London, 1 June 2006
Product name: REMICADE
Procedure number: Remicade-H-240-II-73-AR

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).

PsA is an inflammatory arthropathy associated with psoriasis, which is classified within the group of the spondyloarthritis. Psoriasis affects 1-3% of the population, with approximately a third of patients developing PsA. The estimated prevalence of PsA ranges between 0.1% and 1%. PsA can develop at any time, but for most people it appears between the ages of 30 and 50, and it affects men and women equally. The outcome of the disease varies from low activity to severe disabling disease including mutilating joint disease.

On 23 September 2004, the MAH received the approval for the use of infliximab in combination with methotrexate (MTX) for the treatment of active and progressive PsA, in patients who had responded inadequately to disease-modifying anti-rheumatic drugs (DMARDs).

In November 2005, the MAH submitted the present variation to include improvement of physical function and prevention of worsening of disability claims. Additionally, the MAH proposed a monotherapy claim in patients who show intolerance to MTX or for whom MTX is contraindicated. To support this variation the MAH referred to 2 randomised, multicentre, placebo-controlled trials in patients with active PsA, IMPACT (P02114), and IMPACT 2 (C0168T50).

The MAH proposed to amend the text of the SPC sections 4.1, 4.2, 4.5, 4.8 and 5.1 to reflect the revised indication, and to update the PL accordingly.

2. Clinical aspects

To support the new revision of the PsA indication, the MAH provided new clinical data and made reference to already assessed data, as detailed below:

Study P02114 (IMPACT)
IMPACT was a multicentre study in adults above 18 years of age with PsA and peripheral polyarticular arthritis who had failed at least 1 DMARD. The study design included a 16-week, randomised, double blind, placebo-controlled treatment (Stage I), followed by a 34-week, open-label treatment period (Stage II). This study was assessed as part of the initial variation application for the PsA indication (variation II.46), and was approved on 23 September 2004.
Further to the granting of the PsA indication, the MAH submitted as post authorisation commitments antibody data in October 2004 and the 2-year open label extension study from IMPACT in February 2005.

Study C0168T50 (IMPACT 2)
IMPACT 2 was a multicentre, randomised, double blind, placebo-controlled study. In the 24-week report, assessed as part of the type II.46 variation application (and FUM 087 submitted in October 2004), the primary endpoint evaluated was the proportion of subjects with ACR 20 response[1] at week 14. The MAH submitted the 66-week data for assessment within the present type II variation.

[1] The ACR response criteria were developed for RA. The ACR20 criteria is defined as a ≥20% reduction in the tender joint count, a ≥20% reduction in the swollen joint count and a ≥20% reduction in 3 of 5 additional measures: a) patient assessment of pain, b) patient global assessment of disease activity, c) physician global assessment of disease activity, d) disability index of the health assessment questionnaire (HAQ) and, e) acute phase reactant.

Details of the initial assessment can be found in Module 6 “scientific discussion” of the European public assessment report (EPAR).

2.1 Clinical pharmacology

Pharmacodynamics

Serum was collected in a subset of subjects at baseline and weeks 2, 14 and 24 in IMPACT 2. Baseline serum levels markers of inflammation and bone metabolism were generally comparable between treatment groups. Infliximab reduced serum levels of interleukin 1 receptor antagonist (IL-1Ra), soluble interleukin 2 receptor (sIL-2R), IL-6, matrix metalloproteinase 3 (MMP-3) and vascular endothelial growth factor (VEGF), inflammatory markers that have been associated with disease activity in PsA, as early as 2 weeks following the initiation of treatment. These changes were generally sustained through week 24. In contrast, the serum levels of markers of bone metabolism, reflecting either the formation or resorption of bone, were not notably changed following treatment with infliximab over a period of 24 weeks.
Further to the request for supplementary information, the MAH presented literature evidence to indicate that short treatment with infliximab reduced the number of T-cells and blood vessels in the synovium and psoriatic skin.

2.2 Clinical efficacy

IMPACT 2 (66 week data)

Study participants

The study participants were adults above 18 years of age, with a diagnosis of active polyarticular (5 or more joints involved) peripheral PsA for at least 6 months prior to the first infusion, who had inadequate response to DMARD or non steroidal anti-inflammatory drug (NSAID) therapy. Concomitant MTX at stable doses was permitted, but not required.

Two hundred subjects were enrolled, of which the majority (61%) were men (71% in infliximab and 51% in placebo), Caucasian (95%), and the median age was 47 years of age. With the exception of sex, all baseline characteristics were balanced between treatment groups.
The median PsA duration was approximately 6 years and the median psoriasis duration was 13 years. At baseline, 46% of subjects were taking MTX, 13% were taking corticosteroids, and 72% were taking NSAIDs.
All 200 subjects were analyzed for safety, efficacy, and health economics.

