European Medicines Agency

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ASSESSMENT REPORT
FOR
Remicade

International Nonproprietary Name:
infliximab

Procedure No. EMEA/H/C/II/107

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

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).

Ulcerative colitis is a chronic inflammatory bowel disease of unknown aetiology. In Europe, the incidence of UC is estimated at 5 to 25 per hundred thousand. Although patients of all ages can be affected, UC peaks between 15 and 35 years of age.

Ulcerative colitis is characterised by a uniform and continuous inflammation, without intervening areas of normal mucosa. In 95% of cases, inflammation affects the rectum, and extends proximally for a variable distance. The inflammatory reaction involves the surface mucosa, the crypt epithelium, and the submucosa. The affected mucosa bleeds easily, contains ulcerated areas, and is often completely denuded resulting in bloody diarrhoea, anaemia, and cramping abdominal pain. In severe cases, the bowel wall may become extremely thin, and inflammation may extend to the serosa with the risk of dilatation, toxic megacolon, and subsequent perforation. Toxic megacolon commonly requires an urgent colectomy to avoid perforation, peritonitis, and sepsis.

Ulcerative colitis is associated with an increased risk of colorectal carcinoma. The risk of carcinoma increases with duration and extent of disease: for patients with UC duration of 10 years the risk is 2%; this risk increases to 8% and 18% with a duration of 20 and 30 years, respectively.

Infliximab's initial approval for induction and maintenance treatment of patients with moderately to severely active UC (variation II-65) was based on two studies, ACT 1 and ACT 2. In the present variation application the MAH proposed changes to sections 4.1 and 5.1 of the SPC in relation to the UC indication, based on new data from these studies. The MAH proposed to add information in section 4.1, concerning a claimed reduction in the incidence of colectomy in the same patient population. The information presented included data from the ACT 1 and ACT 2 clinical studies showing a reduction in the incidence of colectomy with infliximab, as well as published data from *Järnerot et al*, 2005 showing a reduction in the incidence of colectomy with infliximab treatment in subjects with moderately or severely active UC refractory to intravenous (IV) corticosteroids.

Clinical aspects

Clinical efficacy[1]

Main studies

ACT 1 and ACT 2 were multicentre, randomised, double-blind, placebo-controlled, parallel-group studies designed to examine the safety and efficacy of infliximab in subjects with moderately to severely active UC. To enter ACT 1 or ACT 2, subjects must have had moderately to severely active UC as defined by a baseline Mayo score[2] between 6 and 12 points, inclusive. Subjects must also have been ambulatory and not considered likely to undergo a colectomy within 3 months of enrollment.

[1] For more detailed information please refer to the Scientific discussion for variation II.65, also published in infliximab's EPAR.

[2] 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

Subjects must also have had endoscopic evidence of active colitis as indicated by an endoscopy subscore of ≥ 2. In addition, subjects must have met at least 1 of the following criteria:

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

The two ACT studies were similar in design with subjects randomised 1:1:1 to receive placebo, 5 mg/kg, or 10 mg/kg at weeks 0, 2, and 6, and then every 8 weeks thereafter. In both studies, the primary endpoint was clinical response at week 8, with clinical response, clinical remission, and mucosal healing also evaluated at week 30. The ACT 1 study also had an additional evaluation at week 54 to establish that efficacy was maintained through a full year. Induction of clinical response, clinical remission, and mucosal healing, and maintenance of clinical response and clinical remission were the primary and major secondary endpoints of both studies.

Colectomy was included as an additional efficacy endpoint, as outlined in the original protocols, even though it was anticipated that the colectomy rate in the ACT study population would be relatively low because the population to be enrolled was ambulatory. The results from ACT 1 and ACT 2 were submitted to various health authorities in clinical study reports and were published by *Sandborn et al* (2005), and by *Rutgeerts et al* (2005a; 2005b). For the primary and major secondary efficacy endpoints examined, in both ACT 1 and ACT 2, both the combined 5 mg/kg and the 10 mg/kg infliximab treatment regimens as well as the individual treatment regimens were significantly more effective than placebo with similar efficacy seen in both infliximab treatment groups.

ACT 1 and ACT 2 study extensions

In October 2003, the protocols for the ACT studies were amended to include a study extension to allow subjects the option of continuing therapy beyond the end of the study as specified in the original study design. Subjects who completed treatment through week 46 in ACT 1 or through week 22 in ACT 2 (with follow-up through week 54 and week 30, respectively), who, in the opinion of the investigator, might have benefited from continued treatment, were eligible for enrollment in the study extension for up to 3 years.

