through Week 54 was somewhat higher in the 6 to 11 years age group (9/15 [60.0%]) compared to the 12 to 17 age group (22/45 [48.9%]). Respiratory system disorders were the most frequently reported infections for both age groups, with a higher percentage being reported in subjects aged 6 to 11 years (7/15 [46.7%]) than in subjects aged 12 to 17 years (7/45 [15.6%]. The only severe infection reported in the younger age group was the SAE of lobar pneumonia. All other infections in this age group were mild to moderate. There were 2 severe infections reported in the 12 to 17 year age group: a non serious AE of abdominal pain and a viral infection.

A greater proportion of subjects in the 6 to 11 years age group reported infections in the GI system disorders class, but a greater proportion of subjects in the 12 to 17 age group reported resistance mechanism disorders and skin and appendage disorders.

Infusion reactions

Four of 22 patients (18.2%) in the q8w group, 3 of 23 (13%) in the q12w group and 1 of 15 (7%) of non-randomized patients had at least one infusion reaction. All infusion reactions were classified as mild or moderate in intensity. One patient discontinued due to infusion reactions of cyanosis and dyspnoea.

The proportion of treated subjects in C0168T72 who reported 1 or more infusion reactions through Week 54 was the same in subjects aged 6 to 11 years (2/15 [13.3%]) as subjects aged 12 to 17 years 6/45 [13.3%]). Dyspnea was reported by 2 subjects in the 6 to 11 year age group and was the only infusion reaction that was reported by more than 1 subject in either age group. The proportion of infusions with an infusion reaction was similar between the 2 age groups. There were no serious infusion reactions, and no possible delayed hypersensitivity or anaphylactic reactions occurred.

Laboratory findings

There were two serious hematologic events reported during the study period; neutropenia and anemia. The most common markedly abnormal change in haematology was decrease in lymphocytes in 15 patients. Ten of these patients received concomitant treatment with immunomodulators during the study. Decrease in haematocrit occurred in 3 patients in the q8w group.

Concerning chemistry changes, abnormal values occurred transiently and according to the MAH did not appear to be of clinical significance.

Antinuclear Antibodies/Anti-double-stranded DNA Antibodies

Treatment with infliximab is associated with the development of anti-nuclear antibodies (ANA) and anti-dsDNA antibodies; however, clinical manifestations of these antibodies in subjects who developed them have been infrequent. Of the 42 subjects evaluated for anti-dsDNA antibodies, all subjects (100%) were negative at baseline and newly positive anti-dsDNA antibodies were detected in 2 (4.8%) subjects (both of whom were in the infliximab 5 mg/kg q8w maintenance treatment group (Table 20).

Table 20 Summary of change from baseline in anti-dsDNA test results using a >=1:160 ANA cut-off, a >=10 IU/mL Crithidia IFA result, and a >=5.4 Farr result for positivity through Week 54; treated subjects

	Subjects Not Randomized at Week 8	Subjects Randomized at Week 8			
		Infliximab 5 mg/kg q8 wks	Infliximab 5 mg/kg q12 wks	Combined	Total
Subjects treated[a]	15	22	23	45	60
Subjects evaluated	3	19	20	39	42
Subjects anti-dsDNA negative at baseline[b]	3 (100.0%)	19 (100.0%)	20 (100.0%)	39 (100.0%)	42 (100.0%)
Subjects anti-dsDNA positive at any time[c]	0 (0.0%)	2 (10.5%)	0 (0.0%)	2 (5.1%)	2 (4.8%)
Subjects anti-dsDNA positive at last evaluation[c]	0 (0.0%)	1 (5.3%)	0 (0.0%)	1 (2.6%)	1 (2.4%)

[a] Data for subjects who stepped up are included according to the regimen received prior to step-up.
[b] Denominator is number of subjects evaluated.
[c] Denominator is number of subjects anti-dsDNA negative at baseline.

In conclusion, in study C0168T72, the most common adverse reactions were upper respiratory tract infection, pharyngitis, abdominal pain, fever, and headache. The most common adverse event was worsening of ulcerative colitis, the incidence of which was higher in patients on the q12 week vs. the q8 week dosing regimen. Overall, 8 (13.3%) of 60 treated patients experienced one or more infusion reactions, with 4 of 22 (18.2%) in the q8 week and 3 of 23 (13.0%) in the q12 week treatment

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

Infections were reported in 31 (51.7%) of 60 treated patients in C0168T72 and 22 (36.7%) required oral or parenteral antimicrobial treatment. The overall incidence of infections in C0168T72 was 13/22 (59%) in the every 8 week maintenance treatment group and 14/23 (60.9%) in the every 12 week maintenance treatment group. Upper respiratory tract infection (7/60 [12%]) and pharyngitis (5/60 [8%]) were the most frequently reported respiratory system infections. Serious infections were reported in 12% (7/60) of all treated patients.

In this study, there were more patients in the 12 to 17 year age group than in the 6 to 11 year age group (45/60 [75.0%]) vs.15/60 [25.0%]). While the numbers of patients in each subgroup are too small to make any definitive conclusions about the effect of age on safety events, there were higher proportions of patients with serious adverse events and discontinuation due to adverse events in the younger age group than in the older age group. While the proportion of patients with infections was also higher in the younger age group, for serious infections, the proportions were similar in the two age groups. Overall proportions of adverse events and infusion reactions were similar between the 6 to 11 and 12 to 17 year age groups.

Comparison of safety data from C0168T72 with REACH (EMEA/H/C/240/II/75)

Both studies were designed as open-labelled studies in which responders to induction treatment were randomized to receive treatment with 2 different dosing intervals. Patients in the REACH study had moderately to severely active Crohn's disease (PCDAI >30 points) and the median age was 13 years (range 6-17 years).

The proportion of treated patients in C0168T72 and REACH that had one or more AE was approximately 95%. In both studies the system-organ class with the highest incidence of AEs was gastro-intestinal disorders (60 and 75%, respectively). Headache was reported in the highest number of patients in the REACH study. A summary of SAEs is shown in Table 21.

Table 21 Summary of number of patients with one or more treatment-emergent SAEs through week 54; treated patients in C0168T72 and REACH.