Treatments

Subjects were randomly assigned (1:1) to infusions of infliximab (5 mg/kg) or placebo at weeks 0, 2, and 6, followed by maintenance doses every 8 weeks up to week 46. The study included a placebo-controlled phase (0 to 24 weeks) and a blinded active treatment phase (24 to 54 weeks). Crossover of subjects from placebo to infliximab therapy occurred at week 16 (early escape) or week 24 (crossover). At week 38, subjects initially randomized to infliximab who had < 20% improvement from baseline in the total number of combined tender and swollen joints were eligible for dose escalation to infliximab 10 mg/kg.

Outcomes/endpoints

In the 24-week report, the primary efficacy endpoint evaluated was the proportion of subjects with ACR 20 response at week 14.

In the 66-week report, the primary objective was to evaluate the efficacy of infliximab in subjects with active polyarticular PsA by assessing reduction in signs and symptoms of arthritis and prevention of structural damage. The primary endpoint was the change from baseline in the total modified van der Heijde modified Sharp (vdH-S)[2] score at week 24.

The major secondary efficacy endpoints were to evaluate the efficacy of infliximab in:

- achieving the ACR 20 sustained response
- achieving the PsA response criteria (PsARC)[3]
- clearing psoriatic skin lesions
- improving quality of life in subjects with PsA.

Concomitant treatment

Stable doses of MTX (mg/week) and oral corticosteroids (mg/day prednisone or equivalent) were permitted for PsA during the study. Subjects were required to maintain their baseline dose through week 54. Despite that, MTX and corticosteroid doses were changed in some of the subjects based on investigator clinical judgment. DMARDs/systemic immunosuppressives other than MTX were not allowed within the 4 weeks prior to the first study infusion and during the course of the study.
At least 1 DMARD was taken by the majority (80%) of subjects prior to study start. More than 2 DMARDs were used by 11% of the subjects. A smaller proportion of subjects used immunosuppressives (11%) or systemic corticosteroids (29%). NSAIDs were used by 82% of all subjects for their PsA.

Statistical Design

The statistical design was considered appropriate.

Results

Patients disposition

With the exception of gender, demographics were generally well balanced between treatment groups. Baseline disease characteristics indicated a population of subjects with active PsA disease.

The CHMP noted that the inclusion criteria with regards to psoriatic skin disease were less stringent that those applied in other studies with infliximab addressing skin psoriasis. The mean/median psoriatic skin disease activity at baseline was rather low, and on a group levels corresponded to mild form of disease. Out of the 200 subjects included, 86% had body surface area (BSA) $\geq$3%. Among those the median BSA% was 10 [IQ range 5, 22] and median psoriasis area and severity index (PASI) score 6.7 [IQ range 3.6, 13.7]. This should be compared with the base line characteristics in EXPRESS (a study evaluating the treatment of moderate to severe plaque psoriasis in adults), where among all subjects (n=375), affected BSA (%) was 34 $\pm$ 19 (mean $\pm$ SD) or 29 [19, 44] (median [IQ range]), and the PASI score was 22.9 $\pm$ 9.2 (mean $\pm$ SD) or 21 [16, 27] (median [IQ range]).

Forty-seven percent and 9% of the subjects in the placebo and infliximab groups, respectively, entered early escape at week 16.

[2] The vDH-S score is a detailed scoring method evaluating erosions, joint space narrowing, (sub)luxation, ankylosis, gross osteolysis, and pencil in cup phenomena.
[3] PsARC response is defined as improvement in at least two of the following four criteria:
a) ≥20% improvement in physician global assessment of disease activity, b) ≥20% improvement in patient global assessment of disease activity, c) ≥30% improvement in tender joint count and d) ≥30% improvement in swollen joint count. One of the criteria improved has to be tenderness joint count (TJC) or swollen joint counts (SJC) and no worsening in any of the criteria should be observed.

Efficacy results

Primary and secondary endpoints

Efficacy was demonstrated for all primary endpoints. Table 1 below presents the ACR 20 at week 14 (primary endpoint). Fifty eight percent of patients achieved ACR 20 at week 14 ($p<0.001$). Further ACR 20, 50 and 70 responders were analysed at various time points.

