London, 26 January 2006
Product name: **REMICADE**
Procedure number: **EMEA/H/C/240/II/65**

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) and psoriasis.

Ulcerative colitis (UC) is a mucosal disease that usually involves the rectum and extends proximally to involve all or part of the colon. About 40 to 50% of patients have disease limited to the rectum and rectosigmoid, 30 to 40% have disease extending beyond the sigmoid but not involving the whole colon, and 20% have a total colitis. The peak age of onset of UC is between 15 and 30 years. The male to female ratio for UC is 1:1.

The core therapy for mild to moderate UC is sulfasalazine and 5-ASA (5-aminosalicylate) compounds. These agents are effective at inducing remission in UC and in maintaining remission in UC. The majority of patients with moderate to severe UC benefit from oral or parenteral corticosteroids. Azathioprine (AZA) or 6-MP (6-mercaptopurine) have been employed successfully as corticosteroids-sparing agents in up to two-thirds of UC patients previously unable to be weaned from corticosteroids. However, despite active treatment, up to 50% of the patients have exacerbations where surgery is currently the only possible alternative. One may think that proctocolectomy might cure UC, but many patients experience social impairment and also side effects from surgery.

TNFα is a highly expressed cytokine in inflamed UC tissue. Systemic and local gut TNFα are elevated in UC and TNFα producing lamina propria cells have been reported to be present in UC and to be associated with disease activity.

The MAH submitted 2 clinical studies (ACT 1 and ACT 2) conducted in patients with UC to support the application for an extension of indication. Based on those, the MAH proposed to extend the indication for Remicade to include the treatment of patients with moderately to severely active UC.

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

2. Clinical aspects

To support the new indication, the MAH submitted 2 clinical studies (ACT 1 and ACT 2), designed primarily for the evaluation of efficacy and safety of infliximab in patients with active UC.

- Study C0168T37 (ACT 1): 54-week study of 364 subjects, designed as a randomised, placebo-controlled, double blind trial to evaluate the safety and efficacy of infliximab in patients with active UC.

- Study C0168T46 (ACT 2): 30-week study of 364 subjects designed as a randomised, placebo-controlled, double blind trial to evaluate the safety and efficacy of infliximab in patients with active UC.

2.1 Clinical pharmacology

Pharmacokinetics (PK)

PK analyses were performed in both studies, on pooled data from 484 infliximab treated subjects through week 30. Dose-dependent median serum infliximab concentrations were observed following multiple infusions of 5 mg/kg and 10 mg/kg infliximab. Subjects treated with infliximab and 6-MP/AZA, with or without corticosteroids, generally had higher serum infliximab concentrations compared with subjects treated with infliximab with 5-ASA compounds or corticosteroids only. These higher infliximab concentrations were more evident in the 5 mg/kg group. This may be related to higher incidence of antibody development in subjects not treated with immunomodulators.

Improvement in clinical signs and symptoms was observed in both dose groups at week 30. However, higher median serum infliximab trough concentrations at week 30 were associated with greater improvement in the Mayo[1] score.

The PK data indicate a correlation between serum levels and sustained efficacy. The CHMP noted that the correlation between development of antibodies and its relation to serum levels and loss of efficacy and also to hypersensitivity reactions are of interest to follow.

Pharmacodynamics

The MAH presented a review of available literature.
The literature review showed that TNFα is highly expressed in gut tissue in UC, and thus supported TNFα as a suitable therapeutic target for UC, which has been confirmed by the use of the anti-TNFα monoclonal antibody infliximab in several clinical studies (*Sands*, 2001; *Chey*, 2001; *Järnerot*, 2005; ACT-1 and ACT-2).

2.2 Clinical efficacy

ACT 1 and ACT 2

Study participants

The study participants were adults above 18 years of age, with active UC at baseline, as defined by a Mayo score between 6 and 12 points. Patients must have had endoscopic evidence of active colitis (endoscopy subscore of ≥2) and at least 1 of the following criteria:

a) current treatment with at least 1 of the following:
ACT 1: oral corticosteroids, 6-MP, or AZA
ACT 2: oral corticosteroids, 6-MP, AZA or 5-ASA compounds.
b) failed to successfully taper, tolerate, or respond to oral corticosteroids within the past 18 months.

