SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Enbrel. This scientific discussion has been updated until 1 October 2004. For information on changes after 1 October 2004 please refer to module 8b.

1. Introduction

Enbrel is indicated for:

Enbrel can be used alone or in combination with methotrexate for the treatment of active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

Enbrel is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

In patients with rheumatoid arthritis, Enbrel used alone or in combination with methotrexate has been shown to slow the progression of disease-associated structural damage as measured by X-ray.

Treatment of active polyarticular-course juvenile chronic arthritis in children aged 4 to 17 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Enbrel has not been studied in children aged less than 4 years.

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate.

Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

Enbrel treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or psoriasis.

In adults the posology for Enbrel is:

<u>Rheumatoid arthritis</u>
25 mg Enbrel administered twice weekly is the recommended dose, alternatively, 50 mg administered once weekly (as two 25 mg injections given at approximately the same time) has been shown to be safe and effective.

<u>Psoriatic arthritis and ankylosing spondylitis</u>
25 mg Enbrel administered twice weekly is the recommended dose. Doses other than 25 mg administered twice weekly have not been studied.

<u>Plaque psoriasis</u>
The recommended dose of Enbrel is 25 mg administered twice weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.

If re-treatment with Enbrel is indicated, the above guidance on treatment duration should be followed. The dose should be 25 mg twice weekly.

In children and adolescents (≥ 4 to ≤ 18 years) with juvenile chronic arthritis, the posology is 0.4 mg/kg (up to a maximum of 25 mg per dose) given twice weekly as a subcutaneous injection with an interval of 3 – 4 days between doses.

The prevalence of rheumatoid arthritis is approximately 0.5 – 1 % of the population. Overall the disease is three times more common in women than in men. The peak age of onset is between ages 45 and 60. Diagnosis is based on a set of criteria, including signs of symmetrical joint inflammation, radiological signs of joint destruction and increased levels of rheumatoid factors. Juvenile chronic arthritis (also known as juvenile rheumatoid arthritis) is the most common rheumatic condition in children, with an estimated prevalence of 1 per 1000.

Enbrel is a recombinant human tumour necrosis factor receptor p75Fc fusion protein. Tumor necrosis factor (TNF) is a dominant cytokine in the inflammatory process of rheumatoid arthritis: TNF has been shown to be present in the synovial fluid and tissue of inflamed joints of rheumatoid arthritis, and, both by itself and by stimulating the production of interleukin-1, to stimulate cartilage and bone to produce proteases which contribute to cell destruction. TNF may therefore be an appropriate target for therapeutic intervention. Enbrel is a competitive inhibitor of TNF that binds to and renders TNF biologically inactive by preventing the binding of TNF to its cellular receptors.

Psoriasis is a chronic inflammatory disorder of the skin characterised by increased epidermal proliferation. Chronic plaque psoriasis is the most common form of psoriasis and its course may have flare-ups and remission. First line therapies are topical (i.e. emollients, tar, dithranol, steroids) and the second line treatments include phototherapy, systemic methotrexate, cyclosporin and retinoids. The levels of tumour necrosis factor (TNF) in serum and in psoriatic lesions are increased compared with levels in uninvolved skin in patients and in normal individuals. TNF levels decrease after effective psoriasis therapy, correlating with clinical improvement. It has been suggested that interfering with the pro-inflammatory effects of TNF may reduce the inflammation seen in psoriatic lesions.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition
The finished product is a lyophilised cake containing etanercept (25 mg), mannitol, sucrose and trometamol. No preservatives are added.

The primary container/closer system consists of a 4 ml type I (Ph. Eur.) glass vial sealed with a butyl rubber lyophilisation stopper, aluminium seal and a flip-off plastic cap.

The lyophilised cake is to be dissolved in 1.0 ml of water for injections. The solvent, if provided, is supplied in pre-filled syringes containing 1 mL of water for injections. The syringe is either a type I (Ph. Eur.) glass barrel with rubber stopper and a fixed stainless steel needle or a type I (Ph. Eur.) glass barrel with rubber stopper and Luer-Lok connector, a vial adapter for reconstitution and one stainless steel needle.

During the development of the product, the level of excipients was selected to provide stability during lyophilisation, satisfactory appearance, shelf life and suitable osmolality of the reconstituted solution.

Active substance
Enbrel is a novel rDNA product containing the cloned fusion protein, etanercept, consisting of the extracellular ligand-binding portion of human tumor necrosis factor receptor (p75) linked to an analog human Fc portion of human IgG1. The Fc component contains the hinge, CH_2 and CH_3 regions, but not the CH_1 region of IgG1. Etanercept (TNFR:Fc) is synthesized by Chinese Hamster Ovary (CHO) cells as a dimeric, secreted, soluble protein. Dimerisation of the Fc region via two disulphide bonds occurs post-translation. Etanercept contains 934 amino acids and has an apparent molecular weight of 150 kDa. The active substance is manufactured at Boehringer Ingelheim Pharma, Germany, or at Amgen Rhode Island, USA.

Gene construct and cell banks
The cDNA for the p75 TNF receptor was cloned from a human fibroblast cell line. Human IgG1 cDNA was cloned by PCR amplification using a published nucleotide sequence. Details of the preparation, storage and distribution of the master cell bank (MCB) have been provided. Description of preparation, storage and current distribution of the working cell bank (WCB) is also summarised. End of production (EOP) cells have been prepared from the WCB. The sterility, freedom from mycoplasma and viral safety of the MCB, WCB and EOP have been demonstrated. The genetic stability of the MCB, WCB and EOP has been established.

Cell Culture
Etanercept is produced by cell culture. Assurance is given that raw materials from animal origin, used during the cell culture process, do not present a risk of BSE/TSE. In-process testing during cell culture includes tests for microbial growth, microscopic contamination, endotoxin, cell density, viability, pH, osmolality, CO_2, glucose, lactate and etanercept production. In-process specifications have defined acceptance criteria.

Purification
The downstream processing of the active substance is a sequence of validated chromatographic and ultrafiltration steps and viral filtration. In-process controls and specifications are adequate to control the quality and consistency of production. Maximum lifetimes for the columns and the ultrafiltration/ diafiltration systems have been set.

Characterisation
The active substance has been characterised using a combination of traditional and state of the art physicochemical techniques.

The active substance is adequately controlled by a combination of physico-chemical, biological and immunological methods. All analytical procedures have been validated. Batch analysis data demonstrate a consistent production of the active substance.

Other ingredients

All excipients and immediate packaging materials meet the requirements of the Ph. Eur.

Product development and finished product

Enbrel is manufactured by Boehringer Ingelheim Pharma Germany, and Dutch State Mines, USA. Assembly, packaging, labelling and final release will be done by Wyeth Laboratories UK or Wyeth Medica, Ireland. The manufacturing processes have been validated. The finished product is adequately controlled by a combination of physico-chemical, biological and immunological methods. All methods used for routine control have been described and validated.

Stability of finished product
The stability results show a good stability profile for the finished product when stored at 2 – 8 °C for a shelf life as indicated in the SPC.
A storage period after reconstitution of 6 hours at 2 – 8 °C is acceptable provided reconstitution is performed under aseptic conditions.

Pre-filled syringes with water for injections
There are two manufacturers for sterile water for injection in pre-filled syringes described: Schering-Plough, Puerto Rico, for the fixed needle diluent syringe and Vetter Pharma, Ravensburg, Germany for the Luer-Lok diluent syringe with removable needles. Manufacture and control are satisfactory for both manufacturers.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics
In vitro studies: In human myelomonocytic cells, etanercept had a 50-fold higher affinity for TNF than for TNFR. It binds to both human TNFα and Lymphotoxin (LTα). *In vitro* in murine L929 cells, etanercept inhibited the cytolytic activities of rhuTNF, rmuTNF, native TNF and LTα. Etanercept did not affect complement activity of human serum.

In vivo studies: Etanercept has been examined for its effects in various animal model systems of inflammation. In various models of arthritis, it reduced the overall arthritis incidence and the severity of the joint disease. Etanercept slowed down or retarded the onset and reduced the severity of arthritic disease. The inhibitory effects of etanercept appeared to be specific to those mediated by TNF and/or LTα.

Etanercept was also evaluated as a TNF antagonist in several other preclinical models of disease such as septic shock, cachexia, allergic asthma, allograft rejection , response to vascular injury and autoimmune encephalomyelitis.

General and safety pharmacology programme: The effect of etanercept was evaluated in several animal models of disease. A conventional package of safety pharmacology was not conducted, but the need for this was obviated by the investigations conducted in the repeat dose toxicity studies. Only cardiovascular safety was assessed, and no change in mean blood pressure, heart rate, or ECG was detected.

Pharmacokinetics

Single-dose and repeat-dose pharmacokinetics
Single-dose data were obtained in mice, whilst single and repeat dose data were obtained in rats, rabbits and cynomolgus monkeys. The dose levels used spanned those used in the toxicity studies. Etanercept serum concentrations were determined by an ELISA method, which may detect ELISA-reactive degradation products as well as the parent compound.

Absorption and distribution
Absorption was slow after s.c. administration, with maximum serum concentration in mice and monkey occurring at 12 and 23 hours post-dose respectively. Following a single s.c. dose, the systemic availability of etanercept was approximately 58 % in mice and 73 % in cynomolgus monkeys.

Distribution was evaluated in: blood, kidney, liver, lung, heart, spleen. Following single s.c. or i.v. administration of radiolabelled etanercept to mice, radioactivity was detected in all tissues examined, with the greatest amount detected in blood. Following single s.c. administration the blood t_{max} was the same as the tissue t_{max} at 720 minutes. Drug-related radioactivity was eliminated more slowly from the blood ($t_{½}$ 19 hours) than from any other tissue ($t_{½}$ 5 to 10 hours). Placental transfer and secretion into the milk were not investigated.

Metabolism and excretion
Since etanercept is a fusion glycoprotein, consisting entirely of human protein components, it is expected to undergo proteolysis. Hence studies were not conducted.

Drug interactions
In the CIA murine model and the rat study, etanercept did not appear to interact with methotrexate.

Toxicokinetics
The kinetics of etanercept were determined in dose-range finding and definitive reproductive toxicity studies in rat and rabbit and repeat-dose toxicity studies in the monkey. The development of antibodies to etanercept and neutralising antibodies was investigated during these studies.

The development of antibodies following repeated s.c. administration in rabbit and monkey was associated with apparent reduction of serum etanercept concentrations. This could be due to the possible interference of the antibodies with the ELISA used to measure the serum etanercept concentrations.

Immunogenicity
The immunogenicity of etanercept was investigated in mice, rats and rabbits following twice weekly s.c. administration. The majority of mice, rats and rabbits developed neutralising antibodies prior to week 4.

Toxicology

All pivotal toxicity studies were conducted according to GLP requirements.

Single dose toxicity
Studies were conducted using the s.c. or i.v. routes of administration in mice and rats.
Etanercept has a low acute toxicity. There were no deaths in either species at the top dose levels of 1000 mg/kg i.v. or 2000 mg/kg s.c. The overt signs of toxicity which occurred at all dose levels (i.v. route) but only at the top dose level (s.c. route) included ataxia, decreased motor activity, ptosis, dyspnoea and low carriage. These signs subsided by 1 hour (i.v. route) or 4 hours (s.c. route) post-dose.

Repeat-dose toxicity
Repeat-dose toxicity studies were performed in cynomolgus monkeys due to the formation of neutralising antibodies in other species. Neutralising antibodies were not found in the majority of monkeys even after 26 weeks of treatment. Enbrel did not illicit dose-limiting or target organ toxicity in cynomolgus monkeys following twice weekly subcutaneous administration for 4 or 26 consecutive weeks at a dose of 15 mg/kg. In the 26 week study the only treatment related effects were an increase in incidence and/or severity of eosinophil and lymphocyte infiltrates at the injection site.

Reproductive toxicity
Conventional fertility and general reproductive and perinatal/postnatal studies in rodents were not performed because the majority of mice and rats developed neutralising antibodies within 2 to 3 weeks following initiation of twice weekly sc administration of etanercept.
The results of the repeated-dose studies in monkeys revealed no treatment related effects on the reproductive and accessory organs. The potential for developmental toxicity was assessed in range-finding and definitive studies in rats and rabbits, while potential perinatal and early postnatal effect were evaluated in rats. The perinatal and early postnatal assessment was conducted as a part of the definitive teratology study. There was no maternal toxicity at the highest dose in the developmental toxicity studies and there was no evidence of harm to the foetus or neonatal rat due to etanercept.

Genotoxicity and Carcinogenicity
Etanercept was considered to be non-genotoxic from a battery of *in vitro* and *in vivo* studies.
Carcinogenicity studies in rodents were not conducted because of the majority of mice and rats developed neutralising antibodies within 2 to 3 weeks following initiation of twice weekly s.c. administration.

The lack of carcinogenicity studies was a concern for the CHMP, but the CHMP concluded that there are probably no meaningful animal studies which can further evaluate the theoretical risk of increased malignancies resulting from chronic TNF inactivation; therefore the company will conduct long-term surveillance for tumours in man.

Local tolerance
Treatment-related reactions at the injection site occurred only in a 26 week study in monkeys and consisted of increased eosinophil and lymphocyte infiltrates. The incidence and/or severity of injection site reactions increased in a dose related manner. These changes were reversible following a 4-week recovery period.

4. Part IV: Clinical aspects

Clinical pharmacology

Pharmacodynamics

Mechanism of action
Etanercept binds to, and neutralises the biological activity of tumour necrosis factor (TNF) and lymphotoxin, competitively inhibiting the binding of both soluble and membrane bound TNF to cell surface receptors and therefore preventing the TNF-mediated signal transduction which requires the cross-linking of cell surface receptors.

Pharmacodynamic studies
The dose is derived from the outcomes of controlled pivotal studies. Enbrel 25 mg administered twice weekly as a subcutaneous injection, is the recommended dose for optimal therapeutic response in rheumatoid arthritis; alternatively 50 mg administered once weekly was been shown to be safe and effective in a subsequent clinical study. 25 mg administered once weekly gives a slower response and maybe less effective.

Pharmacokinetics

General
The pharmacokinetics of etanercept have been studied in more than 300 healthy volunteers and patients. Population pharmacokinetic analysis was also performed on the combined data set.

Serum drug levels were determined by a validated ELISA method. Specificity of the ELISA was demonstrated against a panel of human cytokines and cytokine receptors.

Studies in healthy subjects and adults with rheumatoid arthritis
After administration of radio-labelled etanercept, nuclear imaging showed distribution of the radioactivity to bone, liver, spleen and kidney, with no delay in clearance from any of these organs. Radioactivity was observed in the urine (probably amino acids/polypeptide fragments). Measurements of etanercept concentration in synovial fluid (one week before and 4 weeks after treatment) showed a rise in etanercept concentration, suggesting that etanercept penetrates the synovium.

After s.c. administration of 25 mg, the maximum plasma concentration was reached after 48 hours. Bioavailability after s.c. administration is 76 %. The volume of distribution is small (V_{ss} = 10.4 l for a 70 kg subject). Enbrel is slowly cleared from the body ($t_{1/2}$ = 70 hours). Clearance was reduced in RA patients (0.066 l/h) compared to healthy volunteers (0.11 l/h). The data collected are consistent with the hypothesis that after binding with TNF, the etanercept-TNF complex is broken down by proteolytic processes in the body in the same way as other proteins; the by-products are either recycled or eliminated via urine or bile.

Studies in special populations
Renal and hepatic failure: Based on a study of patients with acute organ failure (n = 15 acute renal failure patients, n = 9 acute hepatic failure patients), no change in dosage has been recommended in the presence of renal or hepatic impairment.

Elderly patients: No impact of advanced age was apparent. The impact of age on pharmacokinetics was studied as a part of population pharmacokinetic analysis.

Gender and ethnic origin: No effect of gender or ethnic origin has been detected.

