European Medicines Agency

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Product name: Remicade
Procedure number: EMEA/H/C/240/II/95

SCIENTIFIC DISCUSSION

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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), adult and paediatric Crohn's disease (CD), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis and ulcerative colitis (UC).

In 2003, Remicade was approved for the treatment of ankylosing spondylitis, with the following indication: *Treatment of ankylosing spondylitis in patients who have severe axial symptoms, elevated serological markers of inflammatory activity and responded inadequately to conventional therapy.* The approval was based on a small investigator-initiated study, where in total 70 subjects were treated for 54 weeks (study P01522). As a condition for the approval, the marketing authorisation holder (MAH) agreed on a follow up measure (FUM 060), namely "*Centocor is currently conducting a Phase 3 placebo controlled trial of two years duration in 275 patients with severe ankylosing spondylitis (C0168T51, ASSERT). The trial is actively enrolling and in addition to safety and efficacy will include pharmacokinetics, immune response, MRI and radiological data. Centocor commits to submitting a clinical study report upon completion of the full 2 years of the trial by 4Q06 as part of a type II variation to expand the AS indication.".*

Ankylosing spondylitis is a chronic inflammatory disease of unknown aetiology. It involves the sacroiliac joints, axial skeleton, entheses, and peripheral joints. Chronic inflammation of entheses leads to new bone formation, syndesmophytes, and ankylosis of joints, primarily in the axial skeleton. It is this axial ankylosis that may lead to loss of range of motion and to disability. The disease may also have nonskeletal manifestations, including uveitis, carditis, pulmonary fibrosis, and cardiac conduction abnormalities. Considered a subset of the spondyloarthropathies, AS is associated with the presence of the HLA[1]-B27 allele. Although patients may experience a variety of musculoskeletal symptoms (arthralgias and morning stiffness), the most common presenting symptom is low-back pain. The low-back pain usually begins before the age of 40, is insidious in onset, associated with morning stiffness, and becomes symmetrical. These musculoskeletal symptoms may be associated with constitutional symptoms, such as fatigue, fever, and weight loss.

To support the current variation application, the MAH submitted the 2 years study report from ASSERT, to fulfil FUM 060, and applied for product information changes based on longer term data from both ASSERT and P01522. The MAH proposed to change sections 4.1 "Therapeutic indication", 4.8 "Undesirable effects" and 5.1 "Pharmacodynamics" of the summary of product characteristics (SPC).

Clinical aspects

Pharmacokinetics/Pharmacodynamics

In the ASSERT[2] study, serum samples for infliximab concentrations were collected prior to an infusion and 1 hour post infusion at each visit with an infliximab infusion.

The serum infliximab concentrations were consistent with the dose administration. There was no evidence of accumulation with the 5 mg/kg or the 7.5 mg/kg used. Higher through levels were achieved with the higher dose, to the extent expected.

Subjects with undetectable preinfusion infliximab concentrations

In general, a majority of the subjects maintained continuous exposure to infliximab when treated with either 5 mg/kg or 7.5 mg/kg infliximab every 6 weeks. A higher percentage of subjects who developed

[1] HLA-human leucocyte antigen

2 For details on the study please see the clinical efficacy section below.

antibodies to infliximab in the 5 mg/kg-escalated to-7.5 mg/kg infliximab group may have contributed to the need for dose escalation for such subjects.
From the data presented it was concluded that the higher occurrence of patients with anti-infliximab antibodies found among those patients with undetectable preinfusion serum infliximab concentrations is plausible and in line with previous findings.

Relationship between serum infliximab concentration and ASAS 20[3] *response*
The proportion of subjects achieving an ASAS 20 response in each category of through infliximab concentration was analysed to explore the relationship between infliximab concentration and clinical response. At week 24, a progressive increase in the proportion of subjects who achieved an ASAS 20 response was noted with increasing serum infliximab concentrations. The proportion of subjects who achieved an ASAS 20 response was lowest in the group that had undetectable serum infliximab concentrations. Of note, in the category of subjects with lowest preinfusion infliximab concentration, 6 of the 10 subjects were confirmed to have developed antibodies to infliximab by week 24.
The MAH argued that the data suggest that ASAS 20 response was associated with higher through serum concentrations of infliximab, thus suggesting an infliximab serum concentration-response relationship. However, the CHMP noted that the described relationship appears plausible, but does not have an impact on treatment strategies. In order to justify dose escalation a clear correlation of low through levels and impaired clinical response and the absence of concurrent safety issues need to be demonstrated. The SPC already contains information that efficacy may be reduced in subjects who have developed antibodies.