	C0168T72		REACH			
Treated subjects 5 mg/kg infliximab	Subjects treated	60	Subjects treated	112		
	Avg duration of follow-up (weeks)	38.0	Avg duration of follow-up (weeks)	47.2		
	Avg exposure (weeks)	29.4	Avg exposure (weeks)	39.2		
	Subjects with 1 or more SAEs	14 (23.3%)	Subjects with 1 or more SAEs	22 (19.6%)		
	SAEs		SAEs			
	Colitis ulcerative	9 (15.0%)	Crohn's disease	10 (8.9%)	Infection bacterial	1 (0.9%)
	Pancreatitis	1 (1.7%)	Intestinal stenosis	3 (2.7%)	Infection viral	1 (0.9%)
	Cellulitis	1 (1.7%)	Abdominal pain	2 (1.8%)	Sepsis	1 (0.9%)
	Infection	1 (1.7%)	Abscess	2 (1.8%)	Furunculosis	1 (0.9%)
	Infection viral	1 (1.7%)	Fever	2 (1.8%)	Rash	1 (0.9%)
	Pharyngitis	1 (1.7%)	Anal fistula	1 (0.9%)	Skin ulceration	1 (0.9%)
	Pneumonia lobar	1 (1.7%)	Blood in stool	1 (0.9%)	Pharyngitis	1 (0.9%)
	Anemia	1 (1.7%)	Colitis	1 (0.9%)	Pneumonia	1 (0.9%)
	UTI	1 (1.7%)	Constipation	1 (0.9%)	Pain	1 (0.9%)
	Neutropenia	1 (1.7%)	Enterocolitis	1 (0.9%)	Migraine	1 (0.9%)
			Intestinal obstruction	1 (0.9%)	Bone fracture	1 (0.9%)
			Intestinal perforation	1 (0.9%)	Suicide attempt	1 (0.9%)
			Pancreatitis	1 (0.9%)	Ecchymosis	1 (0.9%)
			Vomiting	1 (0.9%)	Lymphadenopathy	1 (0.9%)

UTI = urinary tract infection

In REACH 11% of the patients discontinued study agent due to AEs compared to 22% in C0168T72. A larger proportion of patients 6-11 years (40%, i.e. 6 of 15) in C0168T72 had serious adverse event and discontinued the study due to AEs compared with the older age group (18 %) and children in the

REACH study (6-11, 24% and 12-17, 18%). The proportion of patients with infections in C0168T72 was similar to that in the paediatric Crohn's disease study (REACH).

Safety data from the ACT 1 and ACT 2 studies (EMEA/H/C/240/11/65)

Two pivotal studies with infliximab in the treatment of ulcerative colitis with up to 30 weeks data were submitted in the initial application. These studies include adult patients with moderate to severe ulcerative colitis and with non-response to other conventional therapies. A placebo-add-on approach was chosen for the performed studies. The system-organ class with the highest incidence of AEs was Gastro-intestinal disorders (46 and 50%, respectively). In all three studies worsening of the underlying disease was the most common SAE in patients treated with 5 mg/kg infliximab and placebo, see Table 22.

Table 22 Summary of number of patients with one or more treatment-emergent SAEs through week 54; treated patients in C0168T72 and the pooled ACT studies

	C0168T72	ACT 1/ACT 2	
	5 mg/kg infliximab	Placebo	5 mg/kg infliximab
Subjects treated	60	244	242
Avg duration of follow up (weeks)	38.0	32.2	41.1
Avg exposure (weeks)	29.4	22.7	32.6
Subjects with 1 or more SAEs	14 (23.3%)	57 (23.4%)	43 (17.8%)
SAEs		SAEs	SAEs
Colitis ulcerative	9 (15.0%)	Colitis ulcerative 30 (12.3%)	Colitis ulcerative 21 (8.7%)
Pancreatitis	1 (1.7%)	Anemia 4 (1.6%)	Appendicitis 3 (1.2%)
Cellulitis	1 (1.7%)	Abdominal pain 3 (1.2%)	Gastroenteritis 2 (0.8%)
Infection	1 (1.7%)	Vomiting 3 (1.2%)	GI hemorrhage 2 (0.8%)
Infection viral	1 (1.7%)	Abscess 3 (1.2%)	Fever 2 (0.8%)
Pharyngitis	1 (1.7%)	Thrombophlebitis deep 3 (1.2%)	Pneumonia 2 (0.8%)
Pneumonia lobar	1 (1.7%)	Dehydration 3 (1.2%)	Anemia 2 (0.8%)
Anemia	1 (1.7%)	Diarrhea 2 (0.8%)	Thrombophlebitis deep 2 (0.8%)
UTI	1 (1.7%)	Nausea 2 (0.8%)	Abdominal pain 1 (0.4%)
Neutropenia	1 (1.7%)	Renal calculus 2 (0.8%)	Constipation 1 (0.4%)
		Embolism pulmonary 2 (0.8%)	Gastric ulcer hemorrhagic 1 (0.4%)
		Anxiety 2 (0.8%)	Gastritis hemorrhagic 1 (0.4%)
		Diarrhea bloody 1 (0.4%)	Hemorrhage rectum 1 (0.4%)
		GI hemorrhage 1 (0.4%)	Intestinal stenosis 1 (0.4%)
		Hemorrhage rectum 1 (0.4%)	Intestinal ulceration 1 (0.4%)
		Anorexia 1 (0.4%)	Mucositis NOS 1 (0.4%)
		Intestinal perforation 1 (0.4%)	Pancreatitis 1 (0.4%)
		Fever 1 (0.4%)	Herpes simplex 1 (0.4%)
		Infection 1 (0.4%)	Infection fungal 1 (0.4%)
		Infection bacterial 1 (0.4%)	Sepsis 1 (0.4%)
		Chest pain 1 (0.4%)	Chest pain 1 (0.4%)
		Edema peripheral 1 (0.4%)	Fatigue 1 (0.4%)

