Assessment report for

Enbrel

International Nonproprietary Name: Etanercept

Procedure No. Type II variation EMEA/H/C/262/II/134

Assessment Report as adopted by the CHMP with

all information of a commercially confidential nature deleted.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. Scientific discussion

1.1. Introduction

Enbrel contains etanercept, which is a tumour necrosis factor-α (TNFα) inhibitor. Etanercept is a recombinant protein consisting of human p75 tumour necrosis factor receptor (TNFR) fused to the crystallisable fragment (Fc) of human immunoglobulin G1. Etanercept acts as a soluble receptor, which binds both TNFα and TNFß (lymphotoxin), and prevents them from binding to their target receptors on the surfaces of cells thus preventing TNF-mediated cellular responses.

TNF is a cytokine in the inflammatory process of various autoimmune diseases, including rheumatoid arthritis (RA) in adults other diseases such as juvenile idiopathic arthritis (JIA).

Etanercept is authorised for use in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis in children aged 4 to 17 years, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis in adults and paediatric plaque psoriasis in children and adolescents from the age of 8 years.

The MAH submitted this variation application to extend the lower age range for the approved therapeutic indication for paediatric plaque psoriasis from "from the age of 8 years" to "from the age of 6 years" in section 4.1 of the SmPC with consequential changes to section 4.2 and to the package leaflets and section 5.1 of the SmPC where information relating to the long-term (up to 2 years) safety from study 20050111 has been added.

The initially applied for extension of indication reads as follows:

Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of ~~8~~ **6** years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006 as amended the application included an EMA decision (P/236/2010) on the agreement of a paediatric investigation plan (PIP) with a deferral.

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

1.2. Clinical aspects

1.2.1. Introduction

Enbrel is licensed in the EU in adults for rheumatoid arthritis, progressive psoriatic arthritis and moderate to severe plaque psoriasis. Enbrel is licensed in the EU for the paediatric indications of JIA (from the age of 4 years), and plaque psoriasis from the age of 8 years. The latter was licensed in 2008 and the MAH has continued surveillance of this population with an ongoing open label study. The initial application from the MAH for paediatric plaque psoriasis was considered to have too little data on children under the age of 8 years. Additional data collection from the open label study and additional analysis of the age group 6-7 years have been performed by the MAH in an effort to extend the age of licensing of Enbrel in paediatric plaque psoriasis from 8 years down to 6 years. As the indication in paediatric plaque psoriasis is restricted to severe disease where other systemic therapies are unsuitable because of contra-indications or intolerance or have not been effective, Enbrel remains a third line option for children with plaque psoriasis.

The following studies support this variation application:

Study 20030211 was a randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and pharmacokinetics of etanercept 0.8 mg/kg (up to a maximum dose of 50 mg) once weekly (QW) versus placebo in children (aged 4 to 11 years) and adolescents (aged 12 to 17 years) with moderate to severe plaque psoriasis for up to 48 weeks. The final 48-week results of the pre-specified analyses for subjects aged 4 to 17 years in study 20030211 served as the basis for the original approval in paediatric plaque psoriasis (Type II Variation EMEA/H/C/262/II/94 – Commission Decision granted in December 2008) which resulted in the extension of the Enbrel's therapeutic indications to the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years. Some data from this study are presented again here for ease of reference.

Study 20050111 is an ongoing multicenter, open-label extension study for up to 264 weeks for paediatric subjects with plaque psoriasis who participated in study 20030211. Under the agreed PIP, the MAH's obligation was to complete an interim analysis of the first 96 weeks of study 20050111, and to perform a supplementary analysis of data from subjects who were aged 6 or 7 years at any time during study 20030211 or during the first 96 weeks of study 20050111.

1.2.2. GCP

The Clinical trials submitted in support of this variation were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

1.2.3. Pharmacokinetics

The approved dosage forms of etanercept include powder and solvent for solution for injection, and solution for injection in a prefilled syringe. All etanercept dosage forms are intended for subcutaneous (SC) injection. The approved dose for the treatment of chronic, severe, plaque psoriasis in children and adolescents from the age of 8 years is 0.8 mg/kg (up to a maximum of 50 mg per dose) QW for up to 24 weeks.

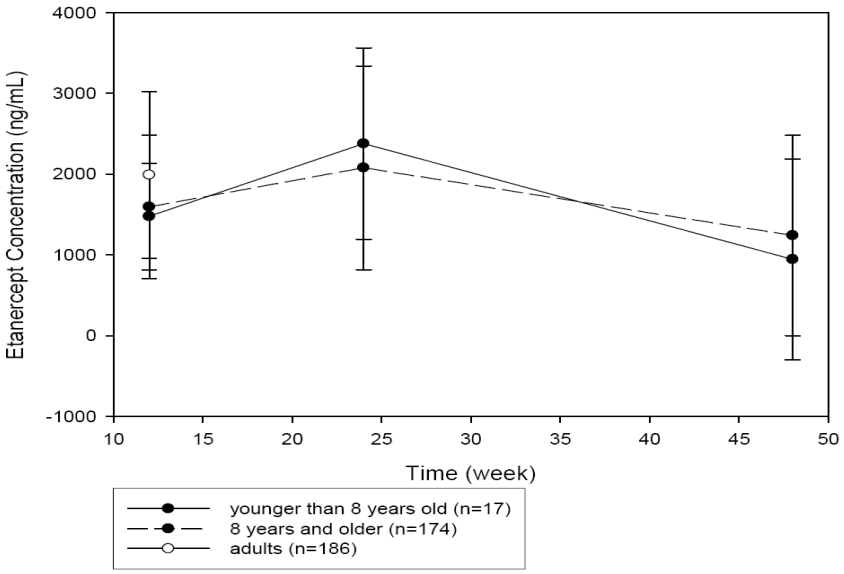
Etanercept pharmacokinetics has been characterized in population PK analyses in adult subjects with RA, AS and psoriasis, in juvenile subjects aged 4 to 17 years with JIA and in juvenile subjects aged 4 to 17 years with psoriasis. Etanercept pharmacokinetics were similar among all these patient populations.

Serum etanercept concentrations were determined from all etanercept-treated subjects in study 20030211 with available samples at baseline (day 1, 124 subjects) and from all subjects with available samples at week 12 (99 subjects), week 24 (191 subjects), and week 48 (106 subjects). Since no PK analyses were done for the subgroup of subjects aged 6 to 7 years, the data from study 20030211 were re-analyzed to determine the mean and median serum steady-state trough concentrations for children aged less than 8 years at enrollment compared with those aged 8 years and older (see Table 1 and Figure 1).

Table 1. Mean and Median Serum Steady-state Trough Concentrations in Pediatric and Adult Subjects with Psoriasis

Week	n	Mean	Standard Deviation	Median
Children Aged < 8 years in Study 20030211				
12	12	1476	659	1387
24	17	2377	1184	2176
48	12	944	1243	231
Children Aged ≥8 Years in Study 20030211				
12	110	1594	886	1549
24	174	2078	1262	1862
48	146	1239	1239	1411
Adults Receiving 25 mg Twice Weekly[4]				
12	186	1900	1110	1800

Figure 1. Mean Serum Steady-state Etanercept Concentrations in Paediatric and Adult Subjects with Psoriasis



Discussion on clinical pharmacology

The pharmacokinetic analyses of the available data from study 20030211 for paediatric subjects with psoriasis aged less than 8 years appear to indicate that they have similar steady-state etanercept concentrations as those aged 8 to 17 years. No significant differences in serum levels were seen in those aged below and those aged above 8 years.

The results from study 20030211, including those of children aged less than 8 years, demonstrate that the mean trough etanercept serum concentrations in paediatric subjects with psoriasis after receiving 0.8 mg/kg etanercept QW (ranging from 1600 ng/mL to 2100 ng/mL) are comparable to the previously reported mean trough steady-state etanercept concentration of 2100 ng/mL observed in subjects with JIA after receiving 0.4 mg/kg etanercept twice weekly (BIW).

In addition, the available data from study 20030211, including those of children aged less than 8 years, seem to indicate that the mean trough etanercept serum concentrations in paediatric subjects with psoriasis after receiving 0.8 mg/kg etanercept QW are comparable to the mean trough etanercept serum concentrations in adult subjects with psoriasis after receiving 25 mg etanercept BIW.

Conclusion on clinical pharmacology

On the basis of the available sample size, the PK analyses appear to indicate no significant differences in steady-state etanercept concentrations in paediatric subjects with psoriasis aged less than 8 years

compared to those aged above 8 years. The posology approved for 0.8 mg/kg in paediatric plaque psoriasis was therefore considered appropriate by the CHMP for the 6-7 years old age group.

1.2.4. Clinical efficacy

The MAH has submitted 2 studies for this variation, study 20030211, which served as the basis for the original approval in paediatric psoriasis in children and adolescents from the age of 8 years, and study 20050111, which is a long-term extension of study 20030211 and provides additional supportive data for children in the age range subject to the present extension application.

Main studies

Study 20030211: Placebo-controlled multicenter study with etanercept to determine safety and efficacy in paediatric subjects with plaque psoriasis

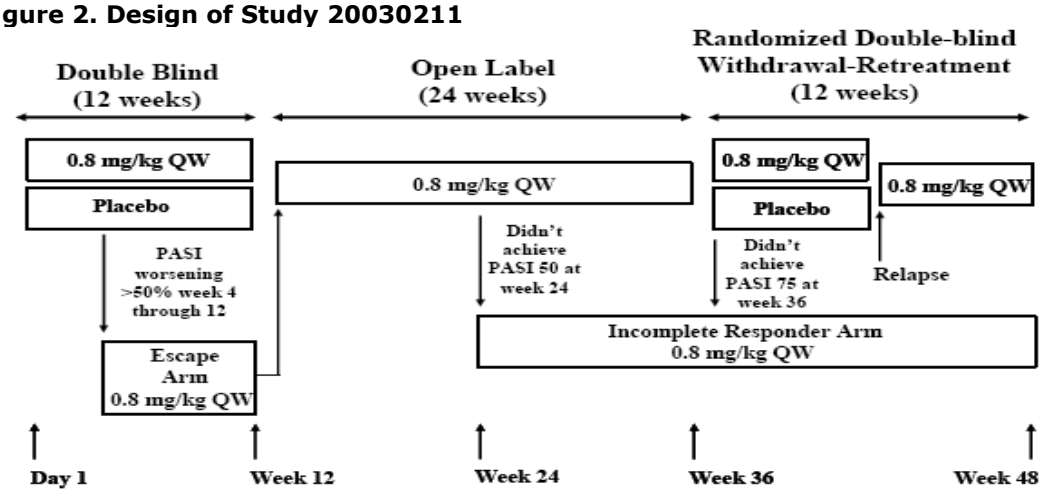
Methods

Study 20030211 was a randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety and pharmacokinetics of etanercept 0.8 mg/kg QW versus placebo in children (aged 4 to 11 years) and adolescents (aged 12 to 17 years) with moderate to severe plaque psoriasis.

Study Participants

The study consisted of an initial 12-week double-blind, placebo-controlled treatment period; a 24-week open-label treatment period; and a 12-week randomized double-blind withdrawal-retreatment period (Figure 2).

Figure 2. Design of Study 20030211



Subjects with substantial worsening of their disease during the double-blind period were given the option to enter an escape arm where they received open-label etanercept therapy. Additionally, during the open-label treatment period, subjects who did not achieve a pre-specified improvement in disease were given the option to withdraw from the study or to enter an incomplete-responder arm and add topical standard of care to the investigational therapy. Subjects who achieved disease control, defined as a Psoriasis Area Severity Index (PASI) 75 response at week 36, were to enter a randomized double-blind withdrawal-retreatment period to evaluate disease relapse and durability of response.

To be eligible for enrollment, subjects had to be 4 to 17 years old with moderate to severe stable plaque psoriasis (defined by a static Physician's Global Assessment of psoriasis [sPGA] score ≥3 [moderate] with a body surface area involvement ≥10% and a PASI score ≥12), and have a history of psoriasis for ≥6 months at the time of randomization. In addition, subjects had to have current or past treatment with phototherapy or systemic psoriasis therapy, or be considered poorly controlled with topical psoriasis therapy.

Treatments

During the double-blind treatment period, subjects received either placebo or etanercept 0.8 mg/kg (up to a maximum dose of 50 mg QW SC); and during the open-label treatment periods, all subjects received etanercept 0.8 mg/kg (up to a maximum dose of 50 mg QW SC).

Objectives

The primary objective of the study was to determine the efficacy of etanercept in paediatric subjects with psoriasis.

Outcomes/endpoints

The primary efficacy endpoint of study 20030211 was the PASI 75 response after 12 weeks of double-blind treatment.