Relationship between antibody-to-infliximab status and serum infliximab concentration
The pharmacokinetics of infliximab generally remained unchanged over time. As expected, the submitted documentation showed that anti-infliximab antibodies can lead to a higher clearance and shorter half-life of infliximab.

Clinical efficacy
The clinical development program for infliximab for the treatment of AS consisted of 2 controlled clinical trials, ASSERT and P01522 (which was previously submitted and assessed within the initial application for AS).

ASSERT (C0168T51)
ASSERT was a phase 3, randomised, multicentre, double-blind, placebo-controlled, 2-arm, parallel study of 279 subjects with AS. The objectives of the study were to assess the reduction in the signs and symptoms of AS and the safety of infliximab (5 mg/kg) therapy in subjects with AS.

Study participants
Subjects eligible were to have had a diagnosis of definite AS, as defined by the 1984 Modified New York Criteria for at least 3 months prior to screening. Active disease at the time of screening was defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[4] score ≥ 4, and a score for spinal pain of ≥ 4 on a visual analogue scale (VAS)[5] of 0 to 10 cm. Concurrent stable treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and tramadol was permitted during the study. Systemic corticosteroids, cytotoxic drugs, or disease-modifying antirheumatic drugs (DMARDs) at the time of screening were not permitted.
For all subjects enrolled, the median AS duration was 8.8 years. The median disease duration in the placebo group was higher than that in the infliximab group (13.2 versus 7.7); the means were similar between treatment groups (11.9 years in the placebo and 10.1 years in the infliximab group) at baseline.

[3] ASAS 20 response is a tool to measure the efficacy of products on the symptoms of AS (see clinical efficacy for details on the criteria).
[4] The BASDAI consists of a one through 10 scale in response to 6 questions pertaining to the 5 major symptoms of AS: fatigue, spinal pain, joint pain/ swelling, areas of localized tenderness, morning stiffness. The higher the BASDAI score, the more severe the patients disability due to their AS.
[5] A VAS is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured, like pain.

Treatment
Subjects were randomly assigned in a 3:8 ratio to 1 of 2 treatment groups, such that 78 subjects were allocated to receive placebo and 201 subjects were allocated to receive 5 mg/kg infliximab. Placebo or 5 mg/kg infliximab was infused at weeks 0, 2, 6, 12, and 18.

Beginning at week 24, placebo-treated subjects crossed over to receive 5 mg/kg infliximab infusions at weeks 24, 26, 30, and every 6 weeks thereafter through week 96. Subjects who received infliximab at randomisation received a 5 mg/kg infliximab infusion at week 24, a placebo infusion at week 26 to maintain the blind, and a 5 mg/kg infliximab infusion at week 30. Starting with the week 36 infusion and continuing through week 96, subjects in the infliximab group who had a BASDAI ≥ 3 at both the current visit and the prior visit (i.e., 2 consecutive visits), received a 7.5 mg/kg infliximab infusion and continued to receive 7.5 mg/kg infusions every 6 weeks through week 96. Subjects with a BASDAI < 3 continued to receive 5 mg/kg infliximab infusions every 6 weeks through week 96. Subjects were followed for efficacy and safety assessments through week 102.

Efficacy variables
The primary endpoint for this study was the proportion of subjects who achieved ASAS 20 response at week 24. A subject was classified as having achieved an ASAS 20 response if the following was achieved:
1. An improvement of ≥ 20% from baseline and absolute improvement from baseline of at least 10 on a 0 to 100 mm scale in at least 3 of the following 4 domains:
- Patient global
- Spinal pain
- Function (Bath Ankylosing Spondylitis Functional Index (BASFI)[6])
- Inflammation (average of the last 2 questions of the BASDAI concerning morning stiffness)

2. Absence of deterioration from baseline (≥ 20% and absolute change of at least 10 on a 0 to 100 mm scale) in the potential remaining domain.

In order to determine whether a subject achieved an ASAS 20 response, postbaseline data from all 4 domains had to be present.

The following were among major secondary endpoints:
- Change from baseline in BASFI at week 24.
- Proportion of subjects achieving an AS major clinical response at week 24.
- Change from baseline in the MRI activity score at week 24.
- Change from baseline in the physical component summary score of the SF-36[7] at week 24.

Safety and efficacy data were presented for the placebo group (data through week 24), the placebo-to-infliximab group (weeks 24 through 102), and the infliximab group (data from week 0 through week 102, which included data for subjects who received an escalated dose of infliximab). Additionally, where appropriate, safety and efficacy data were presented for subjects who received 7.5 mg/kg at any point during the study.