	C0168T72	ACT 1/ACT 2	
	5 mg/kg infliximab	Placebo	5 mg/kg infliximab
		Arthropathy NEC 1 (0.4%)	Abdomen enlarged 1 (0.4%)
		Pharyngitis 1 (0.4%)	Necrosis ischemic 1 (0.4%)
		Sinusitis 1 (0.4%)	Pain 1 (0.4%)
		URI 1 (0.4%)	Arthralgia 1 (0.4%)
		Aphasia 1 (0.4%)	Joint dislocation 1 (0.4%)
		Creatinine increased 1 (0.4%)	Myalgia 1 (0.4%)
		Urinary retention 1 (0.4%)	Myopathy 1 (0.4%)
		Angina pectoris 1 (0.4%)	Adult respiratory distress syndrome 1 (0.4%)
		Hyperglycemia 1 (0.4%)	Respiratory arrest 1 (0.4%)
		Hyperkalemia 1 (0.4%)	Respiratory insufficiency 1 (0.4%)
		Hyponatremia 1 (0.4%)	Sinusitis 1 (0.4%)
		Weight decrease 1 (0.4%)	Arteriosclerosis 1 (0.4%)
		Confusion 1 (0.4%)	Optic neuritis 1 (0.4%)
		Depression 1 (0.4%)	Renal failure 1 (0.4%)
		Edema genital 1 (0.4%)	Urinary tract disorder 1 (0.4%)
		Endometriosis 1 (0.4%)	Embolism pulmonary 1 (0.4%)
		Pregnancy unintended 1 (0.4%)	Adenocarcinoma NOS 1 (0.4%)
		Skin disorder 1 (0.4%)	Rectal carcinoma 1 (0.4%)
		Skin ulceration 1 (0.4%)	Earache 1 (0.4%)
		Pancytopenia 1 (0.4%)	Pemphigus 1 (0.4%)
			Eosinophilia 1 (0.4%)

NEC = not elsewhere classified; NOS = not otherwise specified;UTI = urinary tract infection; URI = upper respiratory infection.

Through week 54 in the pooled ACT studies, 14 (6%) in the 5 mg/kg infliximab treatment group and 23 (9.4%) in the placebo group discontinued the study due to AEs. The proportion of patients with infections in C0168T72 was higher than the proportion in the adults ulcerative colitis studies (ACT 1 and ACT 2).

Supportive safety data from other studies in paediatric populations

The safety profile of infliximab in studies in paediatric Crohn's disease (C0168T23, C0168T559) and in JIA (C0168T32) was consistent with that observed in paediatric UC patients with some exceptions: there were a higher incidence of SAEs and infections (C0168T23) and higher rate of infusion reactions and antibodies to infliximab (C0168T32) in comparison with in study C0168T72.

Long-term follow-up studies and registries

RESULTS UC

The RESULTS UC (C0168T62) program collects long-term safety data in adult subjects with UC who participated in the ACT 1 and ACT 2 studies and in paediatric subjects with UC who participated in the C0168T72 study. As of 08 Jul 2010, follow-up data was available for 33 paediatric subjects who participated in the C0168T72 study.

Safety information collected in the RESULTS UC program includes serious infections (through 1 year after the final safety visit in the primary study), deaths, new malignancies (including colorectal cancer), and new autoimmune diseases (through 5 years after the final safety visit in the primary study). In addition, information on the signs and symptoms of delayed hypersensitivity (serum sickness-like) reactions following readministration of commercial Remicade is collected through 5 years after the final safety visit in the primary study. Additional information on dysplasia of the colon, as determined by follow-up colonoscopy is collected for subjects who were identified in the primary study to be at a high risk of colon cancer (as per protocol, subjects at high risk of colon cancer were defined as those with extensive colitis >8 years in duration or disease limited to the left side of the colon >10 years in duration at the time of screening). The follow-up colonoscopy is to be collected no later than 4 years following the date of the screening colonoscopy.

Through 08 July 2010, for the 33 subjects from C0168T72 in the RESULTS UC program, there have been no deaths or malignancies, 2 serious infections (viral infection and bacterial infection in 1 subject each), 1 autoimmune disorder (psoriasis), and 1 probable delayed hypersensitivity sensitivity reaction.

Within the RESULTS UC report of 2010 data on dysplasia in the subgroup of patients who were identified at high risk for colon cancer were presented (Table 23 below).

Table 23 Summary of biopsy results for subjects at high risk for dysplasia in long-term safety follow-up program; treated subjects in primary study for RESULTS-UC

	Placebo Only	Infliximab
Subjects treated in primary study	243	545
Subjects with long-term safety follow-up	147	345
Subjects identified as high risk for dysplasia	38 (25.9%)	107 (31.0%)
Subjects who had colonoscopy with biopsy[a]	30 (78.9%)	78 (72.9%)
Biopsy results		
No dysplasia	28	58
Dysplasia	2	16
Inconclusive	0	2
Due to inflammation	0	1
Due to other reasons	0	1
Unknown	0	2

[a] Denominator is number of subjects identified as high risk for dysplasia.

DEVELOP registry

DEVELOP (C0168Z02, REMICADEPIB4002, and REMICADEPIB4003) is an ongoing, multicenter, prospective, observational registry of long-term safety and clinical status of paediatric patients with IBD, who were treated with infliximab and/or other medical therapies.

Information is collected on patient demographics, disease characteristics, clinical status, QOL, concomitant medications, and dose and frequency of infliximab administration. Data is collected every 6 months. Patients will be followed for at least 20 years after enrollment in the registry. This company-sponsored registry will include approximately 2,000 paediatric patients with CD who have been exposed to infliximab. The control group for the infliximab-treated patients with CD will include approximately 2,000 paediatric patients with CD who were treated with medical therapies other than infliximab. Approximately 1,000 patients with UC and/or indeterminate colitis will also be enrolled. Consistent with the US and EU Remicade indications for CD in paediatric patients, Remicade-exposed patients in this Paediatric IBD registry had more severe disease activity (including history of abscess/fistula) when compared with the Remicade non-exposed patients at the time of registry enrollment.

From 31 May 2007 through 17 March 2011, data were available for 1,407 patients exposed to infliximab, with 1,854 patient years of follow-up. There were 1,468 patients in the control group, not exposed to infliximab, with 1,585 patient years of follow up.

