European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT
FOR

ENBREL

International Nonproprietary Name:
INN- etanercept

Procedure No. EMEA/H/C/262/II/94

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

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I. SCIENTIFIC CONCLUSION

1. Introduction

Etanercept is an anti-tumour necrosis factor (TNF) agent that has been approved for the treatment of moderate to severe plaque psoriasis in adult patients, Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Psoriatic arthritis (PsA) and Polyarticular Juvenile Idiopathic Arthritis (JIA).

Plaque psoriasis is a common condition affecting 1-3% of the population. In about one third of patients, psoriasis starts in the first or second decade of life (*Benoit and Hamm*, 2007 *Clin Dermatol*.; 25(6):555-62.). Systemic therapy is reserved for a minority of cases (*Leman J, Burden D*. 2001, *Paediatric Drugs*;3(9):673-80). Currently licensed medications for paediatric plaque psoriasis are limited and the options available vary from one country to another.

The marketing authorisation holder (MAH) submitted this Type II variation to extend the indication to "*treatment of chronic moderate to severe plaque psoriasis in children and adolescents aged 4 to 17 years who are inadequately controlled by, or are intolerant to topical or other systemic therapies or photo-therapies*". The posology proposed was 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks and if re-treatment with Enbrel is indicated, the same guidance for treatment duration was applied for.
Consequential changes were proposed to sections 4.2, 4.8, 5.1 and 5.2 of the summary of product information (SPC) and sections 1 and 3 of the Package Leaflet (PL).
In addition, the MAH took the opportunity to relocate one sentence in section 7 of the PL (Instructions for Preparing and Giving an Injection of Enbrel) for the paediatric pack. In the subsection on "Adding solvent to the vial", under step 3, the sentence "Remove the solvent syringe and needle from the vial and discard them." was moved from the end of the paragraph to the beginning of the paragraph. This change places the sequence of steps in the powder reconstitution procedure in the proper order for the patient.

2. Clinical aspects

One clinical study (20030211) was submitted in this dossier to support the use of etanercept in the treatment of plaque psoriasis in paediatric patients.

Main Study
Study 20030211 was a randomised, double-blind, placebo-controlled, multicentre study of 211 subjects, followed by an open-label treatment period and a randomised treatment withdrawal period (total duration 48-weeks), to evaluate the efficacy, safety, and pharmacokinetics (PK) of etanercept 0.8 mg/kg (up to a maximum dose of 50 mg) once a week (QW) versus placebo in children (ages 4 to 11 years) and adolescents (ages 12 to 17 years) with moderate to severe plaque psoriasis who met study eligibility criteria.

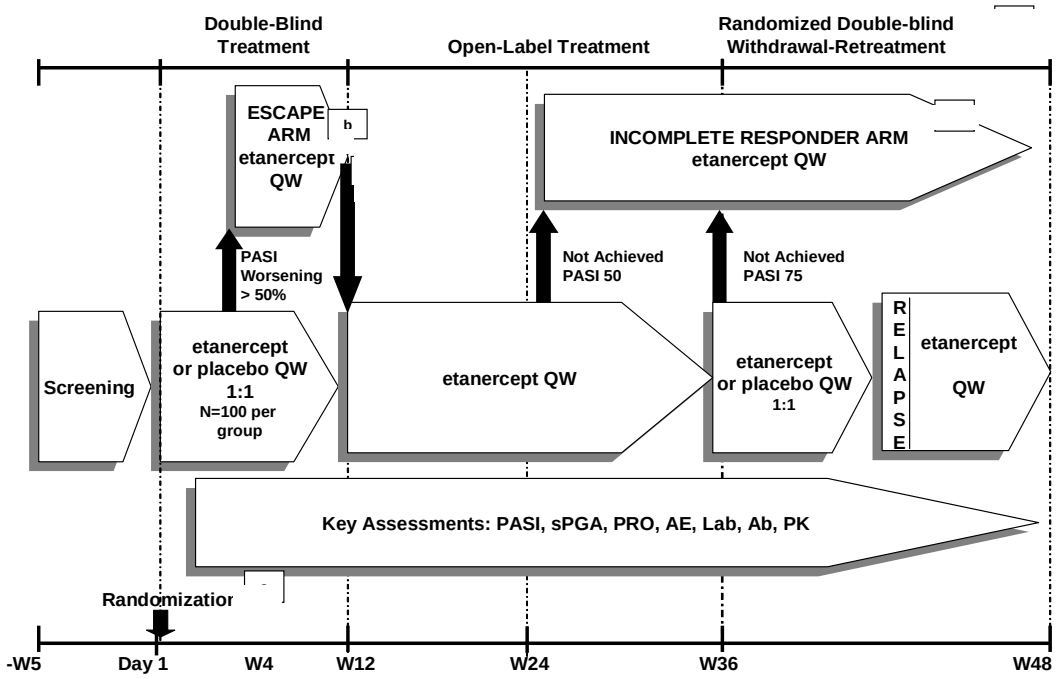
The study consisted of 3 treatment periods (Figure 1):
(1) a double-blind, placebo-controlled treatment period lasting 12 weeks;
(2) an open-label treatment period lasting 24 weeks; and
(3) a randomised, double-blind, withdrawal-retreatment period lasting 12 weeks.
During the double-blind, placebo-controlled treatment period, subjects with substantial worsening of their disease were given the option to enter an escape arm where they would receive open-label etanercept therapy. Additionally, during the open-label treatment period, subjects who did not achieve a pre-specified disease improvement (psoriasis area and severity index (PASI) 50[1] at 24 weeks or PASI 75[2] at 36 weeks) were given the option to withdraw from the study or to enter an incomplete-

[1] A PASI 50 response was defined as a 50% or greater decrease (i.e., improvement) from baseline in PASI score.

[2] A PASI 75 response was defined as a 75% or greater decrease (i.e., improvement) from baseline in PASI score.

responder arm and add topical standard of care to the investigational therapy. Subjects who achieved disease control at week 36 (PASI 75) were re-randomised double-blind to receive etanercept or placebo (the withdrawal-retreatment period) to evaluate disease relapse and durability of response. Subjects who no longer maintained a PASI 75 response could resume treatment with open-label etanercept in the incomplete responder arm.

Figure 1: Design of Study 20030211



Inclusion Criteria

All subjects were anti-TNF therapy naïve and were between 4 and 17 years old inclusive with a history of stable moderate to severe plaque psoriasis (static physician global assessment (sPGA) score of ≥3, PASI score of ≥12, and body surface area (BSA) involvement ≥10%) for ≥6 months at the time of randomisation. Subjects were required to

- Have current or past treatment with phototherapy or systemic psoriasis therapy (e.g. methotrexate, cyclosporin, retinoids), or
- Be considered poorly controlled with topical psoriasis therapy, as evidenced by persistence of moderate to severe psoriasis despite a current or previous treatment course of at least 6-week duration with a corticosteroid of at least moderate potency or a vitamin D analogue. Persistent moderately severe psoriasis during the treatment course was defined as signs and symptoms of psoriasis listed as follows, occurring over a clinically significant portion of the body surface area (BSA), in the opinion of the investigator: erythema – at least moderate red coloration, induration – at least moderate plaque elevation with rounded or sloped edges, scaling – at least coarse scaling.

Exclusion Criteria

The following were specific exclusion criteria:

The presence of guttate, erythrodermic, or pustular psoriasis during the screening period or any other skin condition (e.g. eczema) which would interfere with evaluations of the effect of investigational product on psoriasis: any chronic or recurrent active infection within 6 months of screening: receipt of any systemic psoriasis therapy or oral or parenteral steroids within 14 days before the first dose of investigational product: receipt of any topical therapy (vitamin A or D analogues, anthralin, or calcineurin inhibitor) - other than topical steroids at no higher than moderate strength on the scalp, axillae, and groin - within 14 days before the first dose of investigational product: receipt of any other investigational product within 30 days before the first dose of investigational product: receipt of live attenuated vaccine (e.g. MMR, varicella) within 12 weeks before the first dose of investigational

product, or intranasal influenza vaccine (FluMist). Other relevant exclusion criteria were the diagnosis of multiple sclerosis or any other demyelinating disease; insulin-dependent diabetes mellitus or a history of cancer.

Prior and Concomitant Therapy

Subjects must have had an updated immunisation schedule according to the American Academy of Paediatrics guideline in the US or the Canadian Immunization Guide in Canada to minimise the need for immunisation during the study treatment period.

Throughout the study, investigators could prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care other than the disallowed medications as listed below.

To prevent interference with efficacy assessments, subjects were not to receive the following therapies throughout the duration of the study, including the 30-day follow-up period:

- PUVA, UVA, or UVB therapy
- Any systemic psoriasis therapy (e.g., methotrexate, cyclosporine, etanercept or any other anti-TNF agent(s))
- Oral or parenteral corticosteroids including intramuscular or intraarticular administration (the use of otic, nasal, or inhaled corticosteroids within recommended doses was allowed).
- Topical steroids, topical vitamin A or D analog preparations, or anthralin. The use of topical steroids that are low or moderate potency, per the package insert, was allowed during the study on the scalp, axilla, and groin only. At the investigator's discretion, the use of topical steroids of mild potency, per the package insert, was allowed on the face.
  Exception: Topical standard of care, including those listed above, was allowed for subjects who entered the incomplete-responder arm.
- Topical calcineurin inhibitors
  Exception: allowed for subjects who entered the incomplete-responder arm
- Kineret (anakinra)
- Any investigational product other than etanercept
- Excessive sunbathing or use of tanning salons

Subjects who entered the incomplete-responder arm could be treated with topical standard of care such as vitamin A and vitamin D analogue preparations, anthralin, calcineurin inhibitors, and corticosteroids (mild or moderate, per package inserts).

Topical anaesthetic agents were encouraged for use as local analgesia approximately 30 minutes before SC injections of investigational product or prior to venipuncture.

In the event the subject was exposed to or infected with varicella zoster virus during the study, the subject was treated according to the standard of care for those at high risk of developing severe disease (e.g. varicella zoster immunoglobulin and/or acyclovir).

The CHMP considered the study design adequate according to its objectives. The randomised, double-blind comparison with placebo during 12 weeks allowed for efficacy and safety assessment, while for an evaluation of treatment duration, the open-label and withdrawal retreatment periods are of interest, although the total study duration of 48 weeks was considered insufficient for a full characterisation of an adequate use of a new drug in a chronically remitting and relapsing disease.

In order to ensure an adequate disease control, escape of the treatment allocated was allowed during the study, from as soon as week 4, in order to receive open-label etanercept. Although this can facilitate a disease improvement, it also complicated the analysis and interpretation of study results.

During the study, concomitant therapies for psoriasis, (apart from topical steroids of low to moderate potency in limited areas), were not allowed (except in the incomplete-responder arm); however, in clinical practice, possibly, the combination of both therapies could be beneficial.

The study population was in accordance with the target population of this variation, although the lower age limit of 4 years precluded obtaining information in children of 3 years-old or younger with psoriasis.

2.1 Clinical Pharmacology

Clinical pharmacokinetics

The formulation of etanercept used in study 20030211 was the 25-mg lyophilized vial that is currently approved. Therefore, there was no new important information related to bioavailability that might affect efficacy and/or safety.

