London, 22 March 2007
Product name: Remicade
Procedure number: EMEA/H/C/240/II/75

SCIENTIFIC DISCUSSION

1. Introduction

Infliximab is a chimeric human-murine IgG1κ monoclonal antibody, which binds to both soluble and transmembrane forms of the human tumour necrosis factor (TNF)α and inhibits the functional activity of TNFα.

Remicade (infliximab) is currently approved for the treatment of rheumatoid arthritis (RA), Crohn's disease (CD), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis and ulcerative colitis (UC).

The marketing authorisation holder (MAH) applied for an extension of the indication for infliximab to include treatment of moderate to severe, active Crohn's disease (CD) in children, aged 6 to 17 years, who have not responded to a full and adequate course of conventional therapy, or who are intolerant to or have medical contraindications to such therapy.

Crohn's disease is a chronic relapsing, remitting inflammatory disease of the gastrointestinal tract, the cause of which remains unknown. The disease affects the gastrointestinal tract discontinuously from mouth to anus, but most commonly the disease is located both in ileum and colon (40%)[1], followed by a disease in the small bowel only (30%), and in the colon only (25%). It occurs in a relatively young population and there is no marked sex difference. The incidence of CD in European countries is estimated to be 6-7/100.000. Patients with CD have a normal life expectancy, however, most individuals experience an impact of the disease on their daily life.

It is estimated that 25% of new cases of CD occur in subjects younger than 20 years of age, with the peak frequency of new cases in the paediatric population occurring in the mid-to-late teens (*Motil et al, 1993; Hyams, 1996*). In addition to the perianal disease (e.g., lesions, fistulae, abscesses), anaemia, and weight loss seen in CD at any age, impaired linear growth and delayed sexual maturation are characteristics of the disease in paediatric patients (*Satsangi, 2003*). Other extraintestinal manifestations include arthritis, decreased bone density and bone fractures, skin and eye lesions, hepatobiliary disorders, and acute pancreatitis. Chronic malnutrition in children with CD is thought to result mainly from reduced caloric intake, caused by eating less to avoid painful abdominal cramps and diarrhoea. Cytokines, including TNFα, produced by the inflamed bowel are also considered to be a cause of disease-related anorexia. In addition to the impaired growth caused by malnutrition, CD in children creates challenges with respect to psychological, educational, and social development that are difficult to reverse.

The application for the present type II variation was primarily supported by the results from the phase 3 CD study in 112 paediatric subjects (C0168T47), entitled "*A randomised, multicentre, open-label study to evaluate the safety and efficacy of anti-TNF-α chimeric monoclonal antibody in paediatric subjects with moderate to severe Crohn's Disease* (REACH)."

Additional supportive data was provided by the following two MAH-sponsored clinical trials: C0168T55, entitled "*A phase 1, open-label study evaluating the safety and pharmacokinetics of a single intravenous infusion of a chimeric monoclonal antibody to human TNF-α in paediatric inflammatory bowel disease subjects receiving maintenance treatment with infliximab*" and C0168T23, entitled "*A multicentre study of anti-TNFα chimeric monoclonal antibody in the treatment of paediatric patients with active Crohn's disease*."

Additionally, comparisons to data from adult subjects with CD were included in the submission to support the use of infliximab as a treatment for CD in children.

The MAH proposed to amend the text of the SCP sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 with the results of the above mentioned studies, and to update the PL accordingly.

[1] All figures presented are approximate

2. Clinical pharmacology

Pharmacokinetics (PKs)

Studies C0168T23 and C0168T55, specifically evaluated the PKs in children with CD, additionally to the PK data obtained in study CO168T47. Infliximab was in all three studies analysed with an enzyme-linked immunosorbent assay (ELISA) method. The limit of quantification (LOQ) was 0.1μg/ml.

Study C0168T23
This study aimed to demonstrate that with infliximab at single doses of 5 and 10 mg/kg the PK parameters in the paediatric population were comparable to those previously seen in the adult population. The study involved 21 children (11 to 17 years old; mean age 14.6 years), 19 Caucasians and 2 Black subjects were enrolled, 15 of the subjects were male and 6 female. The study consisted of a single infusion of 1 mg/kg, 5 mg/kg and 10 mg/kg of infliximab. Plasma concentrations were followed for 20 weeks. Pharmacokinetic parameters were determined using a non-compartmental method. The initial timepoint where concentrations fell below quantitation limits was set to half the LOQ (=0.05 μg/ml).

Study C0168T55
Six paediatric subjects ranging in age from 9 to 11 years (mean age 9.5) were enrolled and treated in this study. Each subject received a single intravenous (IV) infusion of 5 mg/kg of infliximab. The infusion was administered over, at minimum, a 2-hour period. Samples for serum concentrations of infliximab and PK analyses were to be obtained prior to the infusion and 2 hours after the end of the infusion, at day 3, week 1, 2, 4, and at the final visit. The PK parameters were determined using compartmental modelling with WinNonLin software.

Study C0168T47
A secondary objective of this phase 3 study was to evaluate the PK in patients aged 6-17 years, with a limited number of patients between 6 and 9 years of age. A total of 112 treated subjects were included and PK data was obtained from 106 subjects.

Blood samples for the measurement of serum infliximab concentration were collected immediately prior to and 1 hour after the infusion at weeks 0, 2, and 6, and at the non-infusion visit (week 10) for all subjects. From patients randomised to the every 8-week dosage, additional blood samples were drawn immediately prior to the infusion at weeks 14, 22, 30, 38, and 46, at 1-hour after the infusion at week 46, and at the non-infusion visit at week 54. For patients randomised to the every 12 week dosage (5 mg/kg infliximab every 12 weeks), additional blood samples were collected immediately prior to the infusion at weeks 18, 30, and 42; at 1-hour after the infusion at week 42; and at the non-infusion visit at week 54. In patients who switched treatment, blood samples were drawn immediately prior to and 1 hour after the infusion at the crossover visit and every visit thereafter. Compartmental modelling was used to obtain the PK parameters.