Patients with polyarticular-course juvenile chronic arthritis: The results of pharmacokinetic studies in 69 patients in a paediatric trial showed that the average steady-state concentration was 2.1 ± 0.8 µg/ml. In absolute terms, children with juvenile chronic arthritis (JCA) had a reduced clearance compared to adults with RA. After normalisation for weight, clearance was increased compared to that of adults

(effect particularly seen in youngest children). Simulation of dosing suggests that while older children (10-17 years) have serum levels close to those seen in adults, younger children may have appreciably lower serum levels.

Patients with chronic heart failure:
Eleven patients with CHF were studied for pharmacokinetics after repeated etanercept doses of 12 mg/m^2. The pharmacokinetics results in patients with CHF in this study were similar to those observed in healthy subjects and in patients with rheumatoid arthritis.

In a large scale study, the pharmacokinetics of serum etanercept were evaluated in patients with CHF following dosing regimens of 25 mg twice weekly, once weekly, or placebo treatments. The mean steady-state etanercept serum concentrations following 25 mg twice weekly observed in this study were comparable to those observed in patients with rheumatoid arthritis following the same dosing regimen. After 12 weeks of 25 mg twice weekly etanercept, the mean steady-state serum concentration was found to be 2.0 µg/mL, which was considered to be in a range comparable to that observed in the previous study.

Interaction studies
No formal drug interaction studies were conducted. It was found that co-administration of methotrexate (MTX) did not alter the pharmacokinetics of etanercept. Human pharmacokinetics data on the effects of etanercept on MTX are not available. No effect of etanercept on the MTX pharmacokinetics has been found in animal studies.

The cytochrome P450 system and other commonly used metabolic pathways are not involved in the metabolism of etanercept, so there is little potential of metabolic drug interactions. There is no scientific nor pharmacological reason that commonly prescribed medications used in the treatment of RA should interact with etanercept.

In studies when patients received concurrent treatment with Enbrel plus anakinra, a higher rate of serious infections compared to Enbrel alone was observed and 2% of patients (3/139) developed neutropenia (absolute neutrophil count < 1000 / mm3). While neutropenic, one patient developed cellulitis that resolved after hospitalisation

Bioequivalence studies
Bioequivalence was demonstrated between clinical study supplies and commercial product.

Clinical efficacy

Studies in Rheumatoid Arthritis, Juvenile Chronic Arthritis, Psoriatic Arthritis

Dose-response studies and main clinical studies
After a small pilot study (Phase I, study 16.0002), 1694 patients with rheumatoid arthritis (RA), of whom 1218 received Enbrel, have been included from 5 controlled studies (studies 16.0004, 16.0009, 16.0014, 300-EU, and 16.0012). Patients with RA also received Enbrel in open-label studies (studies 16.0008, 16.0018, 16.0019, 16.0023, and 301-EU). Sixty-nine (69) children were treated in a Juvenile Chronic Arthritis study (study 16.0016). A total of 265 patients with psoriatic arthritis were treated in studies 16.0612 and 16.0030.

To be included in the RA studies, patients were required to have active disease and to have failed at least 1 disease modifying anti rheumatic drug (DMARD), except for study 16.0012. The previous DMARD treatment was withdrawn for at least one month before the start of the treatment with Enbrel. In all cases, concomitant treatment with NSAIDs and low-dose steroids (≤ 10 mg prednisone or equivalent) was allowed.

Data were analysed using the ACR (American College of Rheumatology) response criteria as standard validated composite endpoints. The ACR 20 response criterion requires at least 20 % improvement in

tender joint count and swollen joint count, plus 20 % improvement in at least three of the following five parameters:

- patient assessment of pain
- patient's global assessment of disease activity
- physician's global assessment of disease activity
- patient's assessment of physical function using the disability domain of the HAQ (standard health assessment questionnaire) index
- acute phase reactant value, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

The ACR 50 % and ACR 70 % require respectively 50 % and 70 % improvement in joint counts and at least 50 % and 70 % improvement in 3 of the 5 remaining criteria.

Main Clinical Studies

Overview of Studies in Support of Efficacy in Rheumatoid Arthritis

Clinical Trial	Phase	Patient Population	Number of Patients
16.0004	II	DMARD failing, active RA patients	180
16.0009	III	DMARD failing, active RA patients	234
16.0014	II/III	DMARD failing, active RA patients	89
16.0016	II/III	Children with JCA	69
300-EU	III	DMARD failing, active RA patients	559
16.0012	III	Early RA, active RA patients, no prior treatment with MTX	632

Study 16.0004 (Phase II)

This was a double blind, randomised placebo controlled trial with 4 treatment arms. Enbrel was used in dosage of 16 mg/m² , 2 mg/m² and 0.25 mg/m² versus placebo.

Painful and swollen joint counts (3 month results)

Dose	**Placebo (n = 44)**	**0.25 mg/m² (n = 46)**	**2 mg/m² (n = 46)**	**16 mg/m² (n = 44)**
Mean % reduction in painful joint counts	28	25	46 #	64 *#+
Mean % reduction in swollen joint counts	24	16	32	58 *#+

* $p < 0.05$ versus placebo

# $p < 0.05$ versus 0.25 mg/m^2 group

+ $p < 0.05$ versus 2 mg/m^2 group

The results from the primary endpoints suggest that Enbrel reduced the joint pain and joint swelling associated with RA with a consistent dose response relationship. The first significant responses were seen at 2 weeks of therapy. Maximum effect was reached by 1 – 3 months. An increase in joint counts was seen 1 – 2 months after cessation of Enbrel therapy, indicating that continued administration of Enbrel is necessary to maintain a therapeutic response.

Study 16.0009 (Phase III)
This was a double-blind, randomised, placebo-controlled trial with 3 treatment arms. Fixed doses of Enbrel of 25 mg and 10 mg twice weekly were tested against placebo.
The primary endpoint was considered the percentage of patients achieving 20 % ACR at 3 months.

Dose	**Placebo (n = 80)**	**10 mg (n = 76)**	**25 mg (n = 78)**
ACR 20 at 3 months	23	45 *	62 *#
ACR 20 at 6 months	11	51 *	59 *
ACR 50 at 3 months	8	13	41 *#
ACR 50 at 6 months	5	24 *	40 *#
ACR 70 at 3 months	4	8	15 *
ACR 70 at 6 months	1	9 *	15 *

* $p < 0.05$ versus placebo
# $p < 0.05$, versus 10 mg

The response was obtained earlier with the higher dose. The consistent results indicating improvements in primary and secondary end-points, in terms of both numbers of patients with reductions in symptoms and in mean change from baseline for assessment of symptoms, signs and laboratory correlates, suggest that Enbrel is effective treatment for RA over a period of 6 months.

Study 16.0014 (Phase II/III)
This was a double-blind, randomised, parallel group, placebo-controlled trial. Fixed doses of Enbrel of 25 mg twice weekly in combination with previously used methotrexate (MTX) were tested against placebo plus MTX.
The primary endpoint is 20 % ACR at 6 months.

Dose	**Placebo + MTX (n = 30)**	**25 mg Enbrel + MTX (n = 59)**
ACR 20 at 3 months	33	66 *
ACR 20 at 6 months	27	71 *
ACR 50 at 3 months	0	42 *
ACR 50 at 6 months	3	39 *
ACR 70 at 3 months	0	15 *
ACR 70 at 6 months	0	15 *

* $p < 0.05$ versus placebo

The addition of Enbrel to MTX produced better results than MTX alone using the ACR 20, ACR 50 and ACR 70 response criteria. Consistent improvements were seen in primary and secondary endpoints, in terms of both numbers of patients with reductions in symptoms, and in mean change from baseline for assessments of symptoms, signs and laboratory correlates.
Although the addition of Enbrel improved the response shown by the group that received MTX in monotherapy, the results obtained did not provide enough efficacy and safety data to reach conclusions about the risk benefit of etanercept in combination of MTX.

Study 300-EU (Phase III)
This was a double-blind, randomised, parallel, placebo-controlled study of 559 patients. All dosing regimens (10 mg once a week, 10 mg twice a week, 25 mg once a week, or 25 mg twice a week) were significantly more efficacious than placebo in relieving the signs and symptoms of RA. The differences were detected with a great degree of consistency in the primary efficacy variables (percent improvement in tender and swollen joints at 3 months) as well as the secondary variables. Statistical separation between each active dose group and the placebo group began at week 1. The response was further improved during the trial and peaked at the 3-month time point. Of the patients who received Enbrel 25 mg twice a week, 70% achieved an ACR 20% response rate, while only 47% of the patients who received the 10 mg once a week treatment registered an ACR 20% response.

The two intermediate Enbrel dose regimens produced similar results as the high-dose group but were associated with slightly lower ACR 20% response rates. The 10 mg once a week treatment was significantly inferior to 25 mg twice a week in terms of the primary variables. The optimal therapeutic dose was determined to be 25 mg twice weekly.

Subgroup analysis*:* Using the pooled population of studies 16.0004, 16.0009 and 16.0014, subgroups were examined for response by factors including age, sex, positive or negative rheumatoid factor at baseline, whether or not the patient was withdrawn from DMARDs at baseline, disease severity at baseline and whether or not concomitants NSAIDs, corticosteroids or MTX were used.
No correlation to clinical response was observed for any subgroup.

Patient disposition*:* The rate of study completion was also studied as a surrogate measure of efficacy, as the vast majority of discontinuations in all groups were due to a lack of efficacy. A significantly greater percentage of Enbrel-treated patients completed the trials compared with placebo treated patients.

Study 16.0012 (Phase III)
The objective of this study was to compare the ability of two fixed doses of etanercept and methotrexate (MTX) to produce improvement from baseline in rheumatoid arthritis activity and decrease the rate of radiographic progression of joint damage.

Study 16.0012 was a randomised, multicentre, double-placebo, active-control Phase III study comparing the efficacy of etanercept and MTX in adult patients with early (≤ 3 years) active RA who had not previously received MTX. The first year of the study was a double-blind period in which 632 patients received the study drug as follows: etanercept 10 mg twice weekly, n = 208; etanercept 25 mg twice weekly, n = 207; and MTX 7.5 escalated rapidly to 20 mg once weekly, n = 217. The study remained double-blinded until the last patient enrolled had completed 12 months of evaluation.

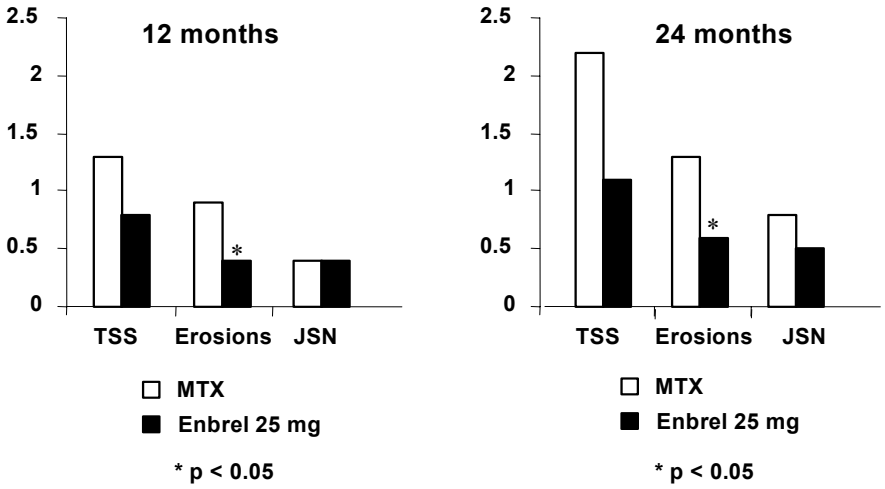
Patients still receiving MTX or etanercept after the study had been unblinded, and who had not experienced adverse events thought to be associated with the study drug, could continue open-label treatment with the study drug to which they were randomised. Patients who discontinued study medication could remain in the study and received standard (non-study) therapy, except etanercept. These patients were included in the statistical analysis.

Patients were at least 18 years of age and fulfilled the 1987 American Rheumatism Association criteria for the classification of RA.

Radiographic progression was a primary endpoint in this study. Total Sharp score (TSS) was calculated by adding each patient's erosion and joint space narrowing scores. The primary clinical endpoint for the double-blind portion of the trial was based on the ACR-N response criteria. Study 16.0012 was designed to allow testing of disability and quality of life as conditional primary endpoints.

Efficacy Results:
Evaluation of radiographic results showed that the changes in joint space narrowing (JSN) scores from baseline to 6, 12 and 24 months of treatment did not differ significantly between the 3 treatment groups. Significantly more patients in the etanercept 25mg group (72%) than in the MTX group (60%) had unchanged erosion scores at 12 months. Enbrel 25mg was significantly superior to MTX for erosion scores at both 12 and 24 months. The differences in TSS and JSN were not statistically significant between MTX and Enbrel 25mg. (please refer to the graph below).

RADIOGRAPHIC PROGRESSION OVER 24 MONTHS



A significantly superior effect of etanercept 25 mg was demonstrated for ACR-N compared with MTX; the mean ACR-N AUC at 6 months being 33% greater in etanercept 25 mg patients compared with MTX patients. The overall tests on HAQ AUC and SF-36 were not significant. The efficacy of Enbrel 10 mg has not been established.

European and North American studies in DMARD refractory patients

The supportive long-term studies showed that the ACR responses achieved by patients receiving etanercept 25mg weekly were maintained up to 3 years.

Efficacy and safety of 50 mg etanercept once weekly dosing regimen compared to 25 mg twice weekly

Study16.0036

Study 16.0036 was a double blind, randomised, active- and placebo-controlled study to evaluate the efficacy and safety of a 50 mg etanercept once weekly dosing regimen compared to the initially approved regimen of 25 mg twice weekly.
Patients with active rheumatoid arthritis (RA) were allowed to receive concomitant methotrexate during the study provided the doses were stable for at least 28 days prior to study start. Randomisation was stratified by usage of methotrexate at baseline based on a 1:4:3 allocation to receive either placebo, etanercept 50 mg once weekly, or etanercept 25 mg twice weekly, respectively.
Treatment was administered twice weekly, with patients receiving 2 injections on the first administration day (dose 1) and 1 injection on the second administration day (dose 2) each week to maintain blinding (patients treated with etanercept also received 1 injection of placebo each week). After 8 weeks of blinded study drug treatment, patients in the placebo group received etanercept 25 mg twice weekly in a blinded fashion for the remaining 8 weeks of the study.

Aim of the study

The primary objective of the study was to evaluate efficacy (ACR 20) and safety of etanercept 50 once weekly in comparison with placebo at Week 8.
The secondary objectives were to evaluate the safety profile of etanercept 50 mg once weekly administered for 16 weeks, the comparative effectiveness of etanercept 50 mg once weekly and 25 mg twice weekly (ACR 20 response after 8 weeks of treatment).In addition, ACR 20 response after 16 weeks and improvement from baseline in individual ACR criteria after 8 and 16 weeks were evaluated.

Patient population
A total of 420 patients were randomised to receive one of the following treatments: etanercept 50 mg once weekly (214), etanercept 25 mg twice weekly (153) or placebo (53).Three hundred eighty one (381) patients (91%) completed 16 weeks of study treatment

Efficacy results

The safety and efficacy profiles of the two Enbrel treatment regimens were comparable in their effect on signs and symptoms of RA.

Use of etanercept in combination with methotrexate (MTX) for the treatment of adult RA, including, the inhibition of the progression of disease-associated structural damage as measured by X-ray

Study 308
The aim of the study was to evaluate the safety and efficacy, including radiographic changes, of etanercept alone, MTX alone, and the combination of etanercept and MTX in patients with active RA who have had inadequate response to at least one DMARD.
In addition, this study evaluated the pharmacokinetics of etanercept with and without concomitant MTX.

Study design
This was a multicentre, double-blind study, which consisted of 2 periods.
Period 1 was a 52-week, randomised, double-blind, parallel design with 3 treatment groups: etanercept only (25 mg twice weekly), MTX only (7.5-20 mg weekly), or etanercept and MTX in combination.
Period 2 is a double-blind extension phase of variable duration (up to 88 weeks), during which patients continue to receive the same treatment as in Period 1 until an administrative decision is made regarding closure of the study.