The secondary efficacy endpoints included PASI 50 and PASI 90 responses at week 12, clear or almost clear status of sPGA at week 12, and percentage improvement from baseline in Children's Dermatology Life Quality Index (CDLQI) at week 12.

Statistical methods

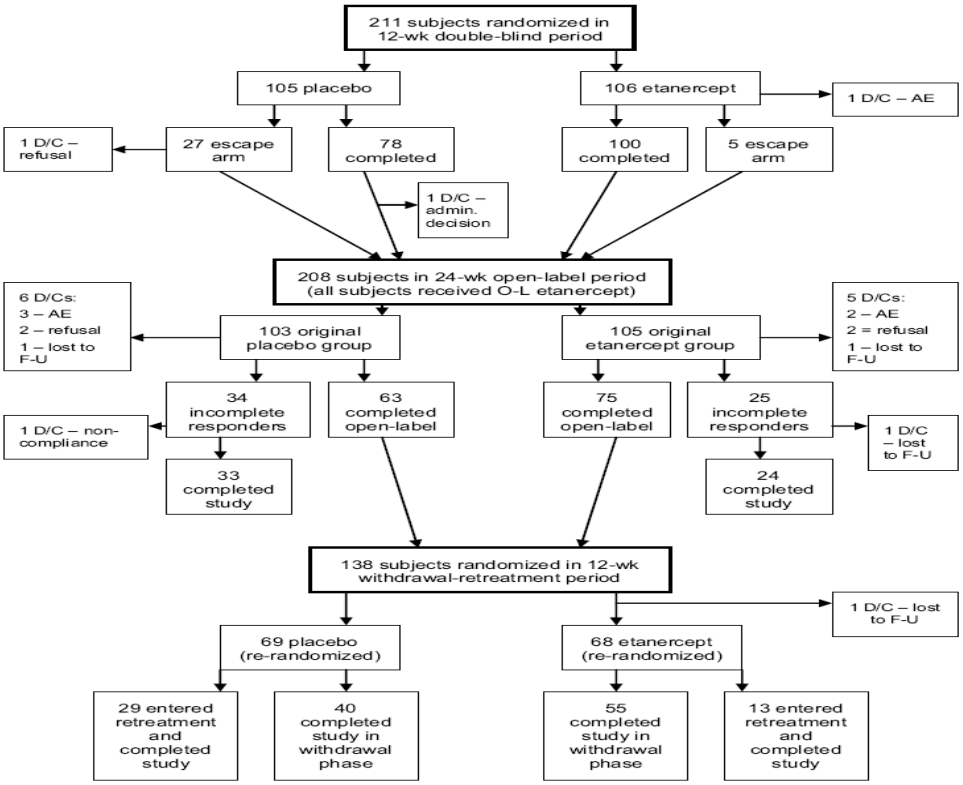
The primary efficacy endpoint was the PASI 75 response at week 12, and was based on an analysis that included all subjects who were randomized, regardless of receipt of investigational product. Subjects who entered the escape arm or who had missing data were considered treatment failures with respect to their original randomized treatment group in the primary analysis. Analysis of the primary endpoint was done using the Cochran-Mantel-Haenszel (CMH) test stratified by age group. 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.

Results

Participant flow

A total of 211 subjects were randomly assigned to receive either placebo or etanercept 0.8 mg/kg QW in the initial 12-week, double-blind period of study 20030211 (Figure 3).

Figure 3. Subject Disposition During the Study 20030211



AE = adverse event; D/C = discontinued; F-U = follow-up; O-L = open-label
Source: Tables 14-1.1.1, 14-1.1.2, and 14-1.1.3

A total of 208 subjects entered the 24-week open-label period and received etanercept 0.8 mg/kg QW. At week 36, a total of 138 subjects were re-randomized to receive either placebo or etanercept 0.8 mg/kg QW during the 12-week withdrawal-retreatment period of the study. Of the 138 subjects who were re-randomized for the withdrawal period, 96 subjects remained on blinded investigational product during the 12-week period and 42 subjects entered the retreatment period. All subjects who entered the retreatment period completed the study.

Subgroup of Subjects Aged 6 to 7 years: Nineteen (19) subjects were less than 8 years of age at some point during study 20030211 or the first 96 weeks of study 20050111. Of these, 17 were 6 or 7 years of age at some point and are thus included in the study 20030211 subgroup analysis.

Baseline data

At baseline, the age distribution of the 17 subjects included in the subgroup analysis for study 20030211 was as follows: 3 (17.6%) aged 4 years, 4 (23.5%) aged 5 years, 3 (17.6%) aged 6 years, and 7 (41.2%) aged 7 years.

Regarding the subgroup aged 6 to 7 years, gender and race in both treatment arms (placebo and etanercept) included a higher percentage of females (58.8 % of the subgroup) and Caucasians (82.5% of the subgroup).

In the overall population of study 20030211, there were a similar number of girls and boys (49.5% and 50.5%, respectively) enrolled and the majority of subjects were white (138 [75.8%]). The mean (SD) age was 12.78 (3.52) years and ranged from 4 to 17 years. The mean (SD) duration of psoriasis at baseline was 6.12 (4.03) years.

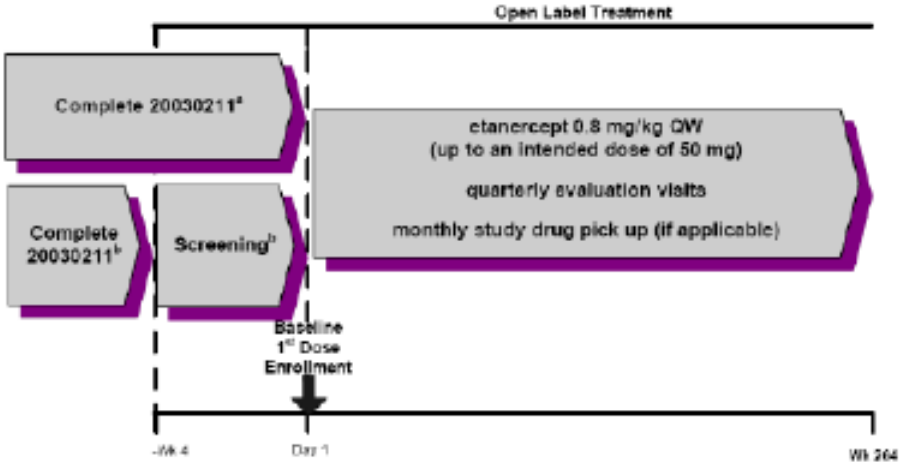
The data on outcome and estimation from study 20030211 with relevance for the present extension application are presented below together with the data from study 2005011.

Study 20050111: An open label extension study to evaluate the safety of etanercept in paediatric subjects with plaque psoriasis.

Methods

Study 20050111 is a multicenter, open-label extension study for paediatric subjects with plaque psoriasis who participated in study 20030211. Subjects have completed week 96 of the study, and the study is currently ongoing and will collect further data for up to 264 weeks (Figure 4).

Figure 4. Study Design and Treatment Schema for Study 20050111



Study Participants

Subjects aged 4 to 17 years from study 20030211 who completed the study or received substantial benefit (achieved a minimum PASI of 50) from etanercept between week 12 and week 48 and did not have a serious adverse event (SAE) or other clinically significant adverse event (AE) considered to be related to the investigational product were eligible for enrollment.

Subjects who were aged 6 to 7 years at any time during the conduct of either the double-blind study 20030211 or the follow-on extension study 20050111 were included in the subgroup analysis.

Treatments

Subjects are receiving etanercept 0.8 mg/kg (up to a maximum dose of 50 mg QW SC) for up to 264 weeks. Subjects have safety and efficacy evaluations every 12 weeks.

Objectives

The primary objective of the study is to evaluate the safety of long-term administration of etanercept in paediatric subjects with moderate to severe plaque psoriasis. The secondary objective is to evaluate the long-term efficacy of etanercept administration in paediatric subjects with moderate to severe plaque psoriasis.

Outcomes/endpoints

The primary endpoint of study 20050111 is a safety endpoint: Incidence of AEs, including infectious episodes, serious adverse events and serious infectious episodes. The secondary safety endpoints are Injection site reactions; Physical examination including height and weight; Vital signs (blood pressure, pulse, respiration rate, temperature); Laboratory toxicity based on the CTC; Anti-etanercept antibody formation.

The following efficacy endpoints were secondary for this study: PASI 50, PASI 75, and PASI 90; percent improvement in PASI score from study 20030211 baseline; sPGA; clear or almost clear status of sPGA; percent improvement from baseline in CDLQI; percent improvement from baseline in CDLQI subscales; and improvement from baseline in joint pain.

The exploratory efficacy endpoint is the improvement from study 20030211 baseline in Harter's Self-perception Profile for Children and Adolescents total scores and subscales.

Due to the small number of subjects in the subgroup aged 6 to 7 years, the efficacy endpoints for this subgroup were summarized using descriptive statistics.

Sample size

Due to the nature of the eligibility criteria, the sample size in study 20050111 is dependent on the number of subjects who participate in study 20030211 and elect to continue etanercept treatment in this study. In study 20030211, there were 17 subjects aged below 8 years old. Table 2 provides the subject disposition for subjects age 6 to 7 years old.

Table 2. Subject Disposition for Subjects aged 6 to 7 years in Study 20050111

	Etanercept
Subjects who were randomized in study 20050111	14
Subjects who completed week 48 of study - n (%)	14 (100.0)
Subjects who completed week 96 of study - n (%)	13 (92.9)
Subjects who are on-going - n (%)	11 (78.6)
Subjects who discontinued study	3
Noncompliance	2 (14.3)
Other	1 (7.1)

Randomisation

Study 20050111 was a non-randomized study for paediatric subjects with plaque psoriasis who participated in study 20030211.

Blinding (masking)

Study 20050111 was an open-label extension study for paediatric subjects with plaque psoriasis who participated in study 20030211.

Statistical methods

All subjects evaluated for all efficacy endpoints, received at least 1 dose of etanercept. All binary or ordinal endpoints were summarized using the number and percent of subjects. All continuous endpoints were summarized using descriptive statistics including mean, standard error, standard deviation, median, minimum, maximum, and number of subjects. Endpoints were summarized up to week 96 using observed data, using treatment failure imputation for missing values and also using last observation carried forward (LOCF) imputation for missing values. In addition, efficacy analyses up to week 96 were also done using descriptive statistics on data using treatment-failure imputation for missing post-baseline data. For binary endpoints, a treatment failure was a non-responder. For ordinal and continuous endpoints, a treatment failure was its baseline value as the endpoint to indicate no change. Since subjects may stop treatment with investigational product at or after week 96 per requirements of the protocol, efficacy data were summarized separately after week 96 and will use observed cases only.

Results

Participant flow

A total of 181 subjects were enrolled and receiving etanercept. The most frequently cited reasons for study discontinuation in the overall population was consent withdrawal (10.5%), lost to follow up (7.2%) and non-compliance (6.1%). Reasons for study discontinuation are provided in Table 3.

Table 3. Reasons for study discontinuation

	Etanercept 0.8 mg/kg QW (N = 181)
Withdrew From Investigational Product	
No	126 (69.6)
Yes	55 (30.4)
Subject Status	
Remain on study	126 (69.6)
Protocol deviation	2 (1.1)
Noncompliance	11 (6.1)
Adverse event	3 (1.7)
Consent withdrawn	19 (10.5)
Lost to follow-up	13 (7.2)
Pregnancy	2 (1.1)
Other	5 (2.8)

N = Number of subjects who received at least 1 dose of investigational product

Subgroup of Subjects Aged 6 to 7 years: Three (3) of the 17 subjects who were 6 or 7 years of age during study 20030211 or the first 96 weeks of study 20050111 were not included in the study 20050111 subgroup analysis (2 did not enroll in the extension study and 1 enrolled but withdrew prior to receiving the first dose of study drug in study 20050111). Therefore, 14 subjects are included in the study 20050111 subgroup analysis. The most frequent reason for discontinuation in the subgroup aged 6-7 years old was non-compliance (see Table 2).

Recruitment

This study was conducted at 37 sites in the United States and Canada. Subjects who satisfied all eligibility criteria were enrolled into this open-label extension. The study period included from 11 August 2005 (first subject enrolled) to 04 September 2008 (last subject completed week 96).

Conduct of the study

There were 3 amendments to this study at the time the report was completed. These amendments are considered as acceptable by the CHMP.

Baseline data

For the 14 subjects included in the subgroup analysis of study 20050111, the demographic and disease characteristic data were based on data collected at the initial visit of study 20030211.

At the baseline of study 20050111, the age distribution of the 14 subjects included in the subgroup analysis for study 20050111 was as follows: 3 (21.4%) aged 5 years, 4 (28.6%) aged 6 years, 2 (14.3%) aged 7 years, and 5 (35.7%) aged 8 years.