An overall comparison between the studies in children CO168T23, CO168T55 and CO168T47, and adults (data collected from study CO168T11) is presented in table 1.

Table 1. Pharmacokinetic parameter estimates in paediatric and adult subjects with Crohn's disease
Dose: 5 mg/kg

	Peadiatrics and adolescents Studies CO168T23, CO168T55 and CO168T47 N= 84 Mean± SD (range)	Study CO168T11 Adults N=5 Mean± SD (range)
CL (ml/day/kg)	6.5±3.0 (2.4-19.4)	7.5±2.7 (5.6-12.1)
AUC_{ss} (µg*day /mL)	918±387 (258-2085)	715±190 (415-891)
C_{max} (µg/mL)	126±34 65-230)	84.5±19.4 (63-108)
$T_{½}$ (days)	12.3±6.1 (2.6-29.2)	6.4±2.5 (2.6-8.3)

Discussion on pharmacokinetics

The MAH investigated the PKs in children aged 6-17 years of age, including a limited number of subjects in the age range between 6-9 years.

In study CO168T23 data suggested a similar exposure in adolescents and adults. In both adolescents and adults a decreased clearance with increased dose was observed. However, since there was a higher frequency of patients administered the 1 mg/kg dose that had their later concentrations set to half the LOQ, the higher clearance may be due to an artefact of the analytical method not being sensitive enough.

Study CO168T55 involved six children aged 9-11 years. Although being a small study; the results indicated a similar exposure in this age group as in adults.

In study CO168T47, PK data were obtained from 106 patients. In this study, subjects were allowed to cross over treatment (either from 5 mg/kg q 12 weeks to either 5 mg/kg or 10 mg/kg q 8 weeks or from 5 mg/kg q 8 weeks to 10 mg/kg q 8 weeks). There was a tendency to higher clearance in those patients who crossed over to other treatments, in particular those who increased the dose. It is unclear if this suggests an increased clearance over time and if this possibly could be caused by formation of antibodies. The MAH stated that there were no signs of any differences between the groups regarding the antibody formation to infliximab. However, the determination of antibodies is to some extent uncertain, as presence of infliximab in plasma could affect the antibody determination.

The adult study (CO168T11), used for comparison of the PK in adults and children, was limited to five patients administered 5 mg/kg. Therefore, additionally to the data that can be presented within the population analysis, a comparison with more extensive PK data in adult Crohn's patients was requested.

Furthermore, initially there was no presentation of individual data vs. age and weight, limiting the assessment of any potential differences in exposure within the paediatric group. A plot of individual clearance values for all paediatric/adolescents versus age was requested together with the corresponding data available in adults. Potential confounders such as antibody formation and insensitive analytical methods were to be discussed by the MAH. The MAH was also requested to perform a population analysis on all data to fully elucidate the influence of e.g. age on relevant PK parameters such as clearance.

The MAH provided answers to the request for supplementary information. From the data presented of the individual plotted variables versus clearance, there did not seem to be any trend that other parameters than weight would explain the differences observed in clearance. Furthermore, the body weight normalised dosing seemed to work appropriately since the pre-infusion serum concentrations in both children and adults reached approximately the same median values and no clear trends were seen indicating any large difference in the distribution of concentrations. The CHMP considered that since there is very limited data, a conclusion regarding the clearance in the paediatric population between 6 and 10 years of age is difficult to make. However, from a PK point of view, this should not be detrimental of the approval of the sought indication.

3. Clinical efficacy

Main study (CO168T47) REACH

Study participants
The study participants were 112 paediatric subjects with moderately to severely active CD (PCDAI[2] > 30) with inadequate response to conventional therapies, ranging in age from 6 to 17 years. Subjects had to have CD diagnosed for at least 3 months prior to screening.

The majority of subjects were boys (60%), Caucasian (82%), with median duration of CD of 1.6 years and median age of 13 years.

The distribution by age group is detailed in the table 2 below.

Table 2 REACH subjects by age group

Age group, years	Number of subjects	%
6 to 8	4	3.6%
9	4	3.6%
10	7	6.3%
11	10	8.9%
12	12	10.7%
13	20	17.9%
≥14	55	49.1%

Treatment
All 112 subjects were to receive 5 mg/kg infliximab induction dosing at weeks 0, 2, and 6. At week 10, 103 subjects who were judged to be in response by the investigators were randomised to 1 of 2 maintenance treatment regimens: 52 subjects were assigned to receive 5 mg/kg every 8 weeks (q8 week maintenance group) and 51 subjects were assigned to receive 5 mg/kg every 12 weeks (q12 week maintenance group). Nine subjects did not enter the maintenance phase of the study. Subjects who lost response during the maintenance phase were permitted to crossover to receive infliximab at a higher dose and/or to receive infliximab more frequently (n=35): 10 subjects had their dose increased from 5 mg/kg q8 weeks to 10 mg/kg q8 weeks, 12 subjects had an increase from 5 mg/kg q12 weeks to 5 mg/kg q8 weeks, and 13 subjects had an increase from 5 mg/kg q12 weeks to 10 mg/kg q8 weeks.