Infliximab-treated patients aged ≥ 6 to ≤ 11 years had a slightly higher rate of AEs and serious infections as compared with infliximab treated patients aged ≥ 12 to ≤ 17 years. However, serious infections reported in patients exposed to infliximab within 91 days prior to the event were similar in the ≥ 6 to ≤ 11 year old and ≥ 12 to ≤ 17 year old age groups. There was no significant difference between the rate of SAEs in the younger age group treated with infliximab compared with the older old age group. As of the cut-off date, 4 malignancies have been reported in patients who were older than 13 years of age at baseline: 3 (0.3 per 100 patient-years) in the infliximab treated patients and 1 (0.1 per 100 patient-years) in the infliximab non-exposed patients. There were no malignancies reported in patients younger than 13 years of age.

Overall, the severity and type of AEs reported during this data accrual period are consistent with those observed in the overall infliximab clinical trials database and in the postmarketing experience for

Remicade. Based on cumulative registry data, the majority of AEs and SAEs were related to the GI system. Infliximab-exposed and Infliximab non-exposed patients displayed similar AE and SAE profiles for these events. Exposure to infliximab trended toward a higher risk of serious infection but this finding was not statistically significant.

Paediatric Inflammatory Bowel Disease Collaborative Research Group Registry

This registry involves paediatric centres in the US and Canada. No infliximab-treated patient experienced a serious opportunistic infection, had a malignancy, or died between Jan 2002 and Aug 2008 (Hyams et al, 2010).

OPUS Registry

The primary objective of the OPUS registry is to collect long-term (5 years) safety data, including data on the incidence of colorectal cancer, in adult subjects with moderate to severe UC exposed to infliximab and to compare this safety profile to that of subjects with UC with similar disease severity treated with standard therapies. As of 10 August 2010 data is available for 591 infliximab treated patients. No unexpected AEs were reported. There were 9 patients (1.7%) in the infliximab group that had infusion-related reactions considered SAEs and 61 patients (12%) had gastrointestinal SAEs. Lymphoproliferative disorders and malignancies were reported for 3 patients (0.6 %).

Postmarketing data

Since the 2006 approval of paediatric Crohn's disease in the EU, each infliximab PSUR has included a separate section analyzing adverse reactions reported in the paediatric population. In general the safety profile is consistent with that seen in adults and with current labelling. Notable exceptions to this are the warnings regarding the risk of paediatric malignancy in general and HSTCL in particular that have been added to the Remicade label.

Since the marketing authorisation approval in 1999 in the EU, there have been 33 cases of malignancies in the paediatric age range (0 to 17 years); 19 non-lymphoma malignancies and 14 lymphomas. Three of these lymphomas were HSTCL, a rare type of T-cell lymphoma that is uniformly fatal. In the entire infliximab postmarketing database, 24 cases of HSTCL have been reported, the majority of which were in adolescent and young adult males with Crohn's disease; all of these patients were taking concomitant AZA/6MP.

Discussion on safety:

Study C0168T72

No clinically relevant differences in safety between children with UC in study C0168T72, children with Crohn's disease in the REACH study and adult UC patients in the ACT studies has been identified. However, the low number of subjects in C0168T72 limits these comparisons. The most commonly reported adverse events were respiratory system disorders and gastrointestinal system disorders. No new safety signals were identified in study C0168T72. There were no obvious differences between the treatment groups in numbers of adverse event, although there was a tendency for worsening of UC in more patients in the q12w group than in the q8w group. Worsening of UC was also the reason for all discontinuations in the q12w group. This can also be seen as lack of effect, increasing the numbers who discontinued due to lack of effect. However, due to low numbers of subjects, no firm conclusions can be drawn concerning differences in safety between the two maintenance treatments.

With respect to the serious AEs, only a few of those reported were considered related to infliximab. There were 40 % (6/15) of patients in the youngest age group that had serious adverse events compared to 17.8% (8/45) in the 12 to 17 years age group. Worsening of UC was the predominant event with severe intensity.

Generally, there were more infections in the lower age group, although only a few serious events were reported overall in the study

During the initial induction phase, the discontinuation rate was higher in the lower age group. There were 6/15 patients aged 6-11 years (40%) who did not continue after the 8 week induction period vs. 9/45 (20%) patients aged 12-17 years. Overall, 31 of the 60 subjects (51.7%) ended their study participation. Of the 15 subjects who were between 6 and 11 years of age, 9 (60.0%) ended their study participation, while 22 of 45 (48.9%) of the subjects who were between 12 and 17 years of age ended their study participation. In the younger age group (6-11 years of age), 6 of the 9 subjects (66.7%) who ended their study participation were not randomized at Week 8, which meant that either they had not achieved clinical response at Week 8 (3 subjects) and therefore were required to discontinue study agent or they had discontinued study agent due to other reasons prior to Week 8 (3 subjects, all due to an adverse event [1 neutropenia, 2 worsening of disease under study]). In the older age group, 9 of the 22 subjects (40.9%) who ended their study participation were not randomized at Week 8 (5 due to not being in clinical response at Week 8 and 4 due to other reasons (2 had a negative varicella titer, 1 had an AE of worsening of disease, and 1 had unsatisfactory therapeutic effect).

Of subjects who were randomized at Week 8, a similar proportion of subjects ended their study participation in the younger age group (3 of 9; 33.3%) compared with the older age group (13 of 36; 36.1%). Within each age category, the number of subjects who ended their study participation before Week 30 was comparable to the number of subjects who ended their study participation after Week 30. The majority of randomized subjects who ended their study participation (13 of 16) did so due to a worsening of the disease under study, while the remaining subjects ended their participation due to an AE (2 subjects, 1 with AEs of shortness of breath and cyanosis and the other with an AE of alopecia) or withdraw of consent (1 subject).

In the older age group, more subjects (10 [52.6%]) randomized to the infliximab 5 mg/kg q12wk treatment group ended their study participation through Week 54 compared with the infliximab 5 mg/kg q8 week group (3 [17.6%]). Within the infliximab 5 mg/kg q8wk group, all 3 subjects ended study participation prior to Week 30, while in the infliximab 5 mg/kg q12 week group, a similar number of subjects ended their participation prior to Week 30 and after Week 30. In the younger age group, the number of subjects in each of the randomized groups is too small to make any conclusions about differences in the number of subjects who ended study participation.