Study population
Six hundred and eighty six (686) patients with active RA (who failed previous DMARD therapy other than MTX) were randomised to receive one of the following treatments:

etanercept 25 mg SC injections twice weekly or methotrexate 7.5 – 20 mg once weekly or
etanercept 25 mg SC injections twice weekly + methotrexate 7.5-20 mg once weekly.
In addition, all patients received folic acid supplementation of 5 mg twice per week.

In total, 682 patients were treated and analysed for safety (four patients did not receive study medication) and 522 patients (77% of 682 patients) completed Period 1 (approximately 52 weeks) of the study.

Efficacy parameters
The primary clinical endpoint was the ACR-N AUC over the first 24 weeks. This was chosen as the primary endpoint for the purpose of comparison to study 16.0012. The AUC mean response over an interval uses all of the data in that interval rather than any specific point and is claimed to be more sensitive to treatment differences than any single point estimate.

Secondary measures of clinical efficacy were also included: ACR 20, 50 and 70 response rates, DAS index (Disease Activity Score), HAQ (Health Assessment Questionnaire), Components of ACR response (Painful and swollen joint counts, Pain Visual Analogue Scale (VAS), Physician and patient global assessment of disease activity, HAQ, erythrocyte sedimentation rate (ESR) (Westergren), C-reactive protein (CRP)) and other disease activity variables (patient's general health on a VAS, EuroQoL VAS, rheumatoid factor (RF), duration of morning stiffness in minutes).The primary radiographic endpoint was the change from baseline in total Sharp score (TSS) at 12 months. Radiographs of hands, wrists and forefeet were taken at baseline, week 24, and week 52, or the final study visit.

The modified Sharp and Van der Heijde method was used to evaluate radiographs. The evaluation of erosions was in a scale from 0 to 10, and each integer increased in the scale approximated a 10% increase in the area of each joint that is eroded. JSN was scored on a scale from 0 to 4.
Secondary radiographic endpoints included**:** Change from baseline in TSS at 6 months, in total erosions at 6 and 12 months, in total joint space narrowing at 6 and 12 months, number of eroded joints at 6 and 12 months, non-progression (TSS change ≤0.5, ≤3.0, and <SDD [smallest detectable difference]) at 6 and 12 months. Results

The primary efficacy endpoint, ACR-N AUC over 24 weeks, was greater for both the combination etanercept + MTX group and etanercept group compared with the MTX group ($p<0.01$).
Additionally, ACR-N AUC was greater for the combination etanercept + MTX group versus the etanercept group ($p<0.01$). The table below presents the mean ACR-N AUC at 24 weeks for the ITT population. There were significant differences in ACR-N AUC among the 3 treatment groups at 24 weeks.

TABLE. MEAN ACR-N AUC (%-Yrs) FOR WEEK 24 (LOCF)

Population	Methotrexate (n = 228)	Etanercept (n = 223)	Etanercept + Methotrexate (n = 231)
ITT	12.2	14.7[X]	18.3[Y,Z]

Pairwise comparisons p-values: **X** = $p < 0.01$ for comparisons of etanercept vs methotrexate; **Y** = $p < 0.01$ for comparisons of etanercept + methotrexate vs methotrexate; and **Z** = $p < 0.01$ for comparisons of etanercept + methotrexate vs etanercept.

Patients in the Enbrel in combination with methotrexate therapy group had significantly higher ACR 20, ACR 50, ACR 70 responses and improvement for DAS and HAQ scores at both 24 and 52 weeks than patients in either of the single therapy groups (52 week results shown in table below).

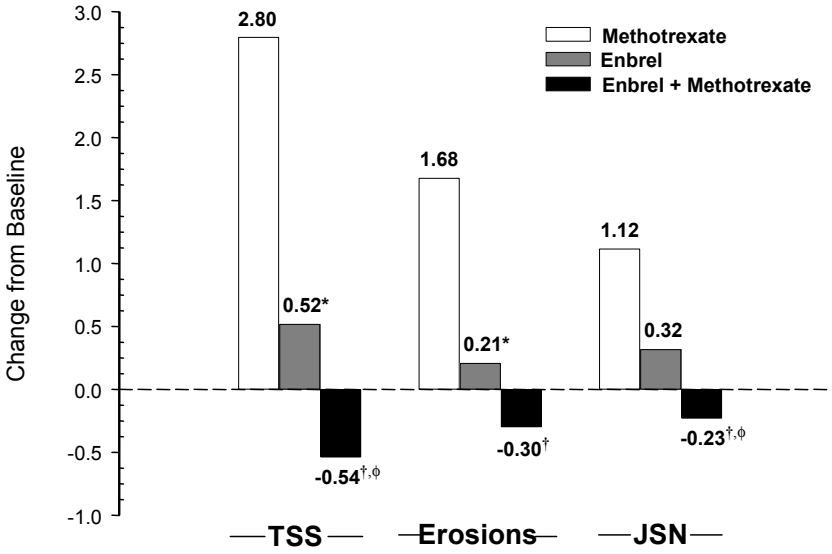
CLINICAL EFFICACY RESULTS: COMPARISON OF ENBREL vs METHOTREXATE vs ENBREL IN COMBINATION WITH METHOTREXATE IN PATIENTS WITH RA OF 6 MONTHS TO 20 YEARS DURATION

Endpoint	Methotrexate (n = 228)	Enbrel (n = 223)	Enbrel + Methotrexate (n = 231)
ACR Responses at week 52			
ACR 20	75.0%	75.8%	84.8% †,ϕ
ACR 50	42.5%	48.4%	69.3% †,ϕ
ACR 70	18.9%	24.2%	42.9% †,ϕ
DAS			
Baseline score[a]	5.5	5.7	5.5
Week 52 score[a]	3.0	3.0	2.3†,ϕ
Remission[b]	14%	18%	37%†,ϕ
HAQ			
Baseline	1.7	1.7	1.8
Week 52	1.0	1.1	0.8†,ϕ

a: Values for Disease Activity Score (DAS) are means.
b: Remission is defined as DAS <1.6
Pairwise comparison p-values: † = $p < 0.05$ for comparisons of Enbrel + methotrexate vs methotrexate and ϕ = $p < 0.05$ for comparisons of Enbrel + methotrexate vs Enbrel

Radiographic progression at week 52 was significantly less in the Enbrel group than in the methotrexate group, while the combination was significantly better than either monotherapy at slowing radiographic progression (see figure below).

RADIOGRAPHIC PROGRESSION: COMPARISON OF ENBREL vs METHOTREXATE vs ENBREL IN COMBINATION WITH METHOTREXATE IN PATIENTS WITH RA OF 6 MONTHS TO 20 YEARS DURATION (52-WEEK RESULTS)



Pairwise comparison p-values: * = $p < 0.05$ for comparisons of Enbrel vs methotrexate, † = $p < 0.05$ for comparisons of Enbrel + methotrexate vs methotrexate and ϕ = $p < 0.05$ for comparisons of Enbrel + methotrexate vs Enbrel

The percentage of patients without progression (TSS change ≤ 0.5) was higher in the Enbrel in combination with methotrexate and Enbrel groups compared with methotrexate at week 24 (74%, 68%, and 56%, respectively; $p<0.05$) and week 52 (80%, 68%, and 57%, respectively; $p<0.05$).

Clinical Studies in Special Populations

Study 16.0016: study in children with Juvenile Chronic Arthritis (JCA)

In the first part of this study, 69 children with JCA received Enbrel subcutaneously twice weekly at a dose of 0.4 mg/kg (max. 25 mg). The inclusion criteria were active disease with at least 5 swollen joints and at least 3 tender/painful joints, and disease refractory to MTX or child resistant to MTX. At the end of the 90 day open-label phase, 51 children who met pre-defined validated response criteria were randomised either to continue treatment with Enbrel or to receive matching injection of placebo for either 4 months or until disease flare occurred. The response criteria were defined as a least 30 % improvement in at least 3 of the following criteria, and with a 30 % or greater worsening in not more than 1 of these criteria: 1. Physician's global assessment ; 2. Patient/parent's global assessment ; 3. Number of active joints ; 4. Number of joints with limitation of movement with pain or tenderness ; 5. Childhood health assessment questionnaire and 6. Erythrocyte sedimentation rate. At the end of the double-blind trial, 28 % (7/25) of children randomised to Enbrel had suffered a disease flare, compared to 81 % (21/26) of the children on placebo treatment. Median time to flare was ≥ 116 days for children on Enbrel versus 28 days for children on placebo. The response to the criteria described above was maintained in the children treated with Enbrel for 4 months, but worsening for all criteria was seen in children treated with placebo. These results show good evidence that the response to Enbrel in JCA is maintained with continued treatment. Given the ethical limitations to undertaking placebo-controlled trials with Enbrel in children, the CHMP agreed that this provided acceptable evidence for the efficacy of Enbrel in the indication Juvenile Chronic Arthritis.

Studies in adults with Psoriatic Arthritis

Two studies are discussed to consider efficacy for Enbrel in the treatment of active psoriatic arthritis (PsA) in adults. A brief description of the studies is presented below.

One Phase II study (16.0612) and one Phase III study (16.0030) have been presented as evidence of efficacy. The Phase III study was a randomised, double-blind, placebo-controlled, multicentre study in 205 patients with active PsA or plaque psoriasis. Randomisation was stratified by concomitant methotrexate (MTX) use. The double-blind phase of the trial lasted 24 weeks and was followed by an open-label extension (OLE) phase in which all eligible patients were treated with Enbrel. The primary endpoint was ACR20 at Week 12. A conditional primary endpoint, only to be tested if a statistically significant effect was observed on ACR20, was Total Sharp score (a measure of radiographic progression) after 12 months. Effects on psoriasis were investigated using the Psoriasis Area and Severity Index (PASI) and target lesion response to therapy. The ITT population was used for the primary efficacy analysis. The psoriasis endpoints were assessed in the subgroup of patients who had at least 3% body surface area affected by psoriasis at baseline

The Phase II study was of similar design. However, the double-blind period was only of 12 weeks duration and the primary endpoint was PsA response criteria (PsARC) at Week 12. Sixty patients were included in this Phase II study.

Efficacy Results:
Both trials achieved their primary and secondary objectives, showing highly statistically significant differences compared with placebo on both PsA and psoriasis endpoints. No treatment by MTX strata interactions were observed. The submitted studies demonstrated that etanercept is more efficacious than placebo in improving clinical symptoms and signs of arthritis and psoriasis in patients with PsA over a period of 24 weeks.

Number (%) of patient achieving ACR 20/50/70 responses in study 16.0030

Endpoint	**Placebo (n = 104)**	**Enbrel (n = 101)**	**p-value**
ACR 20 at 12 weeks	16 (15)	60 (59)	<0.001
ACR 20 at 24 weeks	14 (13)	50 (50)	<0.001
ACR 50 at 12 weeks	4 (4)	38 (38)	0.001
ACR 50 at 24 weeks	4 (4)	37 (37)	0.001
ACR 70 at 12 weeks	0	11 (11)	<0.001
ACR 70 at 24 weeks	1 (1)	9 (9)	0.009

During the 24-week open-label extension of study 16.0612, the PsARC response was maintained in 26 (87%) patients who previously received etanercept. In 28 patients who received placebo in the double-blind phase, 21 (75%) achieved the PsARC at 36 weeks.

Studies in adults with Ankylosing Spondylitis

Study16.0037

This study was a double-blind, randomised, placebo-controlled, multicentre phase 3 study to evaluate the efficacy and safety of etanercept in adult patients with AS as diagnosed by the Modified New York criteria. The planned enrolment was 200 patients, 100 patients in each treatment group.
Adults with active AS were eligible for participation. Patients who met the eligibility criteria were randomly assigned to receive placebo or etanercept, 25 mg administered SC twice weekly, for 24 weeks. The randomisation was stratified on the basis of concomitant DMARDs at baseline.
Efficacy and safety evaluations were performed at weeks 2, 4, 8, 12, and 24.

Study 311-EU

This study was a double-blind, randomised, placebo-controlled, multicentre phase 3 study to evaluate the efficacy and safety of etanercept in the treatment of adult patients with AS. The planned enrolment was 80 patients, 40 patients in each treatment group.

Adults with active AS were eligible for participation. Patients who met the eligibility criteria were randomly assigned to receive placebo or etanercept, 25 mg administered SC twice weekly, for 12 weeks. The randomisation was stratified on the basis of concomitant DMARDs at baseline. The study consisted of a screening period of up to 4 weeks followed by a 12-week double-blind treatment period.
Efficacy and safety evaluations were performed at weeks 2, 4, 8, and 12.

In addition to these 2 multi-centre studies, there was an earlier single-centre study, 16.0626.
Efficacy Endpoints
The primary efficacy endpoint for the 2 phase 3 studies (16.0037 and 311-EU) was the proportion of patients who achieved ASAS 20% response criteria at 12 weeks (≥20% improvement in at least 3 of the 4 Assessment in Ankylosing Spondylitis (ASAS) domains patient global assessments, back pain, BASFI, and inflammation and absence of deterioration in the remaining domain. ASAS 50 and 70 responses used the same criteria with a 50% improvement or a 70% improvement, respectively. Study 16.0037 also had a conditional primary endpoint of the ASAS 20% response criteria at 24 weeks if the primary endpoint established efficacy at 12 weeks. Secondary endpoints included: ASAS 20% at time points other than the final visit, ASAS 50% and 70% responses at all time points, individual components of ASAS response criteria, BASDAI and its components, physician (assessor) global assessment, spinal mobility, peripheral joint counts, acute-phase reactants, and partial remission of AS.

Efficacy Results

Study 16.0037
Compared to placebo, treatment with Enbrel resulted in significant improvements in the ASAS 20, ASAS 50 and ASAS 70 as early as 2 weeks after the initiation of therapy.

RESPONSES OF PATIENTS WITH ANKYLOSING SPONDYLITIS IN STUDY 16.0037

	Percent of Patients	
Ankylosing Spondylitis Response	Placebo N = 139	Enbrel N = 138
ASAS 20		
2 weeks	22	46[a]
3 months	27	60[a]
6 months	23	58[a]
ASAS 50		
2 weeks	7	24[a]
3 months	13	45[a]
6 months	10	42[a]
ASAS 70 :		
2 weeks	2	12[b]
3 months	7	29[b]
6 months	5	28[b]
a: $p<0.001$, Enbrel vs. Placebo		
b: $p = 0.002$, Enbrel vs. placebo		

Among patients with ankylosing spondylitis who received Enbrel, the clinical responses were apparent at the time of the first visit (2 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant therapies at baseline.

Similar results were obtained in the 2 smaller ankylosing spondylitis trials. The studies had different duration of treatment, the Phase II study (16.0626) being for 16 weeks, the Phase III multi-national

study (16.0037) was for 24 weeks and the European study (308) for 12 weeks. Response was maintained over all these periods.

The individual components of the ASAS score and other associated subjective endpoints also all showed a consistent and significant benefit for etanercept. The only component which regularly failed to show any benefit was the swollen joints score. This was considered to be due to the low score at baseline and the small number of patients who actually presented with swollen joints, which did not seem to be a common component in the patients chosen for these studies.

Radiographic results

NUMBER (PERCENTAGE) OF PATIENTS WITH PROGRESSION OF ≤ SDD UNITS FOR TOTAL SHARP SCORE (ITT POPULATION): NUMBER OF PATIENTS / TOTAL NUMBER OF PATIENTS AT TIMEPOINT (%)

Time Points	Methotrexate	Etanercept	Etanercept + Methotrexate
Week 24	192/211 **(91.0)**[a]	202/209 **(96.7)**[x]	216/218 **(99.1)**[Y]
Week 52	187/212 **(88.2)**	203/212 **(95.8)**[X]	212/218 **(97.2)**[Y]

Number of patients / total number of patients at time point (%).
Week 52 values do not include 1-year extrapolated data for patients who did not have week 52 radiograph.

Pairwise comparison p-values: **x** = $p < 0.05$, **X** = $p < 0.01$ for comparisons of etanercept vs methotrexate; **y** = $p < 0.05$, **Y** = $p < 0.01$ for comparisons of etanercept + methotrexate vs methotrexate; and **z** = $p < 0.05$, **Z** = $p < 0.01$ for comparisons of etanercept + methotrexate vs etanercept.

Clinical studies in Plaque Psoriasis

Pharmacokinetics

Pharmacokinetics in patients with psoriasis have been evaluated in the Studies 20021632, 20021639, 20021642, and in the ongoing open-label Study 20030115.

Study 20021632: Serum samples for PK analysis were obtained from all patients before study start, at Weeks 12 and 24, and at the 30-day follow-up visit (for patients who discontinued early).
The concentrations of Enbrel at Weeks 12 (1591 ± 885 ng/mL) and 24 (1634 ±1141 ng/mL) in patients with psoriasis were similar to the concentrations found in patients with RA. The variability in the measured concentrations was high. The Enbrel concentrations did not change significantly between Weeks 12 and 24, suggesting that Enbrel steady state was reached by Week 12.

Study 20021639: Serum samples were obtained from all patients before study start and at Weeks 2, 4, 8, 12, and 24. The concentration time profiles showed dose proportionality, with the concentrations in the Enbrel 50 mg twice weekly group approximately twice as high as the values measured in the Enbrel 25 mg twice weekly group and almost 6 times higher than the levels obtained after the 25 mg once weekly dose. The variability in the measured concentrations in the present study was high, resulting in coefficient of variation (CV) values well in excess of 50%.

Study 20021642: Serum samples were obtained from patients before the study start and at Weeks 2, 4, 8, and 12. The concentration-time profiles of the active treatment groups demonstrated dose proportionality, with the concentrations in the 50 mg twice weekly group approximately twice the values measured in the 25 mg twice weekly group.

Conclusion: The pharmacokinetics of Enbrel in patients with psoriasis were comparable across the studies and showed considerable inter- and intra- variability. All doses produced accumulation after repeated administration, with accumulation ratios ranging from 1.06 to 2.61.
There was a clear dose proportionality after single dose administration and at steady state for 25 mg twice weekly and 50 mg twice weekly dosage regimens.

No interaction studies between Enbrel and other systemic therapies in psoriasis patients have been submitted.

Clinical Efficacy

The efficacy data were obtained from the results of 3 placebo-controlled studies: 200221632, 20021639, and 20021642. The three studies presented are similar in many regards. Each was multicenter, randomised, double blind and placebo-controlled. No active controls were used in the trial programme. Each trial had the same primary endpoint, proportion of patients achieving PASI 75 and analysed the data using a modified ITT population, including only those patients who received study medication. Sample sizes and other pertinent design features are presented in the table below.

Trial	Treatments	Duration of DB treatment / Primary timepoint (weeks)	Extension phase
20021632	E 25mg BW (n=57) P (n=55)	24 / 12	Study completers followed for disease recurrence
20021639	E 50mg BW (n=164) E 25mg BW (n=162) E 25mg QW (n=160) P (n=166) *	24 / 12	Relapsing responders re-started active treatment for 24 weeks. Incomplete responders received E 25g BW
20021642 **	E 50mg BW (n=194) E 25mg BW (n=196) P (n=193)	12 / 12	All continuing patients received E 25mg BW

E – Enbrel, P – Placebo, QW – once-weekly, BW – twice weekly, n – number of patients at the respective dose level, DB – double-blind, * - patients received E 25mg BW from Weeks 12–24. ** Randomisation was stratified by prior receipt of systemic therapy or phototherapy.

Study 20021632

Study design
It was a double blind, randomised study to evaluate the efficacy and safety of Enbrel in patients with chronic plaque psoriasis. The study data was analysed at Week 12 and further treatment (Week 12 to Week 24) remained blinded to all patients and study personnel. Patients who completed 24 weeks of therapy were followed up (off study treatment) until their PASI returned to at least 75% of their baseline PASI or other systemic psoriasis therapy was started.

Efficacy parameters
The primary endpoint was of the proportions of patients who achieved the Psoriasis Area and Severity Index (PASI) 75 response at Week 12 (at least a 75% improvement in the PASI score from baseline).
The secondary endpoints were: PASI at Week 24, target lesion response to study treatment at Weeks12 and 24, Dermatologist Static Global Assessment of target lesion score distribution, Dermatologist Static Global Assessment of psoriasis score distribution.
Additional outcome measures were quality of life (QOL) assessed by the Medical Outcomes Study Short-Form Health, Survey-36 (SF-36), Dermatology QOL assessed by Dermatology Life Quality Index (DLQI) at Week 12, Patient Global Assessment at Week 12. In addition, in a subset of patients, skin biopsies were to be performed at baseline and 12 weeks to measure epidermal thickness, Ki-67 expression, and keratin 16 expression.

Patient population
All patients had chronic plaque psoriasis involving 10% of body surface area (BSA). Patientswho had received at least one previous systemic psoriasis therapy (psoralen ultraviolet A phototherapy [PUVA], ultraviolet B phototherapy [UVB], oral retinoids, cyclosporine, or methotrexate) were randomised to receive placebo or Enbrel 25 mg twice weekly for 24 weeks.
A total of 112 patients who received at least one dose of study treatment (57 received Enbrel and 55 received placebo) were evaluated for safety and efficacy. Fifty three patients (93%) in the Enbrel group completed 12 weeks of study treatment, compared to 40 (73%) patients in the placebo group. At Week 24, 48/57 (84%) patients in the Enbrel group completed 24 weeks of study drug, compared to

12/55 (22%) of patients in the placebo group. The groups were well matched in most characteristics of demography and disease history.

Efficacy results
Primary efficacy endpoint: At Week 12, 17 (30%) of patients in the Enbrel group achieved an improvement in PASI 75, as compared with 1 (2%) patient in the placebo group.
Secondary efficacy endpoints: At Week 24, 32 patients (56%) in the Enbrel group achieved PASI 75, compared to 3 patients (5%) in the placebo group. Differences between the groups were also statistically significant from Week 4 for the PASI 50 and for the percent improvement from baseline in PASI responses, and in all comparisons by Week 12.
Patients in the Enbrel group showed significantly greater improvements from baseline in all measures of target lesion response, compared to patients in the placebo group.
Mean Patient Global Psoriasis assessments improved significantly more in the Enbrel group (62.2%) at Week 24 compared to the placebo group (6.7%). Mean Dermatologist Global Assessments were also significantly better in patients in the Enbrel group than patients in the placebo group. Patients in the Enbrel group demonstrated significantly greater improvement in the DLQI score, compared to the placebo group.
Skin biopsies performed in 31 patients (placebo-14, Enbrel-17) at baseline and at Week 12 showed improvements in skin pathology findings in the Enbrel group compared to the placebo group.
Discontinuations due to lack of efficacy: At Week 24, 60% (33/55) of patients in the placebo group had discontinued due to lack of efficacy, compared to 5/57 (9%) of patients in the Enbrel group.

Follow-up: The relapse of psoriasis signs and symptoms was gradual. Patients in the Enbrel group (n = 12) who achieved the PASI 75 at Week 24 in the controlled study and who entered the extended follow-up observation period (off study treatment) had a mean (median) of 22.6 (26.4) weeks following their last dose of study treatment before they reached at least 75% of their baseline PASI or started other systemic therapy.

Study 20021639

Study design
It was a dose-ranging study evaluating the safety and efficacy of Enbrel 50 mg twice weekly, 25 mg twice weekly and 25 mg once weekly in comparison with placebo.
Part 1 was a 24-week double-blind treatment period (Day 1 to Week 24) and Part 2 was a treatment withdrawal, re-treatment and open-label follow-up period (from Week 24).
Part 1
Patients were randomised to one of the following treatments: Enbrel 50 mg twice weekly, Enbrel 25 mg twice weekly, Enbrel 25 mg once weekly, placebo.
At the end of the double-blind treatment period (Week 24), all patients who completed treatment were categorised as responders (patients having an improvement of >50% from baseline PASI) or incomplete responders.
Part 2
At Week 24, responders discontinued study treatment and were followed until they had a relapse (loss of 50% or more of the improvement in the PASI score between baseline and Week 24). After a relapse these responders started re-treatment with Enbrel at the same dose regimen (50 mg twice weekly, 25 mg twice weekly, or 25 mg once weekly) they received during the first double-blind treatment period.
After 24 weeks of blinded re-treatment, all patients started an open-label Enbrel treatment with Enbrel 25 mg twice weekly for the remainder of the study (up to 72 weeks).
Incomplete responders started an open-label Enbrel 25 mg twice weekly from Week 24. At Week 36, these patients were evaluated whether they had become responders (improvement from baseline PASI of >50%). If they had not responded, patients were given the option to discontinue the study. Patients who responded at Week 36 continued open-label treatment with Enbrel 25mg twice weekly up to 72 weeks.

After Week 72, all patients who had received at least one dose of study treatment were invited to participate in a long-term, open-label Study 20030115 (Enbrel 50 mg once weekly).

Efficacy parameters
The primary endpoint was the proportion of patients in each treatment group who achieved the PASI 75 (at least a 75% improvement in the PASI score from baseline) at Week 12.
Secondary endpoints included: the proportions of patients achieving the PASI 50, PASI 75, and PASI 90, and the mean percent, improvements in the PASI score from baseline at all visits at which the PASI was measured, Dermatologist Static Global Assessment, DLQI, Patient Global Assessment, EQ-5D-FT (visual analogue scale 0 to 100).

Efficacy results
Part 1
Patient population**:** All patients had chronic plaque psoriasis involving at least 10% of body surface, with a minimal PASI score of 10, and had received or had been a candidate to receive systemic psoriasis therapy (in the opinion of the investigator)**.**
A total of 652 patients were randomised and received at least one dose of study treatment. Demographics and disease history were well balanced across treatment groups. Seventy-six percent (76%) of the patients had received prior systemic psoriasis therapy or phototherapy. Twenty two percent (22%) of patients had psoriatic arthritis.

Primary efficacy endpoint: A significantly greater proportion of patients in each of the three Enbrel groups achieved the PASI 75 response at Week 12, compared with the *placebo group.*

At Week 4, the response rates between the Enbrel 50 mg twice weekly group and the placebo group were statistically significantly different. At Week 8, the response rates were statistically significantly different for the Enbrel 25 mg twice weekly group, compared with the placebo group.
At Week 12, the response rates for the PASI 75 were significantly different between the Enbrel 25 mg once weekly group (14%) and the Enbrel 25 mg twice weekly group (34%) and between the 25 mg twice weekly group (34%) and the 50 mg twice weekly group (49%).

Secondary endpoints: From Week 2, statistically significant and dose dependent differences were seen between each Enbrel group and placebo for: mean percent improvement in the PASI response, Dermatologist Static Global Assessment, Patient Global Assessment, and DLQI.
In all three Enbrel groups, the proportions of patients achieving the PASI 50, PASI 75, and PASI 90 responses increased over 24 weeks study duration.
Patients in the placebo group who received Enbrel after Week 12 had similar improvements in the PASI response at Week 24 as those achieved by the Enbrel 25 mg twice weekly group at Week 12.
Patients in each of the Enbrel groups continued to improve from week 12 to week 24 for all dermatologist and patient reported secondary endpoints.

Discontinuations due to lack of efficacy: Eighteen patients discontinued from the study (Day 0 to Week 24) due to lack of efficacy (7 patients in the placebo group, 6 in the 25 mg once weekly group, 2 in the 25 twice weekly group and 3 in the 50 mg twice weekly group).

Subgroup analyses: The subgroup analyses by baseline PASI score, previous systemic therapy or phototherapy and presence of psoriatic arthritis confirmed the primary efficacy analysis. For patients above the median BSA at baseline and in patients in the highest quartiles of weight, the PASI 75 response at Week 12 was lower, though still in favour of Enbrel.

Part 2
Patient population: Of the 652 patients who received at least one dose of study treatment, 573 patients completed 24 weeks of study treatment. Of those, 409 patients were categorised as responders and 160 patients were classified as incomplete responders. Of the 409 responders, 62 patients withdrew from the study before relapse of their psoriasis (46 due to early study closure); 347 patients experienced a relapse (loss of >50% of PASI improvement obtained between baseline and Week 24) and entered the re-treatment period (5 patients withdrew before re-treatment). Two hundred and three

patients (203) completed 24 weeks of blinded re-treatment and 139 patients discontinued during the re-treatment period (118 due to early study closure). One hundred and sixty (160) of incomplete responders entered the open-label period (3 patients discontinued before receiving open-label study drug). Three (3) patients completed 48 weeks of open-label treatment.

12 Weeks

The primary efficacy endpoint was the difference between the PASI 75 score achieved after 12 weeks of re-treatment and the PASI score achieved after 12 weeks of initial treatment.
A total of 297 patients completed 12 weeks of blinded re-treatment (87 patients in the Enbrel 50 mg twice weekly group, 73 in the 25 mg twice weekly group, 63 in the 25 mg once weekly group, and 74 in the placebo/Enbrel 25 mg twice weekly group). The PASI 75 was achieved by 19%, 40%, and 45% in the 25 mg once weekly, 25 mg twice weekly, and 50 mg twice weekly groups respectively, at Week 12 of re-treatment. The absolute mean difference between the initial Week 12 response and the re-treatment Week 12 response for all re-treatment groups was -0.5.
The proportion of PASI 75 responders at Week 12 of re-treatment relative to re-treatment baseline was significantly lower: 22%, 13%, 19% and 24% for patients treated with placebo/25 mg twice weekly, 25 mg once weekly, 25 mg twice weekly and 50 mg twice weekly, respectively.

24 Weeks
A total of 134 patients completed at least 24 weeks of blinded re-treatment (43 patients in the 25 mg once weekly group, 41 in the 25 mg twice weekly group, and 50 patients in the Enbrel 50 mg twice weekly group). The difference mean in PASI scores was -1.5, indicating that most patients had PASI scores approximately 1 to 2 points worse at Week 24 of re-treatment relative to their PASI scores at Week 24 of the initial active treatment. Overall, 113 (84%) patients achieved a PASI 50 response at Week 24 of the re-treatment period.
At Week 24 of re-treatment, the PASI 75 was achieved by 19%, 49%, and 58% in the 25 mg once weekly, 25 mg twice weekly, and 50 mg twice weekly groups respectively. The results were similar to that observed after 24 weeks of blinded treatment.

Open-label period for incomplete responders One hundred and fifty seven (157) patients who improved < 50% from their baseline PASI score and were categorised as incomplete responders at Week 24 of the initial double-blind period received open-label Enbrel at a dose of 25 mg twice weekly. At the end of 12 weeks of open-label treatment, 62 out of 112 patients achieved a PASI 50 response.

Study 20021642

Study design
It was a double blind, randomised, placebo-controlled study to evaluate the efficacy and safety of Enbrel in patients with chronic plaque psoriasis. The study consisted of 2 parts: a double-blind treatment period (Day 1 to Week 12) and an open-label treatment period (Weeks 13 to 48).
Part 1
Patients were randomised to one of the following treatments: Enbrel 50 mg twice weekly, Enbrel 25 mg twice weekly, and placebo twice weekly. Patients were stratified at randomisation into two groups: patients who had previously received systemic therapy or phototherapy and patients who had received no systemic or phototherapy.
Part 2
From Week 12 to Week 48 visit, all patients received Enbrel 25 mg twice weekly in an open-label fashion. The study was closed early during the open-label period of the study to expedite enrolment to Study 20030115. All patients completed 36 weeks of treatment.

Efficacy parameters
The primary endpoint for this study was achievement of PASI 75 at Week 12.
Secondary endpoints included PASI 50 and PASI 90, Dermatologist Static Global Assessment, DLQI, Patient Global Assessment.
Other endpoints included: Medical Outcomes Study - Short Form-36 (SF-36) Health Survey, and discontinuations from the study due to lack of efficacy.

Patient population
All patients had chronic plaque psoriasis involving at least 10% of body surface, a minimal PASI score of 10, and had received or had been a candidate to receive systemic psoriasis therapy (in the opinion of the investigator).
Of the 611 randomised patients, 28 patients withdrew or were excluded before receiving blinded study drug: 11 withdrew consent, 12 were determined ineligible for the study, and 5 were lost to follow-up. A total of 583 patients received at least one dose of study treatment and were analysed for safety and efficacy. The groups were well matched in characteristics of demography and disease history at baseline; 89% of patients had received prior psoriasis therapy (58% received UVB, 91% used topical steroids, 28% received an investigational product, 25% received oral retinoids, 16% received cyclosporine, 34% received PUVA, and 38% received methotrexate). Twenty-six percent of patients had psoriatic arthritis.

Efficacy results
Part 1
Of the 583 patients who received at least one dose of blinded study treatment 559 patients (96%) completed 12 weeks of the study.
Primary efficacy endpoint: The PASI 75 response was achieved in each of the Enbrel groups compared with the placebo group at Week 12. At Week 4, the response rates were statistically significantly different between the Enbrel 50 mg twice weekly group and the placebo group. At Week 8, the response rates were statistically significantly different for the Enbrel 25 mg twice weekly group compared with the placebo.
Response to Enbrel therapy was dose-dependent. At Week 12, the response rates for the PASI 75 response were statistically significantly different between the Enbrel 50 mg twice weekly group (49%) and the 25 mg twice weekly group (34%).
Secondary endpoints: At Week 12, statistically significant improvements were seen in both Enbrel groups in mean percent improvement in the PASI score, in the Dermatologist Static Global Assessment, in the DLQI and in the Patient Global Assessment of psoriasis, compared with the placebo group. The improvements in secondary endpoints were dose-dependent.
Subgroup analyses: The subgroup results for the PASI 75 response at Week 12 by baseline age, and previous systemic therapy were similar to the primary analysis (except for the age group > 65 years). The results in the group of patients > 65 years old were difficult to interpret due to small number of patients.
Part 2
Five hundred and fifty seven (557) patients received at least one dose of Enbrel at a dose of 25 mg twice weekly during the open-label period.
The proportions of patients achieving the PASI 50, PASI 75, and PASI 90 responses increased during the open-label period for patients in the original placebo and Enbrel 25 mg twice weekly groups. Because of the early closure of the study, a majority of patients discontinued between weeks 36 and 48 in the open-label period. The PASI 75 response rate remained relatively constant between weeks 12 and 36 for the group of patients in whom the dose of Enbrel was decreased from 50 mg twice weekly to 25 twice weekly, while the PASI 75 response rate increased between weeks 12 and 36 for patients who remained on Enbrel at a dose of 25 mg twice weekly. Despite a dose reduction from 50 mg twice weekly to 25 twice weekly at week 12, the significant proportion of patients (68%) in the group that were PASI 75 responders at week 12 remained as responders at Week 36. During the open-label treatment, the percent improvement from baseline PASI, Dermatologist Static Global Assessment and percent improvement from baseline in DLQI total score continued to increase for patients originally in the placebo and the 25 mg twice weekly treatment groups. For the patients originally in the 50 mg twice weekly group, the percent improvement from baseline PASI and DLQI total score were maintained when the dose was reduced to 25 mg twice weekly, but the Dermatologist Static Global Assessment decreased upon dose reduction.

The results of the primary and secondary endpoints of studies 20021639 and 20021642 are shown in the table below:

RESPONSES OF PATIENTS WITH PSORIASIS IN PIVOTAL STUDIES

	Study 20021639					Study 20021642		
		Enbrel					Enbrel	
Response	Placebo n = 166 wk 12	25 mg TWICE A WEEK n =162 wk 12	25 mg TWICE A WEEK n =162 wk 24[a]	50 mg TWICE A WEEK n = 164 wk 12	50 mg TWICE A WEEK n = 164 wk 24[a]	Placebo n = 193 wk 12	25 mg TWICE A WEEK n = 196 wk 12	50 mg TWICE A WEEK n = 196 wk 12
PASI 50, %	14	58*	70	74*	77	9	64*	77*
PASI 75, %	4	34*	44	49*	59	3	34*	49*
PASI 90, %	1	12*	20	22*	30	1	11*	21*
Dermatologist static global assessment, clear or almost clear, % (0 or 1 on 0-5 scale)	5	34*	39	49*	55	4	39*	57*
Percent improvement from baseline in PASI, mean	14.0	52.6*	62.1	64.2*	71.1	0.2	56.8*	67.5*
Patient global assessment of psoriasis, median (0-5 scale)	4.0	2.0*	2.0	1.5*	1.0	4.0	2.0*	1.0*
Percent improvement from baseline in Dermatology Life Quality Index, mean	10.9	50.8*	59.4	61.0*	73.8	6.2	65.4*	70.2

*$p \leq 0.0001$ compared with placebo

a. No statistical comparisons to placebo were made at week 24 in Study 1 because the original placebo group began receiving Enbrel 25 mg twice weekly from week 13 to week 24.

Discussion on Clinical Efficacy – Rheumatoid Arthritis

The results of 5 controlled studies in adults with RA show efficacy of Enbrel at the proposed optimal dose of 25 mg twice weekly using predefined endpoints in RA patients. The same dose administered once weekly gives a slower response and may be less effective.

The dose of 25 mg twice weekly is further supported by PK/PD evidence from study 300-EU, which showed optimal response with Enbrel concentrations in the range of 1000-2000 ng/ml; serum levels approximating the upper range of the target concentration were achieved in a higher proportion of patients receiving 25 mg Enbrel twice weekly.

The safety and efficacy of 50 mg Enbrel (two 25mg SC injections) administered once weekly were evaluated in a double blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patients received placebo, 214 patients received 50 mg Enbrel once weekly, and 153 patients received 25 mg Enbrel twice weekly. The safety and efficacy profiles of the two Enbrel treatment regimens were comparable in their effect on signs and symptoms of RA.

Beneficial effects were seen after 1-2 weeks of treatment with Enbrel, and maximum effects appeared to be reached after 1-3 months. Following discontinuation of Enbrel treatment, the therapeutic effect did not persist. Long-term open-label studies of up to 2 years have shown sustained efficacy.

Analysis shows that concomitant use of NSAIDs or corticosteroids did not influence the outcome of the trials.

Combination treatment of Enbrel with methotrexate has been investigated in two controlled studies (studies 16.0014 and 308). The efficacy results were positive. A double blind clinical trial comparing the efficacy of Enbrel alone to Methotrexate in patients who never received treatment with Methotrexate (Study 16.0012) showed a decrease in radiographic progression (erosion scores) at 12 and 24 month for patients receiving Enbrel 25 mg twice weekly. The Study 308 results shows that treatment of RA with the combination of etanercept (25 mg subcutaneously 2x weekly) and MTX (up to 20 mg orally 1x weekly) was superior in reducing disease activity, improving functional disability, and retarding radiographic progression compared with MTX or Enbrel alone.

The clinical trials also provide convincing evidence of activity against Juvenile Chronic Arthritis in the patient age-group of 4 – 17 years. The posology proposed for this population is supported by the population pharmacokinetic study.

The characteristics of the patients chosen seem appropriate. The endpoints used are correct for an anti-rheumatic drug with anti-inflammatory, pain relieving, and disease–controlling actions.

Discussion on Clinical Efficacy and Pharmacokinetics in Plaque Psoriasis

Pharmacokinetics:

The most commonly prescribed systemic medications for psoriasis are MTX, cyclosporine, acitretin, and 8-methoxypsoralen. Based on the known metabolism and elimination pathways of these compounds and etanercept, there is no overlap between the metabolism/elimination pathway for etanercept and those for MTX, cyclosporine, acitretin, or 8-methoxypsoralen; thus, no pharmacokinetic interactions between etanercept and these medications are anticipated.

The results from study 308, which evaluated the efficacy, safety, and pharmacokinetics of the combination of etanercept and MTX in patients with RA, demonstrated that the pharmacokinetics of etanercept was not altered by the concurrent administration of MTX in patients with RA. Furthermore, 2 years of treatment with the combination of Enbrel and MTX has been shown to be well tolerated in patients with RA and did not result in unexpected safety findings. It is expected that a similar safety profile for the combination of Enbrel and MTX would be seen in patients with psoriasis.

However, the following sentence was added to Section 4.4, Special warnings and special precautions for use, under "Combination therapy" of the proposed SPC:

'The use of Enbrel in combination with other systemic therapies or phototherapy for the treatment of psoriasis has not been studied.'

Efficacy

Indication

The efficacy data are based on 1347 patients participating in 3 clinical trials.

The efficacy of Enbrel versus other systemic therapies in patients with moderate to severe psoriasis (responsive to other systemic therapies) has not been evaluated in studies directly comparing Enbrel with other systemic therapies. Instead, the safety and efficacy of Enbrel were assessed in three randomised, double-blind, placebo-controlled studies. The primary efficacy endpoint in all three studies was the proportion of patients in each treatment group who achieved the PASI 75 (i.e., at least a 75% improvement in the Psoriasis Area and Severity Index score from baseline) at 12 weeks.

The CHMP Considered (1) the attributes of the therapies currently used in the treatment of psoriasis, (2) the substantial number of patients with moderate to severe plaque psoriasis who have already failed current therapies due to a loss of efficacy or the occurrence of toxicity, and (3) the lack of clinical trial data directly comparing Enbrel to the currently available systemic agents, (4) the MAH proposal for a second line indication in adult patients with moderate to severe plaque psoriasis in whom conventional systemic therapy or phototherapy has been inadequate or is inappropriate.

However, the proposed wording would allow inclusion of patients who have had some, albeit "inadequate", response to previous therapy. It is preferable that it should be reserved for patients who have failed to respond. Secondly, "inappropriate" is open to interpretation without defining exactly what is meant by the term. It would be better to specify only certain conditions such as "contraindications" and "intolerance" to the other treatments. The CHMP proposed that the indication read as follows:

'Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA. see section 5.1'

Moreover, it is considered that failure to respond should be defined under Section 5.1 both in terms of measurable criteria as well as sufficient length of treatment and adequacy of dosing with the 'failed' treatment

as follows:

Enbrel is recommended for use in patients as defined in section 4.1. Patients who "failed to respond to" in the target population is defined by insufficient response (PASI<50 or PGA less than good), or worsening of the disease while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least each of the three major systemic therapies as available.

Population

The primary efficacy endpoint in all 3 studies was the proportion of patients who achieved the PASI 75 at 12 weeks. Physician and patient global assessments were included as secondary efficacy endpoints.

All patients had moderate to severe chronic plaque psoriasis and had received or had been a candidate to receive systemic psoriasis therapy (in the opinion of the investigator). Overall among all 3 studies, 83% of patients had received prior systemic therapy or phototherapy, and 89% of patients had received prior therapy with topical steroids, 46% with UVB, 29% with PUVA, 14% with cyclosporine, and 36% with methotrexate.

A subgroup analysis of PASI 75 response at 12 weeks by prior systemic therapy was presented for all 3 studies. There was little difference in PASI 75 response between patients who had received previous systemic therapy and those who had not.

For study 20021642 the MAH presented a subgroup analysis of PASI 75 response at 12 weeks by failure of previous systemic therapy or phototherapy. The group that had failed prior therapies represented 337 patients (65% of the total clinical trial population). Based on the results from this subgroup analysis for study 20021642, patients who failed previous systemic or phototherapy responded well to Enbrel.

Dosage and duration of treatment

The primary endpoint, PASI 75, was achieved in all Enbrel groups at 12 weeks. The response rate was dose dependent; 50 mg twice weekly dosage regimen was the most effective with rapid and a significantly better response than the 25 mg twice weekly dose regimen. The results for the secondary endpoints were also dose dependent with 50 mg twice weekly dosage regimen being the most effective. Enbrel 25 mg once weekly was less effective than 25 mg twice weekly and 50 mg twice weekly regimen.

Although the 50 mg twice weekly dose does provide a more rapid response, it is not recommend toe use of the 50 mg twice weekly dose for longer than 12 weeks because of the limited safety data for longer durations of therapy. Thus, the Posology reads:

'The recommended dose of Enbrel is 25 mg administered twice weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly.'

The long-term duration and schedule of treatment have not been evaluated .
Maximum response was observed after initial treatment between Weeks 16 to Week 20; a statement advising to stop treatment at week 12 if no response has been observed should be included in the SPC.

Duration
Both phase 3 studies provide long-term efficacy and safety data from open active periods with up to 72 weeks of Enbrel treatment. Additional design features provide robust qualitative data that are relevant to the long-term clinical use of Enbrel in psoriasis, namely: the safety of Enbrel withdrawal, and the safety and the efficacy of reintroduction of Enbrel following discontinuation. Overall, 1126 patients in the psoriasis program received Enbrel treatment for at least 6 months, 455 patients received Enbrel treatment for at least 1 year, and 289 patients received at least 48 weeks of continuous treatment. The available safety database for patients with psoriasis complies with the ICH guidance for exposure to assess safety (ICH Topic E1A, Population Exposure: The Extent of Population Exposure to Assess Clinical Safety, CPMP/ICH/375/95) and demonstrates an acceptable safety profile. Moreover, the safety profile of Enbrel has been well established during extensive clinical studies and post marketing experience in patients with RA and other rheumatic diseases. In summary, the available clinical trial data support continuous use of Enbrel in psoriasis. However the CHMP noted that there remains a paucity of evidence on duration of treatment and for long-term treatment schedules. In the absence of such data, only weaker evidence on response rates (uncontrolled) and the effect of withdrawal can be considered. There is some evidence that patients with partial response at Week 12 will continue to improve given continued treatment and some evidence that responders continuing treatment will remain in remission (compared with the effect of withdrawing treatment). Clearly, it is appropriate to cease treatment in patients with inadequate response.
therefore. The following sentence was added to Section .2, Posology and method of administration, of the proposed SPC:

'Treatment should be discontinued in patients who show no response after 12 weeks.'

The CHMP considers that there is sufficient evidence of benefit in some patients between Weeks 12 and 24 and that treatment duration should not be limited to 12 weeks based on efficacy considerations. However, there is inadequate evidence of efficacy beyond 24 weeks of treatment therefore this period of treatment should not be exceeded. If re-treatment is warranted, the same principle should be applied. Other current systemic therapies recommend intermittent courses of treatment to induce remission. In addition, there is no evidence of a positive benefit/risk of continuous versus intermittent treatment with Enbrel. Therefore, the posology section recommend that treatment should be stopped

when remission is achieved. The CHMP considered that the risk/benefit ratio would be accurately reflected if the SPC Section 4.2 and 5.1 read as follows:

Section 5.1

'Patients who 'failed to respond to' in the target population is defined by insufficient response (PASI <50 or PGA less than good), or worsening of the disease while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least each of the three major systemic therapies as available.'

Section 4.2.

'Plaque psoriasis
The recommended dose of Enbrel is 25 mg administered twice weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Treatment should be discontinued in patients who shown no response after 12 weeks.

Retreatment
Retreatment with Enbrel for 12 and 24 weeks (compared with 12 and 24 weeks of initial treatment) resulted in PASI 75 response rates similar to the initial treatment for all active treatment groups. However, the assessments did not take into account differences in pre-treatment PASI scores. Once the re-treatment baselines were considered, there was no clear evidence that PASI 75 responses were similar following re-treatment. Moreover, the results were based on small numbers of selected patients. The Enbrel psoriasis clinical trial data, which demonstrates a lack of rebound on withdrawal and the ability to recapture efficacy with retreatment, is particularly relevant to intermittent or episodic treatment, and should be available in the SPC to guide clinicians. Ultimately, the specific duration of treatment, appropriate length of time between treatment courses if any, and the appropriate number of courses of treatment should be determined on an individual patient basis by the prescriber. The issue of whether retreatment with Enbrel resulted in a return of psoriasis control to levels at or near those achieved during initial treatment with Enbrel was addressed in a subset of patients who had responded (achieved ≥ PASI 50 response) to Enbrel treatment during the initial double-blind period of study 20021639. The mean difference between the initial treatment and retreatment 12-week PASI score for the overall retreatment group is neither clinically nor statistically significant**.**

The CHMP agrees that there is some evidence for the benefit of re-treatment. However, as the safety profile in the RA trials is reassuring, it is considered that there are sufficient data to allow treatment or retreatment up to 24 weeks with 25 mg twice weekly.
It is difficult to determine what is the optimal period without treatment before re-treatment is instituted, or the number of iterative courses. Provided it is accepted that the risk/benefit ratio is favourable for the proposed indication, the SPC could allow re-treatment for further 24 week periods if/when a patient, who benefited from the initial treatment, relapses, and the cumulative treatment period does not exceed what has been shown to be acceptable in the RA studies. The CHMP considered that the risk/benefit ratio would be accurately reflected if the SPC Section 4.2 reads:

If re-treatment with Enbrel is indicated, the above guidance on treatment duration should be followed. The dose should be 25mg twice weekly.

Clinical Safety
Presented below are the clinical trial data that supported the initial RA and JCA approvals, as well as data from safety updates from US and European trials, more recent clinical trials, and postmarketing safety reports.

Patient exposure
For the initial approval for RA and JCA, safety information was collected from 849 individuals treated with Enbrel and 154 individuals who received placebo in double-blind and open-label studies. Of the 849 individuals, 531 were patients with arthritis (477 with RA, 54 with JCA) exposed to Enbrel for a total of 3,936 patient months, 130 were individuals without RA (72 healthy volunteers,

45 patients with Crohn's disease, 13 patients with HIV) and 188 individuals participated in 8 studies with different groups (including 108 patients in a sepsis trial). In addition, safety updates were submitted which included 1952 rheumatoid arthritis patients (representing 5832 patient-years). The safety assessments were based on reports of study events, results of routine physical determinations, and vital signs.

Adverse events and serious adverse events/deaths

Safety data from healthy volunteers were obtained from 5 studies. No deaths and no serious adverse events occurred in those studies. Other adverse events reported included injection site reactions, flu syndrome, headache, pharyngitis and rhinitis.

Safety data from RA or JCA patients were obtained from double-blind and open label trials.

The most common adverse events associated with Enbrel treatment were injection site reactions and infections. They occurred in 42% and 58% of Enbrel-treated patients. Other adverse event were: headache (17 % of all Enbrel-treated patients), rhinitis (13 %), rash (13 %), nausea (12 %), abdominal pain (9 %), diarrhoea (8 %), cough increased (8 %), asthenia (7 %), pain (7 %), dizziness (7 %), accidental injury (7 %), pharyngitis (7 %), vomiting (6 %), back pain (5 %), hypertension (5 %), peripheral oedema (5 %). The rates obtained for the pool of placebo-treated patients were not significantly different, except for the injection site reactions.

Injection site reactions occurred early in the course of treatment (often on the first or second injection) and occurred 1 to 2 days after the injection, lasting for approximately 3 to 5 days. Injection site reactions were grade 1 or 2 in severity (erythema and/or pain, swelling or pruritus) and rarely resulted in discontinuation of the treatment.

Rates of infections (the most frequently reported adverse event) were related to the duration of treatment. Upper respiratory tract infections were the most commonly reported type of infection. Increased cough and respiratory disorders ("colds") were found to be significantly more frequent ($p<0.05$) in the high dose group compared to placebo and to the mid dose group. A trend ($p< 0.10$) toward association of fever with Enbrel treatment overall and with high dose treatment as compared to placebo was noted. The majority of fevers were associated with infections or other inflammatory conditions.

In the sepsis clinical trial, 108 patients with documented sepsis were treated with Enbrel and 33 patients received placebo. In this study, the patient group was severely immuno-compromised. A higher mortality was observed in the Enbrel-treated than in the placebo-treated group when the infection was caused by gram-positive or unknown microbes, and the mortality rate was raised in the groups treated with high doses of Enbrel. The increased mortality observed with increasing dose could not be explained by imbalances at enrolment. Mortality was not related to an identifiable direct toxicity of Enbrel.

The susceptibility to infection is increased in RA patients in general, due to a suppressed immune system either occurring within the course of the disease or induced by a concurrent immunosuppressive medication. In the light of post-marketing experience (serious infections and sepsis, including fatalities) with Enbrel in the USA, the text of the SPC has been strengthened to alert the prescriber to the risk of the use of Enbrel in RA patients who are known to have an increased risk of serious infections (e.g., those with advanced or poorly controlled diabetes or active infections, including chronic and localised infections).

Safety-related withdrawals

Of 531 RA and JCA patients treated with Enbrel, 5 % (29 patients) withdrew for safety-related reasons. For the placebo patients, the rate was 5 % as well. Thirteen (13) of the 29 safety-related withdrawals were for events considered by the investigator to be unrelated to study drug.

Serious adverse events and deaths

In the RA group, 8 % of Enbrel-treated patients and 6 % in the placebo and placebo/methotrexate patients had a serious event. Investigators considered that 47 of 49 events in the Enbrel-treated

patients were unrelated to the study drug. The two remaining serious events were hospitalisation for pancreatitis and hypotension.

In the RA groups, 7 patients with Enbrel (out of 531) and one patient with placebo (out of 154) developed cancer while on study. All cancers appeared in patients treated with the high dose of Enbrel. The company has indicated that there is no difference in the malignancy rates between Enbrel and placebo when corrected for the different duration of exposure to Enbrel (0.021 per patient-year) as compared to placebo (0.022 per patient-year). To date no increase in incidence of malignancy has been seen with duration of treatment in the group treated with Enbrel. The observed malignancy rate was similar to that expected for a matched general population.

Safety updates

The safety updates from the US and European studies, double-blind and open label, are based on 1952 RA and JCA patients; 1566 patients treated for at least 12 months, 1375 patients treated for at least 24 months, 1166 patients treated for at least 36 months, and 828 patients treated for at least 48 months. The safety profile that results from the increased exposure data appears to be similar to that observed in the initial safety assessment (on a total of 531 patients).

Laboratory findings

In the placebo-controlled studies that supported the initial RA and JCA approvals, the most commonly occurring laboratory abnormalities were low lymphocytes (62 %) and low albumin. Low albumin occurred in 43 % of Enbrel-treated patients compared with 55 % in placebo patients, and low haemoglobin was 20 % in the Enbrel group and 30 % in the placebo group. Differences were seen in elderly Enbrel-treated patients with respect to renal function. In the etanercept group, 13 % of elderly patients had high serum creatinine levels compared to none in the 18-49 year and 2 % in the 50-64 year age groups; these differences were considered to be normal signs of aging. No worsening of renal function was seen over time. Low sodium was also seen more frequently in the elderly. There were no serious (Grade 3 or 4) abnormalities in serum creatinine or sodium among the Enbrel-treated patients.

A separate analysis of the laboratory toxicity in RA group treated with Enbrel plus methotrexate as compared to placebo and methotrexate did not find extra toxicity in the Enbrel plus methotrexate group.

Autoantibodies

To investigate whether autoantibodies develop in Enbrel-treated subjects, the incidence and titres of antinuclear antibodies (ANA), anti-ds DNA antibodies and anti-cardiolipin antibodies (ACLA) were measured. Anti-ds DNA antibodies occurred in about 3 % (*Crithidia* assay), and ANA in about 11 % (either IgG or IgM isotype). Placebo-treated subjects did not have any anti-dsDNA antibodies. Approximately 5% of placebo-treated patients developed ANA. With regard to ACLA, IgG or IgM antibodies were demonstrated in up to 10 % of the Enbrel-treated patients (not different from placebo). Antibody levels which initially increased, usually returned to normal during continued Enbrel treatment. No overt systemic lupus erythematosus was recorded.

There was no consistent pattern in changes of titres of any of the analysed autoantibodies over time, and eventual shift in occurrence or titres were not associated with adverse events related to the development of signs or symptoms of any other autoimmune disease during the observation time.

Immunogenicity of etanercept
Several assay methods have been developed. The most recent optimised assay indicated that approximately 4 % (4 of 96) of patients treated with Enbrel 25 mg twice a week in a RA trial for up to 3 months were antibody-positive in the screening assays on one or several occasions. They were, however, negative in the assay for neutralising antibodies. No dose effect was observed for the development of anti-etanercept antibodies.
No relationship could be established between the occurrence of antibodies to etanercept and any adverse event or increase or decrease in the efficacy of the drug.

Safety from other RA studies

Study 160012
In this pivotal study, more patients in the MTX group than in the etanercept 25mg group discontinued the study treatment over a period of 2 years due to adverse events. MTX and etanercept have a different mechanism of action and therefore their safety profile may differ. Overall, the incidence of adverse events was similar in all 3 treatment groups, and there were no significant differences in the rates of malignancy and infections between MTX and etanercept.

Enbrel and Anakinra
Patients treated with Enbrel and anakinra were observed to have a higher rate of serious infection when compared with historical controls that were treated with Enbrel. In addition, in a double-blind placebo-controlled trial in patients receiving background methotrexate, patients treated with Enbrel and anakinra were observed to have a higher rate of serious infections and neutropenia than patients treated with Enbrel (see section 4.4).

The MAH has submitted data from clinical trials (20000125 and 20000223) an updated draft SmPC and Clinical Expert report and copies of the CIOMS forms relating to the reports of serious infections.

The study 20000223 was a multicentre, double-blind, randomised, and active-controlled study with a duration of 24 weeks. RA patients on a stable MTX dose of 10-25 mg/week with active disease were randomised to one of 3 treatment arms:

Group 1: Etanercept 25 mg twice weekly
Group 2: Etanercept 25 mg once weekly + anakinra 100mg daily
Group 3: Etanercept 25 mg twice weekly + anakinra 100 mg daily

Therapy was initiated in 242 patients, with 80 patients in Group 1, and 81 patients each in Groups 2 and 3.
The primary efficacy endpoint was the proportion of subjects achieving improvements of 50% according to the American College of Rheumatology (ACR) response criteria at 24 weeks (ACR-50). The secondary efficacy endpoints included the proportion of subjects with improvements of 20% (ACR-20) and 70% (ACR-70) at 12 weeks and 24 weeks.

Efficacy results
The efficacy results showed that there was no benefit in patients receiving combination treatment with Enbrel and anakinra when compared to patients receiving Enbrel alone. Comparisons of the ACR-50 response at week 24 demonstrated no significant differences between the 3 treatment groups, the result were 41%, 39% and 31% in group 1,2 and 3 respectively.

Safety results
Overall, 204 of the 242 patients enrolled in the study completed the study. 75 in group 1, 63 in group 2 and 66 in Group 3. The differences in withdrawal rates in the combined-therapy groups were attributed to occurrence of adverse effects. A total of 13 subjects in the combination groups withdrew due to adverse events, compared to no subjects in the Enbrel alone group. Injection site reactions were reported in 69% of patients receiving combination therapy compared to 40% in the Enbrel alone

group. Other frequently reported adverse reactions were upper respiratory tract infections (15%) and nausea (10%).
A total of 26 patients reported serious adverse events. The proportion of patients in the combination treatment groups who reported serious adverse events (21/162, 13%) was twice the number seen in the Enbrel alone group (5/80, 6%). The most commonly reported serious adverse event were injection site pain (3), pneumonia (3) and cellulitis (3). These were reported in patients taking combination therapy.

Serious infections
Serious infections were experienced by 9/162 (6%) of patients receiving combination therapy. No patients in the Enbrel alone group (Group 1) experienced any serious infections. The reported infections were: Pneumonia (3), Cellulitis (3), Herpes zoster, Pyelonephritis, Pneumonitis (1 each). In 2 cases, one of cellulitis and one of pneumonitis, the investigator considered the infection to be unrelated to the study drugs. Of the 3 patients with cellulitis, one had diabetes requiring insulin therapy, one had an antecedent wound, and all three patients were also being treated with prednisone. Of the three patients with pneumonia, one had asthma and the diagnosis of pneumonia was not supported by laboratory investigations in another patient
One patient had a fatal outcome. This was a 70 year old female who was on concomitant treatment with MTX (15mg/week) and rofecoxib (25mg twice daily). The patient developed a wound infection after seven weeks of therapy. She was subsequently hospitalised with antibiotic associated gastroenteritis. The patient died of acute respiratory failure, which was attributed to pulmonary fibrosis.

Long term safety update - Protocol 16.0023

Protocol 16.0012 was initially designed to compare Enbrel with rapidly dose-escalated methotrexate (MTX) in preventing joint erosions in subjects who had not previously received MTX. Year 1 of the study was a randomized, double-blind, multicenter, double-dummy, active-control, phase 3 trial comparing the safety and efficacy of Enbrel monotherapy (10 or 25 mg twice weekly) with rapidly dose-escalated oral MTX (median of 20 mg/wk after dose escalation).

Protocol 016.0023 was designed to provide all subjects who had participated in Protocol 016.0012 with the opportunity to receive Enbrel treatment in a long-term trial. All subjects were to receive 25 mg Enbrel administered twice weekly.

The primary objectives of Protocol 016.0023 are to evaluate the effects of long-term Enbrel administration in subjects with early RA on safety, health-related quality of life and prevention of disability, structural damage as measured by radiographic progression, and clinical activity (improvement and maintenance of improvement in signs and symptoms of disease).

Study population

The safety data set available for review comprises 558 patients. Forty-nine patients (8.8%) have discontinued the study prematurely. The study treatments can broadly be divided into two groups; patients treated with Enbrel alone (n=415); and patients treated with methotrexate and Enbrel (n=143). There are proportionately fewer males than females (25% and 75%, respectively) and white (86%) in the population studied. The average age of patients was 50 years.

Safety information

The 5-year safety report includes safety data for all subjects who initially received Enbrel in Protocol 016.0012 and for all subjects in Protocol 0116.0023. A total of 558 subjects with early RA are included in the database, representing 1921 subject years of Enbrel exposure.

Deaths**:** Six deaths have been reported, compared to 17 deaths that would be predicted for the general population. Mortality rates remained the same despite increasing exposure to Enbrel.

Serious Adverse Events: One hundred and seventy eight serious adverse events in 115 patients have been reported up to the point at which the database was locked. The rate of serious adverse events has been stable over time and is comparable to those seen in the MTX and Enbrel treatment groups of the initial controlled trial. Serious adverse events were observed most commonly in the cardiovascular, body as a whole, and respiratory systems. Rates of serious adverse events in specific body systems calculated for the 3-year and 5-year reports were comparable.

Withdrawals Due to Adverse Events: Of the 558 subjects treated with Enbrel, 49 subjects (8.8%) have withdrawn either due to death (6 subjects) or other adverse events. Twenty-four subjects withdrew from Protocol 016.0012 and 25 subjects from Protocol 016.0023.

Infections: Approximately 7% of subjects have experienced serious infections. The rate of serious infections is comparable to rates observed for the MTX and Enbrel treatment groups of the controlled trial and similar to rates observed for 2 other cohorts of patients with RA (from the Olmsted County, Minnesota database and the Arthritis, Rheumatism, and Aging Medical Information System database). Rates and types of serious infections have been stable over time.

Malignancies: Eighteen cancers have been observed in 16 subjects. The rates and types of malignancies observed are in the range expected for patients with RA, and exposure-adjusted event rates are stable over time.

Demyelination Events: No neurologic events associated with demyelination have been reported in this cohort of subjects with early RA.

Cardiovascular events: One of the 6 deaths observed in the long-term database was attributed to a cardiovascular event. One subject reported exacerbation of heart failure. Unfortunately, other contributing factors were not collected in this study, therefore, this observation in difficult to interpret.

To date, 2 events of new-onset heart failure have been reported for subjects in the long-term database (subjects 3114 and 6106 in Protocol 016.0023), which, compared to the predicted rate of 5.764 expected for the general population, indicates no increased risk of new-onset heart failure.