All subjects had a history of prior treatment with other CD medications (corticosteroids, immunomodulatory agents, or aminosalicylates). Of the 103 randomised subjects, the majority (99%) received 1 or more concomitant medications at baseline. Of these subjects, 35% received corticosteroids, 98% received immunomodulatory agents and 54% received aminosalicylates. The overall use of immunomodulators and aminosalicylates was balanced between the 2 maintenance treatment groups, but corticosteroids were more commonly used in the q8 week (46%) than in the q12 week (23%) maintenance treatment group. Of the randomised subjects receiving immunomodulatory agents, 90% received 6-MP (6-mercapto purine) or AZA (azathioprine) and 9% received MTX (methotrexate). The use of 6-MP/AZA was balanced between the 2 maintenance treatment groups. MTX was a baseline concomitant medication for 13% of subjects in the q8 week and for 4% of subjects in the q12 week maintenance treatment group. Mesalamine was the most frequently used aminosalicylate in the study. Concomitant medical therapy for CD was stable for a specified period before screening, and through week 54 (excluding corticosteroids). Subjects on oral corticosteroids kept their prescribed dose stable through week 2.

Outcomes/endpoints
The primary efficacy endpoint was to evaluate the efficacy of a 3-dose induction regimen of infliximab in reducing signs and symptoms in paediatric subjects with moderately to severely active

[2] Pediatric Crohn's Disease Activity Index

CD (PCDAI > 30 points). The safety profile of infliximab during induction and maintenance treatment was also evaluated.

The major secondary efficacy endpoints were:
1. To evaluate the efficacy of 2 infliximab maintenance dosing regimens (q8 weeks versus q12 weeks) in maintaining clinical response and inducing clinical remission in paediatric subjects with moderately to severely active CD;
2. To determine the PK profile in paediatric subjects following induction and maintenance dosing with infliximab;
3. To determine the effect of dosing with infliximab on the use of corticosteroids;
4. To determine the effect of maintenance dosing with infliximab on growth over the course of 1 year.

The main objective of the open label extension (OLE) was to offer continued infliximab therapy to the subjects who participated in the study. Additionally, the objectives of the OLE were to assess both the maintenance of clinical response and the safety of infliximab with long-term treatment of CD in the paediatric subject population. The MAH committed to continue the OLE until marketing authorisation is obtained for the use of infliximab for the treatment of CD in paediatric subjects, or for a maximum of 3 years.

Statistics
REACH was an open, non-placebo controlled study. Additionally to these data, the MAH proposed comparisons to data from adult subjects with CD, derived primarily from ACCENT I, a previously assessed multicentre study of adult patients with moderately to severely active CD who had previously failed to respond to usual therapies, such as aminosalicylates, immunosuppressants, and steroids. The CHMP did not agree with the MAH argumentation that the REACH study is very similar to the ACCENT I study. The ACCENT I study was a placebo-controlled study where the effect was measured in the Crohn's Disease Activity Index (CDAI). Improvement in the CDAI of ≥70 points was considered as response. In the REACH study the definition of response was an improvement in PCDAI of ≥ 10 points. The CHMP did not consider that the MAH had presented a rational for how these different scores relates to one another even though it was recognised that the symptoms scored are practically the same. Therefore, direct comparisons of efficacy results from these two studies were not considered as adequate to demonstrate efficacy in REACH. Comparisons between the two dose regimens applied in REACH were considered to hold more value for demonstration of efficacy. Other statistical methods used seemed adequate and satisfactory performed.

Results

Primary endpoint
The proportion of subjects achieving clinical response to infliximab at week 10 was 88%, indicating that the primary objective of the study was reached. The used definition of clinical response was considered clinically relevant in the paediatric population.

Secondary endpoints
Subjects who discontinued the study, did so due to insufficient data to assess their clinical remission status, had a prohibited CD-related surgery, or had prohibited concomitant medication changes. Those who crossed over were considered not to be in clinical remission at the timepoint of interest and at any timepoint thereafter, regardless of their PCDAI score.
A greater proportion of subjects randomised to the q8 maintenance group achieved clinical response as compared to the q12 maintenance group at week 30 (73% vs. 47%) and week 54 (63% vs. 33%). Similarly, a greater proportion of subjects randomised to the q8 maintenance group achieved clinical remission as compared to the q12 maintenance group at week 30 (60% vs. 35%) and week 54 (56% vs. 23%).

There was a reduction in median corticosteroid dose by week 10 that was maintained through week 54. Half of the subjects had discontinued corticosteroid use by the time of their first maintenance treatment visit. In addition, a greater proportion of subjects on corticosteroids at baseline was in remission and off corticosteroids at week 54 in the q8 week maintenance treatment group (46%) than in the q12 week maintenance treatment group (17%).

However, even if nearly all patients had a history of steroid treatment only 35% of patients were steroid treated at inclusion in the REACH study. The MAH was asked to justify the inclusion of patients who were not steroid resistant or dependent and to comment on the fact that the median steroid doses in the q12 week treatment group were higher than in the q8 week treatment group. Further to answers to the request for supplementary information, the CHMP considered that the claim of steroid dependent population did not follow the definition from the European Crohn's and colitis organisation (ECCO), and was therefore not accepted. The number of patients on corticosteroids and the median average daily corticosteroid dose were different at baseline between q8 and q12 week groups. Explanations were proposed and it could be that the q12 week group represented a more severely ill population. The CHMP considered that a flexible regimen could be appropriate.

Other secondary efficacy endpoints included quality of life analysis and a measure of height improvement. Quality of life was assessed using a questionnaire specifically developed and validated for paediatric patients with inflammatory bowel disease (IBD). It was administered only to some of the subjects. The mean changes (negative change indicates improvement) from baseline of the score at weeks 10, 30, and 54 (-22.9, -21.1, and –24.3, respectively) were all significant ($p < 0.001$).
Growth analysis was performed in those patients who had a delay of bone age of at least 1 year ($n = 38$; 23 and 15 subjects in the q8 week and q12 week maintenance regimens, respectively), the z-scores[3] were significantly improved from baseline at both week 30 ($n = 32$, mean change of 0.3, $p < 0.001$) and week 54 ($n = 29$, mean change of 0.5, $p < 0.001$). Considering that multiple factors might be linked to the catch-up growth, like nutrition, reduced inflammation, reduced use of corticosteroids, the MAH was asked to comment on how many of the subjects with delayed bone age were on steroids at baseline. From the data presented in the answers to the request for supplementary information, changes in growth from baseline were not dependent on baseline corticosteroid use. The MAH proposed a shortened wording related to this group of patients for section 5.1 of the SPC, which was agreed.