Table 1 Summary of ACR response over time in IMPACT 2

	IMPACT 2		
	Week 14[a]	Week 24[a]	Week 54[b]
ACR response			
n	100	100	90
ACR 20 response	58.0%	54.0%	58.9%
ACR 50 response	36.0%	41.0%	36.7%
ACR 70 response	15.0%	27.0%	22.2%

[a] Responses are based on all subjects randomised to infliximab.

[b] Responses are based on all subjects randomised to infliximab with evaluable data at week 54.

Table 2 presents the summary of ACR response over time in IMPACT.

Table 2 Summary of ACR response over time in IMPACT

	IMPACT		
	Week 16[a]	Week 50[b]	Week 98[b]
ACR response			
n	52	78	78
ACR 20 response	65.4%	73.1%	61.5%
ACR 50 response	46.2%	50.0%	44.9%
ACR 70 response	28.8%	39.7%	34.6%

[a] Based on all subjects randomised to infliximab

[b] Based on all subjects who entered the year 2 extension.

The proportion of subjects in the infliximab group in IMPACT 2 who achieved PsARC at week 54 was 74% compared with 70% at week 24. The proportion of subjects in the infliximab group (with BSA ≥ 3% at baseline) who achieved ≥ 75% improvement in PASI from baseline at week 54 was 49% compared with 60% at week 24.
The median improvement from baseline in the quality of life questionnaire (both physical and mental components summary score) for the infliximab group was maintained from week 24 to week 54.
A major clinical response (defined as achieving an ACR 70 response for 24 consecutive weeks) was achieved by 12% of infliximab treated subjects at week 54.

At weeks 14, 24, and 54, the proportion of subjects in the infliximab group who achieved ≥ 0.3 units decrease in HAQ was 58%, 54%, and 59%, respectively. In subjects who achieved ≥ 0.3 units decrease in HAQ at week 14 or at week 24, 74% and 89%, respectively, maintained this decrease at week 54.

Discussion on clinical efficacy

The significant and rapid responses initially observed in arthritis and psoriasis outcomes in IMPACT 2 through 6 months and in IMPACT through 1 year, were maintained through the end of the respective studies. Efficacy, as measured by the more stringent ACR 50 and ACR 70 responses, was also evident. Multiple additional efficacy measurements in the 2 studies support the maintenance of infliximab therapy over 1 to 2 years. Dactylitis and enthesopathy, 2 disease-characteristic features of PsA, also demonstrated sustained responses.

At week 2 (after the first infusion of infliximab) in IMPACT 2, 7% of infliximab subjects compared with 0 subjects in the placebo group achieved ≥ 75% improvement in PASI from baseline (p = 0.011). In both IMPACT 2 and IMPACT, a high proportion of subjects achieving ≥ 50%, ≥ 75%, and ≥ 90% improvement in PASI from baseline at 6 months in IMPACT 2 and 1 year in IMPACT, and the substantial PASI responses were sustained through 1 and 2 years in the respective studies.
The MAH also applied for a monotherapy claim in patients who show intolerance to MTX or for whom MTX is contraindicated. A sub-group analysis of the data indicates efficacy of infliximab in patients without baseline use of MTX. The data derived from study IMPACT 2 were considered sufficient to support the use of infliximab in patients who have contraindications to MTX or are intolerant to MTX.
Efficacy in terms of reduction of signs and symptoms (ACR responses) as well as better physical function (HAQ scores) was demonstrated at the time points for the primary efficacy analyses. Therefore, it was considered that the data provided supported sustained effect.

2.3 Clinical safety

Patient exposure

Through week 54, the safety population included 98 subjects who received placebo; 91 subjects in the placebo group who entered early escape to infliximab 5 mg/kg treatment at week 16 or placebo subjects who crossed over to infliximab 5 mg/kg at week 24; 100 subjects who received infliximab 5 mg/kg throughout or subjects in the 5 mg/kg group who received dose escalation to 10 mg/kg infliximab at week 38. Thus, the combined infliximab group includes 191 subjects who received any infusion of infliximab. The average number of weeks of follow-up was approximately 43 weeks for the combined infliximab group versus 20 weeks for the placebo group.

Adverse events (AE)

Overview of AE

The safety profile of infliximab through week 54 was consistent with the safety profile observed through week 24. The proportion of subjects experiencing an AE was 85% in the combined infliximab group. The most frequently reported AE was upper respiratory tract infection, which occurred in 24% of subjects in the combined infliximab group. The frequency of AEs in the combined infliximab group was similar between subjects who received MTX and who those who did not receive MTX at baseline.

Serious adverse events (SAE) and deaths

Approximately 12% of subjects experienced an SAE in the combined infliximab group. The most common were the musculo-skeletal system disorders (including arthritis and bone fracture, reported by 3 patients each). One subject experienced arterial stenosis following dose escalation.