Conclusion

The MAH has provided interim safety data from a long-term open-label study of the use of Enbrel in adults. The data set presented comprises 558 patients with early rheumatoid arthritis aged more than 18 years. In general, patients entering an open label study are a selected subgroup of those initially randomized. Further, the data are uncontrolled and the impact of patient withdrawals/lost-to-follow-ups and missing data are difficult to ascertain. Therefore, it is difficult to distinguish the effect of treatment from the underlying course of the disease/the open label assessment of symptoms. Nevertheless, it appears safety data are consistent with continued positive risk/benefit profile. The data presented do not give grounds for safety concerns.

Safety in Special Populations

JCA patients

In study 16.0016 (children with Juvenile Chronic Arthritis), infections were reported in 43/69 (62 %, 0.38 events per month) of patients (first part of the trial) and 15/25 (60 %, 0.33 events per month) of the patients on Enbrel (second part of trial) versus 8/26 (31 %, 0.28 events per month) of patients receiving placebo. Injection site reactions appear to be a consistent finding following treatment with Enbrel.

Severe adverse events reports included varicella with signs and symptoms of aseptic meningitis which resolved without sequelae, gastroenteritis, depression/personality disorder, cutaneous ulcer, oesophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection. Several adverse events were reported more commonly in 69 juvenile

chronic arthritis patients receiving 3 months of Enbrel compared to the 349 adult rheumatoid arthritis patients: headache , nausea , abdominal pain , and vomiting).

PsA patients

The most common adverse events in the Enbrel group in study 16.0030 were injection site reactions (36%), injection site ecchymosis (12%), accidental injury (8%), headache (8%), and rash (5%). Except for injection site reaction (36% Enbrel versus 9% placebo), no adverse event occurred in a significantly greater proportion of patients in the Enbrel group compared with the placebo group. All occurrences of injection site reactions were of mild or moderate (grade 1 or 2) intensity. Most other adverse events were also of mild or moderate intensity. The most commonly reported infections were upper respiratory infection (21%) and urinary tract infection and sinusitis (6% each). One (1) serious adverse events that was considered possibly related to Enbrel treatment was reported in this study. One (1) patient treated with Enbrel was diagnosed with multiple sclerosis (MS). During a follow-up evaluation, the condition was diagnosed as monosymptomatic demyelinating disease.

CHF patients

Two (2) studies were conducted to investigate the efficacy and safety of Enbrel in patients with NYHA Class II–IV CHF (studies 200-EU and 016.0021). The studies were terminated after an independent analysis of the 2 studies by a Data Safety Monitoring Board showed that it was unlikely that a benefit would be seen with continued Enbrel treatment. There were no unexpected safety findings in either of these studies, and adverse events included those previously reported in the CHF population or those previously associated with Enbrel therapy. Most of the reported adverse events (infectious and noninfectious) were mild to moderate in intensity.

Safety in Plaque Psoriasis

Patient exposure

The overview of safety is a review of information collected from the 1347 patients with chronic plaque psoriasis enrolled in studies 20021632, 20021639, and 20021642.

Of these 1347 patients, 414 were assigned to the placebo group and 933 were assigned to the Enbrel groups (160 in the 25 mg QW group, 415 in the 25 mg twice weekly group, and 358 in the 50 mg twice weekly group). Of the 414 patients in the placebo group, 151 ultimately received Enbrel 25 mg twice weekly from weeks 13 to 24 of study 20021639 and 177 ultimately received Enbrel 25 mg twice weekly during the open-label extension period (weeks 13 to 48) of study 20021642. Therefore, across the 3 studies, 1261 patients received at least 1 dose of Enbrel for a total of 933 patient-years of exposure to any dose level of Enbrel. Furthermore, 1204 patients were exposed to Enbrel for at least 3 months, 1126 patients for at least 6 months, 831 patients for at least 9 months, 455 patients for at least 12 months, and 95 patients for at least 15 months; this includes 289 patients who received Enbrel continuously for at least 48 consecutive weeks.

Safety concerns surrounding the use of the anti-TNF class of agents include opportunistic infections or tuberculosis (TB), malignancies, haematologic reactions including pancytopenia and aplastic anaemia, demyelinating disorders, worsening of congestive heart failure (CHF), and autoantibody formation. In relation to Enbrel use in psoriasis, each of these concerns will be addressed separately.

Adverse events

Enbrel was well tolerated in all 3 studies, with no dose-related adverse events experienced during the initial 12-week, placebo-controlled portion. Additionally, most events, including infections, occurred in similar proportions of patients in each active group compared with the placebo group.

The percentages of patients that reported at least one adverse event in studies 632, 639 and 642 were 51% for the patients that received placebo, 47.5% for patients that received Enbrel 25 mg QW, 56% for patients receiving Enbrel 25 mg twice weekly and 45,5% for patients that received Enbrel 50 mg twice weekly.

The only event that occurred in higher proportions of patients in the Enbrel groups than in the placebo group was injection site reactions (ISRs), which occurred in 6% of placebo patients compared with

11% of patients in the Enbrel 25-mg QW group, 14% in the 25-mg twice weekly group, and 16% in the 50-mg twice weekly group. All ISRs were of mild to moderate intensity (grade 1 or 2). Only 2 patients (1 in the 50-mg twice weekly group and 1 in the 25-mg twice weekly group) withdrew from study 20021642, and 1 patient (25-mg QW group) withdrew from study 20021639 because of an ISR.

Discontinuations for adverse events were similar across treatment groups during the initial 12-week, placebo-controlled portion.

Enbrel continued to be well tolerated during the extended blinded portion (weeks 13 to 24) of studies 20021632 and 20021639. The proportions of patients who reported noninfectious and infectious adverse events decreased when compared with the initial 12-week period. In addition, the incidence of ISRs decreased with longer exposure to Enbrel. During the extended blinded portion (weeks 13 to 24) of studies 20021632 and 20021639, ISRs occurred in a total of 5% of all patients: 6% of patients in the Enbrel 50-mg twice weekly group, 4% of patients in the 25-mg twice weekly group, 5% in the 25-mg QW group, and 7% in patients in the original placebo group who began receiving Enbrel 25 mg twice weekly.

Exposure-adjusted rates of adverse events and infections during the withdrawal/ retreatment/ open-label period of study 20021639 and the long-term, open-label period of study 20021642 were similar to those observed in the initial 12-week double-blind portion of the respective studies.

Serious adverse events and deaths

Serious adverse events () occurred in similar proportions of patients across treatment groups during the initial 12-week, placebo-controlled portion and in each active group compared with the placebo group. During the extended blinded portion (weeks 13 to 24) of studies 20021632 and 20021639, events continued to occur in similar proportions of patients across treatment groups and in each active group compared with the placebo group. Furthermore, the serious adverse events reported during the double-blind treatment period are consistent with those already associated with Enbrel treatment.

Exposure-adjusted rates of serious adverse events during the withdrawal/retreatment/open-label period of study 20021639 were similar to those observed in the initial 12-week, placebo-controlled portion of the study. Additionally, exposure-adjusted rates of serious adverse events during the long-term, open-label period of study 20021642 were similar to those observed in the initial 12-week, placebo-controlled portion of the study.

Drug-related serious adverse events reported in studies 20021632, 20021639, and 20021642 included CNS demyelinating disease, cystitis, gastroenteritis, lymphadenopathy, lymphoma, pancreatitis, papillary thyrocarcinoma, pneumothorax, psoriatic arthritis, pulmonary emboli, and worsening of psoriasis. Of these serious adverse events, pneumothorax is being added to the section of "Serious adverse events reported in clinical trials" (section 4.8) because it was not previously listed in the SPC. Psoriatic arthritis and worsening of psoriasis are not being included in the SPC because the patients in the studies had a prior history of these conditions. CNS demyelinating disease, gastroenteritis, lymphadenopathy, lymphoma, pancreatitis, and pulmonary emboli already appear in the SPC. Papillary thyrocarcinoma is not being added because the risk of malignancies is already adequately addressed in the SPC. Cystitis is not being added because it resulted from an elective procedure to correct a pre-existing anatomic abnormality.

Serious Infections

Serious infections were rare and occurred in similar proportions of patients across treatment groups during the initial 12-week, placebo-controlled portion of the 3 studies. Only 1 serious infection (pneumonia) occurred during the extended blinded portion (weeks 13 to 24) of studies 20021632 and 20021639. Five (5) serious infections occurred during the withdrawal/retreatment/open-label period of study 20021639 and 2 serious infections occurred during the long-term, open-label period of study 20021642 (see table). Overall for serious infections, there were 6 cases of cellulitis, 3 cases of pneumonia, 2 cases of abscess, and 1 case each of furunculosis, pharyngitis, cholecystitis, osteomyelitis, and gastroenteritis reported. No reports of opportunistic infections or tuberculosis occurred in any study.

The following serious infections that were reported in Enbrel-treated psoriasis patients are being added to the section of "Infections" within the SPC (section 4.8): abscess, cellulitis, cholecystitis, gastroenteritis, osteomyelitis, and pneumonia.

Malignancies

Across all 3 studies 25 malignancies were reported, 23 of which occurred in patients who had received Enbrel reported in 21 patients who had received Enbrel the two remaining neoplasms occurred in patients that received placebo. All of these malignancies occurred in the phase 3 studies; there were no malignancies reported in Enbrel-treated patients in study 20021632.

The phase 3 studies included 1038.7 patient-years of observation. For technical reasons, patient-years of exposure accrued in study 20021632 could not be combined with the phase 3 studies and thus are not included in the calculation of patient-years of observation from the psoriasis studies. The tabulations of patient-years of observation for calculating malignancy rates included time on Enbrel as well as time periods when patients were not receiving Enbrel but were still being observed (e.g., during study drug withdrawal period).

Because there is an increased risk of cutaneous malignancy in patients with psoriasis, due in large part to the high prevalence of exposure to ultraviolet phototherapy and to cyclosporin, cutaneous and extracutaneous malignancies are presented separately below.

Overall, 10 patients were diagnosed with extracutaneous malignancies during the 2 phase 3 studies. These 10 cases of extracutaneous malignancies included: 3 cases of prostate carcinoma, 1 bladder carcinoma, 1 pancreatic carcinoma, 2 breast carcinoma, 1 papillary thyroid carcinoma, 1 lymphoma, and 1 oligo dendroglioma. All 10 of these patients were receiving Enbrel at the time of diagnosis of the malignancy, most likely resulting from the fact that patients received Enbrel for the vast duration of the trials. Except for the case of lymphoma and thyroid carcinoma, all cases were considered by the investigator to be unrelated to study drug.

Regarding cutaneous tumours, overall, 12 patients were diagnosed with cutaneous malignancies during the 2 phase 3 studies, however, 1 of these patients had not received Enbrel prior to the time of diagnosis. Therefore, in patients who had received Enbrel, there were 13 cases of cutaneous malignancies in 11 patients: 8 cases of basal cell carcinoma (1 patient had 2 events of basal cell carcinoma) and 5 cases of squamous cell carcinoma (1 patient had 2 events of squamous cell carcinoma).

No cases of melanoma were reported. One (1) case of in situ lentigo maligna (a premalignant lesion) was reported during the open-label period of study 20021642, the patient was withdrawn from the study because of a biopsy diagnosis of in situ lentigo maligna in a preexisting pigmented skin lesion.

Plausible explanations for the higher incidence of skin cancers in Enbrel-treated patients are: (1) the number of patients and the duration of time that patients received Enbrel vastly exceeded that for placebo due to the designs of the trials; and (2) the potential for underlying skin cancers to be unmasked as the patient's psoriatic plaques clear. Six (6) of these patients with cutaneous malignancies had a previous history of the event, and 8 had received prior phototherapy before entering the study. Except for 2 cases of basal cell carcinoma, all cases were considered by the investigator to be unrelated to study drug.

Analysis of the risk attributable to Enbrel of relatively rare events like malignancy can be assessed by comparing the rates observed in the 2 phase 3 studies to those of an appropriate historical population. The observed number of extracutaneous cancers in the Enbrel psoriasis database (10 extracutaneous malignancies/1038.7 patient-years = 1.0 per 100 patient-years) is not significantly different from the expected rate based on calculations using the general population database from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database (0.5 per 100 patient-years; 95% confidence interval [CI] = 0.2-1.1). The SEER database does not include non-melanoma skin cancers. Several studies have confirmed that the risk of malignancy in psoriasis patients exceeds that in the normal population, and standardised incidence ratios of 1.78 (95% CI 1.32-2.40), 1.3 (95% CI 1.2-1.4), 1.37 (95% CI 1.28-1.47), and 1.35 (95% CI 1.22-1.49) have been reported.

A comparison of the overall malignancy rates calculated for patients with severe (defined as any patient who was receiving systemic therapy) and less severe psoriasis with those observed in the Enbrel studies demonstrates that the overall rates of malignancy in the 2 phase 3 studies are very similar to those observed in a large US psoriasis database with a similar psoriasis disease severity. The overall, observed rate of 2.2 events per 100-patient years (23 malignancies/1038.7 patient-years; 95% CI 1.4-3.3) in the Enbrel phase 3 studies was slightly lower than the 95% CI for the severe psoriasis population (2.3-3.6) and slightly above the 95% CI for the less severe psoriasis population (1.8-2.1), as reported by Margolis.

The numbers of squamous cell and basal cell skin carcinomas observed in the Enbrel phase 3 studies also were compared to 2 databases of the general population. The expected numbers of squamous cell and basal cell skin carcinomas were calculated using data from the Southeastern Arizona Skin Cancer Registry; and the expected number of squamous cell carcinomas also were calculated using the Rochester Epidemiology Project. The observed rates of cutaneous malignancies in the Enbrel phase 3 studies are comparable to those expected in these general population studies. Each of the 3 observed rates in the Enbrel phase 3 studies are within the 95% CIs for the expected rates from these studies. Psoriasis patients have an increased risk of cutaneous malignancy, due in large part to the high prevalence of exposure to ultraviolet phototherapy and to cyclosporin, with standardised incidence ratios of 2.46 (95% CI 1.82-3.27) 4.15 (95% CI 2.52-6.84), 2.5 (95% CI 2.0-3.0), and 3.2 (95% CI 2.3-4.4). Taking this into consideration, the rates of cutaneous malignancies from Enbrel clinical trials are less than what would be expected in a population of moderate to severe psoriasis patients.

Demyelinating Disorders

There have been rare reports of demyelinating disorders in Enbrel-treated patients. This issue was reviewed by the CHMP on 2 occasions, and the labeling was revised to include warning language regarding demyelination. For the psoriasis studies, the entire integrated safety database was reviewed to identify any verbatim or preferred terms that might have suggested any new occurrences of demyelinating disorders. One (1) case of demyelination was reported. Approximately 6 weeks after starting blinded retreatment with 25 mg QW, this 43-year old patient experienced symptoms of neuropathy involving both upper extremities. A magnetic resonance imaging scan revealed a solitary lesion in the right parietal periventricular white matter that was considered to be characteristic of a demyelination plaque, in general, and multiple sclerosis, in particular. The patient was withdrawn from the study at week 36 because of this adverse event of demyelinating neuropathy. Follow-up visits on prednisone treatment revealed marked clinical improvement.

Haematology

Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with Enbrel. There were no cases of aplastic anaemia or pancytopenia reported in these studies

Congestive Heart Failure

There have been post marketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking Enbrel. Therefore the integrated safety database from the 3 psoriasis studies was reviewed and it was confirmed that there were no cases reported.

Anti-Etanercept Antibodies

In study 20021632, no patients tested positive for anti-etanercept antibodies. In study 20021639, 40 patients had 1 or more samples that tested positive for non-neutralising anti-etanercept antibodies. Retreatment in study 20021639 was not associated with an increase in antigenicity or the formation of neutralising antibodies to etanercept. In study 20021642, 32 patients had 1 or more samples that tested positive for non-neutralising anti-etanercept antibodies.

Six percent (72/1200) of patients tested positive for non-neutralising anti-etanercept antibodies during at least one time point during the studies. Historically, antibodies to etanercept have been detected at least once over multiple testing points in approximately 3% to 5% of patients with RA. As in the studies of rheumatic conditions, the presence of anti-etanercept antibodies in these patients had no demonstrable effects on the safety or efficacy of etanercept in any of the psoriasis studies.

Deaths

There were a total of 4 deaths in all of the studies. None were drug related.

Laboratory findings

Most laboratory values were normal. Of the laboratory abnormalities that did occur, most were mild or moderate (grade 1 or grade 2) and were balanced across treatment groups.

No grade 3 or grade 4 abnormalities were reported in study 20021632, and no grade 4 abnormalities were reported in any of the studies in the psoriasis program. There were 2 grade 3 laboratory abnormalities reported during the double-blind period of study 20021642: 1 occurrence of increased alanine transaminase (ALT) in a patient in the etanercept 50 mg twice weekly group, who had a later diagnosis of pancreatic cancer, and 1 occurrence of grade 3 increased haemoglobin in a patient in the placebo group.

During the study drug withdrawal, retreatment, open-label after retreatment, and open-label periods of study 20021639, 8 patients reported 9 grade 3 abnormal liver function results. Five (5) patients had transient elevations of liver function test with laboratory values returning to normal during continuous therapy; 1 of these patients experienced non-infectious hepatitis secondary to simvastatin. The other 3 elevations occurred in 3 patients: 1 with an infectious gastroenteritis 1 day prior to the elevation, 1 with a positive hepatitis C serology, and 1 with an abnormal baseline value. One (1) patient withdrew from study 20021642 during the long-term, open-label period because of grade 2 elevated liver enzymes associated with an adverse event of jaundice.

Discussion on Clinical Safety - Rheumatoid Arthritis

There are no significant differences in frequency of adverse events (other than injection site reactions) recorded either between the groups treated with different dosages of Enbrel or between Enbrel and the placebo-treated groups. However, the incidence of most of adverse events described is slightly higher for Enbrel at the proposed dose than for placebo.

In the clinical trials that supported the initial RA and JCA approvals, local injection site reactions were reported frequently (42 %), but rarely led to a withdrawal of Enbrel.

Concerns also remain that patients receiving long-term treatment with Enbrel might develop an as yet unidentified immune defect, rendering them at increased risk of malignancy and of overwhelming sepsis. Long-term inhibition of TNF-alpha could lead to a serious impairment of defence mechanisms against infections (especially opportunistic infections) and against the development of neoplasms.

Additional warnings are included in the SPC on the increased susceptibility to infections in patients who are at risk of developing infections. These warnings were included as a result of post-marketing experience in the USA where serious infections and sepsis, including fatalities, have been reported in patients with or at risk of infection who had received Enbrel.

There is no difference in the malignancy rates between Enbrel and placebo when corrected for the different duration of exposure. To date no increase in incidence of malignancy has been seen with duration of treatment in the group treated with Enbrel.

The detection of anti-etanercept antibodies was also a concern. None of the etanercept antibodies were neutralising antibodies. It seems that anti-etanercept antibodies may be a transitory phenomenon. No dose effect was observed for the development of anti-etanercept antibodies. No relationship could be established between the occurrence of antibodies to etanercept and any adverse event or increase or decrease in the efficacy of the drug.

Post-authorisation experience

By September 2000, 10 cases of serious blood dyscrasias, some with a fatal outcome, in patients with rheumatoid arthritis treated with etanercept have been reported. These 10 reports of serious blood

dyscrasias, from worldwide post marketing experience, include 3 cases of aplastic anaemia and 7 cases of pancytopenia. Five (5) of these 10 cases had a fatal outcome due to sepsis. In the majority of these cases, there was a close temporal relationship between the start of treatment with etanercept and the occurrence of haematological disorders (range 2 weeks to 5 months). Recent or concomitant exposure to other anti-rheumatic medicines known or suspected to have myelosuppressant effects, such as methotrexate, leflunomide, 6-mercaptopurine, cyclophosphamide and azathioprine was reported in some patients who subsequently developed pancytopenia; some patients had no clear past history of haematological abnormalities. As an urgent measure, the prescribing and patient information has been modified through a rapid procedure at the request of the marketing authorisation holder.

Following the availability of data from additional clinical trials and post-marketing experience, the following undesirable effects were added to the product labeling: Infections (including fatal infections and sepsis), blood dyscrasias (including sometimes fatal aplastic anemia and pancytopenia), nervous system disorders (seizures and demyelinating conditions), malignancies (affecting various sites), aggravation of heart failure, autoimmune events (development of autoantibodies and lupus-like syndrome),drug interaction with anakinra (resulting in increased risk of serious infections and neutropenia), bronchospasm, urticaria, rash, several types of injection site reactions, tuberculosis and cutaneous vasculitis

Following the availability of data from additional clinical trials the following adverse events were added to the product labeling:

Among rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and plaque psoriasis patients in placebo-controlled, active-controlled, and open-label trials of Enbrel, serious adverse events reported included malignancies (see below), asthma, infections, heart failure, myocardial infarction, myocardial ischaemia, chest pain, syncope, cerebral ischaemia, hypertension, hypotension, cholecystitis, pancreatitis, gastrointestinal haemorrhage, bursitis, confusion, depression, dyspnoea, abnormal healing, renal insufficiency, kidney calculus, deep vein thrombosis, pulmonary embolism, membranous glomerulonephropathy, polymyositis, thrombophlebitis, liver damage, leucopenia, paresis, paresthesia, vertigo, allergic alveolitis, angioedema, scleritis, bone fracture, lymphadenopathy, ulcerative colitis and intestinal obstruction

Malignancies
Thirty-eight new malignancies of various types were observed in 2,680 rheumatoid arthritis patients treated in clinical trials with Enbrel for up to 48 months, including 231 patients treated with Enbrel in combination with methotrexate in the 1-year active-controlled study. The observed rates and incidences in these clinical trials were similar to those expected for the population studied. No psoriatic arthritis patients developed malignancies in the double-blind placebo-controlled studies of up to 6 months duration involving 131 Enbrel-treated patients. Twenty-three malignancies were reported in plaque psoriasis patients treated with Enbrel in double-blind and open-label studies of up to 15 months involving 1,261 Enbrel-treated patients.

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the post marketing period).

Discussion on Clinical Safety - Psoriasis

Injection Site Reactions
The most frequently reported adverse events were injection site reactions. The incidence of ISRs decreased with longer exposure to Enbrel.
Infections
There were no reports of opportunistic infections or tuberculosis. During the first 12 weeks of treatment there were 12 serious infections (cellulitis-7, pneumonia, furunculosis, pharyngitis, cholecystitis, and gastroenteritis). Exposure-adjusted rates of infections during the withdrawal/re-treatment/open-label periods were similar to those observed during the first 12 week double blind periods.

Non-cutaneous malignancies
All malignancies except of lymphoma and thyroid carcinoma (both cases in the 50 mg twice weekly group) were considered by the investigators to be unrelated to the study treatment.
The rate of non-cutaneous cancers in the submitted studies (1 per 100 patient-years) was higher than the expected rate from the National Cancer Institute (0.5 per 100 patient-years). Published data suggest that the risk of malignancy in patients with psoriasis is higher than in normal population (standardised incidence ratios of 1.3-1.78).

Cutaneous malignancies
The overall observed rate of 1.3 cases per 100 patient-years in the submitted data is comparable to the Southeastern Arizona Skin Cancer Registry. However, the ratios for squamous cell skin cancers were higher in the studied population (0.5 per 100 patient-years) than in the two databases: Southeastern Arizona Skin Cancer (0.3) and Rochester Epidemiology Project (0.1).
An increased incidence in cutaneous cancers in patients with psoriasis can be due to the effects of phototherapy, local skin treatments or systemic therapy. However, it can not be ruled out that a higher incidence of squamous cell carcinoma is not treatment related.

Autoantibodies
Six percent of patients with psoriasis had non-neutralising antibodies against etanercept during the study treatment. This compares to 3% to 5% of RA patients testing positive for anti-etanercept antibodies. There was no correlation between the presence of antibodies and efficacy/safety data.

5. Overall conclusions and benefit/risk assessment

Quality
The application was supported by a comprehensive pharmaceutical dossier. The two specific issues requiring attention were viral safety and active substance/finished product specifications, including analytical methods validation.
Answers to these points were provided as answer to the list of questions. Follow-up measures / commitments are proposed by the company to answer, to an agreed timeframe, the outstanding points identified in the response assessment report.

Preclinical pharmacology and toxicology
Overall, the primary pharmacodynamic studies provided adequate evidence of etanercept acting as an antagonist of TNF biological activity. The pharmacokinetics were studied in mice, rats, rabbits and monkeys. Due to the formation of anti-etanercept antibodies in rodents, the pivotal toxicity studies were performed in cynomolgus monkeys. Etanercept was well tolerated in monkeys following twice weekly s.c. administration at dose levels up to 15 mg/kg for up to 26 weeks. There were no toxicological significant treatment related adverse events.

In development toxicity studies in rat and rabbits, etanercept did not elicit maternal toxicity, embryo-fetal toxicity, teratogenicity or peri-or post-natal toxicity (rats). Etanercept was not genotoxic. The lack of carcinogenicity studies was a concern for the CHMP, but the CHMP concluded that there are probably no meaningful animal studies which can further evaluate the theoretical risk of increased malignancies resulting from chronic TNF inactivation; therefore the company will conduct long-term surveillance for tumours in man.

Efficacy
The activity of Enbrel has been demonstrated on disease activity measures. The results of 5 controlled studies support the recommendation of 25 mg Enbrel twice weekly in the indication for RA (recommended dose for optimal therapeutic effect).
Enbrel has been shown to slow progression of disease-associated structural damage as measured by X-ray in adult RA patients not previously treated with methotrexate. Enbrel was also shown to be effective treatment of active and progressive psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate.

Beneficial effects were seen after 1-2 weeks of treatment with Enbrel, and maximum effect appeared to be reached after 1-3 months. Patients have reached the 48 months time point without loss of efficacy.

Information has also been submitted on the use of Enbrel in Juvenile Chronic Arthritis. The clinical trials provide convincing evidence of activity of Enbrel in JCA in patient age group of 4-17 years. The posology proposed appears to be appropriate.

No formal drug interaction studies were conducted. It was found that co-administration of methotrexate did not alter the pharmacokinetics of Enbrel. There is no scientific nor pharmacological reason that commonly prescribed medications used in the treatment of RA should interact with Enbrel.

Safety

The safety profile shows a reasonable tolerance for Enbrel. The most common adverse events associated with Enbrel treatment were injection site reactions and infections. When the incidence of infections was related to the time on drug, this was not statistically significantly different from placebo. Upper respiratory tract infection was the most commonly reported type of infection. Additional warnings are included in the SPC on the increased susceptibility to infections in patients who are at risk of developing infections. These warnings were included as a result of post-marketing experience in the USA where serious infections and sepsis, including fatalities, have been reported in patients with or at risk of infections.

Adverse events that may be encountered in the indication Juvenile Chronic Arthritis are adequately described in the SPC.

Antibodies to etanercept were detected in approximately 4 % of patients. They were, however, non-neutralising antibodies. No relationship could be established between the occurrence of antibodies and any adverse event or the efficacy of the drug.

There was no difference in the malignancy rates between Enbrel and placebo when corrected for the different duration of exposure to Enbrel. To date, no increase in incidence of malignancy has been seen with the duration of treatment or in relation to predicted malignancy rates for the general population.

Based on post marketing experience, the product information has been modified to include cases of serious blood dyscrasia , autoimmune phenomena, allergic reactions, demyelinating disorders and worsening of congestive heart failure.

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the postmarketing period.

Concurrent administration of Enbrel and anakinra has been associated with an increased risk of serious infections and neutropenia. This combination has not demonstrated increased clinical benefit; such use is not recommended.

Benefit/Risk Assessment

It is the CHMP's view that the quality of the product, including viral safety, has been demonstrated to be satisfactory.

The CHMP judged the preclinical data on the product to be satisfactory.

Rheumatoid Arthritis

Regarding the clinical efficacy and safety data for rheumatoid arthritis, the CHMP discussed several points of concern:

- Updated safety information provided by the applicant, with particular attention to a possible increased risk of sepsis;
- The question whether or not to limit the indication to the treatment of active RA in adults when the response to all usual disease modifying antirheumatic drugs, including MTX, has proved inadequate;
- The question whether or not, given the safety concerns, the treatment should start with 10 mg twice weekly, 25 mg twice weekly being mentioned as the optimal dose;
- The post-approval comparative studies of Enbrel against other anti-rheumatic treatments as single agents;
- The proposed follow-up studies and further epidemiological surveillance studies for sepsis and malignancies.

The CHMP recognised that there might be an increased risk of sepsis and serious infection, but judged that the warnings in the SPC and PL were sufficient to alert the prescriber. The CHMP did not consider it appropriate to restrict the use of Enbrel to patients in whom the response to all DMARDs had proved inadequate. A drafting group was convened, who proposed to the CHMP the following wording : "...when the response to disease modifying anti-rheumatic drugs, including methotrexate (unless contraindicated), has been inadequate." Regarding the dose, it was agreed by the CHMP that the starting dose for use in adults should be 25 mg twice weekly, but that 25 mg once weekly can also be considered (although this gives a slower response and may be less effective). The CHMP agreed with the post marketing studies proposed by the company.

The CHMP also required the applicant to include the indication for Juvenile Chronic Arthritis in the initial authorisation, as it was felt there was a clinical need in this patient population for this new treatment option. In conclusion, the CHMP accepted that Enbrel in monotherapy is effective in rheumatoid arthritis patients when the response to disease modifying anti-rheumatic drugs, including methotrexate (unless contraindicated) has been inadequate. Its activity has been shown on disease activity measures but no results on structural damage have been presented. The CHMP agreed an extension in the treatment of active severe rheumatoid arthritis in adults not previously treated with methotrexate. The CHMP also accepted the following indications: treatment of active polyarticular-course juvenile chronic arthritis in children aged 4 to 17 years who have had an inadequate response to, or who have proved intolerant of, methotrexate, and treatment of active and progressive psoriatic arthritis in adults when the response to the disease-modifying antirheumatic drugs therapy has been inadequate.

Infections including tuberculosis remain a major safety issue associated with anti-TNF therapy. Following review of post marketing reports, the company has strengthened the warnings and precautions in the Enbrel product information to reflect both clinical trials and post marketing experience: Cases of serious blood dyscrasia, autoimmune phenomena, allergic reaction, demyelinating disorders, and worsening of congestive heart failure were added to the safety sections of the product information. Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the post-marketing period).

Plaque Psoriasis

The Evidence of efficacy compared with placebo has been clearly established and replicated. The data support the inclusion of both 25mg twice weekly and 50mg twice weekly (for up to 12 weeks) in the posology, though there was evidence of superior short-term efficacy for the higher dose. There is some evidence to support re-treatment once a responder has relapsed.
Evidence that some patients might benefit from treatment durations longer than 24 weeks is weak and the optimal duration of treatment has not been defined. Maintenance of effect and prevention of relapse have not been fully investigated. The long-term dosing schedules have not been fully evaluated.

Overall, the safety profile in patients with psoriasis did not differ from the safety in other populations of patients. The only exception was an incidence of cutaneous cancers, especially squamous cell carcinoma, which was higher in psoriasis patients treated with Enbrel. Incidence of injection site reactions was dose-dependent during the first 12 weeks of treatment. Enbrel clearly demonstrated short-term efficacy in patients with psoriasis; the safety profile was acceptable up to 24 weeks of treatment. However, long-term risks relative to the established systemic therapies are unknown. Enbrel should therefore be reserved for patients with psoriasis unresponsive or intolerant to other systemic therapy. As described in section 5.1.

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the benefit/risk profile of Enbrel was favourable in the following indications:

Enbrel can be used alone or in combination with methotrexate for the treatment of active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

Enbrel is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

In patients with rheumatoid arthritis, Enbrel used alone or in combination with methotrexate has been shown to slow the progression of disease-associated structural damage as measured by X-ray.

Treatment of active polyarticular-course juvenile chronic arthritis in children aged 4 to 17 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Enbrel has not been studied in children aged less than 4 years.

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate.

Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.