The mean ± SD PASI at baseline was 7.45 ± 9.71 and 5.73 ± 6.05 for the placebo and etanercept treatment arms, respectively. The mean ± SD total CDLQI at baseline was 1.60 ± 3.05 and 4.13 ± 4.19 for the placebo and etanercept treatment arms, respectively. The mean ± SD at baseline total Harter´s Self-Perception Profile for Children was 3.16 ± 0.53 and 2.93 ± 0.60 for the placebo and etanercept treatment arms, respectively. The mean ± SD Patient Assessment Joint Pain at baseline was 0.00 ± 0.00 and 0.33 ± 0.58 for the placebo and etanercept treatment arms, respectively (Table 4).

Table 4. Baseline Disease Characteristics for Subjects aged 6 to 7 years in Study 20050111 (based on Study 20050111 baseline)

	Study 20030211 Placebo (N = 6)	Study 20030211 Etanercept (N = 8)	All (N = 14)
Psoriasis BSA (%)			
N	6	8	14
Mean	10.89	9.99	10.38
SD	21.65	12.31	16.19
Min, Max	0.6, 55.0	0.0, 37.0	0.0, 55.0
Psoriasis Area and Severity Index			
N	6	8	14
Mean	7.45	5.73	6.46
SD	9.71	6.05	7.54
Min, Max	0.5, 26.9	0.0, 16.6	0.0, 26.9
Static Physician Global Assessment of Psoriasis			
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
0	0 (0.0)	2 (25.0)	2 (14.3)
1	3 (50.0)	2 (25.0)	5 (35.7)
2	2 (33.3)	3 (37.5)	5 (35.7)
3	1 (16.7)	0 (0.0)	1 (7.1)
4	0 (0.0)	1 (12.5)	1 (7.1)
5	0 (0.0)	0 (0.0)	0 (0.0)
Total Children's Dermatology Life Quality Index			
N	5	8	13
Mean	1.60	4.13	3.15
SD	3.05	4.19	3.87
Min, Max	0.0, 7.0	0.0, 12.0	0.0, 12.0
Total Harter's Self-Perception Profile for Children			
N	5	4	9
Mean	3.16	2.93	3.06
SD	0.53	0.60	0.54
Min, Max	2.3, 3.6	2.5, 3.8	2.3, 3.8
Patient Assessment of Joint Pain			
N	1	3	4
Mean	0.00	0.33	0.25
SD	.	0.58	0.50
Min, Max	0.0, 0.0	0.0, 1.0	0.0, 1.0

Abbreviations: BSE=body surface area; N=number of subjects who were enrolled; SD=standard deviation.
Treatment groups represent original randomized treatment from study 20030211.

Baseline disease for the overall population is shown in tables 5 and 6:

Table 5. Baseline Disease Summary (based on Study 20050111 baseline)

	Study 20030211 Placebo (N = 92)	Study 20030211 Etanercept 0.8 mg/kg QW (N = 90)	All (N = 182)
Psoriasis BSA (%)			
n	91	89	180
Mean	7.98	6.36	7.18
SD	12.16	7.69	10.20
Min, Max	0.0, 68.0	0.0, 37.0	0.0, 68.0
Psoriasis Area and Severity Index			
n	91	89	180
Mean	5.27	4.39	4.84
SD	5.66	3.82	4.84
Min, Max	0.0, 26.9	0.0, 18.6	0.0, 26.9
Static Physician Global Assessment of Psoriasis			
Unknown	1 (1.1)	1 (1.1)	2 (1.1)
0	7 (7.6)	9 (10.0)	16 (8.8)
1	37 (40.2)	28 (31.1)	65 (35.7)
2	30 (32.6)	39 (43.3)	69 (37.9)
3	15 (16.3)	12 (13.3)	27 (14.8)
4	2 (2.2)	1 (1.1)	3 (1.6)
5	0 (0.0)	0 (0.0)	0 (0.0)
Total Children's Dermatology Life Quality Index			
n	88	84	172
Mean	2.26	2.89	2.57
SD	3.06	3.50	3.29
Min, Max	0.0, 15.0	0.0, 17.0	0.0, 17.0
Total Harter's Self-Perception Profile for Children			
n	38	29	67
Mean	3.13	3.08	3.11
SD	0.54	0.46	0.50
Min, Max	2.3, 4.0	2.4, 3.9	2.3, 4.0

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Treatment groups represent original randomized treatment from Study 20030211
N = Number of subjects who were enrolled

Table 6. Baseline Disease Summary (based on Study 20050111 baseline)

	Study 20030211 Placebo (N = 92)	Study 20030211 Etanercept 0.8 mg/kg QW (N = 90)	All (N = 182)
Total Harter's Self-Perception Profile for Adolescents			
n	45	52	97
Mean	3.08	2.97	3.02
SD	0.44	0.45	0.45
Min, Max	2.3, 3.9	1.9, 3.8	1.9, 3.9
Patient Assessment of Joint Pain			
n	23	13	36
Mean	1.96	1.62	1.83
SD	2.51	2.26	2.40
Min, Max	0.0, 8.0	0.0, 7.0	0.0, 8.0

Treatment groups represent original randomized treatment from Study 20030211
N = Number of subjects who were enrolled

Outcomes and estimation

PASI Response

Study 20030211

Double-blind, Placebo-controlled Period

During the 12-week double-blind period, a higher percentage of subjects aged 6 to 7 years in the etanercept group achieved PASI 50, 75, and 90 responses compared with subjects aged 6 to 7 years in the placebo group as early as week 4. At week 12, 82%, 73%, and 27% of subjects in the etanercept group achieved PASI 50, 75, and 90 responses, respectively, compared with 17%, 17%, and 17% of subjects in the placebo group.

One (1, 9.1%) of the 11 subjects in the etanercept group and 1 (16.7%) of the 6 subjects in the placebo group entered the escape arm during the 12-week double-blind period and were considered treatment failures at week 12.

A comparable result was observed for the overall study population: 75%, 57%, and 27% of subjects in the etanercept group achieved PASI 50, 75, and 90 responses, respectively, at week 12 versus 23%, 11%, and 7% of subjects in the placebo group. Five (5, 4.7%) of the 106 subjects in the etanercept group and 27 (25.7%) of the 105 subjects in the placebo group in this population entered the escape arm during the 12-week double-blind period and were considered to be treatment failures at week 12 (Table 7).

Table 7. Summary of Key Efficacy Endpoints for Subjects Aged 6 to 7 Years and the Overall Study Population in Study 20030211 (Subjects who received at least 1 Dose of Etanercept)

Efficacy Endpoint Time Point	Subjects Aged 6 to 7 Years	Overall Population
PASI Response ≥ 75, n/N (%)		
DB – Wk 12	8/11 (73)	60/106 (57)
PASI Score % Improvement, Mean (SE)		
DB – Wk 12	71.4 (10.1)	67.5 (3.0)
PGA Clear/Almost Clear, n/N (%)		
DB – Wk 12	6/11 (55)	56/106 (53)
CDLQI % Improvement, Mean (SE)		
DB – Wk 12	64.0 (13.4)	52.3 (6.1)

Abbreviations: CDLQI=Children's Dermatology Life Quality Index; DB=double blind; PASI=Psoriasis Area Severity Index; PGA=Physician Global Assessment of psoriasis; SE=standard error; Wk=week.

Open-label Period of Study 20030211

The proportion of subjects aged 6 to 7 years in the original etanercept group who achieved PASI 50, 75, or 90 responses during the double-blind period was maintained during open-label phase (Table 8).

Table 8. PASI Response Through Week 36 of Study 20030211 (ITT Subset With Treatment Failure Imputation; Subjects Aged 6 to 7 Years)

PASI Response	Time Point	Placebo/ Etanercept (N=6) n (%)	Etanercept/ Etanercept (N=11) n (%)
≥50	Week 2 - DB[a]	0/6 (0.0)	2/11 (18.2)
	Week 4 - DB[a]	1/6 (16.7)	5/11 (45.5)
	Week 8 - DB[a]	1/6 (16.7)	8/11 (72.7)
	Week 12 - DB[a]	2/6 (33.3)	10/11 (90.9)
	Week 16 - OL[b]	3/6 (50.0)	10/11 (90.9)
	Week 20 - OL[b]	4/6 (66.7)	10/11 (90.9)
	Week 24 - OL, IR[b]	5/6 (83.3)	10/11 (90.9)
	Week 28 - OL, IR[b]	5/6 (83.3)	10/11 (90.9)
	Week 32 - OL, IR[b]	5/6 (83.3)	9/11 (81.8)
	Week 36 - OL, IR[b]	5/6 (83.3)	8/11 (72.7)
≥75	Week 2 - DB[a]	0/6 (0.0)	1/11 (9.1)
	Week 4 - DB[a]	0/6 (0.0)	2/11 (18.2)
	Week 8 - DB[a]	1/6 (16.7)	6/11 (54.5)
	Week 12 - DB[a]	1/6 (16.7)	8/11 (72.7)
	Week 16 - OL[b]	2/6 (33.3)	7/11 (63.6)
	Week 20 - OL[b]	3/6 (50.0)	8/11 (72.7)
	Week 24 - OL, IR[b]	5/6 (83.3)	9/11 (81.8)
	Week 28 - OL, IR[b]	5/6 (83.3)	8/11 (72.7)
	Week 32 - OL, IR[b]	5/6 (83.3)	9/11 (81.8)
	Week 36 - OL, IR[b]	5/6 (83.3)	8/11 (72.7)
≥90	Week 2 - DB[a]	0/6 (0.0)	0/11 (0.0)
	Week 4 - DB[a]	0/6 (0.0)	1/11 (9.1)
	Week 8 - DB[a]	0/6 (0.0)	2/11 (18.2)
	Week 12 - DB[a]	1/6 (16.7)	3/11 (27.3)
	Week 16 - OL[b]	1/6 (16.7)	5/11 (45.5)
	Week 20 - OL[b]	1/6 (16.7)	4/11 (36.4)
	Week 24 - OL, IR[b]	1/6 (16.7)	4/11 (36.4)
	Week 28 - OL, IR[b]	0/6 (0.0)	5/11 (45.5)
	Week 32 - OL, IR[b]	1/6 (16.7)	6/11 (54.5)
	Week 36 - OL, IR[b]	1/6 (16.7)	5/11 (45.5)

Abbreviations: DB=double blind; IR=incomplete responder; ITT=intent to treat; OL=open label; PASI=Psoriasis Area Severity Index.

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.

Source: 5.3.5.2, Addendum to CSR-77991, Table 5-2.

A comparable result was observed for the overall study population: 87%, 68%, and 41% of subjects from the original etanercept group achieved PASI 50, 75, and 90 responses, respectively, at week 36 versus 86%, 65%, and 38% of subjects from the original placebo group (Table 9). Twenty-five (25, 23.6%) of the 106 subjects from the original etanercept group and 34 (32.4%) of the 105 subjects from the original placebo group entered the incomplete responder arm during the open-label period.

Table 9. PASI Response Through Week 36 (4-17 yrs) (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

Study 20050111 Through Week 96

The treatment response observed in subjects aged 6 to 7 years during the double-blind, placebo-controlled and open-label periods of study 20030211 was maintained through 96 weeks of etanercept treatment in study 20050111 (Table 10). At week 96, 85%, 69%, and 54% of subjects had PASI 50, 75, and 90 responses, respectively.

Table 10. PASI Response for Subjects aged 6 to 7 Years Through Week 96 of Study 20050111 (Observed cases)

Response	Timepoint	Etanercept (N=14)
≥ 50	Week 12	12/ 14 (86%)
	Week 24	10/ 13 (77%)
	Week 36	10/ 13 (77%)
	Week 48	12/ 14 (86%)
	Week 60	11/ 13 (85%)
	Week 72	10/ 13 (77%)
	Week 84	9/ 12 (75%)
	Week 96	11/ 13 (85%)
≥ 75	Week 12	11/ 14 (79%)
	Week 24	9/ 13 (69%)
	Week 36	10/ 13 (77%)
	Week 48	11/ 14 (79%)
	Week 60	8/ 13 (62%)
	Week 72	8/ 13 (62%)
	Week 84	8/ 12 (67%)
	Week 96	9/ 13 (69%)
≥ 90	Week 12	5/ 14 (36%)
	Week 24	7/ 13 (54%)
	Week 36	7/ 13 (54%)
	Week 48	7/ 14 (50%)
	Week 60	6/ 13 (46%)
	Week 72	7/ 13 (54%)
	Week 84	6/ 12 (50%)
	Week 96	7/ 13 (54%)

Abbreviations: PASI=Psoriasis Area Severity Index; QW=once weekly.
Analysis includes all subjects who received at least 1 dose of investigational product in study 20050111.
Subjects previously received up to 48 weeks of treatment with etanercept 0.8 mg/kg QW during study 20030211.