In study 20030211, the posology proposed was 0.8 mg/kg once weekly to a maximum dose of 50 mg. This choice of posology was based on the fact that 0.4 mg/kg twice weekly is used in JIA and that equivalence between posology of 25 mg twice weekly and 50 mg once weekly in adults has previously been demonstrated in AS and RA. Of note is that a marketing authorisation has been granted for once weekly etanercept in adults with PsA, based on population PK data and efficacy data.

Serum etanercept concentrations were determined from all etanercept-treated subjects with available samples (Table 1).

Table 1. Summary Statistics of the Pharmacokinetic Data per Time Point Based on Subjects Who Were Assigned to Etanercept Treatment

	Etanercept Serum Concentrations (ng/mL)					
Time Point	N	Mean	SD	Median	Min	Max
Day 1	124	1.50	3.13	BQL	BQL	16.7
Week 12	99	1614	828	1574	17.3	4224
Week 24	191	2104	1255	1886	2.32	6546
Week 48	106	1650	1126	1621	BQL	4831

At week 12, the mean trough etanercept concentration for subjects who were initially randomly assigned to etanercept was 1614 ng/mL. At week 48, the mean trough etanercept concentration was 1650 ng/mL for all subjects who received etanercept for at least 12 weeks and for subjects who received etanercept during the entire 48-week study, the mean trough etanercept concentration was 1829 ng/mL at week 48.

Etanercept concentrations were determined after receiving 0.8 mg/kg (up to 50 mg) QW etanercept. The mean etanercept concentrations in this study did not differ substantially along the study and neither from those found previously in paediatric juvenile arthritis patients or adult psoriasis patients with 25 mg etanercept BIW, in spite of the different dosing interval.

Analysis of the serum etanercept concentration within the two age groups studied (4-11 years and 12-17 years) was requested. A description of pharmacokinetic results (serum etanercept concentration) according to the age of the study patients and the age distribution within the paediatric age subgroups was provided. These data showed that the serum of etanercept levels were comparable in both age groups.

The MAH also presented the distribution of the study subjects from the minimum age of 4 years to the maximum age of 17 years (Table 2) and clarified that there were more subjects at the upper end of the age interval, reflecting higher prevalence of paediatric psoriasis in adolescents than in children.

Table 2-2: Age Distribution of Subjects in Study 20030211

Age	Placebo (N=105) n (%)	Etanercept (N=106) n (%)	Total (N=211) n (%)
4	2 (1.9)	3 (2.8)	5 (2.4)
5	3 (2.9)	1 (0.9)	4 (1.9)
6	1 (1.0)	2 (1.9)	3 (1.4)
7	2 (1.9)	5 (4.7)	7 (3.3)
8	9 (8.6)	6 (5.7)	15 (7.1)
9	6 (5.7)	7 (6.6)	13 (6.2)
10	5 (4.8)	7 (6.6)	12 (5.7)
11	10 (9.5)	7 (6.6)	17 (8.1)
12	11 (10.5)	6 (5.7)	17 (8.1)
13	9 (8.6)	8 (7.5)	17 (8.1)
14	4 (3.8)	9 (8.5)	13 (6.2)
15	13 (12.4)	10 (9.4)	23 (10.9)
16	15 (14.3)	14 (13.2)	29 (13.7)
17	15 (14.3)	21 (19.8)	36 (17.1)
4 - 11	38 (36.2)	38 (35.8)	76 (36.0)
12 - 17	67 (63.8)	68 (64.2)	135 (64.0)

Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/0881A6 TNR-001 ETANERCEPT (Enbrel) Psoriasis/20030211/emea_apr2008/age_dist_all (28MAR08 09:38).

The CHMP was of the opinion that the breakdown of data by age highlighted a lack of insufficient data in the younger age group (under the age of 8 years). The CHMP therefore recommended that until further data is available in younger children, the license for paediatric plaque psoriasis should be restricted to children over the age of 8 years.

2.2 Clinical efficacy

Efficacy Endpoints

The primary efficacy endpoint was the PASI 75 response at week 12.

The secondary efficacy endpoints included the following:

- PASI 50 response at week 12
- PASI 90 response at week 12
- Clear/almost clear status of sPGA at week 12
- Percentage improvement from baseline in children's dermatology life quality index (CDLQI) at week 12

Other efficacy endpoints included: PASI 50, PASI 75, and PASI 90 responses, clear/almost clear status of sPGA and percentage improvement from baseline in CDLQI at each scheduled visit week (except week 12); sPGA, clear status of sPGA, percentage improvement from baseline in PASI score and CDLQI subscales; improvement from baseline in joint pain, Stein Impact on Family, Paediatric Quality of Life Inventory total score and subscale scores, Harter's Self-Perception Profile for Children (6 subscales), and Harter's Self-Perception Profile for Adolescents (9 subscales) at each scheduled visit week.

In addition, the following efficacy endpoints were analysed as part of the final week-48 analysis: improvement from baseline in photograph-derived nail psoriasis severity index (NAPSI) at each scheduled visit week, and time to disease relapse (i.e., loss of PASI 75 response) for all PASI 75 responders who entered the randomised double-blind withdrawal period at week 36.

Statistical Methods
The primary analysis set for all efficacy analyses with respect to the initial 12-week double-blind, placebo-controlled period was the intent-to-treat (ITT) analysis set, which included all randomly assigned subjects regardless of receipt of investigational product. Analysis of the primary endpoint was done using the Cochran-Mantel-Haenszel test stratified by age group.
Subjects who entered the escape arm or who had missing data were considered treatment failures with respect to their original randomised treatment group in the primary analysis. The efficacy data for subjects who entered the escape arm were changed to non-responder at the time they entered the escape arm. Data for those subjects from before they entered the escape arm were not changed. For subjects who had missing data, their missing data were imputed as non-responder, but their existing data were included as observed. The primary analysis was performed using data through week 12 that were collected in a blinded fashion and, then, unblinded for analysis while the open-label portion of the study was ongoing.
Data collected after week 12 were analysed separately for the open-label treatment period, incomplete-responder arm, randomised double-blind withdrawal period, and retreatment period.
Data from the open-label treatment period and incomplete-responder arm were analysed by the original randomised treatment group for efficacy endpoints and by actual treatment received during the placebo-controlled period for safety endpoints.
Data from the randomised double-blind withdrawal and retreatment periods were analysed by the second randomisation for efficacy endpoints and by actual treatment received during the withdrawal period for safety endpoints.
All analyses for the open-label treatment period, incomplete-responder arm, and randomised double-blind withdrawal and retreatment period were conducted using descriptive statistics as in the week-12 final analysis, without statistical inferences between the treatment groups. Time to disease relapse during the randomised double-blind withdrawal period was assessed for treatment effect without adjusting for multiplicity.
The overall significance level for primary and secondary endpoints was controlled at 0.05 using a sequential testing scheme in the following order: PASI 75 response, PASI 50 response, clear/almost clear status of sPGA, percentage improvement from baseline in CDLQI and PASI 90 response. In this sequential testing scheme, statistical testing is stopped once the first non-significant result is observed. Because the primary efficacy endpoint was significant, the secondary endpoints were tested sequentially at a significance level of 0.05. Subjects who entered the escape arm or who had missing data were considered treatment failures with respect to their original randomised treatment group.
The reported p-values for the analysis of additional efficacy endpoints are nominal and were not adjusted for multiplicity.

The CHMP considered that PASI 75 at week 12 as the primary efficacy endpoint of the study was acceptable to assess short term efficacy, according to the CHMP Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr). Other endpoints (PASI 50 and 90 at week 12, clear/almost clear status of sPGA, among others) were also considered acceptable by the CHMP.
The CHMP also considered that the statistical methods for efficacy assessment were acceptable.

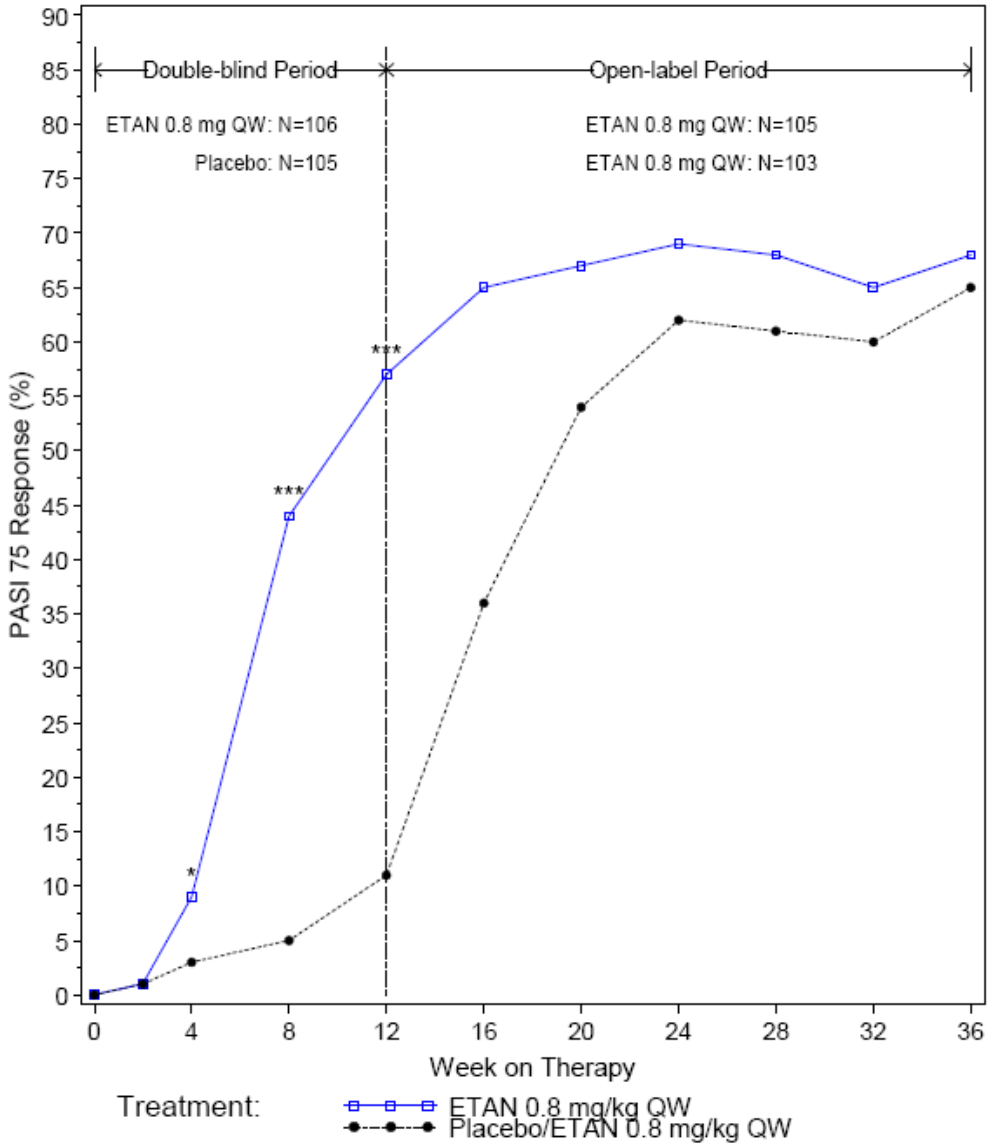
RESULTS
Forty-two sites (30 in the United States and 12 in Canada) randomised subjects in this study. The study population consisted of 108 male and 103 female subjects aged 4 to 17 years.