Of subjects who discontinued their study participation, a greater proportion in the younger age group discontinued by Week 8 compared with the older age group. However, a similar proportion of subjects who were randomized to maintenance treatment discontinued their study participation in each of the age groups. The majority of subjects who discontinued their study participation did so due to a worsening of the disease under study.

Overall there were fewer subjects in the 6 to 11 age group (15/60 [25.0%]) compared with the 12 to 17 age group (45/60 [75.0%]). Although the numbers of subjects in each subgroup are too small to make any definitive conclusions, overall proportions of AEs did not appear to differ among the 6 to 11 and 12 to 17 age groups. The types and frequencies of events were generally consistent between the 2 age groups and are not unusual or clinically concerning given the disease under study (UC), the age of the study population (paediatrics), and the known safety profile of infliximab. There were also higher

proportions of subjects with SAEs, discontinuation of study agent due to AEs, and infections in the younger age group than in the older age group.

RESULTS UC programme

The presentation of data on dysplasia and colorectal malignancy from the RESULTS UC programme led to questions by the CHMP. Among 78 subjects who were identified as at 'high risk for dysplasia' treated with Remicade and who had colonoscopy with biopsy, 16 had developed dysplasia (20%). In the placebo group only, 2 subjects with dysplasia were identified among those 30 with the same data available (7%). Furthermore, among the 16 infliximab-treated subjects with dysplasia, 3 subjects reported colorectal cancers and 1 subject had a dysplasia associated lesion or mass (recorded by the investigator as a malignancy). The MAH clarified that patients participating in the RESULTS UC study and in the long-term follow-up programmes could have received different treatments for various duration including infliximab and other TNF-α agents. The value of comparisons between placebo and active treatment is therefore limited. Of the 109 patients in the RESULT UC study at high risk for dysplasia, colonoscopy in relation to the initial screening was performed after 1 to 7 years in the placebo group and after 0.6 to 7 years in the infliximab group. The corresponding figures for patients with dysplasia were 1.1 to 2.8 and 1.4 to 6.2 years, respectively. In this small and selected group of patients, no clear pattern is discernable apart from the differences concerning the initial treatment (placebo or active). The CHMP concluded that based on the overall information provided in this limited analysis with significant confounding factors, there is insufficient evidence to either confirm or refute a causal role for infliximab in colon dysplasia in patients with UC. However, the imbalance of more cases with Remicade is still noted. These data emphasize the importance of routine surveillance in all patients at high risk for dysplasia as detailed in the RMP. The implications of this analysis to the paediatric population cannot be assessed due to the lack of a clear causal role for infliximab in colon dysplasia in adults and the limited data available on the risk of dysplasia in children with ulcerative colitis. However, in view of the younger age and expected longer disease duration in the paediatric population, the importance of that surveillance is even more reinforced.

IBD registries

Data on dysplasia and CRC was also summarized from 5 IBD registries, including 2 IBD paediatric registries (DEVELOP and the Paediatric Inflammatory Bowel Disease Collaborative Research Group Registry), 2 adult CD registries (TREAT in North America, ENCORE in Europe), and 1 adult UC registry (OPUS in Europe). There were no cases of dysplasia or CRC reported in the infliximab or control cohorts in the paediatric registries. In the TREAT registry, numerically higher incidences of CRC, but not dysplasia, were observed in the infliximab cohort compared with the control cohort; with 0 + 10 (0.06/ 100 pty) cases of colon dysplasia or CRC for infliximab, respectively, and 1 + 3 (0.02 / 100 pty) of the cases not having received infliximab, respectively. In the ENCORE registry, numerically higher incidences of CRC and dysplasia were observed in infliximab treated patients compared with controls; there were 1 + 10 (0.18 / 100 pty) cases of colon dysplasia + CSC with infliximab, respectively, and 0 + 2 cases (0.007 / 100 pty) in the standard treatment group, respectively. In the OPUS registry, there were no cases of dysplasia observed, and one case of CRC in the standard treatment group. The number of patient years is small in OPUS so far (370 pty for Remicade, 464 for standard therapy), and thus these results are insufficient to base any conclusions on. The incidences of dysplasia and CRC in the registries were not adjusted for confounding factors such as higher baseline disease severity in those patients receiving infliximab, or increased frequency of colonoscopies in patients with severe disease, making the results potentially biased.

The MAH has submitted additional analyses from the TREAT and ENCORE registries to address the risk for dysplasia / colorectal cancer in relation to severity of underlying disease. In both registries no consistent pattern of association between the severity of CD and dysplasia and colorectal cancer was identified, but the numbers of patients in each group were small. Detailed analyses are not possible in these two registries given the limited numbers. In addition, the numbers of events are limited to allow definitive conclusions. This is acknowledged by the CHMP.

Post-marketing data

The post-marketing data base SCEPTRE contained 123 cases with dysplasia or CRC in patients receiving infliximab for CD, UC or IBD. Overall, the assessment of the cases was confounded by multiple factors, mostly long-standing disease, and severity of disease. Infliximab is indicated for the treatment of moderately to severely active CD. Therefore, patients with IBD considered for infliximab therapy are at an increased risk for colon cancer due to the severity of their disease. There were cases with a latency period of less than 1 year, which may raise the question regarding a possible role of infliximab in an acceleration of the development of gastrointestinal dysplasia or gastrointestinal malignancy. It is also possible that extended exposure to infliximab may increase the risk of gastrointestinal dysplasia or gastrointestinal malignancy especially in patients with increased documented risk factors. However, the assessments of the majority of the cases with short or long infliximab exposure were confounded and the results are inconclusive.

Based on the cases identified in the post-marketing database, the reporting rate for infliximab for gastrointestinal dysplasia is 0.02 cases per 1,000 patient-years for UC and 0.001 cases per 1,000 patient-years for CD. The incidence rate reported in the literature for dysplasia is 14 per 1,000 patient years for UC. The reporting rate for infliximab for gastrointestinal malignancies is 0.1 cases per 1,000 patient-years for UC and 0.11 cases per 1,000 patient-years for CD. The incidence range reported in the literature for CRC ranged from 0.6 to 7.7 per 1,000 patient-years for UC and 0.6 to 6.2 per 1,000 patient years for CD. The infliximab reporting rates are lower than the range of published incidences for colorectal dysplasia and malignancy in UC and CD.