In the overall population, PASI 50, 75, and 90 responses were maintained through week 96. 89%, 61% and 30% of subjects had PASI 50, 75, and 90 responses, respectively, at week 96 (Table 11).

Table 11. PASI Response Through Week 96 - Study 20050111 (Observed cases)

		Etanercept 0.8 mg/kg QW
≥ 50	Week 12	162/181 (90%)
	Week 24	156/175 (89%)
	Week 36	155/169 (92%)
	Week 48	150/168 (89%)
	Week 60	138/157 (88%)
	Week 72	132/152 (87%)
	Week 84	127/145 (88%)
	Week 96	123/138 (89%)
≥ 75	Week 12	122/181 (67%)
	Week 24	115/175 (66%)
	Week 36	115/169 (68%)
	Week 48	113/168 (67%)
	Week 60	102/157 (65%)
	Week 72	90/152 (59%)
	Week 84	80/145 (55%)
	Week 96	84/138 (61%)
≥ 90	Week 12	64/181 (35%)
	Week 24	64/175 (37%)
	Week 36	62/169 (37%)
	Week 48	55/168 (33%)
	Week 60	54/157 (34%)
	Week 72	48/152 (32%)
	Week 84	45/145 (31%)
	Week 96	41/138 (30%)

Subjects previously received up to 48 weeks of treatment with Etanercept 0.8 mg/kg QW during Study 20030211.

PASI Score Percent Improvement

Study 20030211

Double-blind, Placebo-controlled Period

Mean percent improvement from baseline in PASI scores for subjects aged 6 to 7 years increased more over time for subjects in the etanercept group compared with those in the placebo group. The mean PASI score percent improvement from baseline at week 12 was 71% in subjects aged 6 to 7 years receiving etanercept versus 26% in subjects aged 6 to 7 years in the placebo group (Table 12).

Table 12. PASI Score Percent Improvement From Baseline During Double-blind Period of Study 20030211 (ITT Subset With Treatment Failure Imputation; Subjects 6 to 7 Years of Age)

		Placebo	Etanercept
Week 2	Mean (SE)	11.2 (6.8)	21.3 (9.2)
	SD	16.8	30.7
	Median	7.9	20.8
	Min, Max	-10.0, 36.4	-33.3, 84.1
	N	6	11
Week 4	Mean (SE)	10.8 (16.3)	42.3 (11.8)
	SD	39.8	39.1
	Median	10.4	48.0
	Min, Max	-58.1, 51.1	-50.6, 93.9
	N	6	11
Week 8	Mean (SE)	22.3 (14.4)	61.9 (9.6)
	SD	35.2	32.0
	Median	5.0	76.2
	Min, Max	-1.8, 87.4	0.0, 100.0
	N	6	11
Week 12	Mean (SE)	26.4 (14.9)	71.4 (10.1)
	SD	36.6	33.4
	Median	11.1	79.6
	Min, Max	-1.8, 92.2	0.0, 100.0
	N	6	11

Abbreviations: ITT=intent to treat; PASI=Psoriasis Area Severity Index; SD=standard deviation; SE=standard error.
Subjects who entered the escape arm were considered to be treatment failures at time of entering escape arm.
Source: 5.3.5.2, Addendum to CSR-77991, Table 5-4.

Similar improvements were observed for the overall study population: mean PASI score percent improvement from baseline at week 12 was 68% in subjects receiving etanercept versus 21% in subjects in the placebo group.

Open-label Period of Study 20030211

Mean PASI score percent improvement from baseline at week 36 was 77% in subjects aged 6 to 7 years from the original etanercept group versus 75% in subjects aged 6 to 7 years from the original placebo group (Table 13).

Table 13. PASI Score Percent Improvement From Baseline Through Week 36 of Study 20030211 (ITT Subset With Treatment Failure Imputation; Subjects 6 to 7 Years of Age)

		Placebo/ Etanercept	Etanercept/ Etanercept
Week 2 - DB[a]	Mean (SE)	11.2 (6.8)	21.3 (9.2)
	SD	16.8	30.7
	Median	7.9	20.8
	Min, Max	-10.0, 36.4	-33.3, 84.1
	N	6	11
Week 4 - DB[a]	Mean (SE)	10.8 (16.3)	42.3 (11.8)
	SD	39.8	39.1
	Median	10.4	48.0
	Min, Max	-58.1, 51.1	-50.6, 93.9
	N	6	11
Week 8 - DB[a]	Mean (SE)	30.1 (14.1)	61.1 (10.2)
	SD	34.4	33.8
	Median	23.4	76.2
	Min, Max	-1.8, 87.4	-8.9, 100.0
	N	6	11
Week 12 - DB[a]	Mean (SE)	38.0 (15.3)	77.8 (7.1)
	SD	37.5	23.7
	Median	29.8	79.6
	Min, Max	-1.8, 92.2	17.3, 100.0
	N	6	11
Week 16 - OL[b]	Mean (SE)	51.7 (16.2)	80.2 (6.1)
	SD	39.6	20.3
	Median	45.3	83.3
	Min, Max	13.7, 100.0	34.7, 100.0
	N	6	11
Week 20 - OL[b]	Mean (SE)	65.5 (11.9)	80.1 (5.9)
	SD	29.1	19.5
	Median	72.7	78.8
	Min, Max	21.2, 100.0	35.2, 100.0
	N	6	11
Week 24 - OL, IR[b]	Mean (SE)	72.7 (12.2)	82.5 (5.9)
	SD	29.9	19.7
	Median	80.9	84.9
	Min, Max	13.1, 95.0	32.7, 100.0
	N	6	11
Week 28 - OL, IR[b]	Mean (SE)	72.3 (11.3)	80.6 (6.6)
	SD	27.6	21.8
	Median	82.9	89.4
	Min, Max	16.5, 88.8	31.7, 100.0
	N	6	11
Week 32 - OL, IR[b]	Mean (SE)	74.7 (9.4)	83.0 (7.3)
	SD	23.1	24.4
	Median	81.6	92.7
	Min, Max	28.8, 91.6	27.7, 100.0
	N	6	11

		Placebo/ Etanercept	Etanercept/ Etanercept
Week 36 - OL, IR[b]	Mean (SE)	74.6 (11.7)	76.7 (9.2)
	SD	28.7	30.3
	Median	85.2	86.4
	Min, Max	17.0, 92.7	15.4, 100.0
	N	6	11

Abbreviations: DB=double blind; IR=incomplete responder; ITT=intent to treat; OL=open label; PASI= Psoriasis Area Severity Index; SD=standard deviation; SE=standard error.
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.
Source: 5.3.5.2, Addendum to CSR-77991, Table 5-5.

A comparable result was observed for the overall population: mean PASI score percent improvement from baseline at week 36 was 77% in subjects in the original etanercept group versus 76% in subjects in the original placebo group.

Study 20050111 Through Week 96

Mean percent improvement from study 20030211 baseline in PASI scores in subjects aged 6 to 7 years was maintained through 96 weeks of etanercept treatment in study 20050111. The mean PASI score percent improvement from 20030211 baseline at weeks 48 and 96 was 78% and 81%, respectively, for subjects aged 6 to 7 years (Table 14).

Table 14. PASI Score Percent Improvement for Subjects Aged 6 to 7 Years Through Week 96 of Study 20050111a (Observed Cases)

Time Point		Etanercept (N=14)
Study 20050111 Baseline	Mean (SE)	68.8 (9.2)
	SD	34.2
	Median	78.4
	Min, Max	-14.0, 100.0
	n	14
Week 12	Mean (SE)	74.1 (11.0)
	SD	41.1
	Median	88.2
	Min, Max	-33.1, 100.0
	n	14
Week 24	Mean (SE)	68.4 (13.6)
	SD	48.9
	Median	91.4
	Min, Max	-48.3, 100.0
	n	13
Week 36	Mean (SE)	76.3 (10.0)
	SD	36.1
	Median	93.2
	Min, Max	1.0, 100.0
	n	13
Week 48	Mean (SE)	78.2 (8.6)
	SD	32.1
	Median	91.3
	Min, Max	5.0, 100.0
	n	14
Week 60	Mean (SE)	76.4 (7.8)
	SD	28.0
	Median	88.2
	Min, Max	17.8, 100.0
	n	13
Week 72	Mean (SE)	65.6 (15.9)
	SD	57.2
	Median	91.6
	Min, Max	-101.5, 100.0
	n	13
Week 84	Mean (SE)	76.0 (8.7)
	SD	30.0
	Median	88.1
	Min, Max	20.3, 100.0
	n	12
Week 96	Mean (SE)	80.5 (6.5)
	SD	23.6
	Median	90.6
	Min, Max	30.5, 100.0
	n	13

Abbreviations: PASI=Psoriasis Area Severity Index; QW=once weekly; SD=standard deviation; SE=standard error.
a. Percent improvement from study 20030211 baseline.
Analysis includes all subjects who received at least 1 dose of investigational product in study 20050111.
Subjects previously received up to 48 weeks of treatment with etanercept 0.8 mg/kg QW during study 20030211.
Source: 5.3.5.2, Addendum to CSR-77991, Table 5-6.

This is comparable to the overall population: the mean PASI score percent improvement from 20030211 baseline at weeks 48 and 96 was 78% and 75%, respectively.

Static Physician Global Assessment

The sPGA was used to assess averaged overall lesions (based on induration, erythema, and scaling) of psoriasis at each study visit.

Study 20030211

Double-blind, Placebo-controlled Period

At week 12, 55% of subjects aged 6 to 7 years in the etanercept group achieved a sPGA status of clear/almost clear compared with 17% of subjects aged 6 to 7 years in the placebo group.

A comparable result was observed for the overall study population: 53% of subjects in the etanercept group achieved a sPGA status of clear/almost clear at week 12 versus 13% of subjects in the placebo group.

Open-label Period of Study 20030211

At week 36, 64% of subjects aged 6 to 7 years from the original etanercept group achieved an sPGA status of clear/almost clear compared with 67% of subjects aged 6 to 7 years from the original placebo group (Table 15).

Table 15. Clear/Almost Clear Status of sPGA Through Week 36 of Study 20030211 (ITT Subset With Treatment Failure Imputation; Subjects Aged 6 to 7 Years)

sPGA Status	Time Point	Placebo/ Etanercept (N=6) n (%)	Etanercept/ Etanercept (N=11) n (%)
Clear (0)	Week 2 - DB[a]	0/6 (0.0)	0/11 (0.0)
	Week 4 - DB[a]	0/6 (0.0)	0/11 (0.0)
	Week 8 - DB[a]	0/6 (0.0)	1/11 (9.1)
	Week 12 - DB[a]	0/6 (0.0)	2/11 (18.2)
	Week 16 - OL[b]	1/6 (16.7)	2/11 (18.2)
	Week 20 - OL[b]	1/6 (16.7)	2/11 (18.2)
	Week 24 - OL, IR[b]	0/6 (0.0)	3/11 (27.3)
	Week 28 - OL, IR[b]	0/6 (0.0)	1/11 (9.1)
	Week 32 - OL, IR[b]	0/6 (0.0)	4/11 (36.4)
	Week 36 - OL, IR[b]	0/6 (0.0)	3/11 (27.3)
Clear/Almost Clear (0,1)	Week 2 - DB[a]	0/6 (0.0)	1/11 (9.1)
	Week 4 - DB[a]	0/6 (0.0)	2/11 (18.2)
	Week 8 - DB[a]	0/6 (0.0)	4/11 (36.4)
	Week 12 - DB[a]	1/6 (16.7)	6/11 (54.5)
	Week 16 - OL[b]	2/6 (33.3)	7/11 (63.6)
	Week 20 - OL[b]	3/6 (50.0)	7/11 (63.6)
	Week 24 - OL, IR[b]	4/6 (66.7)	6/11 (54.5)
	Week 28 - OL, IR[b]	3/6 (50.0)	6/11 (54.5)
	Week 32 - OL, IR[b]	3/6 (50.0)	8/11 (72.7)
	Week 36 - OL, IR[b]	4/6 (66.7)	7/11 (63.6)

Abbreviations: DB=double blind; IR=incomplete responder; ITT=intent to treat; OL=open label; SD=standard deviation; SE=standard error; sPGA=static Physician Global Assessment of psoriasis.

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.

Source: 5.3.5.2, Addendum to CSR-77991, Table 5-8.

A comparable result was observed for the overall study population: 53% of subjects from the original etanercept group achieved a sPGA status of clear/almost clear at week 36 versus 56% of subjects from the original placebo group.

Study 20050111 Through Week 96

In the overall population, the majority of subjects had a sPGA of 1 (36%) or 2 (39%) at Study 20050111 baseline indicating minimal to mild induration, erythema, and scaling; these assessment scores were maintained through week 96. 47% of subjects in observed cases maintained the clear/almost clear status of the sPGA through week 96.