Subjects in the study extensions continued to receive the randomised treatment they received during the main portion of the study until the study sites were unblinded. In the study extensions, all subjects, investigators, and coordinators were blinded to subject treatment status until the last subject had completed their 54 week follow-up (week 54 in ACT 1 and week E-24 in ACT 2). Once unblinding occurred, subjects receiving placebo were to be terminated from the study, per protocol, and subjects in the 10 mg/kg group were allowed to decrease their dose to 5 mg/kg. If a subject receiving 5 mg/kg (either randomised to 5 mg/kg or decreased from 10 mg/kg) lost response, the dose of subsequent infusions could be increased to 10 mg/kg. Only a single dose increase was permitted.

RESULTS UC

RESULTS UC was an observational study, designed to collect long-term safety information on death, serious infections, new malignancies (including colorectal cancer), and new autoimmune diseases in subjects previously enrolled in ACT 1 or ACT 2. All subjects who received study agent in either of the ACT studies were eligible to participate in RESULTS UC after completing or withdrawing from the main portions of the studies or the extensions. No study agent was administered in RESULTS UC, but subjects were allowed to take commercial medications including infliximab. Following enrollment into RESULTS UC, investigators were to complete a safety questionnaire at 6 months and at 1 year

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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.

following the subject's last safety visit in an ACT study; investigators were also to complete a safety questionnaire annually for 5 years. Initially, RESULTS UC did not make any provision for the collection of colectomy data, but was subsequently amended to inquire about colectomy.

ACT Combined colectomy analysis

ACT 1 and ACT 2 were both designed to examine the effect of infliximab on the safety and efficacy in subjects with moderately to severely active UC. Induction of clinical response, clinical remission, mucosal healing, and maintenance of clinical response and clinical remission were the primary and major secondary endpoints of both studies. In the original protocols, colectomies through week 54 in ACT 1 and through week 30 in ACT 2 were to be summarised and compared between treatment groups within each study, and no pooled analysis of the data from ACT 1 and ACT 2 was planned.

In 2003, when it was noted during SAE monitoring, that some subjects were discontinuing ACT 1 and ACT 2 and having colectomies that were not being captured in the study databases, the MAH reassessed the way data were being collected. In addition, the higher than expected incidence of colectomy lead to a revision of the planned colectomy analysis, as shown below:

- Collect data on the colectomy status through 54 weeks after their initial infusion for all subjects who participated in either ACT 1 or ACT 2.
- Replace the individual colectomy analyses within each study with a single ITT (intent-to-treat) analysis of the combined incidence of colectomy from both ACT 1 and ACT 2 through 54 weeks after each subject's first study infusion referred to subsequently as the combined colectomy analysis.

Järnerot Study

The Järnerot study (C0168Y06) was a multicentre, randomised, double-blind, placebo-controlled, parallel-group investigator initiated study specifically designed to evaluate the treatment benefit of infliximab in addition to conventional corticosteroid therapy for subjects with moderate to severe UC that was unresponsive to treatment with IV corticosteroids (*Järnerot et al*, 2005).

Subjects (18 to 75 years in age) who were hospitalised with a severe or moderately severe flare-up of UC were potential candidates for enrollment if they were not responsive to IV corticosteroids within 4 to 8 days after initiation of the treatment. This was determined using the fulminant colitis index at day 3 which would allow entry of a severely active population with a high likelihood of an imminent colectomy, or was determined by the Seo index[3] at days 5 to 7 which allowed access of subjects with persistently active UC. Subjects were randomised to receive either a single dose of 5 mg/kg infliximab or placebo. The study was analysed as an ITT analysis. The primary endpoint was the proportion of subjects who had en event (colectomy or death) during the 3 months following study drug administration. Additionally, subjects were followed up to 1 year.

The study was designed to enroll a total of 150 subjects to achieve a statistical power of 80% with a significance level of 0.05, assuming that 60% of placebo-treated subjects and 35% of infliximab-treated subjects would have a colectomy within 3 months. However, due to slow enrollment, an interim analysis was performed after 45 subjects had completed treatment in the study; 24 subjects were randomised to the infliximab treatment group and 21 subjects randomised to the placebo treatment group. Because of the significant reduction in the incidence of colectomy in subjects treated with infliximab, the study was stopped since it was considered unethical to continue.