Results:
Primary Efficacy Endpoint
The proportion of subjects achieving an ASAS 20 response at week 24 in the infliximab group was significantly greater than in the placebo group (123/201 subjects; 61% versus 15/78 subjects; 19%; $p < 0.001$).

Secondary efficacy endpoints
At week 24, a statistically significant larger percentage of infliximab treated subjects achieved an AS major clinical response (22% vs 1.3%); and a BASDAI 50 response (51% vs 11%) compared with

[6] The BASFI consists of 8 specific questions regarding function in AS and 2 questions reflecting the patient's ability to cope with everyday life.

[7] The SF-36 health survey is a short form measure of generic health status in the general population.

placebo. Additional secondary analyses supported that infliximab treatment significantly improved other manifestations of AS, including range of motion, physical function and quality of life (QoL) (SF-36 physical component). The median change from baseline in magnetic resonance imaging (MRI) activity score at week 24 showed a statistically significant ($p < 0.001$) improvement in the infliximab group compared with the placebo group.

In the trial, approximately 10% of patients were HLA-B27 negative. The proportion of responders was similar in this and the HLA-B27 positive subgroup of patients. Hence, efficacy appeared similar in these groups of patients.

Dose escalation and maintenance of effect
The currently approved dose of infliximab for treating the signs and symptoms of AS is 5 mg/kg, administered at weeks 0, 2, and 6, followed by a maintenance regimen every 6 to 8 weeks. There was no proposed change to the current posology.

In ASSERT, a dose escalation up to 7.5 mg/kg infliximab was possible from the week 36 visit. Subjects in the infliximab group who had a BASDAI of ≥ 3 for 2 consecutive visits had their infliximab dose increased from 5 mg/kg to 7.5 mg/kg. There were in total 105 patients out of 201 (53%) who dose escalated up to week 102.

At week 24, the number of ASAS responders was 15/78 (19%) in the placebo group and 123/201 (61%) in the 5 mg/kg infliximab group ($p<0.001$). There were 95 subjects who continued on 5 mg/kg every 6 weeks up to week 102. Among those, 71 were ASAS 20 responders at week 102.

The percentage of subjects achieving an ASAS 20 response with dose escalation generally increased over time. However, a lower percentage of these subjects achieved an ASAS 20 response at any given time compared to subjects who received infliximab 5 mg/kg throughout study treatment. Further, a smaller proportion of subjects in the dose escalation groups maintained response compared to the subjects who received infliximab 5 mg/kg throughout the study.

Study P01522
Data through week 54 of study P01522 was the basis for the current approval in patients with AS. The MAH submitted additional data through 2 years of treatment. The objective of the extension was to assess safety and efficacy of long-term treatment (i.e., up to 2 years) with infliximab in subjects with AS.

Study participants
Study P01522 was an investigator-initiated, phase 3, double-blind, placebo-controlled, single-dummy, clinical study to investigate the efficacy and tolerability of infliximab in 70 subjects with active AS. Subjects eligible for P01522 were to have a diagnosis of definite AS, according to the modified New York criteria (i.e., a pelvic x-ray showing bilateral sacroiliitis ≥ grade 2) with active disease defined by a BASDAI score of ≥ 4 and a spinal pain score of ≥ 4 (last week) on a VAS of 0 to 10 cm.

Treatment
P01522 study had two phases and a long-term extension. In phase A (double-blind, placebo-controlled phase), subjects were randomised to receive 5 mg/kg infliximab or placebo infusions at weeks 0, 2, and 6. At week 12, both groups received a 5 mg/kg infliximab infusion to initiate phase B (noncomparative phase). At week 14, subjects who were randomised to placebo received a 5 mg/kg infliximab infusion (placebo-to-infliximab subjects) and subjects who were randomised to infliximab received a placebo infusion to maintain the original treatment blind. From weeks 18 through 48, all subjects received infliximab (5 mg/kg) infusions every 6 weeks. One-year efficacy was assessed at week 54. The long-term extension of P01522 was open-label. An infliximab infusion (5 mg/kg) was administered at week 54 and every 6 weeks thereafter through week 102.

Efficacy Variables
The primary endpoint in P01522 was the proportion of subjects with ≥50% improvement in BASDAI at week 12.

Results
At week 12, treatment with infliximab resulted in improvement in signs and symptoms, as assessed by the BASDAI, with 57% of infliximab treated patients achieving at least 50% reduction from baseline in BASDAI score (mean baseline score was 6.5 in the infliximab group and 6.3 in the placebo group), compared with 9% of placebo patients ($p<0.01$). Physical function, range of motion, and quality of life (SF-36) were improved similarly.