The proportion of subjects aged 6 to 7 years who had achieved a sPGA status of clear/almost clear during the double-blind, placebo-controlled and open-label periods of study 20030211 was maintained through 96 weeks of etanercept treatment in study 20050111. At weeks 48 and 96, 43% and 54% of subjects aged 6 to 7 years, respectively, had a sPGA status of clear/almost clear (Table 16).

Table 16. Static Physician Global Assessment of Psoriasis Clear and Clear/Almost Clear Status Response for Subjects Aged 6 to 7 Years Through Week 96 of Study 20050111 (Observed Cases)

sPGA Status	Time Point	Etanercept (N=14)
Clear (0)	Week 12	2/ 13 (15%)
	Week 24	4/ 13 (31%)
	Week 36	4/ 13 (31%)
	Week 48	3/ 14 (21%)
	Week 60	3/ 13 (23%)
	Week 72	3/ 13 (23%)
	Week 84	4/ 12 (33%)
	Week 96	3/ 13 (23%)
Clear/Almost Clear (0,1)	Week 12	7/ 13 (54%)
	Week 24	6/ 13 (46%)
	Week 36	9/ 13 (69%)
	Week 48	6/ 14 (43%)
	Week 60	6/ 13 (46%)
	Week 72	7/ 13 (54%)
	Week 84	7/ 12 (58%)
	Week 96	7/ 13 (54%)

Abbreviations: sPGA=static Physician Global Assessment of psoriasis; QW=once weekly.
Analysis includes all subjects who received at least 1 dose of investigational product in study 20050111.
Subjects previously received up to 48 weeks of treatment with etanercept 0.8 mg/kg QW during study 20030211.
Source: 5.3.5.2, Addendum to CSR-77991, Table 5-9.

A comparable result was observed for the overall study population: 49% and 47% of subjects had a sPGA status of clear/almost clear at weeks 48 and 96, respectively.

Children's Dermatology Life Quality Index

Study 20030211

Double-blind, Placebo-controlled Period

For the 6-7 year old subgroup at week 12, the mean percentage improvement from baseline in CDLQI was 64.0% and 52.3% for the etanercept and placebo groups respectively.

A comparable result was observed for the etanercept group of the overall study population at week 12 (mean percentage improvement from baseline in CDLQI was 52.3%); however, the mean percentage improvement in CDLQI at week 12 for the placebo group of the overall study population was 17.5%, much lower than that for subjects aged 6 to 7 years in the placebo group.

Open-label Period of Study 20030211

The mean percentage improvement from baseline in CDLQI was maintained during the open-label period for subjects aged 6 to 7 years in both the original etanercept group and the original placebo group. A comparable result was observed for the overall study population: the mean percentage improvement from baseline in CDLQI was 63.3% at week 36 for the original etanercept group and 59.1% for the original placebo group.

Study 20050111 Through Week 96

Mean percent improvements from study 20030211 baseline in CDLQI in subjects aged 6 to 7 years during the double-blind, placebo-controlled and open-label periods of study 20030211 were well maintained through 96 weeks of etanercept treatment in study 20050111. At week 96, the mean percentage improvement from baseline in CDLQI was 67% for subjects aged 6 to 7 years (Table 17).

Table 17. CDLQI Total Score Percent Improvement From Study 20030211 Baseline: Response for Subjects Aged 6 to 7 Years Through Week 96 of Study 20050111 (Observed Cases)

Time Point		Etanercept (N=14)
Study 20050111 Baseline	Mean (SE)	69.6 (13.0)
	SD	46.7
	Median	93.3
	Min, Max	-40.0, 100.0
	n	13
Week 24	Mean (SE)	62.2 (16.2)
	SD	58.5
	Median	85.7
	Min, Max	-100.0, 100.0
	n	13
Week 48	Mean (SE)	72.7 (13.9)
	SD	50.2
	Median	90.0
	Min, Max	-80.0, 100.0
	n	13
Week 72	Mean (SE)	84.6 (7.3)
	SD	24.3
	Median	90.0
	Min, Max	13.3, 100.0
	n	11
Week 96	Mean (SE)	66.8 (14.3)
	SD	49.5
	Median	88.3
	Min, Max	-60.0, 100.0
	n	12

Abbreviations: CDLQI=Children's Dermatology Life Quality Index; QW=once weekly; SD=standard deviation; SE=standard error.
Analysis includes all subjects who received at least 1 dose of investigational product in study 20050111.
Subjects previously received up to 48 weeks of treatment with etanercept 0.8 mg/kg QW during study 20030211.
Source: 5.3.5.2, Addendum to CSR-77991, Table 5-12.

A comparable result was observed for the overall study population: the mean percentage improvement from baseline in CDLQI was 61% at week 96.

Summary of key efficacy endpoints (Subjects Aged 6 to 7 Years)

The summary of Key Efficacy Endpoints for Subjects Aged 6 to 7 Years and the Overall Study Population in Studies 20030211 and 20050111 is shown in table 18.

Table 18. Summary of Key Efficacy Endpoints for Subjects Aged 6 to 7 Years and the Overall Study Population in Studies 20030211 and 20050111 (Subjects Who Received at Least 1 Dose of Etanercept)

Efficacy Endpoint Time Point (Study)	Subjects Aged 6 to 7 Years	Overall Population
PASI Response ≥ 75, n/N (%)		
DB – Wk 12 (20030211)	8/11 (73)	60/106 (57)
OL – Wk 48 (20050111)	11/14 (79)	113/168 (67)
OL – Wk 96 (20050111)	9/13 (69)	84/138 (61)
PASI Score % Improvement, Mean (SE)		
DB – Wk 12 (20030211)	71.4 (10.1)	67.5 (3.0)
OL – Wk 48 (20050111)	78.2 (8.6)	77.5 (1.6)
OL – Wk 96 (20050111)	80.5 (6.5)	75.4 (2.1)
PGA Clear/Almost Clear, n/N (%)		
DB – Wk 12 (20030211)	6/11 (55)	56/106 (53)
OL – Wk 48 (20050111)	6/14 (43)	81/166 (49)
OL – Wk 96 (20050111)	7/13 (54)	66/139 (47)
CDLQI % Improvement, Mean (SE)		
DB – Wk 12 (20030211)	64.0 (13.4)	52.3 (6.1)
OL – Wk 48 (20050111)	72.7 (13.9)	59.2 (5.4)
OL – Wk 96 (20050111)	66.8 (14.3)	61.1 (5.9)

Abbreviations: CDLQI=Children's Dermatology Life Quality Index; DB=double blind; OL=open label; PASI=Psoriasis Area Severity Index; PGA=Physician Global Assessment of psoriasis; SE=standard error; Wk=week.

Discussion on clinical efficacy

The efficacy data from the randomised, placebo-controlled study 20030211 has previously been assessed and was now re-analysed with particular focus on the data in children aged 6-7 years. Additional 96-week data was provided from the extension study 20050111. The main objective of

study 20050111 was describing the safety profile of etanercept in the paediatric population with moderate to severe plaque psoriasis. The information collected on efficacy (secondary endpoint), growth and development can however be considered supportive. With regard to the efficacy endpoints these were considered relevant.

The number of subjects in the subgroup aged 6 to 7 years old enrolled in the study 20030211 (n=17) was small. Consequently, the sample size in study 2005111 is also very small (n=14); this is a limitation to the study. Due to the small sample size, only descriptive statistics analyses were performed. No inferential statistics or analyses adjusting for covariates were done.

The percentage of subjects who discontinued the study 20030211 in the subgroup aged 6-7 years old (21%) was lower than those who discontinued in the overall population (30%). The main reason for discontinuation was non-compliance. One patient discontinued due to "other" reasons; no further details are provided to describe this item. No subjects discontinued due to lack of efficacy or due to AE. Although the sample size is limited, the absence of discontinuations due to either efficacy or safety reasons supports the extrapolation of the efficacy and safety profile from the authorized population to the 6 to 7 years old one.

The PASI 75 responses at week 12 of study 20030211 for etanercept- and placebo-treated subjects aged 6 to 7 years (73% and 17%, respectively) were slightly higher than those achieved by the overall study population at week 12 (57% and 11%, respectively); however, it is difficult to determine if this difference is clinically relevant because of the small sample size of subjects aged 6 to 7 years. A similar proportion of etanercept-treated subjects in the subgroup achieved an sPGA status of clear/almost clear at week 12 (55%) as did subjects in the overall population (53%). The responses at week 36 of study 20030211 for subjects originally assigned to the etanercept group were comparable between the subgroup and the overall population: PASI 75 response of 73% for the subgroup versus 68% for the overall population and an sPGA status of clear/almost clear achieved by 64% in the subgroup versus 53% in the overall population.

As was observed for the overall population in study 20050111, the efficacy responses were well maintained in the subjects aged 6 to 7 years who received etanercept through 96 weeks in the extension study. The PASI 75 responses at weeks 48 and 96 of study 20050111 for subjects aged 6 to 7 years (79% and 69%, respectively) were comparable to those achieved by the overall study population at weeks 48 and 96 (67% and 61%, respectively).

During the withdrawal period of study 20030211, more subjects in the overall population who were randomly reassigned to the placebo group had disease relapse (loss of PASI 75 response) compared with subjects who were randomly reassigned to etanercept 0.8 mg/kg QW. However, after entering the retreatment period and receiving open-label etanercept, this placebo group again showed improvement in their PASI responses. No subjects had a rebound of their disease (disease rebound was defined as a post-baseline PASI score that was >125% of baseline PASI within 3 months of treatment discontinuation). Thus, the data suggest that disruption of etanercept therapy does not lead to a rebound of disease and the ability to respond to etanercept remains intact even after an interruption in therapy. Withdrawal and retreatment (i.e., disease relapse and rebound) were not formally analyzed for the subgroup of subjects aged 6 to 7 years. Only 7 subjects aged 6 to 7 years entered the withdrawal-retreatment period, 4 subjects in the placebo group and 3 subjects in the etanercept group. One (1) subject in the placebo group experienced disease relapse at the last visit (week 48). Two (2) subjects in the etanercept group experienced disease relapse at week 44. None of these subjects entered the retreatment period.

Conclusion on clinical efficacy

In the overall population of study 20030211, etanercept provided statistically significant improvements to paediatric subjects with moderate to severe plaque psoriasis. Likewise, the efficacy results observed in the subgroup of subjects aged 6 to 7 years were similar to those observed for the overall study population. In study 20050111 the efficacy responses were maintained in the subjects aged 6 to 7 years who received etanercept through 96 weeks in the extension study. The results were comparable to those seen for the overall population.

When reviewing the data from study 20030211 submitted for the original approval for paediatric plaque psoriasis, the available data at that time were considered not sufficient for children below the age of 8 years. These data have now been further substantiated through relevant long-term data, which are considered to provide sufficient support to conclude on the demonstration of clinical efficacy in children 6-7 years. The CHMP acknowledged that the study has limitations in that it relies in terms of numbers on the patients included in study 20030211, however the CHMP considered that the overall dataset is now considered sufficient given that the efficacy results of the subgroup aged 6 to 7 years was consistent with the overall population of study 20050111, in whom efficacy has been demonstrated. There are also no indications to suspect that the efficacy profile should differ in those aged 8 years and above compared with those aged 6-7 years. In this 6-7 year old group the availability of an effective treatment which is restricted to severe disease, under specialist supervision for those who have failed or are intolerant to systemic and phototherapies, will be of benefit to these children. These restrictions will ensure that treatment is aimed only at patients who have no other therapeutic options.

1.2.5. Clinical safety

Patient exposure

Overall, 210 subjects received at least 1 dose of etanercept during the double-blind and open-label periods (through week 36) of study 20030211, and 181 of these subjects received at least 1 dose of etanercept through week 96 of the extension study 20050111, representing 474.2 subject-years of exposure to etanercept in the 2 studies. For the subgroup of subjects aged 6 to 7 years, 17 subjects received at least 1 dose of etanercept during the double-blind and open-label periods (through week 36) of study 20030211, and 14 of these subjects received at least 1 dose of etanercept through week 96 of the extension study 20050111, representing 39.2 subject-years of exposure to etanercept in the 2 studies.