Based on the information provided in the post-marketing cases provided, there is insufficient evidence to assign a causal role to infliximab in dysplasia or gastrointestinal malignancy (i.e. CRC) in patients with UC, CD, or other IBD.

Risk for hepatosplenic T-cell lymphoma

Rare post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF-blocking agents including infliximab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were reported in adolescent or young adult males. All of these patients had received treatment with AZA or 6-MP concomitantly with or immediately prior to infliximab. In the current SmPC for infliximab, there is already a warning that pointing to this potential risk with the combination of AZA or 6-MP and infliximab.

A review of published literature from 2009 onward was performed on HSTCL cases. No new cases of HSTCL associated with the use infliximab were identified that were not already known. Data continue to confirm that HSTCL is a very rare event. The risk for HSTCL associated with use of AZA/6-MP is more and more established, and it is acknowledged that there are no cases with infliximab monotherapy, which is reassuring. The potential risk with the combination of AZA or 6-MP and infliximab should be carefully considered. This risk with the combination of AZA/6-MP and infliximab is already reflected in the current product information. At present this is considered sufficient.

When the paediatric CD indication was approved in 2007, the MAH agreed to expand the education programme to paediatricians. In line with the risk minimization measures as described in the RMP, the education of physicians continues and the MAH implemented an ongoing educational program which includes specific information regarding HSTCL. Consistent results of the 2008 and 2010 surveys indicated a high awareness of risks associated with infliximab treatment and generally high awareness of steps to be taken prior to initiating infliximab therapy. Overall it is therefore considered that awareness among pediatricians who would treat patients with IBD like UC and CD, have a high awareness about the risk of HSTCL. The already agreed education program as described in the RMP will continue and be extended to paediatric UC patients.

Conclusions on the clinical safety

There is no new safety signal observed during the study period. Events more related to the underlying disease were reported frequently i.e. worsening of UC (both adverse events and serious adverse events). There were also 5 patients that underwent a colectomy through week 54.

Available data for children from the CD studies, from DEVELOP (paediatrics IBD registry), and the data from the UC paediatric study do not raise new safety concern. The experience from treatment of adults with IBD with infliximab, from clinical studies as well as ongoing registries in both CD and UC, is extensive, and thus the overall safety profile of infliximab in these patient populations well characterised.

Overall, no signal for dysplasia and CRC was observed in paediatric (UC and CD) population studied. No signal for increased rate of dysplasia or CRC was observed in clinical studies although follow up is limited. Some imbalances were noted with increased rates of dysplasia or CRC in infliximab treated subjects versus comparator group in RESULTS UC study and in some registries. These analyses are routinely complicated by potential or observed increased severity of baseline disease in the infliximab treated population which predisposes the population to increased rates of dysplasia/CRC. The infliximab reporting rates are lower than the published incidences for colorectal dysplasia and malignancy in UC and CD. They do not provide evidence that infliximab has an impact on the overall risk of dysplasia or CRC in the IBD population. Dysplasia and CRC are a safety concern in view of the younger age and expected longer disease and treatment duration in the paediatric population. These risks are already addressed in the product information and the RMP. Based on the data provided in this application no changes to the way they are addressed are deemed necessary. The MAH will continue to monitor gastrointestinal dysplasia or gastrointestinal malignancy as part of ongoing routine pharmacovigilance activities with infliximab as addressed in the RMP.

Postmarketing cases of HSTCL have been reported in adolescents and young adult patients with CD and UC. All patients were taking concomitant AZA/6-MP. HSTCL is a safety concern in view of the younger age and expected longer disease and treatment duration in the paediatric population. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. When the signal of HSTCL was identified, the MAH held two expert meetings. The MAH has presented the most recent initiatives from expert meetings and results from surveys among prescribers relevant for paediatric IBD and particularly the awareness about HSTCL. It is acknowledged that awareness regarding the risk for HSTCL among those prescribers is high. The risk of HSTCL is already addressed in the product information and the RMP. Based on the data provided in this application no change to way it is addressed is deemed necessary. The already agreed education program detailed in the RMP will continue and is expanded to target prescribers of infliximab to patients with paediatric UC.

Overall, although there is no new safety signal identified in the studies and registries analysed, the knowledge on of safety profile of infliximab together with the above-mentioned concerns related to

colon dysplasia, malignancy and HSTCL should be taken into account in view of the younger age, expected longer disease and treatment duration in the paediatric population. Taken together, it is justified to restrict the indication for the most severely ill patients by excluding paediatric patients with moderate active disease. This was accepted by the MAH. Also it remains important to follow the long term safety use of infliximab in paediatric UC patients. The MAH will therefore continue to submit annual update of the DEVELOP registry as detailed in the RMP. The registry will be expanded to include paediatric patients with UC. Patients will be followed for at least 20 years after enrolment in the registry. The protocol will be amended to include paediatric patients with UC. The next update is expected in December 2012.

Risk management plan

The applicant submitted a risk management plan version 6.0, which included a risk minimisation plan: The Paediatric CD Educational Programme has been implemented and is fully active and from this procedure is expanded to educate prescribers of Remicade to paediatric UC patients.

Table 24 Extract from the summary of the risk management plan

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Long-term safety in paediatric CD and UC patients	• Routine pharmacovigilance • Additional surveillance through registries and long-term safety follow-up studies.	Routine activities Additional activities - paediatric educational programme

DEVELOP (C0168Z02, REMICADEPIB4002, and REMICADEPIB4003) is an ongoing, multicenter, prospective, observational registry of long-term safety and clinical status of paediatric patients with IBD, who were treated with infliximab and/or other medical therapies. DEVELOP is already listed in the RMP as pharmacovigilance activity in addition to the use of routine pharmacovigilance. The MAH is submitting regular updates to the EMA. From this procedure the DEVELOP registry will be expanded to include paediatric patients with UC. The protocol will be amended to include paediatric patients with UC.

1.2.6. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: no significant changes impacting the readability of the package leaflet are made.