To examine and confirm the results of this study, the MAH arranged for and supervised the recollection and creation of a source-verified database for analysis. During development of this database, the accuracy of key data elements for the colectomy analysis was also evaluated. Since the

[3] The Seo index is used to measure disease severity. Seo index scores are defined as follows:
• Seo index > 220 = severe UC
• Seo index ≥ 150 to ≤ 220 = moderately severe UC
• Seo index < 150 = mild UC
• Seo index < 120 = Patient Defined Remission (*Higgins et al*, 2005).

initial consent form signed by all participants in the study only noted that data could be reviewed by the study group and regulatory representatives, and did not specifically discuss review of the data by third parties, the MAH elected to reconsent all subjects for the recollection and reanalysis of the data. Of the initial 45 participants, 44 agreed to this data collection.

Results

Data on the impact of infliximab on colectomy in two distinct populations were presented: ambulatory subjects in the ACT trials with active UC, who were treated with a 3 dose induction therapy (5 mg/kg or 10 mg/kg) followed by maintenance therapy; and hospitalised subjects in the Järnerot study with active UC unresponsive to IV corticosteroids treated with single dose (5 mg/kg) induction therapy. The data presented are the time to first colectomy, and the proportion of subjects who underwent a colectomy.

Demographic characteristics

The following table presents an overview of baseline demographics in ACT studies and the Järnerot study. Although different populations were included, the CHMP noted that there were no major differences in the demographic characteristics in the different studies.

Summary of demographics at baseline; randomised subjects in the combined ACT colectomy analysis and in the Järnerot study

	ACT 1 and ACT 2	**C0168Y06**
Randomised subjects	728	44*
Sex		
N	728	44
Male	437 (60.0%)	23 (52.3%)
Female	291 (40.0%)	21 (47.7%)
Age (yrs)		
N	728	44
Mean ± SD	40.9±13.78	37.3±12.02
Median	39.5	38.0
IQ range	(30.0, 51.0)	(28.0, 43.0)
Range	(18, 82)	(18, 61)
Weight (kg)		
N	728	39
Mean±SD	77.9±17.86	68.52±13.724
Median	76.0	68.50
IQ range	(65.0, 88.6)	(59.30, 76.30)
Range	(40, 177)	(46.2, 113.2)
Nicotine use		
N	728	44
Non-smoker	382 (52.5%)	42 (95.5%)
Smoker	32 (4.4%)**	2 (4.5%)

*Randomised subjects who reconsented

**Current smoker: The remaining subjects stopped smoking prior to study entry.

ACT combined colectomy analysis

The cumulative incidence of colectomy was assessed through the analysis of the time to the first partial or total colectomy. Cumulative incidence of colectomy through 54 weeks was 16.5% and 10.1% for placebo and combined infliximab treatment groups, respectively. The comparison was statistically significant with p = 0.015 in favour of the combined infliximab treatment group. In the placebo group 36 out of 244 (14.7%) patients had a colectomy; compared with 28 out of 242 (11.6%, non-significant) patients treated with 5 mg/kg infliximab and 18 out of 242 (7.4%; p=0.011) patients treated with 10 mg/kg infliximab.

Subjects treated with either 5 mg/kg or 10 mg/kg infliximab had a lower risk of undergoing colectomy than those treated with placebo, with the risk of colectomy 29% lower in the 5 mg/kg infliximab treatment group and 53% lower in the 10 mg/kg infliximab treatment group than in the placebo treatment group (p = 0.166 and p = 0.007, respectively).

For the separate studies, there was a significant reduction in the risk of undergoing colectomy between the combined infliximab and placebo treatment groups in ACT 2 with a hazard ratio of 0.41 (p = 0.002), while no difference, was observed within ACT 1.

The CHMP noted that the magnitude of the infliximab treatment effect in reducing the incidence of colectomy varied by dose, and was quite small for the approved dose, 5 mg/kg. Both the 5 mg/kg and the 10 mg/kg infliximab treatment groups had a lower incidence of colectomy than the placebo treatment group, but only the 10 mg/kg infliximab treatment group reached statistical significance of $p < 0.05$. A similar result was seen in the analysis of the proportion of subjects with colectomy through 54 weeks.