Adverse events

- **Adverse Events:**

Study 20030211:

The exposure-adjusted rate of any AEs in subjects aged 6 to 7 years through week 36 of study 20030211 was 766.46 events per 100 subject-years compared with 584.48 events per 100 subject-years in the overall study population. The rate of infections was comparable between the subgroup and overall study population (275.14 events per 100 subject-years versus 238.18 events per 100 subject-years). Serious infections occurred at a rate of 9.83 events per 100 subjects-years in subjects aged 6 to 7 years compared to 2.53 events per 100 subject-years in the overall study population. No subjects aged 6 to 7 withdrew from the study because of a non-infectious AE, whereas the exposure-adjusted rate of non-infectious AEs leading to withdrawal in the overall population was 2.53 events per 100 subject-years. The exposure-adjusted rate of infections leading to study withdrawal was 9.82 and 1.69 events per 100 subject-years in subjects aged 6 to 7 years and the overall population, respectively. No

ISRs occurred in subjects aged 6 to 7 years through week 36 of study 20030211, whereas the exposure-adjusted rate of ISRs in the overall population was 49.83 events per 100 subject-years.

Study 20050111:

The exposure-adjusted rate of AEs in subjects aged 6 to 7 years through week 96 of study 20050111 was 179.4 events per 100 subject-years compared with 185.8 events per 100 subject-years in the overall study population. The rate of infections was slightly lower in subjects aged 6 to 7 years (58.7 events per 100 subject-years) compared with the overall study population (84.9 events per 100 subject-years). No SAEs occurred in subjects aged 6 to 7 years through week 96 of study 20050111, whereas the exposure-adjusted rate of non-infectious SAEs in the overall population was 1.4 events per 100 subject-years.

Noninfectious Adverse Events

Study 20030211

Double-blind, Placebo-controlled Period

During the double-blind period of study 20030211, noninfectious AEs were reported in 83% and 46% of subjects aged 6 to 7 years in the placebo and etanercept groups, respectively. All of the noninfectious AEs were reported in 1 subject each.

In the overall population, noninfectious AEs were reported in 43.8% and 39.6% of subjects in the placebo (n=105) and etanercept (n=106) groups, respectively, during the double-blind period. The most common noninfectious AEs reported in subjects receiving etanercept were headache (13.2%), and dizziness (4.7%). In subjects receiving placebo, the most common noninfectious AEs reported were headache (12.4%) and pharyngolaryngeal pain (4.8%).

Open-label Period of Study 20030211

There were 50 noninfectious AEs reported in subjects aged 6 to 7 years during treatment with etanercept through week 36 of study 20030211 (491.32 events per 100 subject-years).

The majority of the noninfectious AEs were reported in 1 subject each, with the exception of skin fissures and contusion which were each reported at an exposure adjusted rate of 29.5 events per 100 subject-years; and skin hemorrhage, excoriation, arthralgia, pyrexia, and headache which were each reported at an exposure-adjusted rate of 19.7 events per 100 subject-years.

In the overall population, 351 noninfectious AEs were reported during treatment with etanercept through week 36 (296.46 events per 100 subject-years). The most common noninfectious AEs reported were headache, vomiting, arthralgia, nasal congestion, and pharyngolaryngeal pain (36.32, 10.98, 9.29, 8.45, and 8.45 events per 100 subject-years, respectively).

Study 20050111 Through Week 96

There were 33 noninfectious AEs reported in 9 subjects aged 6 to 7 years in study 20050111 (113.9 events per 100 subject-years). The majority of the noninfectious AEs were reported in 1 subject each, except for excoriation which was reported at an exposure adjusted rate of 13.8 events per 100 subject-years, pyrexia which was reported at an exposure-adjusted rate of 10.4 events per 100 subject-years, and viral gastroenteritis which was reported at an exposure-adjusted rate of 6.9 events per 100 subject-years.

In the overall population, 349 noninfectious AEs were reported in 111 subjects (98.1 events per 100 subject-years). The most frequently reported noninfectious AEs were headache, skin papilloma, and cough (7.9, 4.8, 3.1 events per 100 subject-years, respectively).

Infections

Study 20030211

Double-blind, Placebo-controlled Period

During the double-blind period of study 20030211, infections were reported in 17% and 36% of subjects aged 6 to 7 years in the placebo and etanercept groups, respectively. The majority of the infections were reported in 1 subject each, except for gastroenteritis and upper respiratory tract infection which were reported in 2 and 3 subjects each, respectively.

In the overall population, infections were reported in 31.4% and 47.2% of subjects in the placebo and etanercept groups, respectively. The most common infections in subjects receiving etanercept were upper respiratory tract infection (17.0%), influenza (7.5%), nasopharyngitis (7.5%), and gastroenteritis (4.7%). In subjects receiving placebo, the most common infections were upper respiratory tract infection (11.4%), nasopharyngitis (8.6%), pharyngitis (3.8%), and gastroenteritis viral (2.9%).

Open-label Period of Study 20030211

There were 28 infections reported in subjects aged 6 to 7 years during treatment with etanercept through week 36 of study 20030211 (275.14 events per 100 subject-years). The most common infections were upper respiratory tract infection and nasopharyngitis which were reported at exposure-adjusted rates of 59.0 and 49.1 events per 100 subject-years, respectively; and pharyngitis streptococcal and gastroenteritis which were each reported at an exposure-adjusted rate of 29.5 events per 100 subject-years.

In the overall population, 282 infections were reported in subject during treatment with etanercept through week 36 (238.18 events per 100 subject-years. The most common infections were upper respiratory tract infection, nasopharyngitis, influenza, pharyngitis, streptococcal pharyngitis, and viral upper respiratory infection (59.97, 33.79, 16.05, 15.20, 8.45, and 8.45 events per 100 subject-years, respectively).

Study 20050111 Through Week 96

Seventeen (17) infections were reported in 6 subjects aged 6 to 7 years in study 20050111 (58.7 events per 100 subject-years). The majority of the infections were reported in 1 subject each, except for upper respiratory tract infection, pharyngitis streptococcal, and bronchitis which were reported at exposure-adjusted rates of 17.3, 10.4, and 6.9 events per 100 subject-years respectively.

In the overall population, 302 infections were reported in 119 subjects (98.1 events per 100 subject-years). The most frequently reported infections were upper respiratory tract infection, nasopharyngitis, pharyngitis streptococcal, and sinusitis (19.1, 12.9, 7.3, and 6.5 events/100 subject-years, respectively).

Injection Site Reactions

Study 20030211

Double-blind, Placebo-controlled Period

No subjects aged 6 to 7 years experienced injection site reactions (ISRs) during study 20030211. In the overall population, ISRs were reported in 4.8% and 6.6% of subjects in the placebo and etanercept groups, respectively, during the double-blind period.

Open-label Period of Study 20030211

No subjects aged 6 to 7 years experienced ISRs during study 20030211. In the overall population, 59 ISRs were reported in 26 subjects during treatment with etanercept through week 36 (49.83 events per 100 subject-years).

Study 20050111 Through Week 96

Two (2, 14.3%) of the 14 subjects aged 6 to 7 years experienced ISRs through week 96 of study 20050111 (6.9 events per 100 subject-years). In the overall population, 10 ISRs were reported in 10 (5.5%) of the 181 subjects through week 96.

Serious adverse events and deaths

Deaths

No deaths occurred in subjects of any age while participating in either study 20030211 or study 20050111.

Serious Adverse Events

Noninfectious Serious Adverse Events

Study 20030211

Double-blind, Placebo-controlled Period

Consistent with the overall population, no noninfectious SAEs were reported in subjects aged 6 to 7 years during the double-blind period of study 20030211.

Open-label Period

No noninfectious SAEs were reported in subjects aged 6 to 7 years during the open-label period (through week 36) of study 20030211. In the overall population, a 14-year-old female subject experienced a serious noninfectious AE (benign ovarian mass; 0.84 events/100 subject-years).

Study 20050111 Through Week 96

No noninfectious SAEs were reported in subjects aged 6 to 7 years through week 96 of study 20050111. In the overall population, 3 subjects experienced 5 noninfectious SAEs (1.4 events per 100 subject-years): One subject developed anxiety and 1 subject developed a post-operative intestinal obstruction. A third subject developed dehydration and abdominal pain, was hospitalized and subsequently underwent an abortion. Of the 5 serious adverse events none was related to investigational product. There were no opportunistic infections, no malignancies and no deaths.

Serious Infections

Study 20030211

Double-blind, Placebo-controlled Period

Consistent with the overall population, no serious infections were reported in subjects aged 6 to 7 years during the double-blind period of study 20030211.

Open-label Period of Study 20030211

One (1) serious infection was reported in a subject aged 6 to 7 years during the open-label period of study 20030211. A 7-year-old female subject experienced lobar pneumonia during the open-label period and was withdrawn from the study.

In the overall population, an 8-year-old female subject experienced a serious infection of gastroenteritis with dehydration.

Study 20050111 Through Week 96

Consistent with the overall population, no serious infections were reported in subjects aged 6 to 7 years through week 96 of study 20050111.

Discontinuation due to AES

Study 20030211

Double-blind, Placebo-controlled Period

No subjects aged 6 to 7 years were withdrawn during the double-blind period of study 20030211 because of a noninfectious AE. In the overall population, a 9-year-old male subject was withdrawn from the overall population because of a noninfectious AE of bronchospasm. Consistent with the overall population, no subjects aged 6 to 7 years were withdrawn during the double-blind period of study 20030211 because of an infection.

Open-label Period of Study 20030211

No subjects aged 6 to 7 years were withdrawn during the open-label period of study 20030211 because of noninfectious AEs. Three (3) subjects in the overall population were withdrawn because of noninfectious AEs of psoriasis (male, 4 years of age), dermatis atopic (female, 4 years of age), and muscle cramps (female, 16 years of age). None of these events were serious.

Two (2) subjects were withdrawn during the open-label period of study 20030211 because of infections. A 7-year-old female subject included in the subgroup analysis was withdrawn because of a serious infection of lobar pneumonia. In addition, a male subject who was 10 years old and therefore not included in the subgroup analysis of 6- to 7-year-olds withdrew from the study because of a skin infection; the event was not considered to be serious.

Study 20050111 Through Week 96

No subjects aged 6 to 7 years were withdrawn from study 20050111 because of an AE. Two (2) subjects in the overall population withdrew because of an AE. A 9-year-old female subject withdrew from the study because of a noninfectious event of Crohn's disease; the event was not considered serious. A 9-year old male subject withdrew from the study because of a nonserious infection of sinusitis.

Adverse Events of Special Interest

Study 20030211

No cases of lymphoma, malignancy, demyelinating disease, blood dyscrasias, opportunistic infections, or tuberculosis were reported in subjects aged 6 to 7 years during study 20030211.

Study 20050111

No cases of lymphoma, malignancy, demyelinating disease, blood dyscrasias, opportunistic infections, or tuberculosis were reported in subjects aged 6 to 7 years through week 96 of study 20050111.

Laboratory findings

Grades 3 and 4 Laboratory Toxicities

Study 20030211

None of the 17 subjects aged 6 to 7 years experienced grade 3 or 4 laboratory toxicity through week 36 of study 20030211. In the overall population, no grade 4 laboratory abnormalities were reported. There were 3 transient grade 3 elevated hemoglobin concentrations: 1 etanercept subject at baseline and 2 placebo subjects during the open-label period. These elevated hemoglobin concentrations occurred in adolescent boys (all were 15 years old) and the values were within the normal range for adult men. None of the laboratory abnormalities were associated with any clinical reports of AEs.

Study 20050111 Through Week 96

No grade 4 laboratory abnormalities were reported in subjects aged 6 to 7 years during the first 96 weeks of study 20050111.

Samples were collected at screening, baseline, and every 12 weeks for clinical laboratory analyses. Most laboratory abnormalities were mild to moderate (CTC grade 1 or 2), and no CTC grade 4 laboratory abnormalities were reported during the first 96 weeks of the study. During the first 96 weeks of the study there were 6 laboratory abnormalities considered CTC grade 3: hemoglobin (1 increase, 1 decrease), creatinine (increase), platelets (decrease), alanine amino transferase (increase), and white blood cell count (increase). All laboratory abnormalities occurred in only 1 subject each and in all but 1 case laboratory values returned to normal levels (hemoglobin increase occurred at week 96). None of the laboratory abnormalities were associated with any clinical reports of serious adverse events.

One (1) of the 14 subjects aged 6 to 7 years had a grade 3 increase in alanine amino transferase (ALT) at week 24; the subject's ALT values returned to normal for the remaining study visits.

In the overall population, there were 6 laboratory abnormalities considered grade 3: hemoglobin (1 increase, 1 decrease), creatinine (increase), platelets (decrease), alanine amino transferase (increase), and white blood cell count (increase). All laboratory abnormalities occurred in only 1 subject each, and in all but 1 case, the laboratory values returned to normal levels (the hemoglobin increase occurred at week 96). None of the laboratory abnormalities were associated with any clinical reports of AEs.

Ten subjects (5.5%) had positive ANA at baseline of Study 20050111; 9 of these subjects also had positive ANA during Study 20030211. Three subjects had positive ANA at week 96 of Study 20050111; none of these 3 subjects had positive ANA during Study 20030211.