<u>During the 12-week double-blind period:</u>
At baseline of the initial 12-week double-blind study, subject demographics were generally well balanced between the etanercept and placebo groups, although a higher percentage of subjects in the placebo group had psoriatic arthritis at baseline than subjects in the etanercept group (13% vs. 5%, respectively). Mean age was 12 year-old, ranges 4-17 and mean weight was 62 kg, which showed that the proportion of younger children is lower than the older ones. Most patients were white (74.9%).The population included met the inclusion criteria established in the study regarding psoriasis, i.e. mean PASI was 16 and mean duration was 6 years, and it was considered representative of the target population. Previously, 30% of patients had received systemic therapy and 48% phototherapies. This

was similar between the treatment groups. The subject disposition during the study was evaluated during the three study periods. During the initial 12-week comparative period, a high number of patients of the placebo group (27 out of 105) entered the escape arm due to insufficient response, by contrast, only 5 patients of the etanercept group escaped. At the end of this period, all patients entered the open-label period of treatment with etanercept, but, during this second period, a substantial number of patients were also considered incomplete responders. Finally, 138 patients entered the 12 week withdrawal-retreatment period.

Etanercept provided statistically significant improvements in the PASI 75 to paediatric subjects with moderate to severe plaque psoriasis: at week 12, a higher percentage of subjects in the etanercept group achieved a PASI 75 response compared with the placebo group (57% vs. 11%, $p < 0.0001$) (Figure 2).

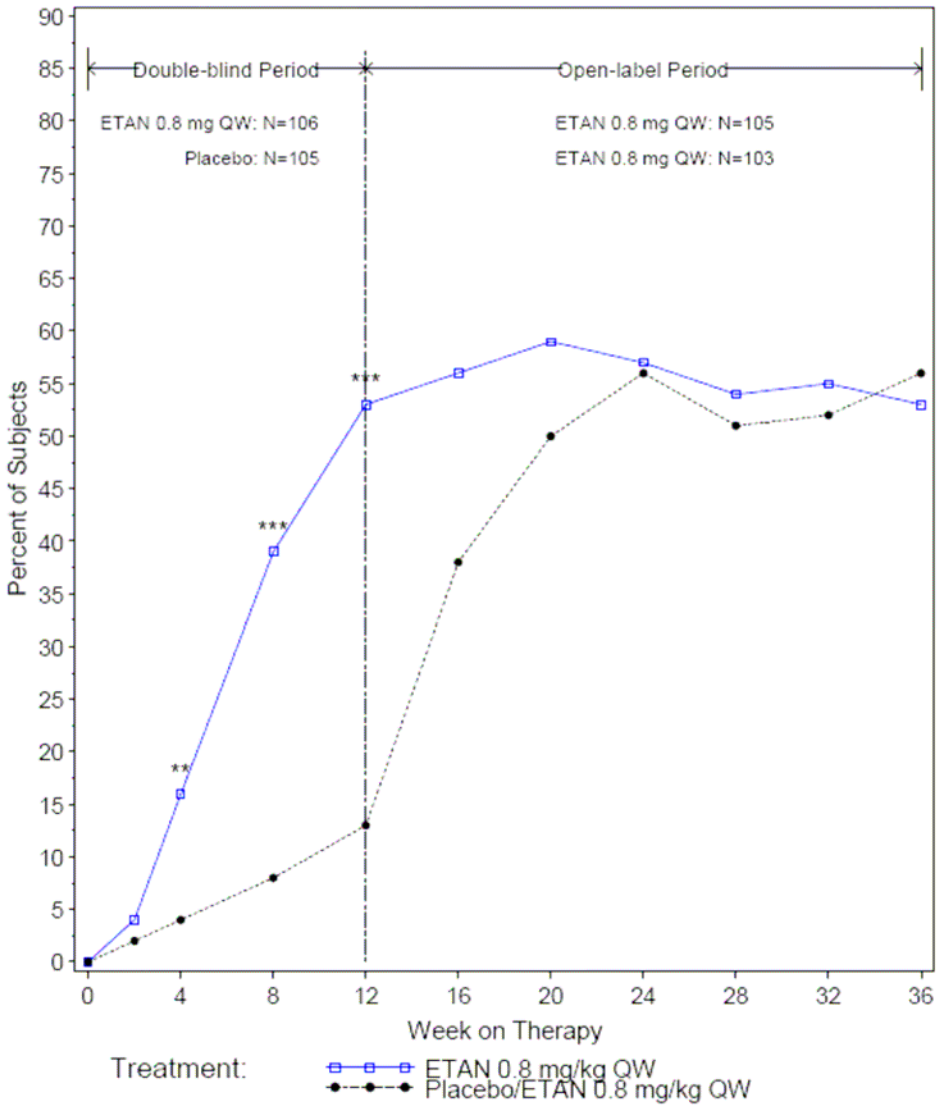
Figure 2: PASI 75 Responses Over Time During the Double-Blind and Open-Label Periods



Abbreviations: ETAN = etanercept; QW = once weekly.
Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.
Note: Subjects who entered the escape arm were considered treatment failures at time of entering escape arm during the 12-week double-blind period.

During the 12-week double-blind period, a significantly higher percentage of subjects in the etanercept group achieved a sPGA status of clear/almost clear compared with the placebo group as early as week 4 (Figure 3).

Figure 3: Percentage of Subjects With a PGA Status of Clear/Almost Clear Over Time During the Double-Blind and Open-Label Periods



Abbreviations: ETAN = etanercept; QW = once weekly.
Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.
Note: Subjects who entered the escape arm were considered treatment failures at time of entering escape arm during the 12-week double-blind period.

The proportion of subjects who achieved a sPGA status of clear/almost clear was maintained during the open-label period in the original etanercept group and continued to improve in the original placebo group when they began receiving open-label etanercept.

The CHMP considered that there was a clear evidence of efficacy of etanercept over placebo in the main psoriasis assessment tools PASI 75 and sPGA. Responders achieved benefit by week 12, with a 10% increase in PASI 75 responders between weeks 12 to 24 in the original etanercept group. However no such further improvement in PASI 75 was seen after 12 weeks of treatment in the original placebo group (62% vs. 65% at weeks 24 and 36 respectively). No further improvement in sPGA was seen after 12 weeks of treatment. The CHMP therefore considered that treatment should be discontinued in those patients who do not show a response at 12 weeks and treatment course should be limited to 24 weeks.

During the 12-week double-blind period, the mean percentage improvement in CDLQI from baseline was significantly greater for the etanercept group compared with the placebo group as early as week 2, and continued to improve during the open-label period for both the original etanercept group and the original placebo group, and was similar by week 36 for subjects in the original placebo group (59.1%) compared with the original etanercept group (63.3%).

This showed a good relative improvement in CDLQI scores compared with baseline and at baseline the scores were similar between the two groups.

The results from the analysis of improvement in joint pain, growth analyses, and photographs and photo-derived NAPSI scores were largely inconclusive because of the small sample sizes (particularly the placebo group). The results of the patient-reported outcomes measures (Stein Impact on Family (completed by parents/caregivers), Paediatric Quality of Life Inventory (completed by parents/caregivers for 4-7 year olds and by subjects 8-17 years old themselves), and Harter's Self-Perception Profile for Children and Adolescents (2 versions – only used for children over 7 years, the 7-12 year old had the child version and the 13-18 yr olds completed the adolescent version) were not statistically significant.

The efficacy results in the double-blind period were independent of age group, with 4-11 year olds having a similar response to 12-17 year olds (Table 3 and 4).

Table 3. PASI Response by Age During Double-blind Period (ITT Subset With Treatment Failure Imputation) 4 to 11 Years old

		Placebo	Etanercept 0.8 mg/kg QW	p-value[a]
≥ 50	Week 2	3/ 38 (8%)	4/ 38 (11%)	0.6916
	Week 4	5/ 38 (13%)	16/ 38 (42%)	0.0048
	Week 8	10/ 38 (26%)	24/ 38 (63%)	0.0012
	Week 12	16/ 38 (42%)	30/ 38 (79%)	0.0010
≥ 75	Week 2	1/ 38 (3%)	1/ 38 (3%)	1.0000
	Week 4	2/ 38 (5%)	5/ 38 (13%)	0.2340
	Week 8	4/ 38 (11%)	15/ 38 (39%)	0.0036
	Week 12	10/ 38 (26%)	22/ 38 (58%)	0.0053
≥ 90	Week 2	0/ 38 (0%)	0/ 38 (0%)	N/A
	Week 4	1/ 38 (3%)	1/ 38 (3%)	1.0000
	Week 8	2/ 38 (5%)	6/ 38 (16%)	0.1349
	Week 12	5/ 38 (13%)	12/ 38 (32%)	0.0540

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Treatment groups represent original randomized treatment
[a]Two-sided Pearson Chi-Square test

Table 4. PASI Response by Age During Double-blind Period (ITT Subset With Treatment Failure Imputation) 12 to 17 Years old

		Placebo	Etanercept 0.8 mg/kg QW	p-value[a]
≥ 50	Week 2	3/ 67 (4%)	5/ 68 (7%)	0.4793
	Week 4	7/ 67 (10%)	34/ 68 (50%)	<0.0001
	Week 8	14/ 67 (21%)	51/ 68 (75%)	<0.0001
	Week 12	21/ 67 (31%)	51/ 68 (75%)	<0.0001
≥ 75	Week 2	0/ 67 (0%)	0/ 68 (0%)	N/A
	Week 4	1/ 67 (1%)	5/ 68 (7%)	0.0985
	Week 8	2/ 67 (3%)	32/ 68 (47%)	<0.0001
	Week 12	11/ 67 (16%)	38/ 68 (56%)	<0.0001
≥ 90	Week 2	0/ 67 (0%)	0/ 68 (0%)	N/A
	Week 4	0/ 67 (0%)	2/ 68 (3%)	0.1573
	Week 8	0/ 67 (0%)	8/ 68 (12%)	0.0038
	Week 12	4/ 67 (6%)	17/ 68 (25%)	0.0023

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Treatment groups represent original randomized treatment
[a]Two-sided Pearson Chi-Square test

Analyses of response by disease duration were presented (Tables 5-8).