Analyses in patients with different disease severity were provided for placebo and infliximab 5 mg/kg. A statistical significance at the 0.05 level was not achieved for these subgroup analyses, however the proportion of subjects with a colectomy was greater in the placebo group than in the 5 mg/kg infliximab group in both the subgroup of patients with more severe disease and the subgroup of patients with less severe disease; greater treatment effects were observed in patients with more severe disease compared to those with less severe disease. The small sample size in each of the subgroups restricted the interpretation of these findings.

UC-related hospitalisations; surgeries and procedures used to treat UC

Subjects in both the 5 mg/kg and 10 mg/kg infliximab treatment groups had significantly fewer UC-related hospitalisations than subjects in the placebo treatment group (p = 0.019 and 0.007, respectively).

In the combined infliximab treatment group subjects had fewer UC-related hospitalisations than subjects in the placebo treatment group (p = 0.003). When expressed as hospitalisations per 100 subject-years, subjects in the combined infliximab treatment group had 20 hospitalisations compared with 40 in the placebo treatment group.

Subjects in the 5 mg/kg infliximab treatment group had fewer UC-related surgeries and procedures than subjects in the placebo treatment group (p=0.145). Subjects in the 10 mg/kg infliximab treatment group had significantly fewer UC-related surgeries and procedures than subjects in the placebo treatment group (p=0.022).

In the combined infliximab treatment group subjects had fewer UC-related surgeries and procedures than subjects in the placebo treatment group (p = 0.026). When expressed as events per 100 subject years, subjects in the combined infliximab treatment group had fewer UC-related surgeries and procedures (20.5) when compared with subjects in the placebo treatment group (34.1).

Järnerot study

The primary endpoint was the proportion of subjects who had an event (colectomy or death) during the 3 months following study drug administration. Subjects were followed up to 1 year. Two datasets were used for analyses. The database used for the published analysis was compiled from summary information obtained from records of 45 subjects randomised in the initial study (*Järnerot et al*, 2005). The Sponsor's database consisted of subject-level data from the 44 treated subjects in the published analysis who consented to have their data recollected.

No subject died during the study. A significantly lower proportion of subjects in the infliximab group (29.2%) had a colectomy within 3 months postinfusion compared with that observed in the placebo group (66.7%; p = 0.017; odds ratio: 0.206, 95% CI: 0.058 to 0.729). The odds of a colectomy being performed within 3 months following a single infusion of 5 mg/kg infliximab were approximately 80% lower than that observed following placebo infusion. In a secondary analysis, the time to colectomy was significantly longer in subjects treated with infliximab compared with placebo (hazard ratio = 0.3; p = 0.007), with half of the subjects in the placebo group undergoing a colectomy by day 10, and fewer than 50% of those treated with infliximab undergoing colectomy by 3 months postinfusion. These results were similar between the first analyses and subjects that reconsented.

Persistence of Efficacy and/or Tolerance Effects

There was no apparent rebound effect on the incidence of colectomies either in the ACT combined colectomy analysis beyond 54 weeks after first infusion of study agent or in the Järnerot study through 1 year. In the ACT combined colectomy analysis, a total of 40 subjects (17 in placebo; 9 in the 5 mg/kg infliximab treatment group; 14 in the 10 mg/kg infliximab treatment group) had a colectomy beyond 54 weeks after first infusion. All but 6 colectomies were reported from RESULTS UC. In the Järnerot study at the 1 year postinfusion visit, 14 (70%) of the 20 subjects in the placebo group and 10 (41.7%) of the 24 subjects in the infliximab group had a colectomy. One additional subject in the placebo group had a colectomy after the 1 year visit.

The differences in follow-up between the infliximab and placebo treatment groups, and the lack of controls on the use of concomitant medications limit conclusions. The CHMP noted that the trend towards a greater proportion of subjects with colectomies in the placebo group than with the two infliximab groups is consistent with the data through week 54 and that these data support that there is no rebound effect on colectomy in patients treated with infliximab. This observation is supported by the data from the Järnerot study although information on the use of infliximab as rescue therapy was not collected during follow-up evaluations and is therefore not available.

Discussion on clinical efficacy:

One important goal in the treatment of UC is to prevent colectomy. The data presented showed that treatment with infliximab reduces the need for colectomy.