Supportive studies

The limited efficacy data from the PK study C0168T23 also supported the efficacy of infliximab in the applied extension of the therapeutic indication for paediatric CD. Although the number of subjects in this study was small (21 subjects), efficacy results, as demonstrated by clinical remission, were comparable to those in the REACH study. In C0168T23, clinical remission was achieved by approximately 48% (17%, 57%, and 62% in the 1 mg/kg, 5 mg/kg, and 10 mg/kg treatment groups respectively) of the evaluated subjects during the first 20 weeks compared with 56% in clinical remission in the q8 week maintenance treatment group and 23% in the q12 week maintenance treatment group at week 54 in the REACH study. All 7 subjects who had fistulising disease had their fistulas closed for at least 1 evaluation visit. Efficacy was not formally evaluated in the PK study C0168T55.

Discussion on clinical efficacy

The CHMP noted that the populations treated and the study designs and scores used for REACH and ACCENT I were substantially different, and therefore did not consider across study comparison sufficient to demonstrate efficacy in the paediatric population. Notwithstanding this fact, comparisons of the two dose regimens (5 mg/kg q8 or q12 weeks) showed statistically significant difference both in terms of clinical response and clinical remission at 30 and 54 weeks. It is remote to believe that the q12 week regimen would be inferior to placebo, and thus this comparison was of importance for demonstration of efficacy.
However, the steroid dose at baseline in the q12 week group (0.6 mg/kg/day) was twice the dose in the q8 week treatment group (0.3 mg/kg/day), which might indicate that the patients in the q12 week treatment group had a more serious disease at inclusion. Furthermore, it was also noted that there were fewer patients on steroids in the q12 week group (12/51) compared to the q8 week group (24/52). When combining the q8 and q12 week data it was shown that subjects on steroids at baseline were able to decrease the dose both at week 10 and throughout to week 54. Even though there was no

[3] The height z-score is a measure of the deviation of the paediatric patient's height from the expected height for a reference population of the same age and sex.

significant difference from baseline between the two regimens according to change from baseline corticosteroid dose through week 54, it seemed that infliximab had a steroid sparing effect.

The height status was improved in a limited group of patients with delayed bone age. The improved height score was an interesting finding but as it was a small group these data have to be interpreted with some caution. Additionally, the quality of life score improved in the subgroup evaluated.

Seventy five percent of patients who lost response and crossed over to a more frequent and/or higher dose regained response. However, the limited experience in 22 patients with the higher dose 10 mg/kg was not considered as sufficient to be reflected in the posology section. The MAH agreed that the data were limited and uncontrolled and thus amended the product information accordingly.
Re-treatment was evaluated in 8 patients in the extension part of study C0168T23. It seemed that the patients had effect but there were signals of more immune mediated events. None of the events was life threatening but in three patients it was judged as hypersensitivity reactions. Based on the available data, the CHMP considered that it would be important to investigate efficacy further in long-term treatment and re-treatment.

4. Clinical safety

Data on clinical safety were primarily derived from the REACH study and supportive data came from the two other studies in paediatric CD (C0168T23 and C0168T55) and the study of adults with CD (C0168T21, ACCENT I). Additionally, safety data in the paediatric population were available from the previously assessed C0168T32 study in juvenile idiopathic arthritis. The safety experience in adults is substantial.

Patient exposure

In the REACH study, the total dose of infliximab that was administered ranged from 15.1 to 65.0 mg/kg in the q8 week maintenance treatment group (n = 53). For the q12 week maintenance treatment group (n = 50), the total dose of infliximab that was administered ranged from 15.0 to 68.8 mg/kg. The median exposures were 40.0 and 31.1 mg/kg for subjects in the q8 week and q12 week maintenance treatment groups, respectively.

Adverse events

The safety profile of infliximab in the paediatric subjects in the REACH study was consistent with that seen in the adult subjects. Through week 10 of the REACH study, 75% of subjects had at least 1 adverse event (AE). The gastrointestinal (GI) system organ class had the highest incidence of AE, which was consistent with what had been seen in the ACCENT I study. Also, the proportion of REACH subjects with AEs in the q8 week maintenance treatment group was comparable to the proportion of subjects across all maintenance groups reporting AEs through week 54 of the ACCENT I study. No new AEs, when compared with existing adult safety experience, were identified. In the sex, age, or race subgroups, the proportions of paediatric REACH subjects with 1 or more AEs were comparable.

The proportions of subjects with AEs were comparable across the maintenance groups, with 96% and 92% of subjects in the q8 week and q12 week maintenance treatment groups experiencing 1 or more AEs, respectively. The largest percentage of treated subjects with an AE occurred in the GI system organ class (74%) and in respiratory system organ class (63%). The most commonly reported AEs in the GI system-organ class were CD (23%), abdominal pain (25%), and vomiting (24%); and in the respiratory system-organ class, upper respiratory infection (URI) (34%), pharyngitis (23%), and coughing (14%).

In cross-over to higher dose or more frequent treatment, the 2 groups in which the dosing interval was shortened each had a greater proportion of subjects with AEs (85% and 83% in the q12 week maintenance to 10 mg/kg q8 week group and the q12 week maintenance to 5 mg/kg q8 week group, respectively) than the group in which the dose was increased (50%; q8 week maintenance to 10 mg/kg

q8 week group). Due to the small numbers of subjects and lack of blinding, no definitive conclusions could be reached and no specific reporting patterns could be discerned.