Table 5. PASI Response by Disease Duration During Double-blind Period (ITT Subset With Treatment Failure Imputation) Duration of psoriasis - 0 to 2 Years

		Placebo	Etanercept 0.8 mg/kg QW	p-value[a]
≥ 50	Week 2	1/ 21 (5%)	1/ 27 (4%)	0.9038
	Week 4	4/ 21 (19%)	14/ 27 (52%)	0.0222
	Week 8	8/ 21 (38%)	19/ 27 (70%)	0.0293
	Week 12	13/ 21 (62%)	21/ 27 (78%)	0.2396
≥ 75	Week 2	1/ 21 (5%)	0/ 27 (0%)	0.2770
	Week 4	1/ 21 (5%)	3/ 27 (11%)	0.4392
	Week 8	2/ 21 (10%)	12/ 27 (44%)	0.0101
	Week 12	9/ 21 (43%)	17/ 27 (63%)	0.1836
≥ 90	Week 2	0/ 21 (0%)	0/ 27 (0%)	N/A
	Week 4	1/ 21 (5%)	1/ 27 (4%)	0.8585
	Week 8	1/ 21 (5%)	4/ 27 (15%)	0.2747
	Week 12	6/ 21 (29%)	8/ 27 (30%)	0.9581

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Treatment groups represent original randomized treatment
[a]Two-sided Cochran-Mantel-Haenszel test stratified by age group
Subjects are required to have a history of psoriasis for >= 6 months at randomization as indicated by the inclusion criteria

Table 6. PASI Response by Disease Duration During Double-blind Period (ITT Subset With Treatment Failure Imputation) Duration of psoriasis >2 to 6 Years

		Placebo	Etanercept 0.8 mg/kg QW	p-value[a]
≥ 50	Week 2	2/ 38 (5%)	3/ 21 (14%)	0.2562
	Week 4	3/ 38 (8%)	10/ 21 (48%)	0.0010
	Week 8	7/ 38 (18%)	14/ 21 (67%)	0.0007
	Week 12	14/ 38 (37%)	16/ 21 (76%)	0.0074
≥ 75	Week 2	0/ 38 (0%)	1/ 21 (5%)	0.2568
	Week 4	1/ 38 (3%)	3/ 21 (14%)	0.1850
	Week 8	2/ 38 (5%)	10/ 21 (48%)	0.0005
	Week 12	8/ 38 (21%)	12/ 21 (57%)	0.0139
≥ 90	Week 2	0/ 38 (0%)	0/ 21 (0%)	N/A
	Week 4	0/ 38 (0%)	1/ 21 (5%)	0.2568
	Week 8	1/ 38 (3%)	5/ 21 (24%)	0.0231
	Week 12	3/ 38 (8%)	6/ 21 (29%)	0.0681

Treatment groups represent original randomized treatment
[a]Two-sided Cochran-Mantel-Haenszel test stratified by age group

Table 7. PASI Response by Disease Duration During Double-blind Period (ITT Subset With Treatment Failure Imputation) Duration of psoriasis >6 to 10 Years

		Placebo	Etanercept 0.8 mg/kg QW	p-value[a]
≥ 50	Week 2	1/ 31 (3%)	5/ 39 (13%)	0.1629
	Week 4	4/ 31 (13%)	21/ 39 (54%)	0.0004
	Week 8	5/ 31 (16%)	28/ 39 (72%)	<0.0001
	Week 12	5/ 31 (16%)	30/ 39 (77%)	<0.0001
≥ 75	Week 2	0/ 31 (0%)	0/ 39 (0%)	N/A
	Week 4	0/ 31 (0%)	4/ 39 (10%)	0.0697
	Week 8	1/ 31 (3%)	18/ 39 (46%)	<0.0001
	Week 12	2/ 31 (6%)	24/ 39 (62%)	<0.0001
≥ 90	Week 2	0/ 31 (0%)	0/ 39 (0%)	N/A
	Week 4	0/ 31 (0%)	1/ 39 (3%)	0.3648
	Week 8	0/ 31 (0%)	5/ 39 (13%)	0.0401
	Week 12	0/ 31 (0%)	11/ 39 (28%)	0.0015

Treatment groups represent original randomized treatment
[a]Two-sided Cochran-Mantel-Haenszel test stratified by age group

Table 8. PASI Response by Disease Duration During Double-blind Period (ITT Subset With Treatment Failure Imputation) Duration of psoriasis 10 or More Years

		Placebo	Etanercept 0.8 mg/kg QW	p-value[a]
≥ 50	Week 2	2/ 15 (13%)	0/ 19 (0%)	0.0942
	Week 4	1/ 15 (7%)	5/ 19 (26%)	0.1646
	Week 8	4/ 15 (27%)	14/ 19 (74%)	0.0113
	Week 12	5/ 15 (33%)	14/ 19 (74%)	0.0317
≥ 75	Week 2	0/ 15 (0%)	0/ 19 (0%)	N/A
	Week 4	1/ 15 (7%)	0/ 19 (0%)	0.2440
	Week 8	1/ 15 (7%)	7/ 19 (37%)	0.0527
	Week 12	2/ 15 (13%)	7/ 19 (37%)	0.1568
≥ 90	Week 2	0/ 15 (0%)	0/ 19 (0%)	N/A
	Week 4	0/ 15 (0%)	0/ 19 (0%)	N/A
	Week 8	0/ 15 (0%)	0/ 19 (0%)	N/A
	Week 12	0/ 15 (0%)	4/ 19 (21%)	0.0713

Treatment groups represent original randomized treatment
[a]Two-sided Cochran-Mantel-Haenszel test stratified by age group

The CHMP noted that although there was no difference in efficacy for those with a history of psoriasis between 2-10 years, there was a lower response in those with a history of >10 years. Those with a short history of psoriasis (<2 years) had a high spontaneous rate of improvement (placebo results: PASI 75 of 43% at week 12 in those with a history of psoriasis of 0-2 years, versus PASI 75 of 6% in those with psoriasis of 6-10 years). The MAH was therefore asked to provide information on length of disease history in each age group by year (e.g. 4-5 year, 6-7 year) and the responses including spontaneous remission in each of these subgroups. The data presented by the MAH showed that although the complete spontaneous remissions were rare at the week 12 time point, it was evident that a higher percentage of patients who had a short duration of disease ≤ 2 years attained a PGA of clear/almost clear on placebo (32%) compared with those with longer disease duration. The CHMP considered this issue as resolved and stated that further data on this finding will be available from the ongoing multicentre, open-label safety trial (study 20050111) which is an extension study for subjects who participated in study 20030211 conducted by the MAH. This study will continue to collect information on efficacy and safety (including immunogenicity, infections and malignancy).

During the 24-week open-label period:

After 12 weeks of open-label etanercept, subjects who were originally randomised to the placebo group in the double-blind period achieved a similar PASI 75 response at week 24 as the etanercept group had achieved at week 12 (62% and 57%, respectively: Table 9).

Table 9. PASI Response Through Week 36 (ITT Subset With Treatment Failure Imputation)

		Placebo/ Etanercept 0.8 mg/kg QW	Etanercept 0.8 mg/kg QW/ Etanercept 0.8 mg/kg QW	p-value[a]
≥ 50	Week 2 – DB[b]	6/105 (6%)	9/106 (8%)	0.4323
	Week 4 – DB[b]	12/105 (11%)	50/106 (47%)	<0.0001
	Week 8 – DB[b]	24/105 (23%)	75/106 (71%)	<0.0001
	Week 12 – DB[b]	37/105 (35%)	81/106 (76%)	<0.0001
	Week 16 – OL[c]	58/103 (56%)	90/105 (86%)	
	Week 20 – OL[c]	77/103 (75%)	94/105 (90%)	
	Week 24 – OL, IR[c]	80/103 (78%)	92/105 (88%)	
	Week 28 – OL, IR[c]	82/103 (80%)	94/105 (90%)	
	Week 32 – OL, IR[c]	88/103 (85%)	90/105 (86%)	
	Week 36 – OL, IR[c]	89/103 (86%)	91/105 (87%)	
≥ 75	Week 2 – DB[b]	1/105 (1%)	1/106 (1%)	1.0000
	Week 4 – DB[b]	3/105 (3%)	10/106 (9%)	0.0466
	Week 8 – DB[b]	6/105 (6%)	47/106 (44%)	<0.0001
	Week 12 – DB[b]	21/105 (20%)	60/106 (57%)	<0.0001
	Week 16 – OL[c]	37/103 (36%)	68/105 (65%)	
	Week 20 – OL[c]	56/103 (54%)	70/105 (67%)	
	Week 24 – OL, IR[c]	64/103 (62%)	72/105 (69%)	
	Week 28 – OL, IR[c]	63/103 (61%)	71/105 (68%)	
	Week 32 – OL, IR[c]	62/103 (60%)	68/105 (65%)	
	Week 36 – OL, IR[c]	67/103 (65%)	71/105 (68%)	
≥ 90	Week 2 – DB[b]	0/105 (0%)	0/106 (0%)	N/A
	Week 4 – DB[b]	1/105 (1%)	3/106 (3%)	0.3184
	Week 8 – DB[b]	2/105 (2%)	14/106 (13%)	0.0019
	Week 12 – DB[b]	9/105 (9%)	29/106 (27%)	0.0004
	Week 16 – OL[c]	22/103 (21%)	36/105 (34%)	
	Week 20 – OL[c]	30/103 (29%)	34/105 (32%)	
	Week 24 – OL, IR[c]	37/103 (36%)	39/105 (37%)	
	Week 28 – OL, IR[c]	31/103 (30%)	39/105 (37%)	
	Week 32 – OL, IR[c]	36/103 (35%)	43/105 (41%)	
	Week 36 – OL, IR[c]	39/103 (38%)	43/105 (41%)	

[a]Two-sided Cochran-Mantel-Haenszel test stratified by age group
[b]Double-blind period
[c]Open-label period or incomplete-responder arm; subjects could enter the incomplete-responder arm at week 24 or week 36

By week 24 of the open-label period, the clear/almost clear status of the sPGA had been achieved by similar proportions of subjects in the original placebo group (56%) compared with the original etanercept group at week 12 (54%).

Incomplete responders

The same proportion of incomplete responders (those who showed substantial worsening of their disease when in the double-blind period, or those who failed to reach the pre- determined responses of PASI 50 at week 24 or PASI 75 at week 36) from the placebo group achieved a PASI 75 response at week 24 (24%) as did incomplete responders from the original etanercept group at week 12 (20%) (Table 10).

Table 10. PASI Response Through Week 48 for Subjects who Entered the Incomplete-responder Arm (Treatment Failure Imputation)

		Placebo/ Etanercept 0.8 mg/kg QW	Etanercept 0.8 mg/kg QW/ Etanercept 0.8 mg/kg QW
≥ 50	Week 2 – DB[a]	1/ 34 (3%)	2/ 25 (8%)
	Week 4 – DB[a]	3/ 34 (9%)	9/ 25 (36%)
	Week 8 – DB[a]	2/ 34 (6%)	11/ 25 (44%)
	Week 12 – DB[a]	5/ 34 (15%)	13/ 25 (52%)
	Week 16 – OL[b]	7/ 34 (21%)	17/ 25 (68%)
	Week 20 – OL[b]	16/ 34 (47%)	16/ 25 (64%)
	Week 24 – OL, IR[b]	17/ 34 (50%)	15/ 25 (60%)
	Week 28 – OL, IR[b]	19/ 34 (56%)	17/ 25 (68%)
	Week 32 – OL, IR[b]	23/ 34 (68%)	16/ 25 (64%)
	Week 36 – OL, IR[b]	24/ 34 (71%)	17/ 25 (68%)
	Week 40 – IR Only[c]	23/ 34 (68%)	19/ 25 (76%)
	Week 44 – IR Only[c]	24/ 34 (71%)	21/ 25 (84%)
	Week 48 – IR Only[c]	23/ 34 (68%)	21/ 25 (84%)
≥ 75	Week 2 – DB[a]	0/ 34 (0%)	0/ 25 (0%)
	Week 4 – DB[a]	0/ 34 (0%)	1/ 25 (4%)
	Week 8 – DB[a]	0/ 34 (0%)	5/ 25 (20%)
	Week 12 – DB[a]	1/ 34 (3%)	5/ 25 (20%)
	Week 16 – OL[b]	2/ 34 (6%)	7/ 25 (28%)
	Week 20 – OL[b]	3/ 34 (9%)	8/ 25 (32%)
	Week 24 – OL, IR[b]	8/ 34 (24%)	8/ 25 (32%)
	Week 28 – OL, IR[b]	6/ 34 (18%)	7/ 25 (28%)
	Week 32 – OL, IR[b]	5/ 34 (15%)	3/ 25 (12%)
	Week 36 – OL, IR[b]	5/ 34 (15%)	2/ 25 (8%)
	Week 40 – IR Only[c]	11/ 34 (32%)	7/ 25 (28%)
	Week 44 – IR Only[c]	10/ 34 (29%)	12/ 25 (48%)
	Week 48 – IR Only[c]	10/ 34 (29%)	10/ 25 (40%)
≥ 90	Week 2 – DB[a]	0/ 34 (0%)	0/ 25 (0%)
	Week 4 – DB[a]	0/ 34 (0%)	1/ 25 (4%)
	Week 8 – DB[a]	0/ 34 (0%)	1/ 25 (4%)
	Week 12 – DB[a]	1/ 34 (3%)	0/ 25 (0%)
	Week 16 – OL[b]	0/ 34 (0%)	2/ 25 (8%)
	Week 20 – OL[b]	0/ 34 (0%)	3/ 25 (12%)
	Week 24 – OL, IR[b]	0/ 34 (0%)	4/ 25 (16%)
	Week 28 – OL, IR[b]	0/ 34 (0%)	0/ 25 (0%)
	Week 32 – OL, IR[b]	0/ 34 (0%)	1/ 25 (4%)
	Week 36 – OL, IR[b]	0/ 34 (0%)	0/ 25 (0%)
	Week 40 – IR Only[c]	0/ 34 (0%)	2/ 25 (8%)
	Week 44 – IR Only[c]	2/ 34 (6%)	1/ 25 (4%)
	Week 48 – IR Only[c]	4/ 34 (12%)	2/ 25 (8%)

[a] Double-blind period

[b] Open-label period or incomplete-responder arm; subjects may enter the incomplete-responder arm at week 24 or week 36

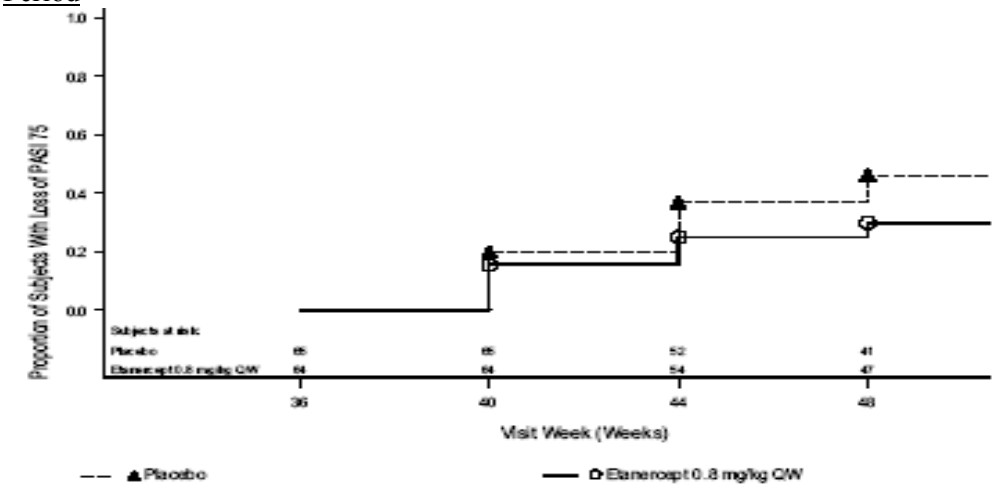
[c] Only includes subjects who continue to receive open-label Etanercept 0.8 mg/kg QW in the incomplete-responder arm

A separate for sPGA clear/almost clear responses for subjects who entered the incomplete-responder arm (with treatment failure imputation for missing data) was also provided.

The CHMP noted that the analysis of subjects who entered the incomplete responder arm showed lower responses to treatment than responders. This may be because they were inherently less responsive to etanercept or were undergoing a flare in their disease which coincided with the onset of the study. The former possibility may be related to lower serum etanercept levels or serum TNF levels in this group compared with responders. The CHMP considered that it would be useful to identify probable non-responders when considering treatment with etanercept, and therefore requested the MAH to provide, for non-responders, information comparing the serum TNF levels and serum etanercept levels in these cases compared with those subjects who had a good initial response to active treatment. The data provided by the MAH showed that non-responders achieve similar serum etanercept concentrations to responders, demonstrating that a lack of response in some patients is not secondary to lower serum levels of etanercept. The CHMP considered the issue as resolved.
The CHMP also requested the MAH to provide a further analysis of the incomplete responders in terms of age, length of disease, serum TNF levels and serum etanercept levels. The data provided by the MAH showed that no difference between the group who were incomplete responders and the group as a whole were found for any of the indices measured. The CHMP considered the issue as resolved.

Efficacy results from randomised withdrawal-retreatment period:
At week 36, subjects who achieved a PASI 75 were considered to be responders to therapy (138 out of the initial 211) and were randomly reassigned to placebo or etanercept QW in a double-blind manner for the 12-week withdrawal-retreatment period of the study to evaluate disease relapse and durability of response.
All subjects were to be followed every 4 weeks and assessed for disease relapse. Relapse was defined as a loss of PASI 75 response or < 75% decrease (i.e. improvement) in PASI score compared with baseline. Upon relapse, subjects were to enter open-label retreatment with etanercept QW through week 48.
During the withdrawal period, no subject had rebound of their disease, defined as a post-baseline PASI score that was > 125% of baseline PASI within 3 months of treatment discontinuation.
Overall, less than 50% of subjects in each group lost their PASI 75 response during the withdrawal period.
The placebo group lost the PASI 75 response more rapidly than did the etanercept group during the withdrawal period. After treatment withdrawal, 75% of subjects in the placebo group versus 81% in the etanercept group retained their PASI 75 response at week 40 (Table 11).

Time to Loss PASI 75 Response for PASI 75 Responders Who Entered Randomised Withdrawal Period



As a consequence, by week 48, more subjects randomly reassigned to placebo (29 of 69, 42%) had entered the retreatment period than had subjects randomly reassigned to etanercept (13 of 69, 19%).

Table 11. PASI Response During Randomised Withdrawal Period (All Subjects Who Were Randomised at Week 36 – Observed Cases)

		Placebo[a]	Etanercept 0.8 mg/kg QW[a]
≥ 50	Week 36 – OL[b]	69/ 69 (100%)	67/ 68 (99%)
	Week 40	62/ 68 (91%)	65/ 67 (97%)
	Week 44	50/ 54 (93%)	53/ 55 (96%)
	Week 48	39/ 40 (98%)	51/ 52 (98%)
≥ 75	Week 36 – OL[b]	65/ 69 (94%)	64/ 68 (94%)
	Week 40	51/ 68 (75%)	54/ 67 (81%)
	Week 44	41/ 54 (76%)	46/ 55 (84%)
	Week 48	34/ 40 (85%)	44/ 52 (85%)
≥ 90	Week 36 – OL[b]	41/ 69 (59%)	40/ 68 (59%)
	Week 40	32/ 68 (47%)	33/ 67 (49%)
	Week 44	26/ 54 (48%)	30/ 55 (55%)
	Week 48	22/ 40 (55%)	32/ 52 (62%)

[a] Treatment groups represent second randomized treatment after week 36
[b] Last visit in open-label period

Similar maintenance of response for sPGA status of clear/almost clear, and percentage improvement from baseline in the CDLQI total score were observed.

The CHMP noted that long-term responders were favoured by the trial design in that the only subjects allowed to remain in the placebo arm during the withdrawal retreatment period were those who maintained their PASI 75 response. Excluding subjects from the placebo group who entered retreatment with etanercept, 34 patients out of the 69 subjects originally randomised for placebo treatment remained on placebo and retained PASI 75 at week 48. Therefore 49% of subjects retained a PASI 75 for 12 weeks after cessation of etanercept treatment. Eighty-five (85)% of those who remained on etanercept retained their PASI 75 at week 48. This demonstrated effective maintenance of response in 49% responders. An alternative possibility is that of disease remission in this group. The CHMP therefore asked the MAH to perform a re-analysis of the subjects who relapsed in the withdrawal-retreatment period of the trial and to identify if they were any differences in this sub-group in terms of demographics and baseline disease characteristics compared with those who retained their PASI 75. The MAH was asked to provide PASI 75 and sPGA scores. The data provided by the MAH showed that there were no baseline disease characteristics or demographic differences between those who relapsed and those who maintained their response in the withdrawal-retreatment period. The PASI 75 and sPGA score data presented were not helpful in view of the small numbers treated for more than 56 days. The CHMP concluded that those who relapse cannot be predicted on the basis of demographics of baseline disease characteristics. The post hoc analysis showing higher efficacy with short-term re-treatment compared to longer retreatment is difficult to explain and is likely to be a spurious result in view of the small number of subjects in these groups. The CHMP considered this issue as solved and noted that further information on efficacy of long-term treatment, and efficacy and safety of re-treatment will become available from the proposed trial 20050111.

The CHMP also requested the MAH to provide information on the ages and length of history of psoriasis in the group who maintained their response and those who relapsed for 12 weeks after cessation of etanercept treatment. The MAH presented a comparison of baseline mean age and mean psoriasis disease duration for subjects who had disease relapse versus the subjects who did not have disease relapse during the withdrawal-retreatment period and concluded that the mean age and disease duration do not appear to be related to disease relapse status. Of subjects who had disease relapse and who entered the retreatment period from the placebo group, 27% had regained a PASI 75 response by week 44 and 36% had regained a PASI 75 response by week 48, after receiving open-label etanercept for 4 to 8 weeks, respectively (Table 12).

Table 12. PASI Response During Retreatment Period (All Subjects Who Received ≥1 Dose of Retreatment After Disease Relapse – Observed Cases)

		Placebo[a]	Etanercept 0.8 mg/kg QW[a]
≥ 50	Week 36 – OL[b]	29/ 29 (100%)	12/ 12 (100%)
	Week 44	12/ 15 (80%)	9/ 9 (100%)
	Week 48	22/ 28 (79%)	11/ 12 (92%)
≥ 75	Week 36 – OL[b]	25/ 29 (86%)	11/ 12 (92%)
	Week 44	4/ 15 (27%)	6/ 9 (67%)
	Week 48	10/ 28 (36%)	7/ 12 (58%)
≥ 90	Week 36 – OL[b]	9/ 29 (31%)	1/ 12 (8%)
	Week 44	2/ 15 (13%)	1/ 9 (11%)
	Week 48	1/ 28 (4%)	0/ 12 (0%)

One subject did not had disease relapse before entering retreatment period and was excluded from efficacy analyses.
[a] Treatment groups represent second randomized treatment after week 36
[b] Last visit in open-label period
All subjects received Etanercept 0.8 mg/kg QW during retreatment period

These results were similar to those observed after subjects had received the initial treatment during the double-blind period: at week 4 of the double-blind period, 9% of subjects in the etanercept group had achieved a PASI 75 response, and by week 8, 44% of subjects had achieved a PASI 75 response.
No subjects had a rebound of their disease, as defined by the National Psoriasis Foundation as a PASI score that is > 125% of the baseline PASI score within 3 months after treatment withdrawal.