Results across studies:
The table 1 below shows results over time in the two studies.

Table 1. Results from Assert and P01522 at different time points.

	Placebo → Infliximab	5 mg/kg Infliximab [a]
ASSERT at week 102		
Subjects randomized	78	201
Subjects evaluated	61	165
Subjects achieving ASAS 20	44 (72.1%)	122 (73.9%)
P01522 at week 54/end of year 1		
Subjects evaluated		53
Subjects achieving BASDAI 50		33 (62.3%)
P01522 at end of year 2		
Subjects evaluated		53
Subjects achieving BASDAI 50		30 (56.6%)

[a] Includes subjects in ASSERT who received a close escalation to 7.5 mg/kg infliximab on or after week 36.

Discussion on clinical efficacy
It can be concluded that the efficacy in AS, including in patients with severe, active disease, has been shown and confirmed by the additionally submitted data. In ASSERT there is limited experience in HLA-B27 negative patients, showing similar efficacy as in HLA-B27 positive.

In ASSERT, the efficacy results indicate an increased number of ASAS 20 responders in patients with baseline CRP (C-reactive protein) >3 and with BASDAI score >7, thus supporting efficacy in patients with severe, active ankylosing spondylitis.
The MAH analysed effect over time and maintenance of effect. At week 24, the number of ASAS responders was 19% vs. 61%, in the placebo and in the 5 mg/kg infliximab groups, respectively. A subset of the patients who continued on 5 mg/kg every 6 weeks were ASAS 20 responders at week 102.
Out of the 201 initially infliximab-treated patients, 106 had a BASDAI score >3 at two consecutive visits at week 36 or thereafter, thereby fulfilling the predefined criteria for an increase in dose, due to insufficient response. It should be pointed out that they could still be ASAS 20 responders. Overall, the CHMP considered there were insufficient data to assess the value of dose escalation. The MAH had no claim in relation to dose escalation.

Clinical safety

Patient exposure
Between week 0 and week 96, each of the 277 subjects who participated in the trial received at least 1 dose of study agent. Subjects in the placebo-to-infliximab group received an average of 11.7 infusions, while subjects in the infliximab group received an average of 15.9 infusions during the study. The median cumulative dose of infliximab was 68.5 mg/kg and 90.5 mg/kg for the placebo-to-infliximab group and the infliximab group, respectively.

Results:

ASSERT

Through week 24 in ASSERT, 3 subjects (2 [1.0%] infliximab-treated and 1 [1.3%] placebo-treated) permanently discontinued study agent infusions because of an adverse event (AE). One subject on infliximab discontinued infusions because of chills (an infusion reaction), another on placebo discontinued infusions because of myelitis, and another on infliximab discontinued infusions because of otitis. Of these AEs, myelitis was the only event considered serious. Through week 102, 26 subjects permanently discontinued study agent infusions because of an AE: 1 (1.3%) placebo-treated subject (through week 24), 7 (9.5%) placebo-infliximab subjects through week 102, and 18 (9.0%) infliximab-treated subjects through week 102, which includes subjects who had an escalation in dose to 7.5 mg/kg. Only 2 events were reported in > 1% of subjects: chills (1.1%) and urticaria (1.1%).

Study P01522

Through week 54 in Study P01522, 11 (16%) subjects had AEs that resulted in the discontinuation of study agent. Through week 12 (Phase A), AEs that led to discontinuation of study agent infusions were granulomatosis of the lung, tuberculosis (TB), and leucopenia, each reported by 1 infliximab-treated subject. All of these AEs were considered serious and all resolved. From weeks 14 through 54 (Phase B), AEs that led to the discontinuation of study agent infusions were lupus-like syndrome (3 subjects), infusion reaction (2 subjects), herpes zoster (1 subject), liver enzymes elevated (1 subject), and skin lupus (1 subject). All of these AEs were considered serious with the exception of infusion reaction (not serious for each subject) and herpes zoster. All of the events resolved. During year 2, 3 (6%) subjects had AEs that led to the discontinuation of study agent. The AEs that led to the discontinuation of study agent infusion were infusion-associated symptoms (2 subjects) and pancreatitis (1 subject). Both cases of infusion-associated symptoms were considered to be severe and probably related to study treatment. The event of pancreatitis was considered to be moderate and unlikely related to study treatment.

Adverse events (AEs)

The AEs observed with infliximab therapy in subjects with AS through 102 weeks in ASSERT and Study P01522 were similar. In addition, the AEs observed in ASSERT and Study P01522 were similar to those observed in previous studies of infliximab in other indications.

The most commonly reported AE in both the placebo-controlled portions and throughout 102 weeks in ASSERT and Study P01522 was upper respiratory tract infection. In ASSERT, the incidence of upper respiratory tract infection increased over a 2-year period of observation. This AE was also the most commonly reported event in subjects who had a dose escalation to 7.5 mg/kg infliximab. However, the frequency of upper respiratory tract infection did not increase as subjects shifted to a higher dose of infliximab: in ASSERT, 47.3% of placebo -infliximab subjects had upper respiratory tract infection through week 102, compared with 31.1% of subjects who escalated to 7.5 mg/kg infliximab.

Serious adverse events and deaths

No deaths were reported through 102 weeks in ASSERT or in study P01522. One subject in ASSERT was diagnosed with lung cancer and subsequently died approximately 1.5 months after terminating study participation due to ventricular fibrillation.

Infections

One or more infections were reported for 79.3% of subjects who received at least 1 dose of infliximab through week 102. The most commonly reported infection was upper respiratory tract infection, which was reported in 48.7% of infliximab-treated subjects during the study. The frequency of serious infections was low among subjects who received at least 1 dose of infliximab: 11 (4.0%) subjects had 1 or more serious infections during the study. Pneumonia was the most common serious infection, occurring in 3 (1.1%) infliximab-treated subjects. The most common infection requiring antimicrobial treatment among infliximab treated subjects was upper respiratory tract infection (12.0%).
No cases of active tuberculosis were identified.

Malignancies
Three malignancies were reported through week 102 in ASSERT. One subject was diagnosed with squamous cell carcinoma of the skin 18 days after the week 66 dose of 5 mg/kg infliximab; this subject also had a basal cell carcinoma of the skin that was not reported as an AE. Another subject was diagnosed with pulmonary carcinoma 40 days after the week 42 dose of 7.5 mg/kg infliximab; the subject was a cigarette smoker (10 to 15 cigarettes/day, with a history of 20 to 30 cigarettes/day). A third subject was diagnosed with breast cancer in the left breast 21 days after the week 36 dose of 7.5 mg/kg infliximab. In addition, 1 subject who participated in ASSERT developed nonseminoma testicular carcinoma after the discontinuation of study participation (nearly 1 year after his last dose of infliximab).
There were no cases of lymphoma through 102 weeks of treatment.

Infusion reactions
The overall proportion of subjects with 1 or more infusion reactions through week 102 was 18.9% in subjects who received at least 1 dose of infliximab. The frequency of infusion reactions was low and similar between placebo infusions (2.6% of all placebo infusions from week 0 through week 24) and infliximab infusions (2.2% of all infliximab infusions through week 102). Two subjects had infusion reactions that were serious
Among infliximab-treated subjects who received prophylaxis at any time, the percentage with infusion reactions following the first use of prophylactic medication was lower (6.3%) than without prophylaxis (12.3%). Altogether prophylactic medication for infusion reactions was given to 32 subjects at any time.

Discussion on clinical safety
No new or unexpected adverse events were identified when infliximab was used for the treatment of AS up to 102 weeks.

Risk management plan

The MAH did not consider there was a need for a Risk Management Plan for this application, as it concerned a revision of an already approved indication, and there were no new or unexpected safety signals identified in the newly submitted data. This view was agreed with by the CHMP.

Overall discussion and benefit/risk assessment

In 2003, Remicade was approved for use in AS. The initial indication was restricted due to sparse clinical data from one small investigator-initiated trial in total 70 patients, treated for up to 54 weeks. To support this variation application the MAH submitted an additional clinical study, ASSERT. These additional data, including long-term data, were requested as a follow-up measure in association with the initial approval.

Benefit
It can be concluded that the efficacy in AS, including in patients with severe, active disease, has been shown and confirmed by the additionally submitted data. In ASSERT; there was limited experience in HLA-B27 negative patients, showing similar efficacy as in HLA-B27 positive patients. Overall, a change of the indication is acceptable. However, due to the general safety concerns with anti-TNF treatment, the new indication should be to "*Ankylosing spondylitis: Remicade is indicated for: Treatment of severe, active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy."*

Maintenance of effect up to week 102 was observed in a subset of the patients who continued on 5 mg/kg every 6 weeks. The CHMP agreed to add the number of responders at relevant time points to section 5.1 of the SPC to present maintenance of effect.

Risk
No new or unexpected adverse events were identified when infliximab was used for the treatment of ankylosing spondylitis up to 102 weeks.

Overall, the benefit /risk balance for this indication remains positive.
No change was proposed to the conditions for the approval of the type II variation.

Conclusion

On 20 September 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.