2. Overall conclusion and benefit-risk assessment

Benefits

Beneficial effects

Infliximab has been approved for the treatment of moderately to severely active ulcerative colitis in adult patients in 2007. Study C0168T72 has been performed in children with moderately to severely active UC (defined as a baseline Mayo score of 6 to 12) who were diagnosed or referred for diagnosis at least 2 weeks before screening and confirmed by biopsy and a Mayo endoscopy subscore ≥2 at a screening sigmoidoscopy. The patients had active disease either despite adequate treatment with 6-MP,

AZA, corticosteroids and/or 5-ASA compounds, or had previously been unsuccessfully treated with 6-MP, AZA, corticosteroids and/or 5-ASA compounds.

The primary efficacy endpoint was evaluated at week 8, before randomisation. It was found that the 3-dose induction regimen induced a clinical response, measured by the Mayo score, in 73 % of the patients. Following randomisation of responders to dosing regimens with different dosing frequency, there were 8/20 and 4/21 patients in remission (PUCAI score) in the q8w and q12w groups at week 30, respectively and there were 8/21 and 4/22 patients in remission week 54, for the same dose groups. Thus, the shorter dosing interval of 8 weeks resulted in a higher degree of responding subjects. The differences were not statistically different at either time point, but these results give support for efficacy for 8 weeks maintenance treatment group.

A corticosteroid-sparing effect over time was observed in both maintenance treatment groups. Both groups had similar values at baseline. For the q8w group, the values had decreased after 8 weeks, and remained very low until Week 54 when a slight increase was observed. For the q12w group the reduction at week 8 was not as large as the reduction observed in the q8w treatment group, but was further reduced before the first maintenance treatment visit at Week 18. However, by Week 54, the values had returned to baseline levels in the q12w treatment group.

Regarding efficacy, the MAH has presented data on clinical remission from ACT 1 and 2, the pivotal UC studies in adults, with data separated by subgroups with moderate and severe disease respectively. Also long-term extension data from these studies were submitted. Although the number of subjects with severe disease at baseline in the studies was limited, there is no difference in the response rate at week 8, 30 or 54. The long-term data beyond 54 weeks should be interpreted with caution as it is open label and from few subjects. However, there is no data showing that long-term efficacy would be different in this subgroup of patients, or that long-term efficacy would be different in UC than in other indications.

Regarding efficacy, translation of efficacy data observed in adult UC patients to paediatric UC patients is considered adequate. The etiology and clinical manifestation of UC in adult and paediatric patients above 6 years as well as the treatment management of the condition and treatment response are considered to be similar. The clinical efficacy results observed in adults with UC can therefore be translated to children above 6 years with UC providing additional support to the efficacy observed in study CT0168T72.

Pharmacokinetic data showed a slightly lower median serum infliximab concentrations in paediatric UC patients than in adult UC subjects following dosing with 5 mg/kg infliximab Weeks 0, 2, and 6, followed by q8w (20-30%) dosing, although the data derived from a low number of subjects. A more flexible dose regimen in paediatric UC was discussed. In the absence of such data in adults and based on the available PK data in children it was agreed that current data are not considered enough to support such approach. The proposed posology is agreed. Overall, it is considered that the previously demonstrated efficacy of infliximab in the treatment of adult UC can be translated to the UC paediatric population.

Taken together, based on the data from C0168T72 and the ACT 1 and ACT 2 studies there is sufficient evidence of benefit of infliximab in paediatric subjects with severe disease, and thus that an indication in severe disease can be justified from an efficacy point of view.

Uncertainty in the knowledge about the beneficial effects

Infliximab induces effects in children with moderate to severe UC with insufficient response to standard therapies; however the magnitude of the effect and its clinical relevance is difficult to measure due to

the design of the study and the rather limited number of patients. Indeed, the overall numbers of patients was small particularly at the week 54 time point (31 patients ended their study participation before week 54, leaving only 29 patients, 18 in the q8w group and 11 in the q12w group for further evaluation). For the age group 6-11 years there were 15 patients included with 9 children evaluable for PUCAI scores at week 54. The support for efficacy in the youngest age group is therefore also relatively weak. However the possible translation of efficacy data from adults to paediatric patients reinforces the results observed in paediatric patients.

After randomisation from week 8 to the q8w or q12 w regimens, 5/45 (1 and 4 on q8w and q12w respectively) patients discontinued due to unsatisfactory effect, and 7/45 (1 and 6 on q8w and q12w respectively) due to worsening of UC (reported as AE). Furthermore, 23 / 45 (9 and 14 on the q8w and q12w respectively) stepped up their dose /dosing frequency, due to loss of clinical response during the maintenance phase. The difference between the two dosing regimens is a support for efficacy of infliximab in paediatric UC. The q8w regimen resulted in 41% of subjects discontinuing or losing response (stepped up in dose). This underlines an uncertainty concerning the long-term effect of the treatment. This uncertainty is addressed through the ongoing DEVELOP registry (detailed in the RMP).

Risks

Unfavourable effects

There is no new safety signal observed during the study period. Events more related to the underlying disease were reported frequently i.e. worsening of UC (both adverse events and serious adverse events). There were also 5 patients that underwent a colectomy through week 54.

Available data for children from the CD studies, from DEVELOP (paediatrics IBD registry) and the data from the UC paediatric study do not raise new safety concern. The experience from treatment of adults with IBD with infliximab, from clinical studies as well as ongoing registries in both CD and UC, is extensive and thus the overall safety profile of infliximab in these patient populations is rather well characterised.

Uncertainty in the knowledge about the unfavourable effects

It appears that younger children (6 to 11 year-olds) have higher incidences of AEs especially infections compared with 12 to 17 year-olds. It is more likely that a young child is hospitalised for infections than an older child. The higher rates may be associated with more severe disease in the younger group. The risk of infections is already addressed in the Product information as well as the RMP.

No new case of HSTCL associated with the use infliximab has been indentified in this procedure. Postmarketing cases of HSTCL have been previously reported in adolescents and young adult patients with CD and UC. All patients were taking concomitant AZA/6-MP. HSTCL is a safety concern in view of the younger age and expected longer disease and treatment duration in the UC paediatric population. Based on data presented it is acknowledged that awareness regarding the risk for HSTCL among the prescribers is high. The already agreed physician’s educational program for paediatric CD patients as described in the RMP will continue and be extended to paediatric UC patients.