However, the ACT studies were made in a patient population with moderate to severe disease, where the risk for colectomy is considered relatively low with only about half of the patients treated with steroids at baseline. The effect on the colectomy incidence with the approved dose (5 mg/kg) was not statistically significant. When subgroup analyses were performed according to disease severity, it appeared that subjects with more severe disease may have had a greater treatment effect that subjects with a less severe disease. However the sample size was considered too small to allow interpretation.

The Järnerot study included patients who had severe or fulminant disease not responding to IV corticosteroids, which is a population with high risk for colectomy. The difference in populations compared to the ACT studies might explain why the data from the Järnerot study was stronger although based on fewer patients. There were no indications that there is a risk, on longer term, for a rebound effect with more colectomies after a single dose of infliximab although data are lacking if any patients in the Järnerot study was treated with commercial infliximab after the study dose; these data were not collected during the post follow-up evaluations.

The CHMP agreed to include data on colectomy outcome and the Järnerot study results in the product information. Additionally, the inclusion of information regarding the impact in the number of hospitalisations and surgeries was agreed.

However, the CHMP did not consider it acceptable to add reduction of the incidence of colectomy as an indication. This outcome is mainly the goal of treatment of UC and not an indication, and in addition, the results from the ACT studies do not show sufficiently convincing effects with the approved dose 5 mg/kg.

Clinical safety

Based on the mechanism of action of infliximab and on previous experience with infliximab both within and outside clinical trials, the adverse events (AEs) of special interest that may occur in infliximab-treated patients include: infections (including tuberculosis (TB) and opportunistic infections), infusion reactions, delayed hypersensitivity reactions, malignancies, autoimmune disorders, neurologic or demyelinating events, haematologic events, hepatotoxicity, and congestive heart failure.

Common adverse events

ACT 1 and ACT 2

As previously reported in the 54-week summary of clinical safety (SCS), the types and frequencies of AEs occurring among subjects in ACT 1 and ACT 2 were consistent with those already described in the current infliximab prescribing information. The proportion of subjects with at least 1 AE was slightly higher in the combined infliximab-treated group (86%) compared with the placebo treatment group (80%) with a longer average follow-up in the infliximab group (41 weeks) compared with the placebo group (32 weeks). No notable differences were observed between the 5 mg/kg and 10 mg/kg infliximab treatment groups in the proportions of AEs (86% and 86%, respectively). The most frequently occurring AEs (≥ 15% of infliximab subjects) were headache (19% and 18%), upper respiratory tract infection (18% and 18%), and worsening of UC (16% and 25%) in the infliximab and placebo groups, respectively. Of note, 10 (2.1%) subjects in the combined infliximab treatment group had pneumonia, but none in the placebo group.

Järnerot study

In the 3-month postinfusion period, a similar proportion of subjects had AEs in the 5 mg/kg infliximab (83.3%) and placebo (75.0%) groups, despite a longer average duration of follow-up among subjects in the infliximab group (10.2 weeks) compared with the placebo group (5.2 weeks). Note that, per protocol, subjects who had a colectomy were discontinued from the study. Overall, no clinically notable differences were observed between treatment groups when AEs were examined by system-organ class or preferred term. Similar results were observed through 1 year.

Through 3 months post-infusion, the most frequent system-organ classes for which AEs were observed in the 5 mg/kg infliximab group (note that proportions shown in parentheses are for the 5 mg/kg infliximab and placebo groups, respectively) were resistance mechanism disorders (6 [25.0%] and 6 [30.0%]) and skin and appendage disorders (6 [25.0%] and 3 [15.0%]). The most commonly occurring AE was oral moniliasis (3 [12.5%] and 0.0%).

Through 1-year postinfusion, a similar number and proportion of subjects in the 5 mg/kg infliximab group (20 [83.3%] subjects) and the placebo group (17 [85.0%] subjects) had 1 or more AEs, despite a longer average duration of follow-up in the infliximab group (31.7 weeks) compared with the placebo group (18.7 weeks). No clinically notable trends were observed between the placebo and infliximab groups in the incidence or types of AEs occurring through 1 year postinfusion.

Deaths

Of the 728 subjects who participated in either ACT 1 or ACT 2, 6 subjects died. None of the deaths occurred within 54 weeks of the first study infusion. One of these subjects was diagnosed with pulmonary histoplasmosis 1 week after the third infusion of the study extension (5 mg/kg group) and died of renal failure and other complications from pulmonary histoplasmosis. The CHMP considered that this infection was likely related to treatment. During the Järnerot study, no deaths occurred in either treatment group through 1 year.