[1] The Mayo score (Schroeder et al, 1987) was developed from the criteria of *Truelove and Witts* (1955) for mild, moderate, and severe ulcerative colitis; and from the criteria of *Baron et al* (1964) for grading mucosal appearance. It consists of the following 4 subscores:
• Stool frequency
• Rectal bleeding
• Findings of endoscopy
• Physician's global assessment
Each subscore was rated on a scale from 0 to 3, indicating normal to severe activity. The Mayo score was calculated as the sum of the 4 subscores and thus ranged from 0 to 12. The partial Mayo score is the Mayo score without the endoscopy subscore and ranged from 0 to 9.

c) failed to tolerate or respond to:

ACT 1: 6-MP or AZA within the previous 5 years.

ACT 2: 6-MP or AZA within the previous 5 years, and failed to respond to 5-ASA compounds within the previous 18 months.

The majority of subjects were men (60%), Caucasian (94%) and the median age was 39.5 years.

At baseline, a total of 11% of subjects had Mayo scores of 11 or 12 indicating severe disease, and 88% of subjects had Mayo scores of 6-10, indicating moderate disease. Three subjects had a Mayo score <6 at baseline and were recorded as protocol violators.
At the time of enrolment, 98% of subjects had a history of treatment with corticosteroids, 74% had received immunomodulatory agents, and 98% had received 5-ASA compounds. At their baseline visit, 56% were receiving corticosteroids, 46% were receiving 6-MP or AZA, and 72% were receiving 5-ASA compounds.

Baseline disease characteristics were generally similar between treatment groups

Treatments

Patients were randomised in a 1:1:1 ratio, to each of 3 treatment groups:

Group I: Placebo (n=244)
Group II: Infliximab 5 mg/kg (n=242)
Group III: Infliximab 10 mg/kg (n=242)

The subjects received induction infusions at weeks 0, 2, and 6, followed by maintenance infusions every 8 weeks (up to week 46 in ACT 1 and week 22 in ACT 2). Stable doses of corticosteroids, 6-MP/AZA, or 5-ASA compounds were allowed, during the study. Tapering of corticosteroids was allowed following the week 8 study visit.

Subjects completing treatment through week 46 (ACT 1) and week 22 (ACT 2), who, in the investigator's opinion could benefit from continued treatment, were allowed to enter a study extension beginning at week 54 and week 30, respectively.

Outcomes/endpoints

The primary efficacy endpoint in both trials was clinical response at week 8. Clinical response was defined as decrease from baseline in the Mayo score by ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

A number of other secondary endpoints were studied including clinical remission and mucosal healing at weeks 8 and 30, and quality of life assessments (IBDQ, SF-36 and EQ-5D). Clinical remission was defined as a Mayo ≤ 2 points, with no individual subscore > 1. Mucosal healing was defined by an endoscopy subscore (from the Mayo score) of 0 or 1.

The chosen efficacy endpoints were considered as relevant to evaluate efficacy in UC patients with moderate to severe disease activity.

Concomitant treatment

During both clinical trials, concomitant treatment with corticosteroids, immunomodulatory agents, antibiotics and symptomatic agents was allowed

The MAH provided data on treatments given at randomisation. In the two trials, 7-10% of patients had received cyclosporine prior to enrolment. Approximately 24% of patients had neither corticosteroids nor immunomodulators at baseline. These figures indicated that this patient group has a less severe disease. On the other hand about 16% of patients had both corticosteroids ≥20 mg and immunomodulators. These patients probably had a more severe disease and may be steroid-dependent. Another 20% of patients were on ≥20 mg corticosteroids but no immunomodulators. Thus, up to approximately 35% of patients included was steroid-dependent, which is a patient group where there is need for alternative treatment to reduce side effects of high doses of steroids and maybe bring down the colectomy rate. The data provided by the MAH was considered acceptable.

Statistical Design

Approximately 360 subjects were enrolled in each of the studies. The method used for sample size calculation was considered acceptable.
Patients were randomised in a 1:1:1 ratio (see *Treatment* section above).
The measures taken for blinding were satisfactory.

Results

Patients disposition

The studies had nearly identical populations, similar dosing regimens, and identical primary and major secondary endpoints. Thus, the data from ACT 1 and ACT 2 were pooled. In the pooled data, a total of 34% of subjects permanently discontinued study infusions, with approximately twice as many subjects in the placebo group (50%) than in either the 5 mg/kg or 10mg/kg infliximab groups.
The same pattern was seen for discontinuation due to lack of efficacy (a total of 25%, and placebo, 37%). Similar data were found in both individual studies.

Efficacy results

Primary endpoint (clinical response at week 8)

Table 1: Clinical response at week 8[a,b]

Clinical response at week 8	Placebo	Infliximab		Combined
		5 mg/kg	10 mg/kg	
ACT 1	N=121	N=121	N=122	N=243
	37.2%	69.4%	61.5%	65.4%
ACT 2	N=123	N=121	N=120	N=241
	29.3%	64.5%	69.2%	66.8%
Pooled data	N=244	N=242	N=242	N=484
	33.2%	66.9%	65.3%	66.1%
p-value		<0.001	<0.001	<0.001

[a] subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in clinical response
[b] Analysis is stratified by corticosteroid refractory status and centre location

The dose regimen with either 5 or 10 mg/kg infliximab infusions at week 0, 2 and 6 followed by further infusions of infliximab every 8 weeks (see clinical response at week 30 below) was effective and the results significantly superior to the placebo group.

Secondary endpoints

The major secondary endpoints evaluated included clinical response at week 30, clinical remission at week 8 and 30, and mucosal healing at week 8 and 30.

Table 2: Clinical response at week 30[a,b]

Clinical response at week 30	**Placebo**	**Infliximab**		**Combined**
		5 mg/kg	**10 mg/kg**	
ACT 1	N=121	N=121	N=122	N=243
	29.8%	52.1%	50.8%	51.4%
ACT 2	N=123	N=121	N=120	N=241
	26.0%	47.1%	60.0%	53.5%
Pooled data	N=244	N=242	N=242	N=484
	27.9%	49.6%	55.4%	52.5%
p-value		<0.001	<0.001	<0.001

[a] subjects who had a prohibited change in medication, had an ostomy or colectomy, discontinued study infusions due to lack of efficacy, or had insufficient data are considered to not be in clinical response

[b] Analysis is stratified by corticosteroid refractory status and centre location

A total of 33% of subjects in the combined infliximab treatment group were in clinical remission at week 8 and the same proportion (33%) was in clinical remission at week 30. In contrast, 10% and 13% of the subjects in the placebo group were in clinical remission at week 8 and week 30, respectively (statistically significant at both weeks ($p < 0.001$)).

The numbers of subjects in sustained remission (remission at both weeks 8 and 30) through week 30 were 5% for placebo and 22% for the infliximab treated group. The comparison placebo vs infliximab treated groups was statistically significant ($p < 0.001$).
In the combined infliximab treated group, mucosal healing was observed significantly in more patients at week 8 and 30 (61% and 51%, respectively) compared to the placebo group (32% and 28%, respectively).

Tapering of corticosteroids

Among subjects who were receiving corticosteroids at baseline, a greater proportion were in clinical remission and not receiving corticosteroids at week 30 in the combined infliximab treatment group (22%) compared with the placebo group (7%, $p < 0.001$). In addition, the percentage of subjects in clinical remission and not receiving corticosteroids at week 30 was similar in the 5 mg/kg and 10 mg/kg infliximab groups, and both were significantly greater than in the placebo group ($p \leq 0.001$, respectively).

Quality of life

Quality of life was significantly improved in the combined infliximab treatment group when compared with the placebo group.

Mayo score

Mayo scores improved until week 8, thereafter only minor changes occurred, but through week 30 the infliximab groups had lower scores than the placebo group.
The improvement in Mayo scores observed in infliximab-treated subjects was also reflected in all 4 Mayo subscores by week 8: stool frequency subscore, rectal bleeding subscore, endoscopy subscore and physician's global assessment subscore.

The MAH submitted the efficacy parameters results based on stool frequency and C-reactive protein (CRP) levels. The clinical response at week 8 and 30 was similar in patients that had mild diarrhoea as compared to patients who had moderate to severe diarrhoea. The same was observed for subjects with normal CRP levels as compared to subjects who had elevated CRP levels.
The clinical remission rate to infliximab at weeks 8 and 30 was greater in patients that had no or mild diarrhoea as compared to patients with moderate to severe diarrhoea. The clinical remission rate at week 8 was higher for subjects with normal CRP levels as compared to subjects who had elevated CRP levels. At week 30, the rate was similar in both groups.
In patients with UC, natural remissions lasting up to several years can occur. Intermittent treatment with infliximab would thus be desirable. The CHMP raised concerns because efficacy and safety data on re-treatment was not available. It was recommended that a study should be undertaken to assess efficacy and safety with episodic treatment, as well as to determine the optimal duration of treatment.

Discussion on clinical efficacy

Efficacy was shown with infliximab 5 mg/kg and 10 mg/kg during 30 weeks in patients with moderate to severe UC, not responding to or having side effects from conventional therapy such as steroids/AZA/6-MP or who had been in remission but with relapse when tapering of corticosteroids. In ACT-2, also non-responders to 5-ASA were included.

In subjects with active UC who had failed conventional therapy clinical response, clinical remission and mucosal healing were rapidly induced and maintained. The corticosteroid sparing effect with infliximab was considered clinically relevant. There was a slight tendency towards tapering of effects for some endpoints, but taking all endpoints into account, efficacy was sufficiently shown up to 30 weeks.
The benefit of infliximab was also shown by an improvement of the Mayo score and from criteria for grading mucosal appearance.

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, $p<0.001$).

The CHMP raised concerns on the fact that the risks of rebound effect with worsening of symptoms, and both infusion reactions and reduced efficacy due to antibody formation if re-treatment after a longer period than approximately 16 weeks had not been assessed. The MAH agreed to follow on this issue.
Relating to the recommended posology, the CHMP considered that the 5 mg/kg dose was relevant for the treatment of moderate to severe UC. It was acknowledged that the 10 mg/kg dose might be of value for some patients, particularly during long-term treatment in a patient developing antibodies to infliximab, as reduced efficacy has been observed in such situation. In the UC studies, the 10 mg/kg dose did not appear to raise safety concerns. However, for other indications an increase in the dose is linked to an increase risk of serious infections. Considering that the results did not show convincing additional efficacy, evident by data for

up to 54 weeks, the benefit / risk balance for the 10 mg/kg dose was not considered favourable. The MAH revised the product information (PI) in accordance with this recommendation.

2.3 Clinical safety

Patient exposure

In both ACT 1 and ACT 2, 364 subjects were randomized to 1 of the 3 treatment groups. The integrated safety analyses described were performed on all treated subjects. All 728 subjects received at least one dose of study drug: 484 subjects received infliximab, either 5 mg/kg (242 subjects) or 10 mg/kg (242 subjects) at week 0, 2, and 6, 14, 22, and 30 (ACT 1 only), and 244 subjects received placebo.

Through week 30, subjects in the combined infliximab treatment group had an average of 22 weeks of treatment and an average of 27 weeks of follow-up compared with those in the placebo group who had an average of 16 weeks of treatment and an average of 22 weeks of follow-up. These lower treatment and follow-up times in the placebo group were due to the higher rates of discontinuation of study infusions and study termination among subjects who were in the placebo group. No notable differences were observed between the 5 mg/kg and 10 mg/kg infliximab groups in either the average weeks of treatment or average weeks of follow-up.

Adverse events (AE)

Overview of AE

The most frequently occurring AEs (≥10% of subjects) among infliximab-treated subjects occurred in a similar proportion of subjects in the combined infliximab treatment group and in the placebo group. These events were headache (17% versus 18%); upper respiratory infection (13% versus 15%); colitis ulcerative (13% versus 19%); arthralgia (12% versus 9%); and abdominal pain (10% versus 12%).

The gastrointestinal (GI) system was the most common system-organ class of AE reported. The most common events in the GI system-organ class coded to the preferred terms of colitis ulcerative (13% versus 19%) and abdominal pain (10% versus 12%). One stricture was reported in a subject in the 5 mg/kg infliximab group. One bowel perforation was reported in a subject in the placebo group. Among subjects in the combined infliximab treatment group, there were no reported cases of intestinal obstructions, peritonitis, or bowel perforations.

The respiratory system was the second most common system-organ class of AEs reported. Upper respiratory tract infection (URI) was most common (13% versus 15%).

A greater proportion of subjects in the combined infliximab treatment group had AEs in the liver and biliary system disorders system-organ class compared with the placebo group (4% versus 1%); transaminase elevation accounted for the majority of these. The markedly abnormal transaminase elevations were transient. No subjects discontinued study infusions due to an elevated transaminase.

AEs of note that occurred more often in the combined infliximab treatment group than in the placebo group included alopecia (3% versus 0%), allergic reaction (1% versus 0%), hypotension (2% versus 0%), and urticaria (1% versus 0%).

The reported AE was generally similar in the 5 mg/kg and 10 mg/kg infliximab groups. The greatest difference between the 2 groups was observed in the respiratory system disorders system-organ class, e.g. sinusitis (6% versus 7%), coughing (3% versus 6%), and pneumonia (0% versus 2%), respectively.

The AE pattern seen in the ACT 1 and ACT 2 studies was similar to that seen in subjects with CD who are treated with infliximab. The proportion of infliximab-treated subjects with AEs in the UC population is less than that reported among subjects with CD (84% versus 91%, for UC and CD respectively). In both diseases, the GI system, followed by the respiratory system, were the most common system-organ classes of the AEs reported. A comparative analysis between the UC and the CD population showed that the common AEs associated with inflammatory bowel disease occurred in a smaller proportion of subjects with UC than those with CD: abscess (2% versus 7%); intestinal perforation (0.0% versus 4%); intestinal stenosis (0% versus 2%); and intestinal obstruction (0% versus 5%). These results were considered consistent with a higher risk of these complications in subjects with CD compared with those who have UC referring to *Glickman*, 1998.

The next table summarises the overall distribution of AEs.

Table 3: Number of subjects with 1 or more common (>5%) AEs (WHOART[1] preferred term)

	Placebo	**Infliximab**		
		5 mg/kg	**10 mg/kg**	**Combined**
Subjects treated	244	242	242	484
Avg weeks of follow-up	22.2	27.2	26.6	26.9
Avg weeks of treatment	16.1	21.9	21.0	21.5
Subjects with 1 or more AE	188 (**77.0%**)	202 (**83.5%**)	202 (**83.5%**)	404 (**83.5%**)
WHOART system-organ class				
Gastro-intestinal system disorders	109 (**44.7%**)	94 (**38.8%**)	97 (**40.1%**)	191 (**39.5%**)
Respiratory system disorders	66 (**27.0%**)	79 (**32.6%**)	95 (**39.3%**)	174 (**36.0%**)
Body as a whole – general disorders	56 (**23.0%**)	61 (**25.2%**)	69 (**28.5%**)	130 (**26.9%**)
Central & peripheral nervous system disorders	59 (**24.2%**)	64 (**26.4%**)	65 (**26.9%**)	129 (**26.7%**)
Skin and appendages disorders	63 (**25.8%**)	67 (**27.7%**)	53 (**21.9%**)	120 (**24.8%**)
Resistance mechanism disorders	52 (**21.3%**)	56 (**23.1%**)	57 (**23.6%**)	113 (**23.3%**)
Musculo-skeletal system disorders	53 (**21.7%**)	61 (**25.2%**)	49 (**20.2%**)	110 (**22.7%**)
Psychiatric disorders	20 (**8.2%**)	18 (**7.4%**)	15 (**6.2%**)	33 (**6.8%**)
Vascular (extracardiac) disorders	17 (**7.0%**)	13 (**5.4%**)	12 (**5.0%**)	25 (**5.2%**)
Cardiovascular disorders, general	1 (**1.6%**)	13 (**5.4%**)	11 (**4.5%**)	24 (**5.0%**)

[1]World Health Organisation Adverse Reaction Terminology

Deaths and serious adverse events (SAE)

➢Deaths

No deaths occurred through week 30 in both clinical trials.
In ACT 1, one placebo treated patient committed suicide 2 months after completing the main part of the study.
In ACT 2 two events were noted. One patient randomized to the 5 mg/kg infliximab group, was diagnosed with pulmonary histoplasmosis (he originated from an endemic region), 1 week after the third infusion in the study extension and died 3 weeks after hospital admission with adult respiratory distress syndrome and renal failure. This event was considered probably related to treatment with infliximab. Another subject randomized to the placebo group,

received commercial infliximab for the treatment of concurrent RA and reportedly died due to unspecified complications of a cerebral vascular accident.

➢SAE

A higher proportion of subjects in the placebo group had an SAE compared with that of subjects in the combined infliximab treatment group (20% versus 13%, respectively). The most frequently reported SAE was colitis ulcerative (ie, worsening UC), which occurred in 11% of subjects in the placebo group compared with 6% in the combined infliximab treatment group. The proportions of subjects with other reported SAEs were similar among the combined infliximab and placebo treatment groups.

There were 3 malignancies reported through week 30 among ACT 1 and ACT 2 subjects. In ACT 1, one subject on 5 mg/kg infliximab, who had a history of elevated prostate-specific antigen (PSA) levels prior to enrolment in the trial, was diagnosed with prostatic adenocarcinoma after the week 8 visit.
In ACT 2, one placebo patient was diagnosed with a basal cell carcinoma. Another patient on 5 mg/kg infliximab, with a 15-year history of UC, was diagnosed as having rectal adenocarcinoma.
The clinical trials presented to support the claimed indication were short-term studies, and the overall exposure of this patient population was insufficient to draw conclusions regarding whether infliximab contributes to the promotion of malignancies or affects the occurrence of e.g. lymphoma. The MAH will undertake long-term follow-up addressing these aspects.

Specific adverse events

➢Infusion reactions

The average number of infusions, proportion of infusions with infusion reactions, and proportion of subjects who had an infusion reaction were similar between the infliximab and placebo treatment groups. The proportion of subjects with infusion reactions was comparable but slightly higher in the 10 mg/kg infliximab group compared with the 5 mg/kg infliximab group (12% versus 10%, respectively). No serious infusion reactions were reported and no subjects discontinued infusions due to an infusion reaction.

➢Serious Infections

In ACT 1 and ACT 2, 11 subjects (2%) in the combined infliximab treatment group had a serious infection compared with 3 subjects (1%) in the placebo group. Serious infections occurred in 3 subjects (1%) in the 5 mg/kg infliximab group and 8 subjects (3%) in the 10 mg/kg infliximab group.

➢Tuberculosis (TB) and opportunistic infections

There was 1 case of pulmonary TB reported (10 mg/kg infliximab). This subject had a negative purified protein derivative skin test and negative chest radiograph at screening.
Herpes zoster (including varicella zoster) was reported in 7 (1%) subjects in the combined infliximab treatment group (5 at 5 mg/kg and 2 at 10 mg/kg infliximab). One subject in the placebo group had herpes zoster. No other serious or systemic potential opportunistic infections were observed during the ACT trials. During the ACT 2 study extension, 1 subject randomized to the 5 mg/kg infliximab group developed histoplasmosis that progressed to death (see *Death* section above).

➢Autoimmune Disorders

There was 1 report of a lupus-like reaction, in a subject randomized to the 5 mg/kg infliximab group who had an ANA titer > 1:320 at baseline. There was 1 report of an autoimmune disorder (ie, autoimmune hepatitis) in ACT 2 in a subject treated with 10 mg/kg infliximab.
A total of 10% of infliximab-treated subjects were newly positive for anti-nuclear antibodies (ANA) and 8% of them also positive for anti-dsDNA antibodies compared with 3% newly ANA positive and 0% newly anti-dsDNA positive patients receiving placebo.

➢Neurologic Events

Neurologic events were observed infrequently and were generally not of clinical concern. One subject experienced increased peripheral neuropathy and another optic neuritis. Both events were considered not related to the study agent and infusions were continued.

➢Laboratory findings

No clinically important differences in any of the haematology laboratory parameters or in any of the chemistry laboratory parameters were noted between treatment groups.
No notable differences were observed between the 5 mg/kg and 10 mg/kg infliximab groups.

The magnitude and duration of transaminase elevations seen in the ACT trials were similar to those seen in subjects treated with infliximab for CD but lower than those noted in subjects with AS and PsA.

➢Antibodies to infliximab and possible reactions to study agent

The incidence of infusion reactions was greater among subjects who were positive for antibodies to infliximab than among those who were negative for antibodies to infliximab. Eight of 17 (47%) antibody-positive subjects in the combined infliximab treatment group experienced infusion reactions through week 30 compared with 7 of 62 (11%) subjects who were evaluated as antibody negative. Six of the antibody to infliximab positive subjects who had infusion reactions were in the 5 mg/kg infliximab group. Among the antibody to infliximab-positive subjects, the infusion reactions were generally mild to moderate, and there were no serious infusion reactions, infusion reactions leading to discontinuation, or possible anaphylactic reactions. One subject in the 5 mg/kg infliximab group had a possible delayed hypersensitivity reaction.

Among the antibody-negative subjects, there were no serious infusion reactions, infusion reactions leading to discontinuation, or possible anaphylactic reactions. One subject in the 10 mg/kg infliximab group had a possible delayed hypersensitivity reaction.

Among the subjects who had an inconclusive antibody to infliximab status through week 30, 28 of 295 (10%) subjects in the combined infliximab treatment group experienced infusion reactions. There were no subjects who had a serious infusion reaction or discontinued infusions due to infusion reactions.

Risk management plan (RMP) and pharmacovigilance plan

Further to the routine post authorisation safety monitoring, the MAH proposed additional pharmacovigilance activities, including risk assessment and risk minimisation action plans.

The MAH will continue to generate long term efficacy and safety data in UC through clinical studies. A European patient registry in patients with moderate to severe active UC will be initiated. Patients will be followed for 5 years following initiation of infliximab or counting

from enrolment in the registry. Periodic safety reporting will also continue in the postmarketing environment through regular surveillance activities utilising a worldwide safety database.
Reference was also made to the available product and safety information, which will be revised on an ongoing basis to incorporate any new relevant information on the use of infliximab in patients with UC.

The current physician awareness and education activities, focusing on TB and other infections will continue and will be extended to UC.

Discussion on clinical safety

The data set for the safety evaluation was based on the ACT1 and ACT2 study. The majority of patients received 7.3 infusions, with an average total dose of 36.5 or 73 mg/kg (5 and 10 mg/kg infliximab group). The followed up period for all treated patients was at least 30 weeks. Overall, the treatment with infliximab was well tolerated with no new or unexpected safety signals.
The safety profile of infliximab in the treatment of UC was considered similar to safety during treatment of other approved indications, in particular CD.

The incidence of AEs was slightly greater among the infliximab arms than in the placebo group. The GI system was the body system mostly affected. Other common events were headache, URI, arthralgia and abdominal pain.
No patient died and none of the three malignancies were considered related to infliximab by the investigators. There was one pulmonary TB (10 mg/kg infliximab) in a patient with negative PPD result and negative chest radiograph at screening.

The incidence of ANA antibodies and anti-dsDNA as well as the incidence of anti-infliximab antibodies appeared lower than that observed in previous clinical studies. Approximately 5% of patients treated with infliximab developed antibodies to infliximab. The presence of anti-infliximab antibodies was associated with an increase in infusion reactions. The findings were considered consistent with that of other clinical trials.

The CHMP noted that infections were the most common side effects and continuing surveillance, in particular of serious infections including TB, was considered important. A contributing effect of infliximab on the promotion of tumours such as adenocarcinoma of the colon is not known and should be monitored.

The MAH clarified that the ACT 1 and ACT 2 studies were not designed to investigate effects on colectomy and that the study population had stable UC, which might indicate a low colectomy rate. This issue is to be further studied.
The CHMP raised concerns that infliximab could affect the risk of malignancy associated with UC, considering that anti-TNF therapy is suspected to have a potential tumour promoting effect. Further to the request for supplementary information, the MAH included a warning in the SPC.
The ACT trials excluded patients hospitalised and patients with signs of fulminant colitis. Fulminant colitis was an exclusion criterion in the pivotal studies, but limited data from another, recently published, study does not raise concerns.

The MAH submitted a European RMP, together with a pharmacovigilance plan. The RMP was based on the safety experience and in the specific safety issues regarding the risk of dysplasia and colorectal cancer in UC patients treated with infliximab. The pharmacovigilance plan included open label extensions of clinical trials and an observational registry study. The available prescribing information will focus on the need for screening

through colonoscopy and biopsies, with differential schemes according to recommendations of professional societies. These recommendations appear to be well founded. Furthermore, the MAH proposed to implement the Physician Awareness and Education activities that aim to help prescribers pay attention to the known safety problems, in UC. Moreover, all patients should get the Patient Alert Card already approved.

3. Overall discussion and benefit/risk assessment

Ulcerative colitis is a new area for treatment with anti-TNF therapy and currently not approved for any other anti-TNF or biologic agent. The rationale for the treatment is based on findings of increased levels of TNF in patients with active UC.

Two pivotal studies with infliximab in the treatment of UC were submitted in the application. These studies include 364 patients each, with moderate to severe UC and with non-response to other conventional therapies. A placebo-add-on approach was chosen for the performed studies.

The assessment concluded that efficacy had been shown for up to 54 weeks. Disease activity, evaluated with the Mayo score, was reduced. Clinical response and clinical remission occurred in a significantly higher number of patients in the active groups compared with placebo. A clinically relevant corticosteroid sparing effect as well as fewer infliximab treated patients who discontinued due to lack of efficacy, also speak in favour of infliximab treatment compared with the add-on placebo treatment.

No new safety signals were observed in the trials for up to 54 weeks, however, the (S)AEs in the studies confirm the already known safety issues that are typical for Remicade. Events more specifically related to UC, such as gut perforations and cases of fulminant colitis were not reported in the UC studies. One stricture was reported in a subject in the 5 mg/kg infliximab group. One bowel perforation was reported in a subject in the placebo group.
Colectomy outcome was not studied in ACT 1 and ACT 2, an issue considered of relevance for efficacy and safety. One reason to discuss colectomy is the often dysplastic character of the disease, and the potentially tumour-promoting effect of anti-TNF therapy that by protracting colectomy might in the long term lead to a rise in malignancies. The fact that a potentially tumour-promoting drug is given to a patient population with a precancerosis remains a potential problem.
Further data evaluating colectomy and malignancy rates, as well as episodic treatment will be collected by the MAH.

The CHMP considered that the use of infliximab in patients with moderate to severe UC is approvable in cases where other treatments have failed and the patient is steroid dependent. Changes where introduced to the product information.

4. Conclusion

On 26 January 2006 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.

The CHMP adopted on 26 January 2006 an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation, as amended.