Serious adverse events and deaths

In the REACH study, the proportion of all treated subjects with serious adverse events (SAEs) was 20%. The most frequently reported SAEs (in 2 or more of all treated subjects) were: worsening of CD (9%), intestinal stenosis (3%), and abdominal pain, abscess and fever (2% each). No new SAEs compared with existing adult safety experience were identified.
There were no deaths, malignancies, central nervous system (CNS) demyelinating disorders, optic neuritis, or seizures through week 54 in the REACH study. Likewise, no such events were reported through week 20 of study C0168T23 or in study C0168T55. One subject died during the re-treatment extension of Study C0168T23, from central respiratory depression due to morphine toxicity 26 weeks after the subject's last re-treatment infusion and approximately 2 weeks after receiving a commercial infliximab infusion.

The most commonly reported infection was URI (21%), followed by pharyngitis (15%). The proportion of subjects with AEs noted by their investigator as an infection was higher for subjects in the REACH q8 week maintenance treatment group than for subjects in the q12 week maintenance treatment group (74% and 38%, respectively).

By week 10, a greater proportion of the subjects who would be randomised to the q8 week maintenance treatment group had at least 1 AE reported as an infection than those subjects who would be randomised to the q12 week maintenance treatment group (32% and 20%, respectively), even though they had received identical treatment. This difference was less evident when considering only AEs that required treatment (47% and 28%, respectively).

Through week 54, the proportion of subjects with an URI reported as an AE was similar in the two treatment groups (36% and 32%, respectively), even though the proportion of subjects with an URI reported as an infection in the q8 week maintenance treatment group was nearly twice that reported in the q12 week maintenance treatment group (32% and 14%, respectively). In this open-label study subjects in the q8 week maintenance treatment group were seen and evaluated for infection more frequently than those subjects in the q12 week maintenance treatment group.

With the exception of abscess, viral infection, and bronchitis (all of which occurred in a greater proportion of subjects in the q8 week maintenance treatment group) and pharyngitis and fever (both of which occurred in a greater proportion of subjects in the q12 week maintenance treatment group), AEs were comparable in the respiratory and resistance system-organ classes between the 2 maintenance treatment groups.

The overall numbers of subjects with at least 1 infection reported as an SAE were similar in the q8 week and the q12 week maintenance treatment groups, 6% and 8%, respectively.

In REACH, pneumonia was reported in 3 subjects, 2 in the q8 week and 1 in the q12 week maintenance treatment groups. Herpes zoster was reported in 2 subjects in the q8 week maintenance treatment group.

Only 1 of the 9 subjects with serious infections had an infection that was not related to CD. There were no reports of TB through week 54. The proportion of infliximab-treated paediatric subjects with serious infections (in both the REACH and C0168T23 studies) was higher than that seen for adult subjects. Although the number of subjects was smaller in these paediatric clinical studies, in general, it appears that a higher rate of infections noted to be serious were observed in paediatric subjects with CD treated with infliximab than in adult subjects with CD from the ACCENT I study.

The proportion of infliximab-treated REACH paediatric subjects with infusion reactions was comparable to that for infliximab-treated adult subjects.

Laboratory findings

Results of safety-related laboratory analyses and immune response analyses were unremarkable. The proportions of REACH subjects with markedly abnormal ALT (alanine aminotransferase) results were comparable to those seen in the adult ACCENT I study (no markedly abnormal ALT results were observed in the q8 week maintenance treatment group in REACH).

Overall, in the REACH study, 3% of subjects were positive for antibodies to infliximab with titers ranging from 1:10 to 1:40. In the C0168T23 study (through week 20) and C0168T55 study, none of the subjects developed detectable antibodies to infliximab. Of the 8 subjects enrolled in the re-treatment extension of Study C0168T23, 3 subjects demonstrated antibodies to infliximab. Two of these 3 subjects developed both infusions reactions and delayed hypersensitivity reactions.

The MAH was asked to discuss the relatively low rate of antibody formation in these studies, as compared to other infliximab studies, such as the juvenile idiopathic arthritis study were the percentage of patients with antibodies was 30%. Further to the assessment of the answers to the request for supplementary information, the CHMP noted that no obvious explanation for the difference was identified.

Supportive Safety Findings

Through week 20 of the C0168T23 study, 90% of all treated subjects had at least 1 AE. The most commonly reported AEs occurred in the GI (67%), resistance mechanism (48%), and respiratory (33%) system-organ classes. The most commonly reported AEs were similar to those seen in the REACH study, (worsening of) CD (38%), nausea and URI (29% each), and vomiting (24%). When data from subjects who received re-treatment with additional infliximab infusions were included, the proportion of subjects and type of AEs were not notably different than those observed during the 20 weeks following the initial single infusion. Among the 8 subjects participating in this re-treatment extension, 6 experienced AEs. The most frequently reported AEs were (worsening of) CD (3 subjects), and arthralgia, flushing, and nausea (2 subjects each). No AEs were reported in study C0168T55.

Worldwide Marketing Safety Experience

Results of the review of serious paediatric adverse events, supplemented with an interim review of all paediatric events in the periodic safety update reports, were consistent with the information contained in the current prescribing information for infliximab. In the review regarding the postmarketing use of infliximab (not from clinical studies), the distribution of AEs reported as serious spontaneous cases in the paediatric population was similar to that reported with all serious spontaneous cases. The review of postmarketing data suggest, although based on limited data, that children may have increased rates of infusion-related or delayed hypersensitivity events (34% reporting rate for the paediatric serious cases compared with 17% reporting rate for all serious cases). However, the infusion reaction rate in paediatric REACH subjects with CD was not higher than that observed in ACCENT I in adults with CD.