Discontinuations

Through week 54, 21% subjects discontinued the study. Sixteen subjects in the combined infliximab group permanently discontinued study agent infusions due to an AE. Elevated liver function tests were the most frequent reasons for discontinuing infliximab treatment.

Specific adverse events

Infections

The proportion of subjects who had at least 1 infection was 55% in the combined infliximab group; upper respiratory tract infection was the most common infection. The frequency of infections in the combined infliximab group was similar in subjects who received MTX and who did not receive MTX at baseline.

Serious infections occurred in 2% of subjects in the placebo group (cellulitis and bronchitis), and 3% of subjects in the infliximab only group (infectious hepatitis, cellulitis and pneumonia). Despite the discrepancy in follow-up between the placebo groups, there was not an increased occurrence of serious infections in the infliximab group. There were no events of tuberculosis or potential opportunistic infections.

Infusion reactions

The infusion reaction rate with infliximab infusions was 2% for the combined infliximab group (in total 1376 infliximab infusions were given); 12% of subjects in this group had an infusion reaction. The majority of infusion reactions were mild in intensity; there were no serious infusion reactions. There were no possible anaphylactic reactions or possible delayed hypersensitivity reactions.

Subjects in the combined infliximab group who were receiving MTX at baseline were less likely to experience infusion reactions (6%) compared with subjects not receiving MTX at baseline (17%). Subjects treated with placebo had a similar incidence of infusion reactions regardless of baseline MTX usage (9% of subjects receiving MTX at baseline versus 6% of subjects not receiving MTX at baseline).

Malignancies

There were 2 malignancies reported: 1 basal cell carcinoma (placebo only subject) and 1 stage I Hodgkin's lymphoma (infliximab only subject).

Other AE of interest

There was 1 case of leukopenia, a haematologic event, and 3 neurologic events of interest. There were no autoimmune disorders, central demyelinating events, or occurrences of congestive heart failure.

Laboratory findings

Treatment with infliximab had no clinically significant adverse effects on haematologic values. With the exception of elevations in ALT and AST, the proportion of subjects with markedly abnormal post-baseline chemistry values was very low and comparable between treatment groups. Markedly abnormal ALT and AST values occurred in 4% and 2% of subjects, respectively, in the combined infliximab group. A markedly abnormal gamma glutamyltransferase (GGT) value was reported in 4% of subjects in the combined infliximab group. No subjects had a markedly abnormal total bilirubin. Infliximab treated subjects with elevations in ALT or AST did not develop liver failure. More infliximab-treated subjects not receiving MTX at baseline had a markedly abnormal ALT or AST as compared with infliximab treated subjects receiving MTX at baseline. Similarly, more subjects in the combined infliximab group who were not receiving MTX at baseline had an ALT or AST value that shifted from normal to high.

The proportion of subjects who were newly positive for ANA (defined by $\geq$ 1:160 titer) through week 66 was 41% in the combined infliximab group. The proportion of these subjects who became newly positive for anti-dsDNA antibodies was 9% in the combined infliximab group.

Antibodies

Among the combined infliximab group, 15% were positive for antibodies to infliximab through week 66. In subjects receiving MTX at baseline, 4% tested positive for antibodies to infliximab compared with 26% who were not receiving MTX at baseline.

Discussion on clinical safety

From the one-year data of IMPACT 2 no new safety signals are apparent. However, the CHMP noted that concomitant use of MTX with infliximab resulted in lower incidences of antibodies as well as infusion reactions. Furthermore, infusion reactions were approximately 3 times more common in subjects on monotherapy (17%), compared with those receiving infliximab together with MTX (6%). This finding is similar to the previous experience with infliximab.

3. Overall discussion and benefit/risk assessment

In September 2004, infliximab was approved for treatment of PsA, based on data from IMPACT. For the present application, the MAH applied for a revision of the indication, based on results from an additional study, IMPACT 2.
In IMPACT 2, efficacy in terms of reduction of signs and symptoms (ACR responses) was demonstrated at the different time points.
With respect to the monotherapy option, data have now been submitted, which support efficacy and general safety profiles irrespective of concomitant MTX. However, the data showed, as also known from previously submitted data, that concomitant use of infliximab and MTX reduces antibody development, as well as results in lower incidences of infusion reactions. Thus, the proposal by the MAH to recommend monotherapy only in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated, was endorsed.
The CHMP, having considered the data submitted, was of the opinion that no additional risk minimisation activities were required beyond those included in the product information.

IV. CONCLUSION

On 1 June 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.