Serious Adverse Events

ACT 1 and ACT 2

As previously reported in the 54-week SCS, a smaller proportion of subjects in the combined infliximab treatment group than in the placebo treatment group had a serious adverse event (SAE) (18.4% versus 23.4%, respectively) and the most frequently occurring SAE was worsening of UC, which was reported in 40 (8.3%) subjects in the combined infliximab treatment group and 30 (12.3%) subjects in the placebo treatment group. Pneumonia was reported as an SAE in 5 (1.0%) subjects in the combined infliximab treatment group and in no subjects in the placebo treatment group. Among the 37 subjects whose retrospective data through 54 weeks were available, 12 subjects (6 placebo and 6 infliximab) had an SAE of worsening of UC or lack of improvement of UC.

Beyond 54 weeks after the first infusion in ACT 1 and ACT 2, the types of SAEs that occurred were consistent with the data through 54 weeks of treatment. SAEs occurred in 11 (5.0%) subjects in the infliximab treatment group and 5 (8.6%) subjects in the placebo group.

Järnerot Study

Within 3 months postinfusion, 1 (4.2%) subject in the 5 mg/kg infliximab group had SAEs of fever, infection, and pulmonary infiltration. In the placebo group, 3 (15.0%) subjects had SAEs, including 1 subject each with abscess, wound infection, and hepatotoxic effect.

From 3 months postinfusion through 1 year, 3 additional subjects in the 5 mg/kg infliximab group had SAEs. All 3 subjects had SAEs of flare of UC, 1 of whom also had an SAE of anaemia. In the placebo group, 2 additional subjects had SAEs after the 3-month visit, including 1 subject with flare of UC and 1 subject with atrioventricular block.

The CHMP noted that the higher incidence of SAE in the placebo groups appears driven by more UC-related events, than in the infliximab group.

AEs Leading to discontinuation of study agent

As previously reported in the 54-week SCS for ACT 1 and 2, 34 (7.0%) subjects in the combined infliximab treatment group discontinued study infusions due to an AE compared with 23 (9.4%) subjects in the placebo treatment group. The most frequent AE leading to discontinuation of study infusions in both treatment groups was worsening of UC, occurring in 10 (2.1%) subjects in the combined infliximab treatment group and 16 (6.6%) subjects in the placebo treatment group. During the Järnerot study, no subject discontinued from the study due to an AE.

Malignancies

Four malignancies were reported in the 54-week period in ACT studies. These included: a prostatic adenocarcinoma (5 mg/kg); a rectal adenocarcinoma (5 mg/kg); and 2 basal cell carcinomas 1 placebo and one subject in the 10 mg/kg group. Beyond 54 weeks after the first infusion in ACT 1 and ACT 2 through the database lock, no malignancies were reported. Neoplasms were reported in 2 subjects (breast neoplasm benign and a lipoma), neither of these neoplasms was malignant. After the database lock, the Sponsor became aware of 3 subjects with malignancies.

In the RESULTS UC study, 4 subjects who had previously received infliximab had malignancies during long-term follow-up. Nonmelanoma skin cancers occurred in 3 subjects, and 1 subject was diagnosed with prostate cancer. No malignancies were observed in the placebo treatment group.
An additional malignancy was identified during review of the pathology reports for the colectomy narratives in a subject previously treated with 5 mg/kg infliximab, who had an incidental adenocarcinoma limited to the mucosa, which was identified in a bowel specimen obtained during his colectomy surgery. This event was not reported as an SAE.

No malignancies were reported through 1 year postinfusion in the Järnerot study.

Infections

Any Infection

As reported in the 54-week SCS, more subjects in the combined infliximab treatment group had infections than in the placebo treatment group (40.1% and 32.8%, respectively). Infections occurred more frequently in the 10 mg/kg infliximab treatment group than in the 5 mg/kg infliximab treatment group (41.3% versus 38.8%, respectively). Upper respiratory tract infection was the most common infection in both the combined infliximab and placebo treatment groups (11.6% and 11.9%, respectively). Of note, pneumonia occurred in 9 (1.9%) subjects in the combined infliximab treatment group and in no subjects in the placebo treatment group. One additional case of pneumonia (5 mg/kg infliximab treatment group in ACT 1) occurred, but was not reported by the investigator as an infection.

As reported in the 54-week SCS, TB was reported in 1 subject in the 10 mg/kg infliximab treatment group in ACT 1. This subject had both a negative purified protein derivative (PPD) skin test and negative chest radiograph at screening. Study infusions were discontinued.

Beyond 54 weeks after the first infusion in ACT 1 and ACT 2, infection occurred in 50 (22.5%) subjects in the infliximab group and 16 (27.6%) subjects in the placebo group

In the Järnerot study, through 3 months postinfusion, there were no clinically notable differences between treatment groups in the incidence or type of infections reported. Nine subjects (37.5%) in the 5 mg/kg infliximab group and 6 subjects (30.0%) in the placebo group had 1 or more infections. The only infection that occurred in more than 1 subject in the 5 mg/kg infliximab group was oral moniliasis (3 [12.5%] subjects in the infliximab group and 0 subjects in the placebo group). Through 1 year postinfusion, 9 subjects (37.5%) in the 5 mg/kg infliximab group and 7 subjects (35.0%) in the placebo group had 1 or more infections.

Serious Infections

As reported in the 54-week SCS for the ACT studies, serious infections occurred slightly more frequently in the combined infliximab treatment group (19 [3.9%]) than in the placebo treatment group (6 [2.5%]). A higher proportion of subjects in the 10 mg/kg infliximab treatment group had serious infections compared with the 5 mg/kg infliximab treatment group (12 [5.0%] and 7 [2.9%], respectively). The most frequent serious infections among infliximab-treated subjects were pneumonia (2 subjects in the 5 mg/kg group and 3 subjects in the 10 mg/kg group), abscess (3 subjects in the 10 mg/kg group), and gastroenteritis (2 subjects in the 5 mg/kg group and 1 subject in the 10 mg/kg group).

In the RESULTS UC study, 7 subjects had serious infections during long-term follow-up through 1 year; 1 subject (previously treated with placebo) had received commercial infliximab. Of these 7 subjects, 3 subjects had previously received infliximab and 4 subjects had previously received placebo.

In the Järnerot study, through 3 months postinfusion, 1 subject (4.2%) in the 5 mg/kg infliximab group had a serious infection, recorded as infection, fever, and pulmonary infiltration. In the placebo group, 2 subjects (10%) had a serious infection, including 1 with abscess and 1 with wound infection.

Infusion Reactions

In the ACT studies, the proportion of infusions that led to infusion reactions was similar in the combined infliximab and placebo treatment groups (2.9% and 2.5%, respectively; however, the proportion of subjects who had an infusion reaction was greater in the combined infliximab treatment group than in the placebo treatment group (13.4% versus 9.4%, respectively). This difference was largely due to the greater percentage of subjects with infusion reactions in the 10 mg/kg infliximab treatment group compared with the 5 mg/kg infliximab treatment group (16.1% versus 10.7%).

Infusion reactions beyond 54 weeks occurred in 17 (7.7%) subjects in the infliximab group. No placebo infusions resulted in an infusion reaction. The most common infusion reactions were chest pain, flushing, infusion syndrome, pruritus, and rash, which each occurred in 3 (1.4%) subjects.

In the Järnerot study, no subject was identified as having an infusion reaction according to the definition noted. However, on review of individual subject data in the Järnerot study, 3 subjects in the 5 mg/kg infliximab group had an AE on the day of their infusion that was considered an infusion reaction by the Sponsor.

Possible anaphylactic or delayed hypersensitivity reactions

In the ACT studies, no possible anaphylactic reactions occurred among subjects in either the placebo or the combined infliximab treatment group. Similar proportions of subjects in the combined infliximab and placebo treatment groups had 1 or more possible delayed hypersensitivity (serum sickness like) reactions (0.6% and 0.8%, respectively). No possible anaphylactic reactions or delayed hypersensitivity reactions occurred among subjects in either the placebo or the combined infliximab treatment group beyond 54 weeks after the first infusion.

In the RESULTS UC study, 2 (1.2%) subjects who were in the infliximab treatment group and 4 (3.4%) subjects who were in the placebo treatment group received commercial Remicade and had possible delayed hypersensitivity reactions.

No subjects reported an AE of anaphylactic reaction in the Järnerot study.

Dysplasia

Through 54 weeks of follow-up in the ACT 1 and ACT 2 studies, 1 subject (5 mg/kg infliximab) was reported to have developed dysplasia. In the study extensions beyond 54 weeks after the first infusion, no subject was reported to have developed dysplasia.