Due to the risk for HSTCL, predominantly seen with concomitant use of AZA/6-MP and anti-TNF agents, it appears desirable that infliximab is used as monotherapy in young subjects with UC. The presented data show that there is no consistent pattern of differences in maintenance results between subgroups receiving infliximab monotherapy or concomitant AZA/6-MP. The possible advantage of monotherapy in terms of reduced risk for HSTCL has to be considered in relation to the possible increase of antibody development, potentially leading to reduced efficacy with time, as well as a higher risk for infusion

reactions. In certain patients there may be a need for combination therapy to achieve sufficient efficacy. The SmPC already warns that the potential risk of HSTCL should be carefully considered with the combination of AZA or 6-MP and infliximab.

The potential risk of malignancy associated with the disease is of special concern in the present population with UC. The MAH has submitted data from various sources to address the risk for dysplasia/colorectal cancer. Overall, no signal for dysplasia and CRC was observed in the paediatric population studied. No signal for increased rate of dysplasia or CRC was observed in clinical studies although follow up is limited. Some imbalances were noted with increased rates of dysplasia or CRC in infliximab treated subjects versus comparator group in RESULTS UC study and some registries. These analyses are routinely complicated by potential or observed increased severity of baseline disease in the infliximab treated population which predisposes the population to increased rates of dysplasia/CRC. The infliximab reporting rates are lower than the published incidences for colorectal dysplasia and malignancy in UC and CD. They do not provide evidence that infliximab has an impact on the overall risk of dysplasia or CRC in the IBD population. Data from the TREAT and ENCORE registries have been evaluated in relation to severity of underlying disease. In both registries no consistent pattern of association between the severity of CD and dysplasia and colorectal cancer was identified but the numbers of patients in each group were small. Overall, due to the limited number and the changing disease severity over time the interpretation of the analysis is limited. Dysplasia and CRC are safety concerns in view of the younger age and expected longer disease and treatment duration in the paediatric population. These risks are already addressed in the product information and the RMP. Based on the data analysed in this application this is considered sufficient at the present time. The MAH will continue to monitor gastrointestinal dysplasia or gastrointestinal malignancy as part of ongoing routine pharmacovigilance activities with infliximab as described in the RMP. In addition the MAH will provide regular safety updates in paediatric UC patients through DEVELOP i.e. the registry in paediatric IBD.

Overall, although no new safety signal has been identified in the presented studies or registries, the safety data from the paediatric population, especially the youngest age group remain limited due to the limited number of patients. Dysplasia, CRC and HSTCL are safety concerns in view of the younger age and expected longer disease and treatment duration in the paediatric population. Follow up of long-term safety is of importance to address and expand on the currently limited information available and will be made through the DEVELOP registry as described in the RMP.

Balance

Importance of favourable and unfavourable effects

Infliximab treatment induced a clinical response by week 8, and maintained remission in a number of subjects by week 54. Due to the study design, the relatively high number of subjects who discontinued or dose escalated and the overall limited remaining number of patients evaluable, the clinical relevance of these effects remains limited. However, it was showed that the 3-dose induction regimen induced a clinical response and the observed differences in effect between the two treatment groups indicate that there is a clinical effect of infliximab treatment. In addition, data translated from studies in adult's patients with UC provide a support to the observed treatment effect in paediatric patients.

Treatments with infliximab as well as alternatives for ulcerative colitis are associated with potentially serious adverse events. The disadvantages with steroid treatment in young individuals with effects on growth and bone structure is well characterised and also the increased risk for infections. The safety profile for AZA/6-MP is also serious with increased risks of bone marrow suppression, malignancy / lymphoproliferation, hepatic events and pancreatitis. Main safety concerns for treatment with infliximab are the increased risk of infections and the potential risk of lymphoproliferative disorders or

malignancies including HSTCL. More rare potential safety concerns include risk for demyelination. Thus, the safety of infliximab in comparison with the safety of alternatives for the treatment of UC is of clinical relevance.

Benefit-risk balance

In study C0168T72 conducted in children with UC a treatment effect has been demonstrated based on comparisons of the two dose regimens studied. With support from the data with infliximab in UC in adults, there is sufficient data to accept treatment with infliximab of paediatric UC from a benefit perspective.

UC in paediatric patients is characterized by well recognized short term and long term complications. The disease course in paediatric patients can lead to an important degree of morbidity and a poor quality of life due to e.g. intra-abdominal surgeries, extra intestinal manifestations and permanent growth deficits. Increased mortality has been reported in paediatric UC patients. Current therapies are limited to aminosalicylates, corticosteroids and immunomodulators (AZA/6-MP). 5-ASA is not sufficiently effective in patients with more severe disease. The use of corticosteroids and immunomodulators is associated with significant safety risks. Long-term use of corticosteroids is not desirable, particularly in growing children due to the adverse event profile, including growth failure, osteoporosis, hypertension, hyperglycemia, and cushingoid features. Thus, a possibility to taper such treatment is an important opportunity. AZA/6-MP is associated with serious adverse events as well, such as neutropenia, pancytopenia, pancreatitis, hepatotoxicity, and lymphoma, HSTCL. Surgical options are associated with notable morbidity and mortality, and significantly impact a paediatric patient's quality of life and physical and emotional development. Consequently, there is a need for additional treatment options for these children with more severe UC.

Although there were no new safety signals identified during the study period, the knowledge on the safety profile of infliximab together with the concerns related to colon dysplasia, malignancy and HSTCL should be taken into account in view of the younger age, expected longer disease and treatment duration in the paediatric population. Taken together, it is therefore justified to restrict the indication for the most severely ill patients by excluding paediatric patients with moderate active disease. This was accepted by the MAH.

Overall, based on the available efficacy data and the extensive knowledge about the safety profile of infliximab, as well as the additional pharmacovigilance measures particularly the long-term safety registry DEVELOP, the benefit risk balance of infliximab is considered positive for the treatment of severely active ulcerative colitis, in paediatric patients aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

The following indication is therefore agreed for section 4.1 of the SmPC:

Paediatric ulcerative colitis:

Remicade is indicated for treatment of severely active ulcerative colitis, in paediatric patients aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

3. Conclusion

On 19 January 2012 the CHMP considered this variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.