Antibody Data and Their Relationship to Safety Data

Study 20030211:

Serum samples to test for anti-etanercept antibodies were obtained from subjects at baseline, at 12 weeks post-dose, and at week 48 or the early termination visit. Of the 211 subjects who were randomized in study 20030211, 208 had predose and postdose serum samples available for testing for antibodies to etanercept and 20 of these (9.6%), had samples that were positive for anti-etanercept antibodies. All samples were negative for neutralizing anti-etanercept antibodies. One (1) of the 17

subjects aged 6 to 7 years in study 20030211 tested positive for anti-etanercept antibodies at week 12 and was then negative at week 48.

Study 20050111:

Per the protocol for study 20050111, anti-etanercept antibody formation was not analyzed for the 96-week interim analysis of study 20050111, and all serum samples collected at weeks 48, 96, 144, 168, and 264 will be analyzed for anti-etanercept antibodies at the end of the study.

Safety in special populations

- Measures of Growth

Growth data were collected throughout studies 20030211 and 20050111. Mean percentile and mean percentile change from baseline in height, weight, and body mass index (BMI) were assessed for the overall population as well as for the subpopulation of subjects aged 6 to 7 years. Post hoc analyses using standard z-score calculations were conducted for height, weight, and body mass index (BMI) for subjects aged 6 to 7 as compared to the general pediatric population. z-Scores were calculated based on height-for-age, weight-for-age, and BMI-for-age charts provided by the United States Centers for Disease Control and Prevention website for children from birth to 240 months.

Study 20030211 Through Week 36

The z-scores for height were relatively consistent over time for subjects aged 6 to 7 years in study 20030211. Specifically, there was no evidence in a decline in growth velocity in height over time. The z-scores for weight and for BMI were relatively consistent over time for subjects aged 6 to 7 years.

Study 20050111 Through Week 96

The z-scores for height were relatively consistent over time for subjects aged 6 to 7 years in study 20050111. Specifically, there was no evidence in a decline in growth velocity in height over time. The z-scores for weight were relatively consistent over time for subjects aged 6 to 7 years. The z-scores for BMI decreased after baseline for subjects aged 6 to 7 years and then remained consistent throughout the study.

Post marketing experience

Post-marketing Experience in Etanercept Patients 8 Years of Age or Under

A review of events that were reported regarding children aged 1 to 8 years who received etanercept (any indication) revealed that the events were very similar to those reported in all paediatric users. Accidental overdose was reported more frequently in children below the age of 4 years. In children 6 to 8 years of age, there was 1 report of accidental overdose. Among spontaneous, medically confirmed reports regarding patients 8 years of age and under who received etanercept for any indication, there were 7 reports of deaths and 2 of malignancies. The malignancies included 2 reports of acute lymphocytic leukaemia, which occurred in etanercept patients who were 3 and 7 years of age.

Through 02 February 2010, there were 181 spontaneous, medically confirmed events (in 69 cases) reported in patients under the age of 18 (range, 6 to 17 years; mean age, 14 years; median age, 14 years) who received etanercept for the treatment of psoriasis. The reported events were similar to those received for the overall etanercept population. The most frequently reported serious events were herpes zoster and viral infection (3 each). The most frequently reported non-serious events were psoriasis, injection site pain, condition aggravated and drug ineffective. There were no reported deaths or malignancies among the paediatric psoriasis patients. Of the events reported in paediatric psoriasis patients, 4 (1 serious and 3 non-serious) occurred in children age 8 or below. The serious report

described an 8-year-old female who received etanercept for the treatment of psoriasis and psoriatic arthropathy. The patient had good response for the arthritic symptoms. Approximately three to four months later, the patient began to have pins and needles sensation of the left thigh initially that progressed to both thighs and then involved the knees to the ankles. The patient experienced fever with one episode of needle-like leg pain. The patient saw a paediatric neurologist. Results of a neurology evaluation and nerve conduction studies were normal. The impression was "neuropathic pain and dysesthesia, most likely due to neurotoxins." Etanercept therapy was discontinued and the patient was treated with a trial of tocopherol and gabapentin. At the time of the report, the patient has not recovered from the dysaesthesia or neuralgia. In addition, she experienced an injection site reaction.

The non-serious reports included a report of "Drug ineffective" in a 6-year-old, "Drug ineffective and Kidney infection" in a 7-year-old, and "Atopic Dermatitis" in a 7-year-old.

Literature Reports of Etanercept Use in Children 8 Years of Age or Under

Etanercept has been approved for chronic severe plaque psoriasis in children and adolescents from the age of 8 years in the EU since December 2009. The use in younger children with psoriasis has been documented in the safety database and in published literature. Medical literature was searched for any publications that described use of etanercept for the indication of psoriasis in children under 8 years of age. Besides the publication describing the phase 3 placebo-controlled study to determine safety and efficacy in paediatric subjects, which included children and adolescents from age 4 to 17 years, there were case reports of efficacy and good tolerability in a 22-month-old with suberythrodermic, recalcitrant psoriasis, in a 4-year-old with generalized pustular psoriasis who had a flare after 1-year of infliximab therapy, in a 6-year-old who experienced total remission of psoriasis, and in a 7-year-old with severe, recalcitrant psoriasis. One (1) publication described use of etanercept in a 3-year-old with severe generalized psoriasis. After 4 weeks there was improvement; however, after 16 weeks, the skin symptoms increased again.

Discussion on clinical safety

Data from a subgroup analysis of patients aged 6 to 7 years from studies 20030211 and 20050111 was provided.

The exposure-adjusted rate of infections was lower in subjects aged 6 to 7 years (58.7 events per 100 subject-years) compared with the overall study population (84.9 events per 100 subject-years).

No SAEs occurred in subjects aged 6 to 7 years through week 96 of study 20050111, whereas the exposure-adjusted rate of non-infectious SAEs in the overall population was 1.4 events per 100 subject-years.

No new safety signal emerged from the open label study up to 96 weeks. Specifically there were no additional safety concerns in the 6-7 year old group. There were no serious infections from week 48-96 in the whole population.

The exposure-adjusted rate for any AEs and serious infections were higher in the 6 to 7 year old subgroup. However the difference in rates for AEs in the 6-7 year old group compared with the overall population was small and for serious infection was as a result of one subject. The finding that through week 96 the AE rates and SAE rates were lower in the 6-7 year group compared with the overall population is consistent with the position that there are no major safety signals that are apparent between the 6-7 year group and the overall paediatric population.

No cases of lymphoma, tuberculosis, malignancy, or death were reported in the subjects aged 6 to 7 years or in the overall population. There were no deaths in the whole study population.

Regarding laboratory findings, no special concerns have been identified. No data from antibodies has been submitted by the MAH. In view of the maintenance of efficacy over 96 weeks and the lack of high rates of injection site reactions, these results are not considered necessary for this application. It is also of note that no neutralising antibodies were detected in study 20030211.

Data from discontinuations show a higher rate of withdrawals in the overall population. No subjects aged 6 to 7 years discontinued from study 20050111 because of an AE.

In the overall population, data from measures of growth appears to show the null effect of etanercept on the children's growth development. The same trend is observed in the subjects aged 6 to 7 years, although no conclusive data can be obtained because of the number of subjects analyzed.

Since there are limited data available about the long-term effects of etanercept in paediatric psoriasis, the MAH was requested further to the approval of the original paediatric psoriasis variation to conduct a registry of paediatric psoriasis including patients from the European Union. As detailed in the RMP, this product registry is used for a multicenter, long-term, prospective, observational, cohort study conducted to evaluate the long term safety and effectiveness of etanercept prescribed by dermatologists to children for the treatment of plaque psoriasis (PURPOSE STUDY). The objectives of this registry are to describe the risk of serious and pre-specified opportunistic infections, the long term risk of incident malignancy and to identify any new, serious potentially unrecognized ADRs in paediatric plaque psoriasis patients who received etanercept. Although the primary focus of this registry is safety, in addition, the study will assess effectiveness by describing patterns of treatment with etanercept including premature discontinuation of etanercept and subsequent treatment with systemic therapies (including re-treatment with etanercept). The total duration of the registry is approximately 9 years, including 4 years for patient enrolment and 5 additional years to complete follow up on all enrolled patients. The registry will recruit 100 to 200 patients from 11 EU countries. The inclusion criteria for this registry is age ≤ 17 years old at time of enrolment, but there is no lower age limit. An update on the progress of the PURPOSE study was presented in the most recent Enbrel PSUR. The recruitment of registry physicians and sites started on 29 September 2009. The registry targets recruitment of 100 to 200 patients. The study is scheduled for completion in 2018 and enrolment of the first and only study patient occurred in November 2010.

The CHMP is of the opinion that the collection of data from this study is expected to address the risks of immunosuppressive adverse events (serious and pre specified opportunistic infections and malignancy) specifically in paediatric psoriasis patients.

Conclusions on the clinical safety

Overall, the safety results observed in the subgroup of subjects aged 6 to 7 years receiving etanercept were generally similar to those observed for the overall study population during the double-blind, placebo-controlled and open-label periods of study 20030211 and the 96-week extension study 20050111. Although these results are limited due to the small sample size of subjects in the 6 to 7 years old subgroup, there no any major difference from the overall population.

In addition, the PURPOSE study described in the risk management plan is appropriate to generate further data which will confirm the safety profile.

In conclusion, the safety profile described in this study does not show any special safety concerns within the well described safety profile of Enbrel.

1.2.6. Risk Management Plan

The MAH submitted a risk management plan, which included a risk minimisation plan.

Table 19 Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)						
Important Identified Risks - All Indications							
Malignancy	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA[a]	JIA	AS	PsA	PS	Ped PS
	BSRBR	√		√	√		
	RABBIT	√					
	ARTIS	√	√	√	√		
	ESC questionnaire	√	√	√	√	√	√
	BSPAR		√				
	German JIA registry		√				
	LTE 20040210					√	
	BADBIR					√	
	LTE 20050111						√
	0881X1-4654 (PURPOSE)						√
	B1801023		√				
	0881A1-3338-WW		√				
							SPC section 4.4 Special warnings and precautions SPC section 4.8 Undesirable effects

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)						
Important Identified Risks - All Indications (cont'd)							
Serious Infection	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	BSRBR	√		√	√		
	RABBIT	√					
	ARTIS	√	√	√	√		
	BSPAR		√				
	German JIA Registry		√				
	LTE 20040210					√	
	BADBIR					√	
	LTE 20050111						√
	0881X1-4654 (PURPOSE)						√
	0881A1-3338-WW		√				
	B1801023		√				
							SPC section 4.3 Contraindications SPC section 4.4 Special warnings and precautions SPC section 4.8 Undesirable effects Patient alert card
Lupus-like reactions	Routine PV						

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)						
	Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	LTE 20040210					√	
	LTE 20050111						√
	0881A1-3338-WW		√				
							SPC section 4.4 Special warnings and precautions SPC section 4.8 Undesirable effects
Sarcoid/granuloma	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	LTE 20040210					√	
	LTE 20050111						√
	B1801023		√				
	0881A1-3338-WW		√				
							SPC section 4.8 Undesirable effects
Important Identified Risks - All Indications (cont'd)							
Central demyelinating disorders	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	BSRBR	√		√	√		
	RABBIT	√					
	ARTIS	√	√	√	√		
	ESC questionnaire	√	√	√	√	√	√
	0881A1-3338-WW		√				
	B1801023		√				
	BSPAR		√				
	German JIA registry		√				
	LTE 20040210					√	
	BADBIR					√	
	LTE 20050111						√
							SPC section 4.4 Special warnings and precautions SPC section 4.8 Undesirable effects
Peripheral demyelinating events (CIDP and GBS)	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	LTE 20040210					√	
	LTE 20050111						√
	B1801023		√				
	0881A1-3338-WW		√				
							SPC section 4.4 Special warnings and precautions SPC section 4.8 Undesirable effects

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)						
	ESC questionnaire	√	√	√	√	√	√
	RABBIT	√					
Important Identified Risks - All Indications (cont'd)							
Injection site reactions	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	LTE 20040210					√	
	LTE 20050111						√
	0881A1-3338-WW		√				
	B1801023		√				
							SPC section 4.8 Undesirable effects
Allergic reactions	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	LTE 20040210					√	
	LTE 20050111						√
	0881A1-3338-WW		√				
	B1801023		√				
							SPC section 4.3 Contraindications
							SPC section 4.4 Special warnings and precautions
							SPC section 4.8 Undesirable effects
							SPC section 4.8 Undesirable effects
Aplastic anemia and pancytopenia	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	BSRBR	√		√	√		
	RABBIT	√					
	ARTIS	√	√	√	√		
	ESC questionnaire	√	√	√	√	√	√
	B1801023		√				
	0881A1-3338-WW		√				
	LTE 20040210					√	
	BADBIR					√	
	LTE 20050111						√
							SPC section 4.4 Special warnings and precautions
							SPC section 4.8 Undesirable effects
Important Identified Risks - Specific Indications							
Change in morphology and/or severity in	Routine PV Additional PV Activities by Individual Risks and Indications						

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)						
psoriasis - adult and pediatric psoriasis		RA	JIA	AS	PsA	PS	Ped PS
	LTE 20040210					√	
	LTE 20050111						√
Important Potential Risks - All Indications							
AI Renal disease	Routine PV						
	Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	LTE 20040210					√	
	LTE 20050111						√
	ESC questionnaire	√	√	√	√	√	√
	B1801023		√				
	0881A1-3338-WW		√				
Pemphigus/ pemphigoid	Routine PV						
	Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	LTE 20040210					√	
	LTE 20050111						√
Amyotrophic lateral sclerosis	Routine PV						
	Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	Adult PS	Ped PS
	LTE 20040210					√	
	LTE 20050111						√
	B1801023		√				
	0881A1-3338-WW		√				
Important Potential Risks - All Indications (cont'd)							
Myasthenia gravis	Routine PV						
	Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	LTE 20040210					√	
	LTE 20050111						√
	ARTIS	√	√	√	√		
	B1801023		√				
	0881A1-3338-WW		√				
	ESC questionnaire	√	√	√	√	√	√

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)						
Encephalitis/ leukencephalomyelitis	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	Adult PS	Ped PS
	LTE 20040210					√	
	LTE 20050111						√
	B1801023		√				
	0881A1-3338-WW		√				
Liver events in patients with history of hepatitis	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	LTE 20040210					√	
	LTE 20050111						√
	ESC questionnaire	√	√	√	√	√	√

SPC section 4.4 Special warnings and precautions

Important Potential Risks - All Indications (cont'd)							
Liver failure	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	LTE 20040210					√	
	LTE 20050111						√
	B1801023		√				
	0881A1-3338-WW		√				
	ESC questionnaire	√	√	√	√	√	√
Hepatic cirrhosis and fibrosis	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	LTE 20040210					√	
	LTE 20050111						√
	B1801023		√				
	0881A1-3338-WW		√				
	ESC questionnaire	√	√	√	√	√	√
Severe hypertensive reactions	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	LTE 20040210					√	
	LTE 20050111						√

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)							
	B1801023		√					
	0881A1-3338-WW		√					
	ESC questionnaire	√	√	√	√	√	√	
Important Potential Risks - All Indications (cont'd)								
Adverse Pregnancy Outcomes	Routine PV Additional PV Activities by Individual Risks and Indications							
		RA	JIA	AS	PsA	PS	Ped PS	
	LTE 20040210					√		
	LTE 20050111						√	
	BADBIR					√		
	ESC questionnaire	√	√	√	√	√	√	
	B1801023		√					
	0881A1-3338-WW		√					
	OTIS	√	√	√	√	√		
Potential for Medication Errors (Pre-filled Pen)	Routine PV	RA	JIA	AS	PsA	PS	Ped PS	Clear Package Leaflet Instructions for use of the pre-filled pen. Education to patients, care givers and HCPs on the appropriate of the pre-filled pen. Enhanced educational materials and clarified instructions for use. Visual teaching guide to facilitate HCP training of patients. Availability of a needle free demonstration devise. Instructional materials in both print and DVD format. Training of Pfizer staff on the correct use of the PFP.
Important Potential Risks - All Indications (cont'd)								
Male Infertility	Routine PV Additional PV Activities by Individual Risks and Indications							
		RA	JIA	AS	PsA	PS	Ped PS	
	0881A1-3338-WW		√					
	B1801023		√					

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)						
Weight Gain	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	0881A1-3338-WW		√				
	B1801023		√				
Important Potential Risks - Specific Indications							
Growth and development - JIA and pediatric psoriasis	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	LTE 20050111						√
	0881A1-3338-WW		√				
	B1801023		√				
Acute ischemic CV events - all adult indications	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	BSRBR	√		√	√		
	RABBIT	√					
	ARTIS	√	√	√	√		
	ESC questionnaire	√		√	√	√	
	LTE 20040210					√	
Important Potential Risks - Specific Indications (cont'd)							
CHF - all adult indications	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	BSRBR	√		√	√		
	RABBIT	√					
	ARTIS	√	√	√	√		
	LTE 20040210	√				√	
Inflammatory bowel disease - JIA	Routine PV Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	0881A1-3338-WW		√				
	B1801023		√				

SPC section 4.4 Special warnings and precautions
SPC section 4.8 Undesirable effects
Patient alert card

SPC section 4.4 Special warnings and precautions

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)							
Important Missing Information - All Indications								
Use in hepatic and renal impaired patients	Routine PV	RA	JIA	AS	PsA	PS	Ped PS	SPC section 4.2 Posology and administration SPC section 4.4 Special warnings and precautions
Use in different ethnic origins	Routine PV Additional PV Activities by Individual Risks and Indications							
		RA	JIA	AS	PsA	PS	Ped PS	
	LTE 20040210					√		
	LTE 20050111						√	
Important Missing Information - All Indications (cont'd)								
Pregnancy	Routine PV Additional PV Activities by Individual Risks and Indications							
		RA	JIA	AS	PsA	PS	Ped PS	SPC section 4.6 Pregnancy and lactation
	BSRBR	√		√				
	RABBIT	√						
	ESC questionnaire	√	√	√	√	√	√	
	OTIS	√	√	√	√	√		
	BADBIR					√		
	LTE 20040210					√		
	LTE 20050111						√	
	0881A1-3338-WW		√					
	B1801023		√					

a. To further investigate the question of relationship between etanercept use and malignancies in children: European Pediatric Psoriasis Registry, Standardized Incidence Ratio Analysis of Cancer in Etanercept Treated Children with JIA using 3 Registries, and 2 Epidemiologic Studies to Understand the Background Risk of Malignancy in JIA.

The below pharmacovigilance activities in addition to the use of routine pharmacovigilance is needed to investigate further some of the safety concerns:

Description	Due date
Study 0081X1-4654- The PURPOSE Study; A Long-Term, Prospective, Observational Cohort Study of the Safety and Effectiveness of Etanercept in the Treatment of Paediatric Psoriasis Patients in a Naturalistic Setting: A Post-Authorisation Safety Study (PASS). The MAH will provide interim progress reports annually and the final report at the completion of the eight year registry, to the EMA as part of the Periodic Safety Update Report (PSUR) and updated etanercept risk management plan.	Study to be completed in 2018. The final report will be submitted within 6 months of study completion.

1.2.7. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable as the changes proposed for the package leaflets as part of the variation to extent the paediatric plaque psoriasis indication to include patients from 6 years of age were minimal.

2. Benefit-Risk Balance

Benefits

Beneficial effects

The double-blind, placebo controlled study that served as the basis for the approval in paediatric patients with psoriasis from the age of 8 years, study 20030211, demonstrated that etanercept at a dose of 0.8 mg/kg QW (up to a maximum dose of 50 mg QW) was associated with significantly greater improvements in the measures of psoriasis compared with placebo. Subgroup analyses were subsequently performed to describe the efficacy and safety profile of etanercept in a subpopulation of paediatric psoriasis subjects aged 6-7 years in study 20030211.

The improvements in efficacy observed during study 20030211 in subjects aged 6-7 years were maintained through 96 weeks of treatment in the extension study 20050111. The data provided in study 20050111 is supportive of efficacy in the age group 6-7 years old. Since the results of this subgroup in terms of efficacy were similar to the overall population, it is acceptable to conclude that these results can be considered supportive of efficacy in this group.

Uncertainty in the knowledge about the beneficial effects

Because the efficacy results are from a small number of subjects (n=17 for the 36 week study and n=14 for the 96 week study), the evidence for efficacy is limited. However what has been shown is that the efficacy responses were well maintained in the subjects aged 6-7 years who received etanercept through 96 weeks in the extension study. Furthermore, for all endpoints the results for the 6-7 year group are consistent with the overall population. As the mechanism of the disease is expected to be the same in 6-7 year olds and in those over 8 years, it is reasonable to extrapolate efficacy from the older paediatric population to those aged 6-7 years. The consistency of the data over time and across age ranges is therefore supportive to the conclusion that the available data are sufficient.

Risks

Unfavourable effects

The safety profile in the age group 6-7 years appears is generally similar to the one observed for the population from 8 years of age, for which the product is already approved. The unfavourable effects are well documented, highlighted in the SmPC and under continual surveillance as described in the RMP. These include increased risk of infection including TB, reactivation of Hepatitis B, allergic reactions, antibody development to etanercept, development of autoantibodies, blood dyscrasias, reduced vaccine responses and demyelination. Also an increased risk for the development of malignancies, including lymphoma cannot be excluded. The SmPC and the Risk Management Plan adequately address these safety-related topics.

Uncertainty in the knowledge about the unfavourable effects

In general there are uncertainties with regard to the use of immunosuppressants in children where an earlier introduction of immunosuppression may lead to an increased risk of malignancy, including virally associated tumour development. In order to collect more information in this patient population

the MAH has already set up the PURPOSE registry (a multicenter, long-term, prospective, observational, cohort study conducted to evaluate the long term safety and effectiveness of etanercept prescribed by dermatologists to children for the treatment of plaque psoriasis) as part of the initial approval of the use of etanercept in paediatric plaque psoriasis. This registry also covers the age range of the present extension application, and allows the identification of any common serious or new potentially unrecognized ADRs in paediatric plaque psoriasis patients who received etanercept. The registry will recruit between 100-200 patients and is currently enrolling patients. Data from this ongoing registry will address the safety concerns of etanercept in paediatric psoriasis. The MAH provides interim progress reports annually as part of the PSUR and the RMP. The MAH will submit the final report at the completion of the eight year registry as described in the RMP.

Balance

Importance of favourable and unfavourable effects

The balance of favourable and unfavourable effects has to take into account that the extension of age is from 8 years to 6 years and is supported by randomised controlled data albeit in a small number of patients and long-term open label data which is supportive of maintenance of efficacy.

Furthermore, from a clinical point of view, in patients in which all other available therapeutics alternatives have failed, and without any other viable alternatives, the use of Enbrel constitutes a significant advantage for these patients with severe plaque psoriasis in terms of disease control (PASI, PGA). The disadvantages include the known side effects of etanercept which are highlighted in the SmPC and under continued pharmacovigilance as detailed in the RMP.

Benefit-risk balance

The benefit of etanercept in the treatment plaque psoriasis in patients between the ages of 6-7 years was demonstrated in study 20030211 in a limited number of patients. These data were further substantiated through the open label study 20050111, where the efficacy was maintained over time and the benefits of etanercept treatment in paediatric plaque psoriasis for those aged 6-7 years was similar to that of the overall population. The safety profile in the age group 6-7 years appears to be similar to the paediatric population for which the use of the product is already approved. A registry will collect further long-terms safety data. The benefit-risk balance is therefore considered favourable.

Discussion on the benefit-risk assessment

The efficacy of etanercept in plaque psoriasis in children aged 8 -17 years was demonstrated in study 20030211 and this led to the approval of etanercept in a plaque psoriasis children aged 8 years and above. In addition although the efficacy in children under the age of 8 years was also shown in study 20030211, the numbers were very limited and the length of the trial was 48 weeks. The additional long-term data from the open label study 20050111 in the paediatric population overall and for the subset of patients who at any time were between the ages of 6 and 8 years, are supportive of both safety and maintenance of efficacy in the 6-7 year old subgroup. The maintenance of efficacy and safety profile for the 6-7 year olds and are similar to the results of the overall paediatric population in the open label study. The availability of an effective treatment in children where no alternative therapeutic options are available is considered a benefit.

The safety profile for those aged 6-7 years did not differ from the overall paediatric population in the open label study for up to 96 weeks. These risks are highlighted in the SmPC and are monitored with the ongoing study 20050111 (for up to 5 years) and by pharmacovigilance activity and the PURPOSE registry as described in the RMP.

The benefits of earlier introduction of treatment with etanercept in paediatric patients aged 6-7 years with severe plaque psoriasis who are inadequately controlled by, or are intolerant to, other systemic

therapies or phototherapies is expected to provide similar benefit as has been formally demonstrated in children aged 8-18 years. The earlier control of resistant disease is expected to lead to a favourable clinical outcome in terms of symptom control, development and quality of life. For children who need treatment with etanercept and who respond to treatment, the benefit is very significant. With improved control of their disease these children will be expected to have a better quality of life and improved growth.

Based on the CHMP review of data on safety and efficacy, the CHMP considered that the risk-benefit balance of Enbrel in the treatment of paediatric plaque psoriasis in children from the age of 6 years was positive.

The following indication is therefore agreed for section 4.1 of the SmPC:

Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of **6** years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

3. Conclusion

On 21 July 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.