The CHMP considered that the randomised withdrawal-retreatment period, conducted in responders to etanercept, was useful to assess the duration of treatment effect and adequacy of retreatment. Overall, less than 50% of subjects in each group lost their PASI 75 response during the withdrawal period. As expected, the placebo group lost the PASI 75 response more rapidly than did the etanercept group, as after 4 weeks (week 40), 75% and 81% of patients, respectively, retained the response. It was also informative that, after 12 weeks (week 48), more subjects reassigned to placebo had entered the retreatment period than had subjects randomly reassigned to etanercept (42% vs. 19%) and that they were able to regain a PASI 75 response in a similar proportion to that found during the initial double-blind period. From this data it can be concluded that, although the results of part I and II of the study showed that the treatment with etanercept during 36 week was useful to control the disease in a substantial proportion of patients, in many of the responders, this treatment period was insufficient; after cessation of etanercept administration, 42% of patients had to enter the retreatment period. The CHMP therefore asked the MAH to provide results (efficacy and safety) obtained in study patients during the follow-up after 48 weeks. The MAH provided data on between 17 and 22 children for PASI results, serum etanercept levels, anti-etanercept antibody status and vital sign measurements. Ten out of twenty-one (10/21) subjects retained their PASI 75 at the follow-up visit. The CHMP considered that the relevance of these findings was limited in view of the small sample size. The data on serum etanercept levels was not helpful because of the small numbers of subjects comprising largely of those who had completed the end of study visit early in the study. The CHMP considered, as many subjects are enrolled into the long-term safety trial, that more complete data will become available from the follow on study 20050111.

In addition the group of patients who entered the third phase of the study were those who had shown a good response to initial treatment. Because of the potential risks of repeated immunosuppression in children (effects on developing immune system and growth) and the lack of long-term safety data the optimal duration of therapy and frequency of retreatment needed to be addressed by the MAH. The identification of factors associated with a rapid loss of response would prevent frequent re-treatment in those least likely to respond. The data provided (analysis to ascertain whether any predictive factors existed at baseline to predict those subjects who had relapse in disease following cessation of active treatment) did not reveal any predictive indictors for clinicians to determine which patients may experience a more rapid loss of response.

Discussion on clinical efficacy

The clinical study submitted to support a paediatric plaque psoriasis indication for etanercept included a total of 211 children aged 4 to 17 years-old with moderate to severe plaque psoriasis who were poorly controlled with topical psoriasis therapy or had received phototherapy or systemic therapy. Etanercept at a dosage of 0.8 mg/kg QW was efficacious in paediatric subjects with moderate to severe plaque psoriasis. At week 12 of the double-blind period, significantly more subjects in the etanercept group had positive efficacy responses compared with those in the placebo group, as assessed by PASI 75, sPGA and CDLQI. During the open-label period, subjects originally from the placebo group had responses in efficacy measures at week 24 (after 12 weeks of etanercept treatment) that were similar to the original etanercept group at week 12 of the double-blind period. Some quality of life assessments (patient-reported outcomes measures (Stein Impact on Family (completed by parents/caregivers), Paediatric Quality of Life Inventory (completed by parents/caregivers for 4-7 year olds and by subjects 8-17 years old themselves), and Harter's Self-Perception Profile for Children and Adolescents (2 versions – only used for children over 7 years, the 7-12 year old had the child version and the 13-18 yr olds completed the adolescent version) did not yield major differences between placebo and etanercept groups. During the withdrawal period, more subjects who were randomly reassigned to the placebo group had disease relapse (loss of PASI 75 response) compared with subjects who were randomly assigned to etanercept 0.8 mg/kg QW. Subjects who had relapsed and entered the retreatment arm showed improvement in their PASI responses but this was less that the original responders and took longer to become evident. No subjects had a rebound of their disease. Thus, the data suggest that disruption of etanercept therapy does not lead to a rebound of disease within 12 weeks. From the results obtained in this 3-period study, it can be concluded that etanercept at a dosage of 0.8 mg/kg QW has shown short-term efficacy, compared with placebo, in the study population. This is consistent with its mechanism of action (immunosuppressant) and the previous findings in adult population with chronic plaque psoriasis. Additionally, the treatment effect duration (including withdrawal and retreatment) was investigated in this study, but more data are required to reach solid conclusions. Psoriasis is a chronic relapsing disease and the possibility of repeated courses in subjects who relapse quickly is a concern since there is limited safety data available in this group.

As only a total of 19 children under the age of 8 years were included in study 20030211, the CHMP was of the opinion that Enbrel's indicated age group should be from 8-17 years. The indicated group should be restricted to chronic severe plaque psoriasis, until further safety data is available. Where the standard practice is to administer systemic therapy or phototherapy with a well known safety profile to such cases, Enbrel should be reserved for those who have failed to respond to systemic therapies or phototherapies. The limitation of prescription of etanercept in this indication to physicians experienced in the treatment of plaque psoriasis will ensure that only those with severe plaque psoriasis for whom limited options are available will be given etanercept.

3. Clinical safety

Patient exposure

Two hundred and eleven (211) subjects received at least 1 dose of test article (106 received etanercept 0.8 mg/kg QW and 105 received placebo) in the 12-week double-blind period. A total of 208 subjects entered the 24-week open-label period and received etanercept 0.8 mg/kg QW. 138 subjects completed the open-label period and were randomly reassigned in the 12-week withdrawal-retreatment period.

The mean exposure to etanercept during the 12-week double-blind period was 21.67 doses over 77.20 days for the etanercept treatment group. The mean exposure to etanercept during the open-label period was 47.20 doses over 175.05 days for the original etanercept group and 48.87 doses over 182.03 days for the original placebo group. Because etanercept was administered QW using 1 or 2 vials of etanercept at a concentration of 25 mg/mL, 1 dose is counted as an injection from 1 vial in the calculation of mean doses above.

The overall exposure to etanercept through 48 weeks was 153.6 subject-years.
No significant change in body measurements (height, weight BMI) was evident in either age group over the initial 12 week double-blind placebo controlled part of the study.

Over the 48 week period an increase in the weight and BMI percentiles were noted in the group as a whole and a slight drop was noted in the height percentiles (Table 13).

Table 13. Weight Percentiles/Body Mass Index (BMI)/ Height/ Height Standard Deviation Scores (SDS) by Visit

	Weight Percentiles by Visit	Body Mass Index (BMI) Percentiles by Visit	Height Percentiles by Visit	Height Standard Deviation Scores (SDS) by Visit
	Etanercept 0.8 mg/kg QW (N=210)			
Baseline				
n	210	209	209	209
Mean	74.88	74.96	57.21	37.10
SD	27.46	28.03	29.53	162.44
SE	1.89	1.94	2.04	11.24
Median	86.57	87.39	60.82	36.19
Min	0.4	2.2	0.3	-510.4
Max	100.0	100.0	99.4	406.8
Week 48				
n	189	188	188	188
Mean	75.59	81.31	56.07	32.42
SD	26.77	22.61	30.23	166.47
SE	1.95	1.65	2.20	12.14
Median	86.66	92.34	58.67	35.99
Min	4.2	11.0	0.6	-452.3
Max	100.0	100.0	99.7	439.3

N= Number of subjects who received at least 1 dose of Etanercept 0.8 mg/kg QW

The CHMP commented that the height percentile showed a drop from baseline at week 48. The height SDS table was found difficult to interpret. The data provided by the MAH (height SDS in the format of age stratified (4-11 years, and 12-17 years) height SDS scores at baseline and at 48 weeks demonstrated that that there were no detectable adverse effects on growth, with the limited data available using the two age groups, 4-11 years and 12-17 years. To obtain an accurate estimate of growth in each sub-group, growth would need to be compared with age and sex- matched controls over a period of a year, in order to get a good estimate of growth rate for a particular group. As they were a very small number of children under the age of 8 years, it was very difficult to exclude an adverse effect on growth within this younger population. Concerns remained about the lack of data in children under the age of 8 in this study. As the ongoing safety study includes only those who completed study 20030211, this will not constitute enough safety data for this group. The marketing authorisation was therefore restricted to children aged 8-17 and those under the age of 8 years will need to have more data collected before authorisation can be granted for this younger age group.

During the initial 12-week double-blind period, the proportions of subjects reporting adverse events or infections were generally similar between the etanercept group (64.2%) and the placebo (59.0%) group (Table 14). There were no serious adverse events (SAEs).

Table 14. Summary of Subject Incidence of Selected Adverse Events During Double-blind Period

Types of Events	Escape Arm Etanercept 0.8 mg/kg QW (N=32) n (%)	Placebo (N=105) n (%)	Etanercept 0.8 mg/kg QW (N=106) n (%)
At least 1 Event	16 (50.0)	62 (59.0)	68 (64.2)
At least 1 Non-infectious Adverse Event	9 (28.1)	46 (43.8)	42 (39.6)
At least 1 Infection	9 (28.1)	33 (31.4)	50 (47.2)
At least 1 Serious Non-infectious Adverse Event	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
At least 1 Serious Infection	0 (0.0)	0 (0.0)	0 (0.0)
At least 1 Grade 3 Non-infectious Adverse Event	0 (0.0)	3 (2.9)	0 (0.0)
At least 1 Grade 3 Infection	0 (0.0)	0 (0.0)	0 (0.0)
At least 1 Non-infectious Adverse Event Leading to Withdrawal From Study	0 (0.0)	0 (0.0)	1 (0.9)
At least 1 Infection Leading to Withdrawal From Study	0 (0.0)	0 (0.0)	0 (0.0)
At least 1 Injection Site Reaction	1 (3.1)	5 (4.8)	7 (6.6)

Treatment groups represent actual treatment received
N = Number of subjects who were randomized and received at least 1 dose of investigational product

Table 15. Subject Incidence of Adverse Events ≥5% by Preferred Term in Descending Frequency During Double-blind Period

Preferred Term	Escape Arm Etanercept 0.8 mg/kg QW (N = 32) n (%)	Placebo (N = 105) n (%)	Etanercept 0.8 mg/kg QW (N = 106) n (%)
Number of Subjects Reporting Adverse Events	16 (50.0)	62 (59.0)	68 (64.2)
Upper Respiratory Tract Infection	4 (12.5)	12 (11.4)	18 (17.0)
Headache	1 (3.1)	13 (12.4)	14 (13.2)
Influenza	0 (0)	2 (1.9)	8 (7.5)
Nasopharyngitis	0 (0)	9 (8.6)	8 (7.5)
Gastroenteritis	1 (3.1)	0 (0)	6 (5.7)

Treatment groups represent actual treatment received
N = Number of subjects who were randomized and received at least 1 dose of investigational product

Table 16. Injection Site Reactions by Preferred Term in Descending Frequency During Double-blind Period

Preferred Term	Escape Arm Etanercept 0.8 mg/kg QW (N = 32) n (%)	Placebo (N = 105) n (%)	Etanercept 0.8 mg/kg QW (N = 106) n (%)
Number of Subjects Reporting Adverse Events	1 (3.1)	5 (4.8)	7 (6.6)
Injection Site Pain	0 (0)	0 (0)	2 (1.9)
Injection Site Reaction	0 (0)	0 (0)	2 (1.9)
Injection Site Anaesthesia	0 (0)	0 (0)	1 (0.9)
Injection Site Bruising	0 (0)	4 (3.8)	1 (0.9)
Injection Site Pruritus	1 (3.1)	0 (0)	1 (0.9)
Injection Site Erythema	1 (3.1)	0 (0)	0 (0)
Injection Site Haemorrhage	0 (0)	1 (1.0)	0 (0)
Injection Site Warmth	1 (3.1)	0 (0)	0 (0)

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Treatment groups represent actual treatment received
N = Number of subjects who were randomized and received at least 1 dose of investigational product

The CHMP commented that compared to the study of etanercept in juvenile rheumatoid arthritis the side effects profile in this double-blind period of the study was similar, except that no SAEs occurred in study 20030211 during the first 12 weeks and the incidence of injection site reactions (ISRs), upper respiratory tract infections (URTIs), gastrointestinal (GI) infections and headache was lower than in the study with juvenile rheumatoid arthritis.