Hepatosplenic T-cell lymphoma

On 4 May 2006, the MAH submitted a report entitled "*Response to the US FDA regarding the sBLA for the pediatric Crohn's disease indication: Report on Lymphoma in pediatric and adults patients treated with Infliximab (Remicade)*". In total, six cases of hepatosplenic T-cell lymphoma (HSTL) in CD patients treated with infliximab had been identified. Five of them were in the age range of 12 – 19 years. Four of the cases were classified as gamma-delta type T-cell non-Hodgkin's lymphoma (NHL) and 2 of the cases were classified as alpha-beta T-cell NHL. All patients had been previously and concomitantly treated with an immunomodulator (6-MP or AZA). Hepatosplenic T-cell lymphoma was only recognised as a distinct lymphoma subtype since early 1990's and was added to the Revised European American Lymphoma (REAL) classification in 1994. It is therefore probable that this lymphoma was historically misclassified. The true incidence of this lymphoma is unknown. As the pathogenesis of this malignancy still is being elucidated, there is incomplete knowledge about its causes and predisposing factors. In the absence of a better understanding of this newly described disease, it was concluded that it is currently not possible to estimate the background risk of HSTL.

The CHMP considered that the reports of HSTL were of medical concern given the nearly universal fatal outcome associated with this subtype of T-cell lymphoma and the fact that a causal relationship to infliximab treatment could not be excluded. The MAH submitted a type II variation (variation II.84) to update relevant sections of the product information on this finding, which received a CHMP positive opinion in May 2006, and Commission decision in July 2006.
In June 2006, the MAH organised an expert meeting to discuss the 6 cases of HSTL. The expert panel made some recommendations when not to treat children/adolescents/young adults with infliximab, such as in cases of unexplained hepatosplenomegaly with/without B symptoms (fever, fatigue, weight loss) and AZA/6-MP induced leukopenia. The conclusions of the expert panel were considered for the assessment of this variation.

By November 2006, in total 8 cases were reported in patients with inflammatory bowel disease (IBD)..The CHMP considered that the benefit / risk ratio for use of infliximab in paediatric patients with moderate to severe, active CD was not yet possible to conclude on, and considered that an ad hoc expert group meeting on the use of infliximab in paediatric CD needed to be convened. The meeting was held at the EMEA on 30 November 2006, and the overall conclusions, as endorsed by the CHMP are described below:

- The benefit /risk balance was considered positive for use of infliximab in a very restricted paediatric population with CD. It would correspond to those having failed conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy. The description of treatment failure was considered important, as a patient with 'severe' disease does not necessarily respond poorly to 1st or 2nd line therapy.

- A flexible dose regimen was recommended, as experience has shown that several patients need treatment more often than every 8 weeks.

- The treatment from 6 years of age was recommended.

- Monotherapy was not a favoured option due to lack of data, and experience showing need for combination therapy to obtain sufficient effect.

- Severe CD often is a chronic disease. Maintenance therapy is therefore likely needed, as patients in many cases relapse when infliximab is stopped.

- Infliximab was considered a promising tool for the treatment of fistulising disease, but a clinical trial in this setting was considered of importance.

- It was considered a need for a clinical trial addressing monotherapy, where also the possibility to taper immunomodulators could be addressed. Data on how to use steroid to avoid infusions reactions were also considered of interest.

- Setting up registries in the EU was considered crucial. The MAH proposed registry in the United States (US) was not considered sufficient e.g. due to different treatment strategies in the EU and the US.

Discussion on clinical safety

The CHMP considered that short-term safety in REACH was similar to the adult experience even though the frequency of infections (and frequency of serious infections) was higher in the paediatric population. However, it was noted that the long- term safety in this population is not known, for example, if the risk for malignancies is increased.

Even though the q8 week regimen showed better efficacy, there were markedly more AEs in this group compared to the q12 week regimen, especially infections. It seemed that for some patients treatment q12 weeks may be sufficient. There appeared to be a relatively small proportion of patients

who developed antibodies and the markedly lower infection incidence in the q12 week treatment group support that this regimen may be justified in certain subjects for safety reasons. Flexibility regarding the infusion interval (8-12 weeks) after an induction treatment was therefore recommended. Since there were so few patients treated with 10 mg/kg, the safety of this dose could not be assessed. Considering the cases of HSTL, the CHMP expressed concerns pertaining to the concomitant use of infliximab with AZA/6-MP. However, the fact that there is a lack of data on infliximab monotherapy in this population was noted and the need for a clinical trial to address monotherapy was discussed. It was considered that the general safety of monotherapy will be sufficiently monitored within the registry setting. However, in terms of efficacy, the experts at the November 2006 meeting expressed doubts that infliximab monotherapy would be sufficiently effective, and that there for many cases would be a need for additive effects of infliximab and an immunomodulator. Such additive effects are not unexpected. Furthermore, even if a difference in terms of efficacy would be found in an additional trial, such finding would be difficult to interpret and to base detailed prescribing recommendations on, particularly considering the third/fourth line indication recommended. Another important factor, which may affect both efficacy and safety, is the potential for increased development of anti-infliximab antibodies, if infliximab is used as monotherapy. Based on experience from the juvenile RA study with infliximab, there are doubts that data from adults are fully predictive for the paediatric population. However, the MAH proposed to undertake a substudy in the planned registry to investigate immunogenicity. Although data from the registry are likely to be less sensitive compared to a controlled study, it will be possible to collect data from a larger number of subjects than realistically could be included in a controlled trial. As pointed out by the MAH; an additional trial would be of small size, and given the previous results, only few subjects are expected to develop antibodies, and therefore data can be expected to be rather uncertain. Thus, by the MAH's proposal to undertake these analyses in the registry, the uncertainties related to antibody development are considered sufficiently addressed. Given the issues listed above, and the last line indication where individualised treatment should be opted for, it is considered acceptable not to require an additional monotherapy study.

The CHMP recommended that treatment should be exclusively for the more severely ill paediatric patients. Therefore, the indication should not include moderate CD.

5. Risk management plan

Pharmacovigilance plan

Proposal for assessing long-term safety in children exposed to infliximab.

Safety Surveillance in Ongoing Studies
The MAH will continue safety surveillance in ongoing programs in children and adolescents, including the 3-year open-label extension (OLE) to the REACH (C0168T47) trial (60 subjects entered the OLE) and the 5-year long-term safety follow-up program (RESULTS, C0168T45).

Paediatric Registry
The MAH proposed to set up a registry for paediatric CD in the US. The MAH justified that patient data from this North American registry would address epidemiologic questions regarding children exposed to infliximab for CD in Europe. However, it was noted that there are somewhat different therapy traditions in the US and EU. Further to the ad hoc expert group meeting, the CHMP discussed the need to develop a plan for a registry in the EU. The MAH committed to set up a registry in 3-5 European countries which would collect data for 20 years on paediatric subjects, noting the comments from the CHMP on data collection.

Periodic Safety Reporting
The MAH will also continue to report on safety of paediatric patients in the postmarketing environment through regular surveillance activities. The safety experience in children treated with infliximab for any indication will continue to be reported in the Experience in Special Patients Groups section of the PSUR. Special efforts will be made to collect all available data on postmarketing cases of lymphoma (in particular HSTL), non-lymphoma malignancies, and TB.

Prescribing Information

Reference safety information for infliximab will be revised on an ongoing basis to incorporate any new relevant safety information on the use of infliximab for paediatric patients.

Risk Minimisation Plan

The SPC serves as the primary tool for risk minimisation for paediatric CD patients treated with infliximab.

In 2002, the MAH initiated the TB Awareness and Educational program, which has resulted in a substantial decrease in the incidence of TB in Europe. The MAH will now expand the education program to physicians treating paediatric Crohn's patients

A summary of the risk management plan for infliximab highlighting the safety concerns specific to the paediatric CD population is presented below:

Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Identified Risks - Tuberculosis - Opportunistic infections - Infusion reactions - Delayed hypersensitivity reactions - Auto-immune events	Routine pharmacovigilance activities - Periodic safety reporting - Prescribing information Open label extension from T47 REACH Safety surveillance (Long-Term Safety Follow-Up) from adult and paediatric studies. Paediatric Registries - North American Paediatric Inflammatory Bowel Disease Collaborative Registry. - Paediatric IBD Registry (North America & Europe)	Product Information texts - Warnings in Section 4.4 of SPC - Listed as ADR in Section 4.8 of the SPC TB Awareness and Educational Program extended and tailored to the new paediatric Crohn's patient population, with regular assessment of program effectiveness. Patient alert card.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Potential risks - Occurrence of lymphomas including hepatosplenic T-cell lymphoma	Routine pharmacovigilance activities - Periodic safety reporting: the MAH will provide updates on the number of reported cases of HSTCL in the annual REMICADE PSUR as well as yearly estimates of post-marketing infliximab exposure in Crohn's disease and Ulcerative Colitis by age category. - Prescribing Information: the MAH will re-evaluate the need to change the Remicade Core Data Sheet (CDS) and EU labelling whenever a new case is reported. Open label extension from T47 REACH Safety surveillance (Long-Term Safety Follow-Up) from adult and paediatric studies. Paediatric Registries - North American Paediatric Inflammatory Bowel Disease Collaborative Registry. Specific questionnaires on lymphoma are utilised to obtain additional information on these events. - Paediatric IBD Registry (North America & Europe)	Product Information texts - Warnings in Section 4.4 of the SPC - Listed as ADR in Section 4.8 of the SPC TB Awareness and Educational Program extended and tailored to the new paediatric Crohn's patient population, with regular assessment of program effectiveness. Medical letter for HSTCL Centocor/Schering-Plough Medical Affairs have developed a Medical Letter for HSTCL, which is available to prescribers upon request. The Medical Letter, which is updated twice per year to coincide with the PSURs, provides information on the cases of HSTCL reported in association with infliximab.
Collection of additional Information - Long-term safety in paediatric Crohn's patients - Safety of infliximab monotherapy / infliximab episodic therapy in paediatric Crohn's patients	Routine pharmacovigilance activities - Periodic safety reporting - Prescribing Information Open label extension from T47 REACH Safety surveillance (Long-Term Safety Follow-Up) from adult and paediatric studies. Paediatric Registries - North American Paediatric Inflammatory Bowel Disease Collaborative Registry - Paediatric IBD Registry (North America & Europe). This prospective observational registry will collect information on the dose and frequency of infliximab administration.	Product Information texts - Statement in Section 4.1 of the SPC that infliximab has only been studied in combination with conventional immunosuppressive therapy in paediatric Crohn's patients

Discussion on risk management plan

The additional proposals to address the new population of paediatric CD include long-term safety follow up with in RESULTS, expanded risk minimisation and safety educational tools, and patient registries in the US and EU. These were all agreed with.

With respect to risk minimisation, the proposed activities appear appropriate. Annex II was updated regarding the conditions to ensure the safe and effective use of the medicinal product. Furthermore, the MAH committed to performing the studies and additional pharmacovigilance activities detailed in the pharmacovigilance plan.

In the safety specification provided by the MAH, reference was made to the SPC, PSURs, follow-up measures (FUMs), among others, regarding a description of the safety profile of Remicade (both known and potential risks) in the adult population, as it has been reviewed in detail and is well characterised and described within these documents. The MAH committed to submit an updated RMP as per the CHMP Guideline on Risk Management Systems for medicinal products for human use, covering all indications.