In the RESULTS UC study, 77 (27%) subjects were identified at screening during the main studies to be at high risk for dysplasia. Thirty-three of these 77 subjects had a colonoscopy with biopsy, and 28 subjects had biopsy results indicating no dysplasia. Two subjects (1 subject who had previously received placebo and 1 subject who had previously received infliximab) had biopsy results indicating dysplasia. One subject who had previously received placebo was inconclusive due to inflammation. Additionally, the status of 2 subjects was unknown. No malignancies have been reported for these subjects.

Data concerning dysplasia was not collected in the Järnerot study. Per protocol, the signs and symptoms of UC were not to be reported as an AE unless there was reasonable cause to believe that the event was caused by study medication, that the event met the criteria for serious, and/or the symptom was inconsistent with the natural history of the disease in the judgment of the investigator.

Discussion on clinical safety

The safety profile presented in this variation application was consistent with the known safety profile for infliximab with the well known increased risk for infection and in particularly, opportunistic infections. There were no evident signals of increased incidence of adverse events in patients receiving a three dose induction and 8 weekly administration of infliximab. The clear signal of increased incidence of pneumonia and interstitial lung disease was already reflected in the product information through another type II variation (II/108). A potentially increased risk for malignancy remains a concern. Therefore, from a safety point of view the proposed the change to the UC indication is not accepted but should be reflected in the product information.

Risk management plan

The MAH argued that there was no need for a risk management plan (RMP) to be provided for the current variation application. The CHMP agreed with this approach.

Changes to product information

The MAH proposed to add information to sections 4.1 and 5.1 of the SPC, regarding reduction of the incidence of colectomy in UC. The CHMP did not consider it acceptable to add this as an indication, as it reflects an outcome of treatment of UC. However, the inclusion of information regarding colectomies, hospitalisations and surgical procedures in section 5.1 was agreed. Information from the ACT 1, ACT 2 and Järnerot studies was included. The MAH took the opportunity to update the ATC code in accordance with the WHO ATC/DDD alterations.

Benefit risk assessment

Infliximab is currently approved for treatment of adult patients with moderately to severely active UC who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies. The approvals for treatment of adult UC were based primarily on data from two multicentre, randomised, double-blind, placebo-controlled studies, ACT 1 and ACT 2. In the present variation application submission, the MAH proposed to add information to sections 4.1 and 5.1 of the SPC.

Benefit
The MAH applied to change the current UC indication to reflect the reduction of the incidence of colectomy in this patient population. The CHMP did not consider it acceptable to add this as an indication, as it reflects an outcome of treatment of UC and not an indication. In addition, the results from the ACT studies did show sufficiently convincing effects with the approved dose 5 mg/kg.
The data from the Järnerot study was considered stronger although based on fewer patients. There were no indications that there is a risk, on longer term, for a rebound effect with more colectomies after a single dose of infliximab. Data on the use of commercial infliximab after the study dose were not collected.
Regarding hospitalisations and surgical procedures, the data indicates that treatment with infliximab decreases the number of these events.

The CHMP considered that it would be relevant for the prescriber to include data on colectomy, hospitalisations and surgical procedures outcome in section 5.1 of the SPC.

Risk
The safety profile seen through 54 weeks in the combined ACT population was similar to that seen in other indications and is consistent with the current infliximab prescribing information. The safety findings are notable in the overall similarity between the placebo and the combined infliximab treatment groups. Pneumonia and elevated transaminases, which occurred with greater frequency in the infliximab treatment groups than the placebo treatment group, are already outlined in the current prescribing information.
The predictable occurrence of infections such as herpes zoster, pulmonary TB, and a single case of fatal histoplasmosis in the ACT 2 study extension, emphasize the importance, that both patients and physicians be aware of the risk of opportunistic infections. Furthermore, a potentially increased risk for malignancy remains a concern.

No notable differences were observed between the 5 mg/kg and 10 mg/kg infliximab treatment groups in the proportions of AEs (86.0% and 86.4%, respectively).
There were no evident signals of increased incidence of adverse events in patients receiving a three dose induction and 8 weekly administration of infliximab. The product information was already approved regarding the noted increased incidence of pneumonia and interstitial lung disease within variation II.108.

Benefit-Risk Balance
The benefit/risk balance for the use in moderately to severely active UC in patients who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies remains positive.

Conclusion

On 21 February 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.