Long-term safety analyses through week 48 were based on exposure-adjusted rates, as all subjects received etanercept during the open label period of the study. In this analysis, treatment groups represented the actual treatment received at the time of the event. The overall rate of AEs through week 48 associated with etanercept treatment was 554.8 events per 100 subject-years versus a rate of 685.3 events per 100 subject-years associated with placebo treatment.
Although times of exposure to etanercept (E = 153.6 subject-years) and placebo (E = 30.1 subject-years) were very different, most events in the etanercept group occurred at a similar or lower exposure-adjusted rate than in the placebo group. Three (3) exceptions to this included streptococcal pharyngitis, gastroenteritis, and arthralgia, which occurred at exposure-adjusted rates of 14.3, 9.8, and 8.5 events per 100 subject-years, respectively, in the etanercept group compared with 3.3, 0, and 0 events per 100 subject-years, respectively, in the placebo group.

The most frequently reported adverse events during the study were all mild to moderate in severity, except for 1 case of gastroenteritis, which was reported as severe (also reported as SAE).

Table 17. All Events Through Week 48 Exposure-adjusted Rates by Preferred Term in Descending Frequency (Treatment Groups Represent Actual Treatment Received at Time of Event

Preferred Term	Placebo (N = 149) (E = 30.1) n	r	Etanercept 0.8 mg/kg QW (N = 210) (E = 153.6) n	r
Total Number of Events	206	(685.3)	852	(554.8)
Upper Respiratory Tract Infection	20	(66.5)	83	(54.0)
Headache	21	(69.9)	51	(33.2)
Nasopharyngitis	12	(39.9)	50	(32.6)
Pharyngitis Streptococcal	1	(3.3)	22	(14.3)
Influenza	5	(16.6)	21	(13.7)
Vomiting	3	(10.0)	19	(12.4)
Pharyngolaryngeal Pain	9	(29.9)	17	(11.1)
Cough	7	(23.3)	15	(9.8)
Gastroenteritis	0	(0.0)	15	(9.8)
Skin Papilloma	1	(3.3)	15	(9.8)
Nasal Congestion	6	(20.0)	14	(9.1)
Arthralgia	0	(0.0)	13	(8.5)
Injection Site Bruising	4	(13.3)	13	(8.5)
Injection Site Pruritus	0	(0.0)	12	(7.8)

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N = Number of subjects who were randomized and received at least 1 dose of investigational product
E = Total number of exposure years
n = Number of adverse events
r = Exposure-adjusted event rate per 100 subject years (= n / E * 100)

During the randomised withdrawal period, 52.9% of subjects receiving etanercept and 46.4% of subjects receiving placebo reported ≥1 adverse event or infection. The most frequently reported adverse events included nasopharyngitis (10.3% etanercept vs. 2.9% placebo) and headache (8.8% etanercept vs. 2.9% placebo).

The CHMP noted that subject incidence of adverse events must be interpreted with caution during the retreatment period because of the small sample size. The most frequently reported adverse events reported during this period were upper respiratory tract infection (25.0% etanercept vs. 10.0% placebo) and sinusitis (8.3% etanercept vs. 6.7% placebo).

3.1 Safety-Related Discontinuations

Six subjects were withdrawn from the study because of an adverse event or infection. One subject in the etanercept group was withdrawn during the double-blind period because of bronchospasm. Five subjects were withdrawn during the open-label period because of psoriasis progression, atopic dermatitis, muscle spasms, skin infection, and lobar pneumonia (the case of pneumonia was considered a serious infection)
The 2 subjects who withdrew during the open-label period because of infections were from the original etanercept group, and the other 3 subjects were from the original placebo group. No subjects were withdrawn during the randomised withdrawal or retreatment periods.

It was noted that it was of interest that those who withdrew because of infection had a higher cumulative dose of etanercept than those who withdrew for other reasons. Data presenting the incidence of infection and all other AEs against the cumulative dosage of etanercept received were provided showing that there was no evidence over the 48 week period of an increase in rate of non-serious AEs. No SAEs were seen in the 1-85 day exposure period and the 4 SAEs in the trial occurred after that time.

3.2 Serious Adverse Events

No non-infectious SAEs or serious infections occurred during the 12-week double-blind period or during the randomised withdrawal or retreatment periods of the study. Four SAEs were reported in 3 subjects during the open-label period.

1. A 14-year-old female subject from the original etanercept group developed an ovarian mass, which was later determined to be benign. The right ovary and mass were surgically removed and pathology revealed fibrous tissue with marked chronic inflammation.

2. A 7-year-old female subject from the original etanercept group with a history of asthma developed pneumonia and was withdrawn from the study because of the event; the subject recovered without sequelae.

3. An 8-year-old female subject from the original placebo group developed gastroenteritis and dehydration (2 SAEs) while receiving etanercept in the incomplete-responder arm. This subject's symptoms of nausea, vomiting, diarrhoea, and abdominal pain developed 2 weeks after a tonsillectomy, and resulted in hospitalisation for dehydration and gastroenteritis.

The SAEs of ovarian mass, gastroenteritis, and dehydration were considered not related to test article, and the SAE of pneumonia was considered related.

The CHMP concluded that it was reasonable to expect that the gastroenteritis was related to the test article as gastroenteritis is a common side effect of etanercept therapy in children

Deaths
No deaths occurred during the study.

Malignancies
No malignancies were reported during the study.

Clinically Important Laboratory Test Results
Transient elevated haemoglobin concentrations were reported: all occurred in adolescent boys (all 15 years old) and were within the normal range for adult men. None of the laboratory abnormalities were associated with any clinical reports of SAEs.

Safety in special populations

No studies have been conducted in special populations in the paediatric psoriasis group.

Anti-nuclear antibodies

Table 18. Summary of Anti-Nuclear Antibody (ANA) Titre Status

		Placebo (N=105)	Etanercept 0.8 mg/kg QW (N=106)
Titer Status - n(%)			
Baseline	NEGATIVE	89 (84.8)	97 (91.5)
	POSITIVE	12 (11.4)	7 (6.6)
Week 48	NEGATIVE	41 (39.0)	47 (44.3)
	POSITIVE	5 (4.8)	5 (4.7)

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Treatment groups represent original randomized treatment from initial 12-week double-blind period
N = Number of subjects who were randomized and received at least 1 dose of investigational product

At baseline, the background rate for ANA was 6.6-11.4%. Those in the original placebo group at week 48 did receive etanercept in the open label period of the study. Of note is that the data presented in table 23 gives percentages calculated on the total number in each group rather than the total number of subjects with test results at each time point. Calculations of the percentage positive at week 48 in the etanercept group would give a result of 5/52 (9.6%). Data were also provided on the titre of ANA at baseline and 48 weeks, the ages of those positive for ANA, the AE profile and whether any further tests were performed in ANA positive cases (such as ENA and dsDNA testing). These data showed that there were only small number of subjects tested for ANA and no clear correlation with age or AE profile emerged from the limited data set.

Anti-etanercept antibodies
No analysis of the 20 cases with anti-etanercept antibodies was performed. Data assessing whether the presence of anti-etanercept antibodies had any effects on efficacy or safety were provided showing that there were no statistically significant differences in efficacy of AE profile between subjects who developed antibodies to etanercept and those who did not at week 12. At week 48 the efficacy responses were lower in the antibody positive group but this was not statistically significant. There were no significant differences between the two groups in terms of efficacy or AE profile.

Of the 211 subjects who were randomly assigned to the study, 208 had predose and postdose serum samples available for testing for antibodies to etanercept. Of these 208 subjects, 20 (9.6%) had at least 1 sample that was positive for anti-etanercept antibodies at ≥ 1 time point. Ten (10) of the 208 subjects (4.8%) had samples that were positive for anti-etanercept antibodies at week 48 or at the end-of-study time point.
All samples were negative for neutralising anti-etanercept antibodies.

Table 19. Summary of Anti-Etanercept Antibodies

		Any Etanercept 0.8 mg/kg QW
Titer Status		
All Time Points	Positive	20/207 (10%)
	Neutralizing Positive	0/ 20 (0%)
Week 12	Positive	9/187 (5%)
	Neutralizing Positive	0/ 9 (0%)
Week 48	Positive	10/179 (6%)
	Neutralizing Positive	0/ 10 (0%)

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Program: /userdata/stat/amg916/derm/20030211/analysis/final/tables/t_antibody.sas
Output: t14-07_007_001_antibody.rtf (Date Generated: 26APR07:12:58:24) Source Data: ab.sas7bdat

ANA and anti-etanercept antibody results on the cases with arthralgia were provided and clarified that 3/11 (27%) of cases with arthralgia and related AEs were positive for ANA and/or anti-etanercept antibodies. Although there was limited data no association between the presence of these antibodies and the development of arthralgia was evident.
Data on those with anti-nuclear antibodies in terms of demographics, baseline disease characteristics, PASI 75, sPGA scores, adverse events including arthralgia as a function of total cumulative dose received were also provided showing that the demographic and baseline disease characteristics of the ANA-positive subjects were comparable to those of the ANA-negative subjects and that the efficacy was similar between these 2 groups and no correlation between arthralgia and ANA positivity was found.

3.3 Risk management plan

In the initial application no revision of the etanercept risk management plan (RMP) was submitted. As part of the etanercept RMP, two paediatric registries were set up (UK and Germany) in order to evaluate the safety profile of etanercept in children and adolescents with juvenile idiopathic arthritis. However, because psoriasis may need multiple courses of treatment, the MAH was requested to submit a RMP addressing this specific paediatric population as well as to consider setting up a registry for paediatric psoriasis.
A RMP was therefore submitted which addressed only the plaque psoriasis indication for this product. A summary of the RMP (distinguishing between identified risks, potential risks and missing information and providing clear indication as to what additional PV activities are planned) is included in the below table.

Safety Concern – Planned Actions

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Identified Risks		
Serious infection	Routine PV and Additional PV: -Long-term extension study 20050111	SPC Section 4.4 Special warnings and precaution SPC Section 4.8 Undesirable effects Patient alert card (see Section 8.7)
Lupus-like reactions	Routine PV and Additional PV: -Long-term extension study 20050111	SPC Section 4.4 Special warnings and precautions SPC Section 4.8 Undesirable effects
Injection site reactions	Routine PV and Additional PV: -Long-term extension study 20050111	SPC Section 4.8 Undesirable effects
Allergic reactions	Routine PV and Additional PV: -Long-term extension study 20050111	SPC Section 4.3 Contraindications SPC Section 4.4 Special warnings and precautions SPC Section 4.8 Undesirable effects
Central demyelinating disorders	Routine PV Additional PV: -Long-term extension study 20050111 -Events of special circumstance questionnaires	SPC Section 4.4 Special warnings and precautions SPC Section 4.8 Undesirable effects
Aplastic anemia and pancytopenia events	Routine PV and Additional PV: -Long-term extension study 20050111	SPC Section 4.4 Special warnings and precautions SPC Section 4.8 Undesirable effects

Safety Concern – Planned Actions (Cont'd)

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Potential risks		
Malignancy	Additional PV: -Long-term extension study 20050111 -Events of special circumstance questionnaires	SPC Section 4.4 Special warnings and precautions SPC Section 4.8 Undesirable effects
Change in morphology and/or severity of psoriasis	Routine PV and Additional PV: -Long-term extension study 20050111	-
Growth and development	Routine PV and Additional PV: -Long-term extension study 20050111	-
Missing information		
Use in pregnant women	Routine PV and Additional PV: -Long-term extension study 20050111 -Organization of Teratology Information Services (OTIS) - autoimmune diseases in pregnancy project -Events of special circumstance questionnaires	SPC Section 4.6 Pregnancy and lactation
Use in hepatic and renal impaired subjects	Routine PV	SPC Section 4.2 Posology and administration SPC Section 4.4 Special warning and precautions
Use in different ethnic origins	Routine PV and Additional PV: - Long-term extension study 20050111	-

Wyeth is proposing to conduct a single-arm, open-label, long-term, , prospective, observational cohort study of safety and effectiveness of pediatric psoriasis patients treated with etanercept (ie, registry).

In its initial RMP, the MAH mentioned that the British Association of Dermatologists Biological Interventions Register (BADBIR) was recently established with the primary purpose of evaluating the long-term safety of biological agents used to treat psoriasis. It is a prospective longitudinal cohort study consisting of two cohorts, psoriasis patients treated with biological interventions and a control group (presumably with similar disease characteristics) exposed only to non-biological systemic therapies. The primary objective of BADBIR is active surveillance for potential adverse events, which have not been detected in the relatively short-term clinical trials, and those which are perceived as clinically important. Safety outcomes of interest include malignancy, cardiovascular events, demyelinating disease, serious infection, and tuberculosis. The register aims to recruit all patients receiving all approved biologic agents, including etanercept, until the required cohort size has been attained. Currently, the investigators have approval for the inclusion of adult psoriasis patients. The MAH has been in communication with the BADBIR investigators regarding the possibility of including pediatric psoriasis patients who are treated with etanercept in the register.

3.4 Discussion on clinical safety

During the clinical study submitted to support this variation, there were no unexpected safety findings associated with etanercept therapy in paediatric plaque psoriasis. The most frequently reported adverse reactions were upper respiratory tract infections, gastrointestinal infections and injection site reactions.

The AE profiles for the retreatment group as a function of length of treatment showed that there were no baseline disease characteristics or demographic differences between those who relapsed and those who maintained their response in the withdrawal-retreatment period. The overall AE rate was higher in those who received etanercept in the withdrawal phase (69% vs. 31%) compared with those receiving placebo. The data showed that infection and infestation rates were lower in those on placebo (26.67%) compared with those on etanercept (66.67%). Infections and infestations were higher in those treated for 29-56 days. The CHMP concluded that those who relapse cannot be predicted on the basis of demographics of baseline disease characteristics.

Because of the potential risks of repeated immunosuppressive therapy in children (effects on developing immune system, immunogenicity and growth) and the lack of long-term safety data, the CHMP requested the MAH to discuss the optimal duration of therapy and frequency of retreatment. The identification of factors associated with a rapid loss of response would prevent frequent re-treatment in this group and the MAH was also asked to comment on this.
Similarity in PK, safety, and efficacy in adult and paediatric subjects with psoriasis was noted. Treatment duration of "up to 24 weeks" recommended for the adult population can therefore be recommended in the paediatric population. In the absence of a response to treatment after 12 weeks, it is recommended that etanercept therapy be discontinued for paediatric patients (in line with the adult patients recommendation). If retreatment is clinically indicated, the same regimen should be employed with regard to dose and duration. However, further data will be provided from the open-label extension study 20050111.This long-term safety trial (20050111) has recruited from subjects in study 20030211 and will therefore not provide sufficient safety data in younger children. The MAH acknowledged that only 17 subjects under the age of 8 years were enrolled in study 20050111 from study 20030211 and therefore, safety data collected during the study will be insufficient to establish a safety profile in this young psoriasis population. Psoriasis affects approximately 2% of the world's population. The prevalence of psoriasis in children has been estimated at 0.55% to 1.4%, the large majority of which is comprised of mild disease. Consequently, there are significant challenges with the recruitment of children with severe psoriasis aged 4 through 7 years. Due to the small number of patients with psoriasis under 8 years of age, the MAH was of the opinion that it is not feasible to conduct a robust, controlled clinical trial in this population, and proposed to conduct a single-arm, open label, long-term, prospective, observational cohort study. An outline protocol for this study has been submitted. The planned study is a single-arm open-label long-term prospective observational study, aiming to recruit at least 100 European paediatric psoriasis patients and as many as 200, across 5 countries over the first 3 years of the study. Patients will be followed up every three months for the first 2 years and every six months for years 3 through to 5. The objectives of this study are to describe the risk of serious infection associated with current or recent treatment with etanercept in paediatric psoriasis; to describe the long-term risk of malignancy in paediatric psoriasis patients who have ever received etanercept; to identify any new, potentially unrecognized ADRs by collecting SAE data in this population; and to assess effectiveness by describing patterns of initial treatment with etanercept, premature discontinuation, and subsequent treatment with systemic therapies including re-treatment with etanercept.

Analyses of infections, SAEs, and treatment patterns will be descriptive. Should any patient develop cancer during follow-up, standardized incidence ratios (SIRs) will be calculated for malignancies, adjusted for age and gender, using geographically appropriate population-based reference rates.
The MAH does not plan to request blood samples to be taken from children during the study for immunogenicity testing. The anti-etanercept assay developed for use in clinical trials is not commercially available, and it cannot be used to test ad hoc blood samples since the assay methodology requires a baseline sample to determine whether a post-exposure sample meets the criteria for the presence of anti-etanercept antibodies. Thus, even if testing for antibodies were to be limited to patients only where indicated, *all* patients would need to provide a sample at baseline. Inclusion of phlebotomy for study participation would likely dissuade parents and physician from patient enrolment in the study (since the medicinal product would otherwise be readily available), thereby diminishing the already limited patient population for the study.

The CHMP considered the outline protocol as appropriate.

The CHMP also considered that whilst it is regrettable that blood samples cannot be collected from patients for immunogenicity testing, the MAH's argument that this will not be feasible within this study is accepted. Also immunogenicity data is to be collected in paediatric psoriasis patients in study 2005011, the long term trial extension.

4. Overall conclusion and benefit risk assessment

The evidence presented showed that etanercept is an effective short-term treatment for paediatric patients with severe plaque psoriasis and who respond within 12 weeks of treatment compared with placebo. Although the side effect profile demonstrates an increased risk of infection, other rarer side effects will only become evident with prolonged pharmacovigilance in this patient group, which will be provided by the MAH.
In view of the lack of long-term safety data in patients with paediatric psoriasis, the CHMP was of the opinion that only those with severe plaque psoriasis who are inadequately controlled by or are intolerant to systemic therapies or phototherapies should constitute the indicated group.

The CHMP was of the opinion that the breakdown of data by age highlighted a lack of insufficient data in the younger age group and was considered insufficient. The CHMP therefore recommended that until further data is available in younger children, the license for paediatric plaque psoriasis should be restricted to children over the age of 8 years and to amend section 4.1 of the SPC accordingly. The CHMP therefore considers that the etanercept indication in treatment of severe plaque psoriasis in children and adolescents should be limited to children over the age of 8 years.

The CHMP also pointed out that the long-term safety trial has recruited from subjects in study 20030211 and will therefore not provide sufficient safety data in younger children. The lack of sufficient data on younger children and the need for longer term efficacy and safety data in paediatric plaque psoriasis is to be addressed with an open label observational study with at least 100 patients from 4-17 years, to assess the safety and efficacy in paediatric plaque psoriasis. This study will collect data on efficacy, safety – particularly in relation to infection, malignancy and loss of efficacy - and will also collect information on dose length and frequency of courses. The aim to collect immunogenicity in such a long-term study cannot be fulfilled due to the need for baseline blood samples for all entrants to the study – which is likely to reduce the number of entrants as the majority of these children and adolescents (from the age of 8 years) could be treated without the need for extra blood tests. Long-term data on immunogenicity will be available from the open-label long term safety trial (study 20050111) and the results will be submitted within 6 months of completion and will provide long-term safety and immunogenicity data on the subjects from study 20050111. This study aims to recruit at least 100 European paediatric psoriasis patients (from the age of 4 years) and as many as 200, across 5 countries over the first 3 years of the study.

The other concern is that in a relapsing remitting disease such as plaque psoriasis the possibility of multiple serial courses being administered before further long-term safety data is available arises. In the absence of long-term safety and growth data maximum treatment duration should follow the current SPC for adults with moderate to severe plaque psoriasis and be limited to 24 weeks.

By restricting the indication to severe disease in those who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies and by restricting the age group to those over 8 years, the benefit/risk balance for etanercept in paediatric plaque psoriasis was considered positive.

II. CHANGES TO THE PRODUCT INFORMATION

Section 4.1 of the SPC was updated as follows:
"Paediatric plaque psoriasis
Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies". The PL was updated accordingly.

Section 4.2 was updated to limit the prescription of Enbrel in this indication to physicians experienced in the treatment of plaque psoriasis which will ensure that only those with severe plaque psoriasis for whom limited options are available will be given Enbrel.
This section also states that treatment should be discontinued in those patients who do not show a response at 12 weeks and treatment course should be limited to 24 weeks. The PL was updated accordingly.

Whilst accepting the restriction to the age range for the indication, section 4.8 of the SPC reflects whole age range of study 20030211 and was updated as follows:

"Undesirable effects in paediatric patients with plaque psoriasis
In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis."

At the CHMP's request, section 5.1 of the SPC includes information about the randomised withdrawal period.

Annex II was updated to include the new version of the RMP approved with this indication and to reflect the recommendation from the CHMP regarding future RMP submissions.

The MAH has also taken the opportunity to relocate one sentence in section 7 of the Package Leaflet (Instructions for Preparing and Giving an Injection of Enbrel) for the paediatric pack. In the subsection on "Adding solvent to the vial", under step 3, the sentence "Remove the solvent syringe and needle from the vial and discard them." is moved from the end of the paragraph to the beginning of the paragraph. This change places the sequence of steps in the powder reconstitution procedure in the proper order for the patient.

The MAH has also made a correction in section 4.8 of the 50 mg presentations' SPC. The sentence "There were 4 reports of macrophage activation syndrome in juvenile idiopathic arthritis clinical trials." was missing in this section and was therefore included.

The other wording proposed by the MAH was agreed by the CHMP.

III. CONCLUSION

On 20 November 2008 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.