6. Overall discussion and benefit/risk assessment

Crohn's disease often begins during childhood and adolescence with sometimes debilitating consequences from malabsorption and low quality of life. The MAH has performed a study in 112 paediatric subjects with moderate to severe CD and submitted data up to 54 weeks. Comparisons of the two dose regimens (5 mg/kg every 8 or 12 weeks), showed statistically significant difference both in terms of clinical response and clinical remission at 30 and 54 weeks versus placebo. A greater proportion of subjects randomised to the q8 maintenance group achieved clinical response and remission as compared to the q12 maintenance group. However, given the lower infection frequency in the q12 week group compared with the q8 week regimen, the possibility to use this regimen was considered justified. The relatively limited experience of 10 mg /kg was not considered sufficient to be reflected in the posology.

The steroid dose at baseline in the q12 week group (0.6 mg/kg/day) was twice the dose in the q8 week treatment group (0.3 mg/kg/day). This may imply that the patients in the q12 week treatment group had a more serious disease at inclusion. However, it is also noted that there were fewer patients on steroids in the q12 week group (12/51) compared to the q8 week group (24/52). This is probably explained by the fact that there were more patients in the q12 week group that had a steroid resistant disease or had developed steroid toxicity. This points to that the q12 week population may have a more severe disease. The MAH was not able to exclude that in their answer.

A steroid-sparing effect of infliximab therapy was shown and since long-term corticosteroid treatment in childhood has well-known side effects (*Hyams and Markowitz 2005*), the steroid sparing effect may be important for long time health benefits in children with CD. In a small group of patients (n=38) with a 1-year delay in bone age at inclusion improved height status was shown for 17 of those at week 54.

There were only 8 patients <10 years in REACH, which may be seen as insufficient to support use in children younger than 10 years. Nevertheless, the expert meeting held on 30 November 2006 supported an age range from 6 years of age, and this position was endorsed by the CHMP.

The pattern and frequency of AEs in the paediatric studies was similar to the safety profile in the adult population, except that in the REACH study there seemed to be a higher frequency of serious infections compared to ACCENT I. However, there are theoretically additional risks in the current population, due to the treatment of a growing individual.

In CD in the adult population, infliximab is approved only for severe disease. The CHMP considered that it is not acceptable to include moderate disease for the paediatric population since long-term

safety experience is limited, the finding that children had more frequent infections compared to adults and the potential issue with hepatosplenic T-cell lymphoma. Furthermore, the CHMP did not agree with the inclusion of treatment of fistulising disease in the indication as the data is very limited. Notwithstanding this fact, the CHMP agreed with the inclusion of the findings in section 5.1.

The RMP was accepted, however an update of the RMP including all indications will be presented by the MAH in agreed timelines. The MAH expanded the planned registry in the US, to include 10-15 sites in 3-5 EU member states. The patient follow up will be 20 years. Additionally, a substudy to assess immunogenicity in the registry was proposed. Overall, the planned registry was endorsed and encouraged. Minor comments regarding data collection could be taken into account.
The proposed risk minimisation activities included in the RMP were considered appropriate. The CHMP considered that the conditions regarding the safe and effective use should be reflected in the annex II.

Concerning the studies on episodic treatment the MAH referred to the fact that episodic treatment is to be investigated in the adult population with UC and psoriasis. The CHMP considered of importance to study episodic treatment in this population considering the long life time expectancy in young patients and thus that the need for treatment may change considerably during life-time. Considering the rapid onset of effect of infliximab together with the safety profile and especially the high risk of infections, it is not justified to recommend maintenance treatment year after year. Decreasing exposure to or stopping infliximab in patients with stable disease or in remission were proposed by the expert panel organised by the MAH in June 2006, as one option to reduce the risk for HSTL. The MAH proposed to study episodic treatment within the registry setting, and intend to submit a protocol early next year. This approach was considered acceptable.

All patients were treated with immunomodulators at inclusion in the REACH study. This may explain the quite low frequency of infliximab antibodies (approximately 3%) compared to the adult population in the ACCENT I study (approximately 15%). The MAH was not in favour of restricting the treatment to a combination with immunomodulators but recommended to leave the decision to the treating physician. One reason for this position was the recent reports of HSTL, and the potential link between the combined treatment and these events. However, since all patients in the REACH study were treated with immunomodulators, there are no controlled data on monotherapy. Although there was a small subset of patients treated with MTX in combination with infliximab in REACH, there are insufficient data to recommend MTX as the specific concomitant immunomodulator to use. Each therapeutic option must be assessed by the treating physician. The experts participating in the meeting on 30 November 2006, were of the opinion that infliximab monotherapy was often not sufficient to obtain adequate response. They generally questioned monotherapy as an option, also due to lack of data regarding efficacy and safety of monotherapy in the paediatric population. The MAH strongly argued against undertaking a monotherapy trial. Several of the problems identified by the MAH are acknowledged, and understood. Further, since the MAH proposed to monitor immunogenicity in a substudy in the registry, one of the main uncertainties with monotherapy, i.e. antibody development, will be further studied. Taken together and considering the third/fourth line indication which the MAH has agreed to, the lack of a commitment for an additional monotherapy study was accepted.

The experts participating in the meeting on 30 November 2006, reported that the use corticosteroids and anti-histamines for premedication is common in clinical practise because infusion reaction are observed and the treating physicians opt for continued treatment. Further information on the use of premedication may increase the possibility for monotherapy is of interest. The MAH will explore this in the planned registry setting. At present, there is insufficient data to amend the current SPC with respect to use of premedication.

In conclusion, the REACH study has shown that Remicade is effective in treating children with moderate to severe CD, but several issues were identified in previous assessments which needed to be further addressed. After having considered the view of the expert meeting held on 30 November 2006, the benefit /risk balance for use of Remicade in a very restricted population is positive.

IV. CONCLUSION

On 22 March 2007 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet