London, 27 July 2005
Product name: **REMICADE**
Procedure number: **EMEA/H/C/240/II/61**

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) and ankylosing spondylitis (AS) and psoriatic arthritis (PsA).

Psoriasis vulgaris is a common, immunologically mediated disorder of the skin, characterized by a relapsing-remitting clinical course of elevated, erythematous, scaling plaques of the skin, affecting approximately 2% of the population. Psoriasis is not a life-threatening disease, but in relation to the extent and location of the plaques can lead to serious social and psychological impairment. The disease affects both women and men in an equal manner, and is mostly diagnosed already at young age.

TNFα is considered a key player in physiological and pathophysiological inflammatory processes. In some autoimmune diseases, the molecule was found to be a major contributor to inflammation. Since elevated TNFα levels were found in psoriatic skin lesions capable of mediating keratinocyte proliferation, and increased serum levels were correlated with disease activity, there is a rationale for evaluation of treatment of moderate to severe psoriasis with infliximab.

The MAH proposed to extend the indication for Remicade in the treatment of patients with psoriasis in patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate.

The MAH proposed to amend the text of the SPC, sections 4.1, 4.2, 4.4, 4.8 and 5.1, and to update the PL accordingly.

2 Clinical aspects

To support the new indication "Psoriasis", the MAH submitted 2 clinical studies (EXPRESS and SPIRIT) for the evaluation of efficacy and safety of infliximab monotherapy in patients with moderate to severe plaque-type psoriasis.

- Study C0168T38 (EXPRESS): Phase III study, "European Infliximab for Psoriasis (Remicade) Efficacy and Safety Study"
- Study C0168T31 (SPIRIT): Phase II study, "Study of Psoriasis with Infliximab (Remicade) Induction Therapy"

The MAH submitted also the clinical study IMPACT 2 (in PsA), which had already been submitted in a previous application.

2.1 Clinical Pharmacology

Pharmacokinetics

Pharmacokinetics (PK) analyses were performed in both studies. The serum half-life in SPIRIT for 5 mg/kg was 9.1 days. This parameter was not evaluated in EXPRESS, but serum concentrations at respective timepoints were similar in both studies. There was no evidence of accumulation of infliximab concentration over time during maintenance therapy in the EXPRESS study.

The PK was comparable in patients with psoriasis and PsA, reaching higher pre-infusion serum concentrations than in patients with RA or CD. The CHMP requested further discussion of this finding. The MAH submitted data that suggest that over time pre infusion levels were becoming similar to those evaluated in other populations, and that maintaining detectable pre-infusion serum levels were associated with clinical response.

2.2 Clinical efficacy

Study C0168T38 (EXPRESS)

EXPRESS was a phase 3, double blind, placebo-controlled trial in moderate to severe plaque psoriasis in 378 subjects, candidates for phototherapy or systemic therapy. An induction regimen of infliximab 5 mg/kg infusions at Weeks 0, 2, and 6 was followed by maintenance treatment (every 8 weeks) through Week 46.
The application included 50-week safety and efficacy data from the EXPRESS study as well as 66-week antibody data as a separate report.

Methods

Study participants

Adult patients with a diagnosis of plaque-type psoriasis for at least 6 months were included in this trial. Concerning severity, patients were required to have a baseline PASI score ≥ 12 and a baseline body surface area (BSA) involvement ≥ 10% (moderate to severe plaque-type psoriasis). Patients must have been candidates for phototherapy or systemic therapy, but were not necessarily required to be pre-treated.

The majority of the patients were men, 70.9% and median age was 42 years.

In EXPRESS, 98.4% of subjects had previously used topical agents, 66.4% of subjects had used UVB, 43.1% had used PUVA (phototherapy combining psoralens and ultraviolet light A), 42.6% had used methotrexate (MTX), 29.2% had used acitretin, and 30.4% had used cyclosporin.
Overall, 43.1% of subjects had previous treatment with ≥2 systemic agents (including MTX, cyclosporin, acitretin, and PUVA), 23.0% of subjects had previous treatment with ≥ 3 systemic agents, and 7.7% of subjects had previous treatment with ≥ 4 systemic agents. Eighteen percent of subjects had used at least 1 systemic agent systemic agent for ≥ 3 years.
At baseline, 16.4% of subjects had previously been treated with biologics.

The inclusion criteria were considered acceptable and adequate to recruit the addressed patient population of moderate to severe plaque-type psoriasis in a second-line therapy setting. The CHMP requested supplementary information on the fact that the present studies did not specifically address adult patients "who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, MTX or PUVA". The MAH justified that subjects' psoriasis medication history was collected and analysed, however the data on the response to the previous psoriasis medication were not collected. This was agreed with and reflected in the SPC.

Treatments

Patients were randomised in a 4:1 ratio, stratified by investigational site, to two groups:

Group 1 (infliximab arm):	
(n=301)	Infliximab 5mg/kg at weeks 0, 2, and 6 (induction phase), followed by Infliximab 5mg/kg every 8 weeks through week 46 (maintenance phase). Placebo infusions were given at weeks 24 and 26 to maintain the blind
Group 2 (placebo cross-over arm):	
(n=77)	Placebo at weeks 0, 2, and 6, followed by Placebo every 8 weeks through week 22 (placebo maintenance phase), cross-over to infliximab 5mg/kg at weeks 24, 26, and 30 (induction phase), followed by infliximab 5mg/kg maintenance therapy every 8 weeks through week 46

During the first 10 weeks all topical corticosteroids were prohibited, thereafter low-potent topical steroids were allowed in face/groin (max. 30 g/week). Other steroids (except inhalations, otic, ocular

or nasal), phototherapy or any systemic therapy were not permitted during the first 50 weeks. Intraarticular injections in no more than 2 sites were allowed.

Evaluations and blood sampling were performed at weeks 0, 2, 6, 10, 14, 22, 24, 26, 30, 38, 46, 50 and 66.

Outcomes/endpoints

The primary efficacy endpoint was the proportion of subjects achieving ≥ 75% improvement in PASI (referred to as PASI 75) from baseline at week 10.

Major secondary endpoints were:

- PASI ≥ 75% from baseline at week 24
- Change in DLQI (Dermatology Life Quality Index) from baseline to week 10 and week 24
- The proportion of subjects achieving a PGA (Physicians global assessment of improvement) score of cleared (0) or minimal (1) at week 10

Further to these, other efficacy measures were employed; both measured at week 10 and 24:

- PASI ≥ 50%, representing "clinically meaningful response"
- PASI ≥ 90%, representing "significant" or "marked" response, also referred to as "clear or almost clear"
- NAPSI (Nail Psoriasis Severity Index)
- SF-36 (36-item Short Form Health Survey)

Results

Efficacy results

The following table shows the proportion of subjects achieving PASI 75 over time in the respective groups. In the placebo group the switch over to infliximab at week 24 should be noted.

Table 1. Summary of PASI response through Week 50 by visit; randomized subjects

	Placebo → Infliximab 5mg/kg (at Week 24)	Infliximab 5mg/kg
Subjects randomized	77	301
Week 2		
n	77	298
≥ 90% improvement	0 (0.0%)	3 (1.0%)
≥ 75% improvement	0 (0.0%)	16 (5.4%)
≥ 50% improvement	3 (3.9%)	106 (35.6%)
Week 6		
n	77	295
≥ 90% improvement	1 (1.3%)	94 (31.9%)
≥ 75% improvement	4 (5.2%)	184 (62.4%)
≥ 50% improvement	6 (7.8%)	264 (89.5%)
Week 10		
n	77	301
≥ 90% improvement	1 (1.3%)	172 (57.1%)
≥ 75% improvement	2 (2.6%)	242 (80.4%)
≥ 50% improvement	6 (7.8%)	274 (91.0%)
Week 24		
n	77	276
≥ 90% improvement	1 (1.3%)	161 (58.3%)
≥ 75% improvement	3 (3.9%)	227 (82.2%)
≥ 50% improvement	5 (6.5%)	248 (89.9%)
Week 50		
n	68	281
≥ 90% improvement	34 (50.0%)	127 (45.2%)
≥ 75% improvement	52 (76.5%)	170 (60.5%)
≥ 50% improvement	61 (89.7%)	193 (68.7%)

Serum infliximab concentrations and correlation with psoriasis area and severity index:

Serum concentration was correlated to disease activity, where response was defined as ≥ PASI 75%. At week 10, the proportions of patients achieving PASI 75 were similar (78%-89%) in all detectable concentration ranges but lower (44%) in subjects with undetectable levels (below 0.1 µg/ml). At week 24, the proportion of patients with PASI 75 was lower (64%) in the undetectable group than in groups with detectable concentrations. At week 50, 82%-88% of patients with concentrations above 1 µg/ml had PASI 75 but the percentage of PASI 75 responders was decreased at <0.1 µg/ml and 0.1 - 1 µg/ml concentrations (29% and 50% respectively).
Subjects losing response seemed to clear infliximab more rapidly, which was indicated by median preinfusions-infliximab concentrations below the 'lower limit of detection'.

Physician´s Global assessment (PGA) (in EXPRESS)

At week 50, PGA cleared/minimal was reached by 53% of the infliximab 5 mg/kg group and by 68% of placebo/infliximab. The timepoint with the highest percentage of clear/minimal response was at week 10 in the infliximab group, with 82.9% reaching PGA cleared/minimal.

Nail psoriasis (NAPSI score)

At week 24, the NAPSI score improvement from baseline was 2 in the infliximab group and 0 in the placebo group.

Dermatology life quality index ((DLQI)

Significant differences were seen between the infliximab and placebo groups at Weeks 10 and 24. At Week 24, the infliximab group had a -9.0 median improvement from baseline in DLQI score versus no median change in the placebo group. At Week 50, both treatment groups showed a similar median improvement from baseline in DLQI (-7.0 in the placebo/infliximab group and -6.0 in the infliximab

group). This however represents a drop in the median DLQI score from Week 24 for the infliximab group. This was considered most likely driven by the proportion of subjects who lost responder status (defined by PASI improvement).

SF-36

The infliximab group showed a significant (median 3.9 and 3.4) improvement from baseline in the SF-36 physical component score in comparison with the placebo group at Weeks 10 and 24.
At Week 50, both the placebo/infliximab and infliximab groups showed a median improvement from baseline in the SF-36 physical component score, with a change of 1.8 in the placebo/infliximab group and 0.7 in the infliximab group. This is a median decrease from Week 24 for the infliximab group.
At Week 50, both the placebo/infliximab and infliximab groups showed a median improvement from baseline in the mental component of the SF-36, with a median change of 1.0 in the placebo/infliximab group and 1.5 in the infliximab group. This was a decrease from Week 24 for the infliximab group.

Conclusion on efficacy

The CHMP considered that efficacy in the short-term seems excellent. In EXPRESS, there was a trend towards a decrease in efficacy from week 24 to week 50 in a small proportion of subjects who initially responded.. The identified lowering of serum concentrations of infliximab, development of antibodies and decrease in effect are of concern in maintenance therapy with infliximab.

Study C0168T31 (SPIRIT)

SPIRIT was a phase 2, double blind, placebo-controlled trial evaluating the efficacy and safety of infliximab induction therapy in patients with plaque-type psoriasis (249 subjects with severe psoriasis) who had previously received PUVA or other systemic therapy. An induction regimen of infliximab 3 mg/kg or 5 mg/kg infusions at Weeks 0, 2, 6, was followed by the possibility of retreatment with the same dose at Week 26. The SPIRIT study was complete and included 30 weeks of safety and efficacy data and a final HACA (Human Antichimeric Antibodies) evaluation at week 46. Efficacy data through Week 30 was previously submitted in support of the PsA type 2 variation.

Methods

Study participants

The study participants were adults suffering from plaque-type psoriasis for at least 6 months. SPIRIT required that the patients were already pre-treated with systemic therapy or PUVA. In addition, subjects were required to have a baseline PASI score ≥ 12 and a BSA involvement of at least 10%. The inclusion criteria were considered acceptable and adequate to recruit the addressed patient population of moderate to severe plaque-type psoriasis in a second-line therapy setting.

The majority of patients were male (69.9%), in median 44.0 years old.

Treatment

Patients were randomised in a 2:2:1 ratio to three groups:

Group 1: (n=99)	Infliximab 3mg/kg at weeks 0, 2, and 6 (induction therapy only) At week 26, subjects with a PGA score of ≥ 3 were retreated with a single infusion of infliximab 3mg/kg
Group 2: (n=99)	Infliximab 5mg/kg at weeks 0, 2, and 6 (induction therapy only) At week 26, subjects with a PGA score of ≥ 3 were retreated with a single infusion of infliximab 5mg/kg
Group 3: (n=51)	Placebo infusions at weeks 0, 2, and 6 At week 26, subjects with a PGA score of ≥ 3 were retreated with a single infusion of placebo

Outcomes/endpoints

The primary efficacy endpoint was the proportion of subjects achieving ≥ PASI 75 improvement from baseline at week 10.
Major secondary endpoints were:

- The proportion of patients positive for HACA
- The proportion of patients with infusion reactions at week 26
- The proportion of patients with an infusion reaction at week 26 by HACA status at week 26
- PASI ≥ 75% from baseline at week 26

Further to these, other efficacy measures were employed; both measured at weeks 10 and 26:

- PASI ≥ 50%, representing "clinically meaningful response"
- PASI ≥ 90%, representing "significant" or "marked" response, also referred to as "clear or almost clear"

Results

Efficacy results

Efficacy results are presented in the table below and further addressed in the discussion on clinical efficacy.

Table 2. Summary of PASI response at each visit through week 26; randomized subjects[a]

		Infliximab		
	Placebo	3 mg/kg	5 mg/kg	Combined
Subjects randomized[a]	51	99	99	198
Time post initial infusion				
Week 2				
n	50	98	98	196
≥ 90% improvement	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.5%)
≥ 75% improvement	0 (0.0%)	3 (3.1%)	7 (7.1%)	10 (5.1%)
≥ 50% improvement	2 (4.0%)	33 (33.7%)	39 (39.8%)	72 (36.7%)
Week 4				
n	47	96	95	191
≥ 90% improvement	0 (0.0%)	8 (8.3%)	19 (20.0%)	27 (14.1%)
≥ 75% improvement	0 (0.0%)	34 (35.4%)	45 (47.4%)	79 (41.4%)
≥ 50% improvement	4 (8.5%)	68 (70.8%)	79 (83.2%)	147 (77.0%)
Week 6				
n	49	96	97	193
≥ 90% improvement	0 (0.0%)	18 (18.8%)	35 (36.1%)	53 (27.5%)
≥ 75% improvement	0 (0.0%)	56 (58.3%)	68 (70.1%)	124 (64.2%)
≥ 50% improvement	7 (14.3%)	78 (81.3%)	91 (93.8%)	169 (87.6%)
Week 8				
n	45	95	93	188
≥ 90% improvement	0 (0.0%)	36 (37.9%)	54 (58.1%)	90 (47.9%)
≥ 75% improvement	2 (4.4%)	67 (70.5%)	79 (84.9%)	146 (77.7%)
≥ 50% improvement	8 (17.8%)	82 (86.3%)	91 (97.8%)	173 (92.0%)
Week 10				
n	51	99	99	198
≥ 90% improvement	1 (2.0%)	45 (45.5%)	57 (57.6%)	102 (51.5%)
≥ 75% improvement	3 (5.9%)	71 (71.7%)	87 (87.9%)	158 (79.8%)
≥ 50% improvement	11 (21.6%)	83 (83.8%)	96 (97.0%)	179 (90.4%)
Week 26				
n	42	87	90	177
≥ 90% improvement	0 (0.0%)	5 (5.7%)	13 (14.4%)	18 (10.2%)
≥ 75% improvement	4 (9.5%)	12 (13.8%)	27 (30.0%)	39 (22.0%)
≥ 50% improvement	6 (14.3%)	27 (31.0%)	51 (56.7%)	78 (44.1%)

Relapse in SPIRIT.

Relapse was defined as having a >50% loss of the improvement seen in PASI between baseline and week 10 at a visit subsequent to week 10.
The proportion of PASI responders at week 10 who relapsed at or before week 26 was slightly greater among subjects in the 3 mg/kg infliximab group (34/70, 48.6%) compared to that observed in the 5 mg/kg group (33/83, 39.8%).

The median time to relapse among subjects in each infliximab group was > 16 weeks from week 10.

For the subset of subjects who were retreated at week 26 (11 subjects in the placebo group, 52 subjects in the 3 mg/kg group, and 51 subjects in the 5 mg/kg group), the proportion of subjects who were

PASI responders at week 30 was 23.1% in the infliximab 3 mg/kg group, 34.0% in the infliximab 5 mg/kg group, and 18.2% in the placebo group. These results indicate that the majority of subjects who lost response were not able to regain response in 4 weeks after one single infusion. No rebound was observed.

This limited experience from retreatment after an induction regimen with one single infliximab dose after an interval of 20 weeks suggests reduced efficacy. The study protocol was not designed to evaluate the meaning of this finding as no further infliximab dose was administered after week 26.

Clinical efficacy across trials

Subgroup analyses:

In both EXPRESS and SRIRIT, PASI response was consistent across PASI and BSA subgroups indicating similar efficacy in both moderate and severe psoriasis. Additionally, the PASI response was consistent in EXPRESS across previous systemic agent subgroups supporting infliximab as being efficacious in those who may have been intolerant to or resistant to other medications.

Onset of efficacy:

As seen in tables 1 and 2, onset of response was rapid. For instance, nearly two-thirds of the 5 mg/kg group in each study achieved > 75% improvement in PASI at Week 6.

Maintenance of efficacy:

Maintenance of efficacy in an induction/maintenance regimen

In EXPRESS, 82.2% of subjects in the infliximab group achieved > 75% improvement in PASI from baseline at Week 24 and 60.5% at Week 50. When subjects were evaluated using a per-protocol analysis, which primarily removed data after subjects discontinued study infusions for reasons other than unsatisfactory therapeutic effect or missed at least 2 study infusions, 70.5% of subjects in the infliximab group achieved ≥ 75% improvement in PASI from baseline at Week 50. When considering only subjects who responded at Week 10 (i.e., achieved the primary endpoint), 65.1% of infliximab subjects maintained ≥ 75% improvement in PASI from baseline at Week 50.
In EXPRESS, a loss of response (< 75% improvement in PASI from baseline) was observed in a small proportion of subjects who initially responded. Serum infliximab levels and antibody to infliximab status were examined to assess any relationships to efficacy.

Supportive studies

Study C0168T50 (IMPACT 2)

IMPACT 2 had already been submitted in a previous application. This trial was a multicentre, randomised, double blind trial in 200 patients with active, polyarticular PsA who had inadequate response to current or previous therapies. All patients also had concomitant active psoriasis. The data submitted included week 24 data. Infliximab was administered as 5 mg/kg at weeks 0, 2 and 6 followed by every 8-week maintenance, including a subset of patients in the infliximab arm where dose was escalated to 10 mg/kg. Nearly half of the patients were treated with MTX at baseline. Median BSA was 10.0% (range 3.0% to 91.0%). The median PASI at baseline was 6.6.
The degree of psoriasis was considerably more variable than in EXPRESS and SPIRIT.

The primary endpoint, the proportion of patients who reached an ACR 20 response (American College of Rheumatology) of PsA, demonstrated significant improvements in favour of infliximab. Concerning improvement of psoriatic skin lesions, efficacy was demonstrated in a subset of patients with at least 3% BSA involvement (85.9%). The efficacy of infliximab showed an extent comparable to EXPRESS

and SPIRIT with an early onset. However, these data are considered supportive only, since the severity of psoriasis was markedly heterogeneous.

Discussion on clinical efficacy

The baseline characteristics were comparable across the EXPRESS and SPIRIT studies and across the treatment arms and balanced with regard to demographic, baseline and disease characteristics.
These baseline data enable for an assessment of infliximab efficacy and safety in a clinically meaningful target population for an anti-TNF agent, i.e. after failure of previous therapies.

The primary endpoint was reached by 80.4% (EXPRESS) and 87.9% (SPIRIT) of infliximab-treated patients as compared to 2.6% and 5.9% in the respective placebo groups, which reflects a profound and clinically meaningful efficacy of this treatment.

The clinical efficacy was also consistently demonstrated for the secondary outcome measures. Of note, a profound clinical efficacy, reflected by a PASI response of ≥90% and a PGA of cleared or minimal, was apparent by a considerable number of patients. Also nail psoriasis was improved, although the NAPSI score represents a score where no accepted definition of a clinically relevant improvement exists so far. The improvement of the quality of life parameters was considered supportive evidence of efficacy.

The onset of efficacy for the key efficacy variables (PASI, PGA) was rapid. After two infusions (5 mg/kg), approximately two-thirds achieved a PASI 75 response and approximately one-third reached a "marked" response (PASI 90).

Some subjects had a late onset of efficacy. 16 subjects achieved only a PASI improvement of less than 50% at week 10 (i.e. they failed to reach the primary endpoint), but three patients reached a PASI 75 at week 24. Subjects who achieved already a PASI improvement between 50 and 75% at week 10 were more likely to achieve responder status at week 24 (20/30 patients, 66.7%).
The CHMP requested adequate definitions on non-responders, and how long they should be treated before infliximab is to be discontinued due to inefficacy. The MAH submitted a clarification, namely to amend the wording of the SPC, and the wording was considered adequate.

A tapering of efficacy from 80% PASI 75 at week 10-24 to 60% at week 46 was found. The reduced effect over time was discussed by the MAH and low serum levels together with impairment of efficacy might be due to antibody formation. The CHMP considered that further data on long-term efficacy and safety would be of value.

2.3 Clinical Safety

Patient exposure

The safety analysis includes 50-week data from the EXPRESS study and 30 week data from the SPIRIT study, complemented by 24-week data from IMPACT 2 (PsA). For EXPRESS, 66-week HACA data were available in a separate report.

In the EXPRESS study, through week 50, 375 received at least one dose of study agent and a total of 366 subjects received at least one dose of infliximab. Through week 50, the infliximab group had an average follow-up of 48.7 weeks.

In total (EXPRESS, SPIRIT, IMPACT 2), 615 patients were exposed to at least one dose of 5 mg/kg and 98 patients exposed to at least one dose of 3 mg/kg.

Safety evaluations were based on subjects who were randomly assigned and received at least 1 infusion (full or partial) and were summarized by actual treatment received. Two types of summaries were provided, through Week 24 and Week 50.

Cumulatively, 576,000 patients have been exposed to infliximab for a total of 1,347,000 person-years elapsed since first exposure.

Adverse events

Serious adverse events, deaths and malignancies

(a) Serious adverse events (SAE)

In the placebo-controlled period of the EXPRESS trial (i.e. through week 24), 17 (5.7%) subjects in the infliximab 5 mg/kg group experienced at least 1 SAE, compared to 2 (2.6%) subjects in the placebo group, the SAE in these placebo cases being psoriasis. Through week 50, 22 patients (one in the placebo group, two in the infliximab group after cross-over, and 19 in the infliximab group) reported SAEs that were reasonably related to study drug, the most common being abscess (n=3).

In SPIRIT, a total of 12 patients (6.1%) reported SAEs through week 30, including 4 patients in the 3 mg/kg group and 8 patients in the 5 mg/kg group. 4 of these 12 patients reported SAEs that were considered reasonably related to study drug: squamous cell carcinoma of the skin, cholecystitis/cholelithiasis, diverticulitis, sepsis/pyelonephritis. Other SAEs included basal cell carcinoma, brain haemorrhage, and others.

(b) Deaths

One death occurred in the EXPRESS trial. It was a 47-year old caucasian male patient with a 9-year history of psoriasis who died due to bacterial sepsis and cardiac arrest following necrotizing fascitis involving the right neck with Streptococcal group A infection. According to the investigator, the cardiac arrest and sepsis had an unlikely relationship to study agent, and the necrotizing fascitis was considered not related to study agent.

(c) Malignancies

In EXPRESS, malignancy occurred in 6 patients through week 50. Five of these patients received prior PUVA and/or narrow band ultraviolet light B (UVB) therapy for psoriasis, 4 of them for over one year. The malignancies were characterized as follows:

1. squamous cell carcinoma of the lower lip at week 24, (placebo/infliximab group, i.e. before cross-over to infliximab)
2. Basal cell carcinoma on the tip of the nose (week 50, infliximab group)
3. Bowenoid keratosis actinica (squamous cell carcinoma in situ) on the left thigh, week 6 (infliximab group)
4. Spinocellular carcinoma on the right lower leg, week 6 (infliximab group)
5. Basal cell carcinoma on the forehead at approximately week 6 and a basal carcinoma on the left side of the nose at week 24 (inflximab group, discontinued from week 14)
6. Bowenoid papulosis, week 38 (coded as squamous cell carcinoma, benign lesion), infliximab group.

In SPIRIT, through week 30, 3 (1.5%) subjects had a malignancy, with two of the patients having been pre-treated with previous PUVA and/or UVB therapy. Two patients developed a squamous cell carcinoma of the skin 2 to 3 weeks after the Week 6 infusion of 3mg/kg infliximab. One subject discontinued from the study due to the event. The third patient developed a basal cell carcinoma of the skin approximately 5 weeks after the Week 26 infusion of 5mg/kg infliximab.
Specifically, 2 of 3 subjects in SPIRIT and 4 of 6 subjects in EXPRESS were diagnosed with skin malignancy in the course of infliximab therapy.
In both studies, no patients in either placebo group developed a malignancy.
No cases of lymphoma were reported for both studies.

Specific adverse events

Infections

In the EXPRESS study, through Week 24 a similar proportion of subjects reported infections (39.5% of the placebo and 41.9% of the infliximab group). Through Week 50, 65.8% in the infliximab groups reported infections, which was a higher proportion of patients than in the first half of the study, as compared to 39.7% in the placebo/infliximab group through week 50. Most commonly reported infection was upper respiratory tract infection (URI, 28.9% through week 50). Infectious events that were at higher incidence in the second half of the study (weeks 25 to 50) were pharyngitis (8.4%), flu syndrome (7.4%), and herpes simplex (5.4%).
In SPIRIT, the proportion of patients with one or more infections was greater in both infliximab groups than in the placebo group (31.6% and 37.4% versus 21.6%). With the exception of sinusitis, infections generally occurred at comparable incidence in both infliximab groups. Again, most frequently reported infection was URI.

a) Serious infections

In EXPRESS, 8 serious infections were reported through week 50, 3 of which occurred before week 24. Most common was abscess (n=4, 1.3%), 3 of them being perianal abscesses (two treated by incision, one treated with systemic antibiotics). Study drug was not discontinued. The fourth abscess was a throat abscess. The other four serious infections were fasciitis and sepsis, appendicitis with subumbilical wound infections, neuroborreliosis, and bronchitis.
In SPIRIT, one patient had a serious infection (pyelonephritis), followed by sepsis, probably related to infliximab. He was hospitalized, and the event resolved after treatment.

b) Opportunistic infections

In EXPRESS, 9 patients were reported of having experienced a potential opportunistic infection, all of them occurring while being on treatment with infliximab. These consisted of herpes zoster (n=2), candida infections (n=4), oral candida infections (n=2), esophageal candidiasis (n=1), and intestinal candida (n=1). Two patients had genital fungal infections, and one subject reported a possible fungal infection of the feet. Of these 9 events, 4 were resolved, 5 were ongoing as of the last follow-up visit.
In SPIRIT no case of opportunistic infection was reported.

c) Tuberculosis

No cases of active tuberculosis were observed in either study.

Infusion reactions

An infusion reaction was defined in both studies as any AE occurring during an infusion or within one hour after the completion of an infusion. In EXPRESS, the incidence of infusion reactions was 2.0% in the placebo group (347 infusions) vs. 2.7% in the infliximab group through week 24 (1416 infusions); for the subjects having crossed to infliximab from the placebo group, the incidence was 3.6% (334 infusions). Total incidence of infusion reactions through week 50 in the infliximab group was 2.1% (2652 infusions). The majority of the reactions were mild or moderate.
In SPIRIT, the occurrence of infusion reactions was comparable between both dosage groups (3mg/kg: 5.2%, 288 infusions, 5mg/kg: 6.5%, 292 infusions), but higher than in the placebo group (0.7%, 136 infusions).

a) Serious infusion reactions

Four patients in the EXPRESS study had serious infusion reactions The rate of serious infusion reactions (1.1% in EXPRESS) was consistent with the rate across other infliximab studies. In EXPRESS, one patient in the placebo/infliximab group (1.3%) and 8 patients (2.7%) in the infliximab group permanently discontinued the drug due to an infusion reaction. In SPIRIT, two (2.0%) patients in the infliximab 3mg/kg group permanently discontinued study infusions due to an infusion reaction.

b) Infusion reactions following re-treatment (SPIRIT study)

The infusion reaction rate for the 5mg/kg infliximab group was higher at the Week 26 re-treatment than for the 3 mg/kg infliximab group and higher than the rate observed in this group through Week 6. The infusion reaction rate for the 5mg/kg infliximab group was 13.7% at Week 26, compared to 6.5% through Week 6. The infusion reaction rate for 3mg/kg infliximab group at Week 26 (7.7%) was similar to the rate in this group through Week 6 (5.2%).
For the 11 placebo subjects who received a single placebo infusion at Week 26, none experienced an infusion reaction.

Anaphylactic and delayed hypersensitivity

There were 4 reports of delayed hypersensitivity in the EXPRESS and 3 reports in the SPIRIT trial, respectively.
One patient in the EXPRESS study experienced a moderate anaphylactic reaction during the week 30 infusion. The study drug was permanently discontinued.
No patient in the SPIRIT trial was reported with an anaphylactic reaction.

Immunological events

In the EXPRESS study, four cases of autoimmune disease occurred through 50 weeks. Three patients experienced lupus-like syndrome, primarily manifesting as arthritis associated with development of ANA and anti-dsDNA antibodies. In one patient, Sjögren's syndrome was diagnosed. All symptoms improved with treatment or with discontinuation of infliximab.
No case of autoimmunity was observed in the SPIRIT study.

No case of CNS demyelination was seen in either study.

One of the patients with lupus-like syndrome had concomitant chronic hepatitis, being treated with oral prednisone for suspected autoimmune hepatitis.
The occurrence of newly positive antinuclear antibodies (ANA, defined as titre ≥1:40) was 37.3% in the infliximab group, compared to 1.5% in the placebo group, in the EXPRESS trial. Also in SPIRIT, a markedly higher incidence of ANA was measured in the infliximab groups as compared to placebo (22.9% in the 3mg/kg group, 25.0% in the 5mg/kg group versus 2.3% in the placebo group).
The incidence of newly positive anti-dsDNA antibodies was 17.0% in the infliximab/infliximab group, 12.3% in the placebo/infliximab group vs. 0% in the placebo group before switching to infliximab in the EXPRESS study. In the SPIRIT study, incidences were 3.3%/4.3% for infliximab groups vs. 2.1% of subjects in the placebo group.

Antibodies to infliximab

In both SPIRIT and EXPRESS trial efficacy was correlated with the serum concentrations of infliximab in a subset of patients. Serum concentrations below 1µg/ml in the SPIRIT trial were related to declining efficacy. Also, in EXPRESS, the proportion of patients with a PASI 75 improvement was reduced when pre-infusion levels fell below the 1µg/ml level. It was concluded that subjects losing response cleared infliximab more rapidly. However, there were exceptions to this, since some patients lost response despite adequate serum levels and, vice versa.

The CHMP noted that serum concentration levels above 1 µg/ml seemed to be clinically important to achieve. The MAH was requested to further consider if the monitoring of serum levels was of value. The CHMP concluded that clinical evaluation of the individual patient is supported, but long-term strategies are needed. However, serum levels and antibody status do not seem relevant as predictors of efficacy.

HACA positivity was associated with lower median serum infliximab concentrations during the maintenance phase and was generally associated with diminished maintenance of clinical response at week 50. 30/42 (71.4%) subjects who were HACA positive and were responders at Week 10 failed to maintain clinical response at Week 50; the majority had undetectable serum infliximab levels at Week 46. However, there were also subjects who showed a loss of response through week 50 despite initial response who were HACA negative (19/31, 61.3%).

In the EXPRESS study, the majority of subjects (62.4%) were inconclusive for antibodies to infliximab through Week 50. The combined incidence of subjects positive for antibodies to infliximab through Week 50 was 19.7%. The majority of subjects presented with titres of < 1:40. This was consistent with the incidence of antibodies to infliximab observed in SPIRIT.
There was an approximate 1.5-fold increase in the incidence of infusion reactions among antibody to infliximab positive subjects compared with subjects negative for antibodies. The majority of infusion reactions were of mild to moderate intensity. The incidence of serious or possible delayed type hypersensitivity reactions was comparable between antibody to infliximab positive and negative subjects.

The CHMP requested further clarification on the possible relationship between antibody and infliximab concentrations. The MAH provided the requested justification. Antibody positivity seems to be correlated to lower serum levels. Patients inconclusive to antibodies seem to maintain higher serum levels of infliximab in a higher degree than those who are negative, making it plausible that inconclusive most often indicate "no antibodies". The definition of "inconclusive" (measurable serum levels and negative for antibodies) in contrast to "negative" (low serum levels and no antibodies) makes this interpretation possible. The explanation for why antibody negative patients have low serum levels is more difficult to understand. This group of patients might be those who would benefit from dose escalation. Antibody positive patients might benefit from combination therapy with e.g. MTX. The issue was considered resolved.

In the SPIRIT study, the subjects in the 3mg/kg infliximab group that were antibody positive had a higher baseline PASI score at week 26 before re-treatment was initiated. This could be in line with a clinically relevant inhibitory effect of anti-infliximab antibodies. The longer-term impact of this finding, e.g. if such loss of efficacy could be overcome by repeat dosing, is not known, as SPIRIT was not designed to evaluate this further.

This finding raised concerns with regard to re-administration of infliximab after a longer time period in terms of safety, but also in terms of efficacy. Since it in the treatment of psoriasis might not in every case be justified to keep a permanent maintenance therapy, infliximab might in some patients be discontinued after a sustained clinical remission.
Additionally, the CHMP considered that the high incidence of HACA is still of concern and that higher rates were observed in psoriasis. Therefore, the CHMP recommended that the SPC should reflect these findings. The MAH agreed with the CHMP proposal.

Discontinuations due to AES

In EXPRESS, 5 patients in the placebo group (6.6%) and 27 patients (9.1%) in the infliximab groups discontinued due to one or more AEs (through week 24). Among patients in the placebo group, most common was psoriasis (5.3%), among infliximab-treated patients increased liver enzymes (1.3%), the latter being a pre-defined cause for planned discontinuation required by the protocol. One (1.5%) patients in the placebo/infliximab group and 8 (2.7%) patients in the infliximab group permanently discontinued due to an infusion reaction. AEs leading to discontinuation through 50 were similar to those reported through week 24, being 13.8% for infliximab from week 0 to 50. In SPIRIT, the

incidence of discontinuations due to an AE was not increased in patients receiving a higher dose of infliximab. Through week 26, eleven patients permanently discontinued because of an AE (7 in the infliximab 3mg/kg group, 3 in the 5mg/kg group, and 1 in the placebo group). These AEs affected various system-organ classes without a trend towards any specific AE.

Laboratory findings and vital signs

Clinically significant abnormal haematologic and serum chemistry values were rare, whilst elevation of liver enzymes, predefined as <150 U/L and ≥ 100% increase from baseline were markedly abnormal. Such elevations of ALT/SGPT (alanine aminotransferase/ serum glutamate pyruvate transaminase) and AST/SGOT (aspartate aminotransferase/serum glutamic-oxaloacetic transaminase) occurred in 6.4% and 2.0% of infliximab-treated patients in the placebo-controlled period of the EXPRESS study , increasing to 8.4% in the infliximab group through week 50. Bilirubin was not markedly elevated in either of these subjects. Approximately one-third of the patients continued treatment, one-third was discontinued, and one third was temporarily suspended. The elevation of liver enzymes resolved in all but two patients. No such elevations of liver enzymes were observed in the placebo groups. There was no correlation between serum infliximab concentrations and abnormal liver function tests, although patients treated with infliximab showed a higher frequency of markedly abnormal levels of liver enzymes in comparison to placebo. The MAH was requested to further explain this and provided the necessary explanation.
In SPIRIT, such findings were reported less frequently.

Safety in special populations

There were 6 pregnancies reported during the EXPRESS study, whereof 3 were unwanted and electively terminated. One normal premature boy was born and one normal in full time (and one unknown).

Discussion on clinical safety

In EXPRESS and SPIRIT no new safety signals were raised.

Increased ALT levels were found in previous studies with infliximab in PsA and ASIn EXPRESS, elevated enzyme levels were found in 8.5% infliximab treated patients through week 50 but in 0% with placebo, which is in line with previous findings. However, no serious hepatic AE, except one with markedly elevated enzyme levels, were reported.
Integrated safety analyses (as of June 2004) suggest disease-specific differences, since such elevated liver enzymes were more frequent in patients with AS and PsA than in patients with RA or CD.
Data suggest that also psoriasis is accompanied with an increased risk for the development of elevated liver enzymes. This elevation of liver enzymes appears to be mainly a problem of continuous therapy with infliximab.
Additional events in EXPRESS included 1 infliximab-treated patient with a single episode of decreased neutrophils, 1 placebo/infliximab subject with a single episode of decreased lymphocytes, and 11 infliximab subjects with decreased lymphocytes (5 subjects with more than 1 abnormal value).

Anti-dsDNA was found in 9.9% at week 24 and in 17% through week 50 in the infliximab group (0% for placebo at week 24).

3. Overall Discussion and benefit/risk assessment

Efficacy in psoriasis has been satisfactorily shown for the treatment of patients with moderate to severe plaque psoriasis,. The highest response rates were found approximately 10-26 weeks after start of treatment. A PASI75 response was reached in approximately 80% of the patients during this time period. At week 50 60% of patients achieved a PASI 75 response. Beyond that time-point, no information is available on the duration of efficacy. Although loss of response is frequently associated with low serum concentrations and the presence of antibodies to infliximab, the correlation between these parameters appears uncertain. With the current knowledge, detailed recommendations on how to handle a patient who looses response with time cannot be given. Moreover, data on intermittent therapy would be of importance in the treatment of psoriasis, and some data will become available later this year from EXPRESS II.

Safety in patients with psoriasis is similar to previously approved indications with the exception of elevated hepatic enzyme levels. However, no alarming hepatic events or safety signals were reported in the studies in psoriasis and further monitoring of hepatic events should continue.

In common with the already approved indications, there is an identified risk for serious infections, including opportunistic infections and TB. Malignancies continue to be followed as well as other events of concern, as per normal PSUR procedures.

Benefit/risk is in favour of infliximab as monotherapy for the indication " treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, MTX or PUVA".

CONCLUSION

The CHMP considered this Type II variation to be acceptable and agreed on the proposed wordings to be introduced into the Summary of Product Characteristics and the Package Leaflet, based on the observations and the appropriate conclusions.

The CHMP adopted on 27 July 2005 an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation.