Assessment report for

Enbrel

International Nonproprietary Name: Etanercept

Procedure No. Type II variation EMEA/H/C/262/II/126

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 7718 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.

The MAH submitted this variation application to extend the lower age range for the approved therapeutic indication for polyarticular juvenile idiopathic arthritis (JIA) "from the age of 4 years" to "from the age of 2 years" with consequential changes to section 4.1, 4.2 and to the package leaflets. Information relating to the supporting clinical trial (20021626) has been added to section 5.1.

The initially applied wording for extension of indication reads as follows:

Polyarticular juvenile idiopathic arthritis

Treatment of active polyarticular juvenile idiopathic arthritis in children and adolescents from the age of ~~4~~ **2** years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Enbrel has not been studied in children aged less than ~~4~~ **2** years.

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

3.2.1 Introduction

In support of this variation the MAH provided

1. The CSR 75813 for study 20021626 (assessed in FU2 096.3, AR adopted in March 2009 with conclusions that there was no change to the positive benefit/risk for Enbrel)
2. an Addendum to the final study report which analysed safety and efficacy data on the 2 to <4 year old subjects with polyarticular JIA

As the registry study 20021626 was assessed previously (FU2 096.3) only the summary of the main study will be presented and this assessment report will then focus on the Addendum examining safety

and efficacy in the 2-4 year old age group under the Ancillary analysis section. Comparison with the safety and efficacy of the whole overall group (aged 1-18 years) will be made.

3.2.2 GCP

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

The applicant 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.

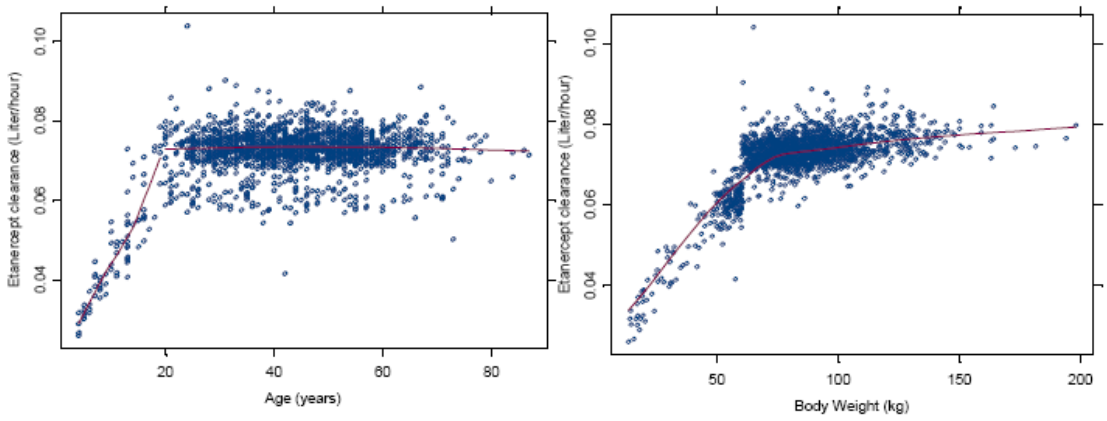
3.2.3 Pharmacokinetics

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. For the treatment of JIA in children ≥4 years, the approved dosage of etanercept is 0.4 mg/kg (up to a maximum of 25 mg per dose) twice weekly (BIW; 72 to 96 hours apart). For the treatment of psoriasis in children and adolescents from the age of 8 years, the approved dosage of etanercept is 0.8 mg/kg (up to a maximum of 50 mg per dose) QW.

The formulation of etanercept used in registry 20021626 was identical to the 25 mg/ml powder and solvent for solution for injection for paediatric use that is currently approved in the EU for JIA. The dosage regimen used in registry 20021626 was 0.8 mg/kg QW, up to a maximum dose of 50 mg. This varies from the 0.4 mg/kg BIW regimen, up to a maximum dose of 25 mg per dose approved in the EU for the treatment of JIA in children ≥4 years.

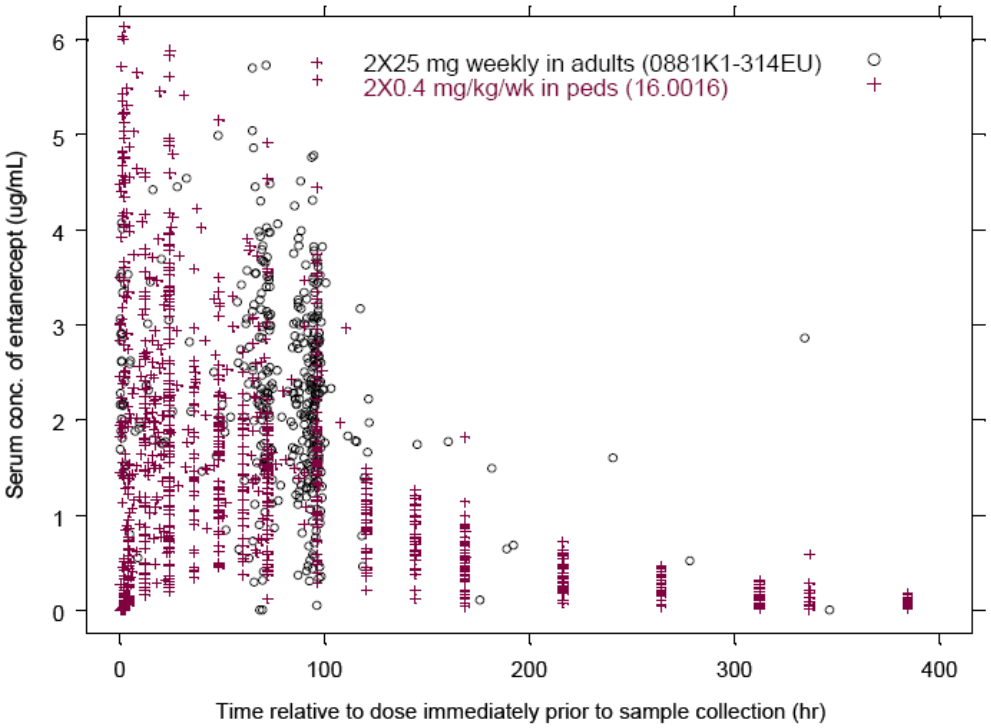
There was no pharmacokinetic investigation in registry 20021626 and there are no etanercept PK data available in JIA subjects aged 2 to <4 years. However, based on existing knowledge of etanercept pharmacokinetics, the serum etanercept exposure in JIA subjects aged 2 to <4 years receiving 0.4 mg/kg BIW is expected to be in the same range as JIA subjects aged 4 to 17 years receiving 0.4 mg/kg BIW or adult RA subjects receiving 25 mg BIW. Etanercept pharmacokinetics have been well characterized in adult subjects with RA, AS and psoriasis, and data is available in juvenile subjects aged 4 to 17 years with JIA and in juvenile subjects aged 4 to 17 years with psoriasis in population PK analyses, and etanercept pharmacokinetics were similar among all patient populations. Adult (age >17 years) healthy subjects and adult subjects with RA have consistent PK exposure with no significant effect of age and body weight (Figure 1).

Figure 1: The Relationship of Etanercept apparent clearance with Age and Body Weight



The 0.4 mg/kg BIW dose has been studied in JIA subjects (study 16.0016, the CSR of which was submitted during the original Marketing Authorisation Application [MAA; EMA/H/C/262], approved in February 2000). As shown in Figure 2, trough etanercept concentrations in JIA subjects following 0.4 mg/kg BIW doses were comparable to those of adult subjects receiving a fixed dose of 25 mg BIW. Body weight-adjusted apparent clearance is comparable between paediatric JIA subjects and adult subjects; thus, adjusting the dose in JIA subjects for body weight (0.4 mg/kg BIW) achieved blood concentrations similar to that observed in adult subjects who received 25 mg BIW in study 088A3-314-EU (CSR was submitted in support of procedure EMA/H/C/262/II/66, approved in April 2006 (Figure 2)).

Figure 2: Sparse and Trough Etanercept Concentrations in JIA Subjects Following 0.4-mg/kg Twice Weekly Dose and in Adult subjects Following 25-mg Twice Weekly Dose



Body weight is expected to increase with age in male and female paediatric patients under the age of 18 years, with an average 2- to 4-year-old normally weighing between 10 to ~15 kg. Assuming that etanercept clearance would decrease with body weight in 2- to 4-year-olds in a manner similar to that for 4- to 17-year-olds, the expected drop in clearance in a 2- to 4-year-old would require the same dose adjustment based on a smaller body weight as applied to patients 4 to 17 years old. The lower etanercept dose in JIA patients aged 2 to 4 years together with a slower etanercept clearance is expected to produce etanercept exposure comparable to JIA patients aged 4 to 17 years.

In addition, the 0.8 mg/kg QW regimen used in registry 20021626 is expected to produce exposure similar to the 0.4 mg/kg BIW dose regimen. The etanercept pharmacokinetics in paediatric subjects was initially assessed in JIA subjects in study 16.0016. After repeated BIW doses of 0.4 mg/kg, the children had a mean serum etanercept concentration of 2100 ng/mL. In the paediatric psoriasis study 20030211 (the CSR of which was presented in variation EMA/H/C/262/II/94, approved in December 2008), etanercept pharmacokinetics were assessed in paediatric subjects with psoriasis who received 0.8 mg/kg QW. Mean and median steady-state trough concentrations were similar across visits (range from 1600 ng/mL to 2100 ng/mL). For subjects who received etanercept during the entire 48-week study, the mean trough etanercept concentration was 1829 ng/mL, which was 10% to 20% lower than the mean trough steady-state etanercept concentration of 2100 ng/mL observed in subjects with JIA after receiving 0.4 mg/kg etanercept BIW. This is consistent with the expected approximately 20% lower trough concentrations of the QW regimen as compared to the BIW regimen. Given the inter-subject variability observed, the mean trough etanercept serum concentrations following 0.8 mg/kg etanercept QW in paediatric psoriasis subjects are generally comparable to those observed following 0.4 mg/kg etanercept BIW in JIA subjects. Similar results were seen when comparing 25 mg BIW and 50 mg QW in adult RA subjects. Based on these results, it is expected that the safety and efficacy profiles of 0.4 mg/kg BIW and 0.8 mg/kg QW will be similar.

Discussion on clinical pharmacology

The MAH has presented a clinical registry study in children with JIA between 2 and 17 years old. In this study the dose used was 0.8 mg/kg QW up to a maximum dose of 50 mg peer week, whereas the dose approved in children with JIA between 4 and 17 is 0.4 mg/kg BIW.

The MAH was not in a position to provide the additional PK data for children based on serum samples collected in study 20021626 as requested by CHMP. The CHMP also noted the recruitment challenges for some studies where additional PK data could have been generated. Therefore, despite the lack of this additional information the CHMP considered that the available data and the PK modelling are supportive of a weight based dosing in children aged 2-3 years.

Conclusion on clinical pharmacology

The CHMP considered that:

- The mechanism of disease is considered to be the same for 2- <4 yr olds compared with children above the age of 4 years.
- PK data is available in children from the age of 4 yrs
- No difference would be expected in the 2-< 4 yr old group compared with older children.

Therefore, the absence of more detailed PK in children aged 2-<4 years was deemed acceptable.

The similar exposure from 0.4 mg/kg twice weekly and 0.8 mg/kg weekly is accepted and has been demonstrated for adults with RA and children above the age of 8 years with paediatric psoriasis. Therefore the posology of 0.8 mg/kg once weekly for JIA in study 20021626 can be accepted as providing similar levels as the EU approved posology of 0.4 mg/kg twice weekly.

3.2.4 Clinical efficacy

Study 20021626 was an open-label, multicenter registry for children aged 2 to 18 years with a diagnosis of polyarticular-course or systemic JIA. The objective of the registry was to determine the long-term safety of etanercept administered with or without MTX compared to MTX alone in paediatric subjects with polyarticular-course or systemic JIA. Eligible subjects received etanercept alone, etanercept plus MTX, or MTX alone. Subjects were also allowed to be on other concomitant DMARDs. Etanercept was administered SC at a dose of 0.8 mg/kg per week (up to maximum dose of 50 mg per week) for up to 36 months. In the comparator group, MTX was dosed at the investigator's discretion at a dose of at least 10 mg/m^2/week but not to exceed 1 mg/kg/week. Safety data, including adverse events and medically important infections, were collected on all subjects. A limited set of effectiveness and health outcomes data were also collected. All subjects were followed in this registry for up to 36 months.

It is of note that both polyarticular and systemic JIA cases were included in the trial. As the current approved indication in JIA is restricted to the polyarticular subtype, the Addendum provided by the MAH (see under Ancillary analysis) focuses on polyarticular JIA in those aged 2 to <4 years.

Main studies

Study 20021626: a Phase IV registry of etanercept in children with juvenile rheumatoid arthritis.

Methods

This was an open-label, multicenter, registry study to assess the long-term safety of etanercept in children with polyarticular course or systemic JRA. Approximately 400 subjects received etanercept alone or etanercept plus methotrexate or other DMARDs, and approximately 200 subjects received methotrexate alone or methotrexate with other DMARDs for 36 months.

Subjects who enrolled into the study on methotrexate but who subsequently switched to etanercept (alone or in combination with methotrexate or other DMARDs) were eligible to be re-enrolled into the etanercept arm of the study if they had not been in the study for more than 30 months. Subjects who enrolled into the study on the etanercept arm were not re-enrolled into the methotrexate arm if they discontinued etanercept and continued or started methotrexate.

Safety data, including significant adverse events and infections, was collected on all subjects.

Study Participants

Inclusion Criteria

Eligible subjects met the following criteria:

- Boys or girls age 2 to 18 years (inclusive) with a diagnosis of systemic, polyarticular, or pauciarticular JRA defined by the American College of Rheumatology (ACR) criteria
- Duration of disease long enough for the subject to have been given an adequate trial of nonsteroidal anti-inflammatory drug (NSAID) and/or prednisone.
- Co-administration of other DMARDs that did not specifically inhibit TNF (e.g., infliximab, thalidomide, D2E7 [adalimumab]).
- Parent or legal guardian able and willing to give informed consent.
- Disease course must have been polyarticular or systemic with active arthritis in ≥3 joints at the time of starting methotrexate alone or methotrexate in combination with other DMARDs, etanercept alone or etanercept added to ongoing methotrexate or other DMARDs.
- Pre-pubescent, or if post-pubertal at any time during the study and of childbearing potential must practice adequate contraception.

Etanercept Arm:

- Newly started etanercept or began etanercept within 6 months of enrollment into the study.

Methotrexate Arm:

- Newly started methotrexate or began methotrexate within 6 months of enrollment into the study.

Exclusion Criteria

Subjects were excluded from the study if they met any of the following criteria:

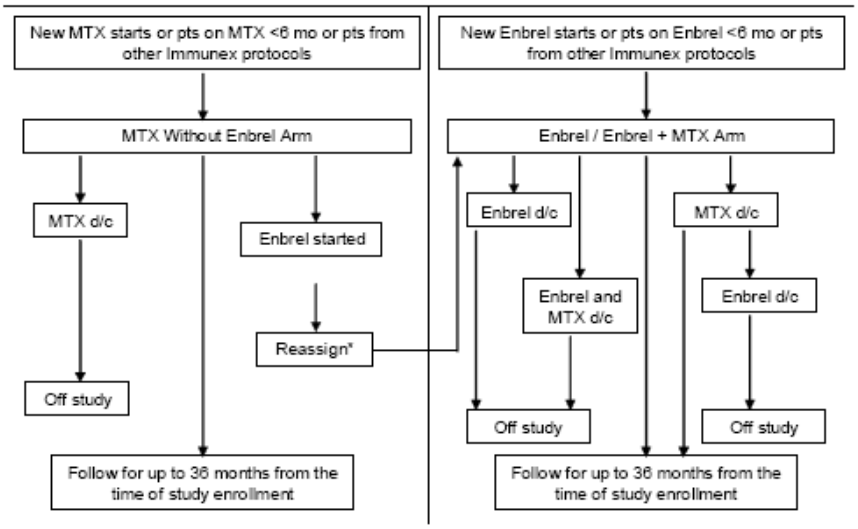
- Pregnant or nursing
- Receipt of antibody to TNF (infliximab, adalimumab, or other anti-TNF), antibody to CD4 (anti-CD4), or diphtheria interleukin-2 fusion protein (DAB-IL-2)
- Participation in a study of an investigational drug or biologic other than etanercept that required informed consent ≤6 months

- Receipt of any of the following DMARDs: TNF inhibitors other than etanercept such as infliximab, thalidomide, adalimumab; cyclophosphamide; experimental agents; or other biologic agents
- Any serious concurrent medical condition, either acute or chronic, which would compromise the subject's ability to cooperate with the protocol requirement
- History of alcohol or drug abuse
- Prior malignancies unless the subject had been disease free for at least 5 years
- Serious concurrent medical conditions, either acute or chronic (including infections) that prevent the subject from receiving a TNF inhibitor

Treatments

This was a non-randomized study. Subjects who satisfied all eligibility criteria were enrolled into 1 of 3 cohorts in the study based on their baseline treatment (Figure 3).

Figure 3: Study Design and Treatment Schema



*Reassign only if patient has been in Registry for ≤ 30 months.
d/c = discontinued; MTX = methotrexate

Objectives

The primary objective was to determine the long-term safety of etanercept administered with or without other DMARDs in paediatric subjects with polyarticular course or systemic juvenile rheumatoid arthritis (JRA) compared to a control cohort of subjects with polyarticular course or systemic JRA receiving methotrexate (with or without other DMARDs).

Outcomes/endpoints

Assessments included adverse event assessments, Tanner scores (by physical examination), behavioral assessment (Achenbach CBCL appropriate by age group), paediatric quality of life,

physician's global assessment of overall disease activity (scale 0 to 10), and paediatric joint assessment.

Sample size

Sample Size Considerations

Table 1 provides event rates for etanercept and methotrexate with approximately 80% power to detect a treatment difference (using a 2-sided, 95% confidence interval for the difference in proportions).

Table 1 Event Rates Whose Difference is Detectable with 80% Power

Event Rate	Sample Size (per arm)	
methotrexate	200/100	400/200
0.01	0.10	0.06
0.05	0.17	0.12
0.10	0.24	0.19
0.15	0.30	0.25
0.20	0.36	0.31
0.25	0.42	0.37

At full enrollment (400 subjects in the etanercept arm and 200 subjects in the methotrexate arm) the trial has 80% power to detect an increase from 0.10 to 0.19 in the proportion of subjects with an event (relative risk = 1.9).

Statistical methods

Descriptive summary statistics for observed data are provided for each study endpoint. For categorical endpoints, the summary statistics contain the frequency and percentage. For continuous endpoints, the summary statistics contain the number of observations, mean, standard deviation, median, minimum, maximum, and 95% confidence interval for mean (except for the safety laboratory assessment). The interested comparison for any study endpoint was between methotrexate and etanercept, with significance level of 0.05. Possible confounding factors were examined to adjust for the potential difference between cohorts and adjust for subjects who switched from methotrexate to etanercept or etanercept plus methotrexate. Study centers were pooled for all analyses and summaries. Missing values were not imputed for the primary and secondary endpoints in this study.

Efficacy analyses

Paediatric joint assessments and the physician's global assessment were summarized with descriptive statistics at each visit, by treatment group. Due to the non-randomized nature of this study and the possibility that some subjects could have changed treatment arms mid-study, there may be some selection bias in treatment group assignment with regards to disease severity, type, or duration. For this reason, no inferential statistics were performed on the efficacy endpoints.

Growth Data

Growth data (height, age, and weight) and Tanner scores (approximately 30% of subjects) were compared between treatment cohorts. Height, weight, and body mass index (BMI) were also compared using percentiles from standardized growth charts. Each subject's baseline and last on-study height, weight, and BMI were compared to the charts for their age and sex, and the percentile for each height, weight, and BMI was recorded. The change in percentile from baseline to end of study was compared between the treatment arms, using an analysis of covariance (ANCOVA), adjusted for possible confounders.

Quality-of-Life Analyses

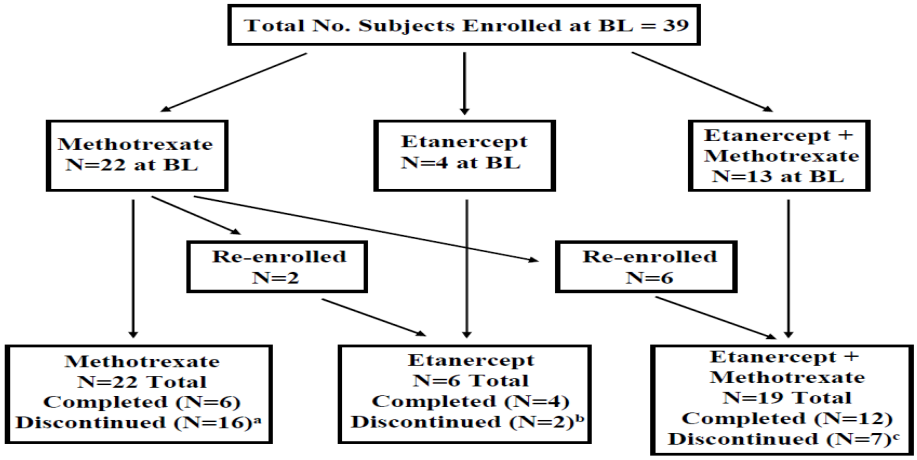
Paediatric Quality of Life (PedsQL™) Inventory Module and PedsQL Arthritis Module scores, child behavior checklist sub-scales and total scores were summarized with descriptive statistics at each visit, by treatment arm.

Safety Analyses

Adverse event rates, serious adverse event rates, infection rates, and medically important infection rates were compared between treatment arms. Poisson regressions adjusted for age, sex, baseline disease characteristics, and treatment crossover were used to compare etanercept with methotrexate for cancer, grade 3 or 4 adverse events, autoimmune events, medically important infections, or psychiatric and behavioural problems. Treatment arms were compared with respect to the occurrence of any new autoimmune disease. Cancer rates for each treatment arm were to be compared between arms. Infection was summarized as reported by the treating physician.

Results

Participant flow



a. Eight (8) out of 16 subjects who discontinued from the methotrexate arm re-enrolled in the etanercept only arm or etanercept + methotrexate arm. The remaining 8 subjects permanently discontinued from the registry.
b. Following discontinuation from the methotrexate only arm, none of the patients who re-enrolled in the etanercept only arm discontinued from the registry.
c. Following discontinuation from the methotrexate only arm, 2 of the patients who re-enrolled in the etanercept + methotrexate arm discontinued from the registry.

Recruitment

The study was conducted at 32 study centers (28 in the United States and 4 in Canada).

Subjects who satisfied all eligibility criteria were enrolled into 1 of 3 cohorts in the study based on their baseline treatment. Subjects were registered by contacting the Paediatric Rheumatology Collaborative Study Group and assigned a study number. The final subject's last visit occurred in January 2008, and the final clinical study report (CSR) was prepared in November 2008.

Conduct of the study

There were 5 amendments to this study at the time this report was completed. These amendments are considered as acceptable by the CHMP.

Baseline data

Demographics and Baseline Disease Characteristics

Gender and race were consistent across the 3 treatment groups, with a higher percentage of females and Caucasians observed in both the overall population (Table 2).

Table 2. Demographic Characteristics

	Methotrexate Only (N = 197)	Etanercept Only (N = 103)	Etanercept + Methotrexate (N = 294)
Sex - n (%)			
Male	52 (26.4)	20 (19.4)	80 (27.2)
Female	145 (73.6)	83 (80.6)	214 (72.8)
Race - n (%)			
Asian	1 (0.5)	4 (3.9)	6 (2.0)
African American	12 (6.1)	5 (4.9)	29 (9.9)
Caucasian	151 (76.6)	78 (75.7)	214 (72.8)
Hispanic	24 (12.2)	7 (6.8)	29 (9.9)
Native American	0 (0.0)	1 (1.0)	1 (0.3)
Other	9 (4.6)	8 (7.8)	15 (5.1)
Age (Years)			
n	197	103	294
Mean	9.02	10.78	10.09
SD	4.40	4.10	4.69
SE	0.31	0.40	0.27
95% CI Mean	8.40, 9.63	9.97, 11.58	9.55, 10.63
Median	9.00	11.00	10.00
Min, Max	1.0, 18.0	2.0, 18.0	1.0, 18.0
Age Category - n (%)			
Age <= 4	38 (19.3)	9 (8.7)	47 (16.0)
5 <= Age <= 7	41 (20.8)	15 (14.6)	56 (19.0)
8 <= Age <= 12	66 (33.5)	41 (39.8)	85 (28.9)
13 <= Age <= 18	52 (26.4)	38 (36.9)	106 (36.1)
JRA Disease Duration (Months)			
n	197	97	267
Mean	20.15	58.11	40.66
SD	30.69	44.53	41.68
SE	2.19	4.52	2.55
95% CI Mean	15.84, 24.47	49.13, 67.08	35.64, 45.68
Median	8.90	50.20	21.90
Min, Max	0.2, 189.5	1.9, 179.0	0.3, 199.5

Page 1 of 2

N = Number of subjects enrolling into the registry and completing at least 1 evaluation while on methotrexate or etanercept

	Methotrexate Only (N = 197)	Etanercept Only (N = 103)	Etanercept + Methotrexate (N = 294)
Height (cm)			
n	197	102	292
Mean	133.02	141.19	137.20
SD	25.29	22.79	26.23
SE	1.80	2.26	1.54
95% CI Mean	129.47, 136.57	136.72, 145.67	134.18, 140.22
Median	135.40	144.05	141.35
Min, Max	78.0, 179.0	85.6, 195.0	80.0, 197.4
Weight (kg)			
n	197	102	293
Mean	37.18	42.68	40.14
SD	20.82	22.82	21.84
SE	1.48	2.26	1.28
95% CI Mean	34.25, 40.10	38.19, 47.16	37.63, 42.65
Median	33.80	38.65	38.20
Min, Max	9.4, 119.6	10.9, 151.0	9.5, 120.0
BMI (kg/m^2)			
n	197	102	292
Mean	19.26	19.92	19.67
SD	5.05	5.83	5.19
SE	0.36	0.58	0.30
95% CI Mean	18.55, 19.97	18.77, 21.06	19.08, 20.27
Median	18.04	18.63	18.69
Min, Max	12.2, 45.8	12.5, 39.7	12.7, 45.0

Page 2 of 2

N = Number of subjects enrolling into the registry and completing at least 1 evaluation while on methotrexate or etanercept

The mean duration of JIA was approximately 2 times longer for subjects receiving etanercept only and etanercept + MTX compared with those receiving MTX only.

Baseline Disease Characteristics

Subjects in the etanercept only arm had the longest mean (SD) duration of JRA with 58 months (44.5) while the subjects in the methotrexate only arm had the shortest mean (SD) duration of JRA (20 months [30.7]); the etanercept + methotrexate arm had a mean (SD) duration of JRA of 41 months (41.7). The range for the etanercept only arm was 1.9 to 179.0 months; the overall range was 0.2 to 199.5 months. The majority of subjects in each arm had polyarticular JRA with a polyarticular onset. Most subjects were negative for rheumatoid factor. Although 1 subject (etanercept only arm) was reported to have had a history of cancer, this was later determined to be incorrect and therefore a database errata was created.

The median (range) number of active arthritic joints was 6 (0 to 47) for the methotrexate only arm, 4 (0 to 46) for the etanercept only arm, and 6 (0 to 59) for the etanercept + methotrexate arm.

At enrollment, subjects were to provide a list of all anti-rheumatic medications taken since their diagnosis with JRA. 86% in the etanercept only arm had a history of MTX use. In the overall population 86-100% had a history of MTX use and >98% in the etanercept only and etanercept plus MTX groups had a history of etanercept use. In the MTX arm only 0.5% had prior history of etanercept use.

Subjects were also asked to specify which medications they were currently taking for the treatment of their JRA. Based on the categories for medications used, a large percentage of subjects were taking NSAIDs at baseline; 91% of subjects in the methotrexate only arm, 73% in the etanercept only arm; and 85% in the etanercept + methotrexate arm. The dose of MTX in the study ranged from a dose of at least 10 mg/m^2/week but not to exceed 1 mg/kg/week. Over half of the subjects in the methotrexate only and etanercept + methotrexate arm were also on folinic or folic acid at baseline,

61% and 68%, respectively. Only 9% of the subjects in the etanercept only arm were taking folinic or folic acid at baseline.

Numbers analysed

Enrollment and Disposition of Subjects

A total of 594 subjects were enrolled; 197 subjects were receiving methotrexate only, 103 subjects were receiving etanercept only, and 294 subjects were receiving etanercept + methotrexate. Per the protocol, subjects in the methotrexate only arm who discontinued from methotrexate and switched to etanercept treatment or added etanercept to existing methotrexate within 30 months of enrollment were allowed to re-enroll in the etanercept only or etanercept + methotrexate arms of the study. However, subjects who discontinued etanercept were not eligible to re-enroll in the methotrexate only arm. In this study, 32 subjects were allowed to re-enroll; 8 subjects re-enrolled into the etanercept only arm and 24 subjects re-enrolled into the etanercept + methotrexate arm.

Thirty-one (31) patients have switched from MTX only arm. Eight (8) switched to the etanercept only arm and 23 to the etanercept + MTX arm. Of the 31 cases that were re-enrolled, 7 were re-enrolled after 1 year and so the follow-up for these cases is short.

The most frequently cited reasons for study discontinuation in the methotrexate only arm was insufficient therapeutic effect (18.3%), other (15.2%), and remission (12.2%); in the etanercept only arm was other (15.5%); and in the etanercept + methotrexate arm was insufficient therapeutic effect (20.1%) and other (16.3%).

Protocol Deviations and Treatment Compliance

The protocol deviations were predominantly missed visits.

Treatment compliance was not monitored as part of this registry study because investigational product was supplied via prescription by the treating physician.

Outcomes and estimation

Efficacy Results:

At year 3, the mean (SD) percentage improvement in the number of active arthritic joints was 57% (93.6) for the methotrexate only arm, 63% (56.2) for the etanercept only arm, and 59% (75.8) for the etanercept + methotrexate arm (Table 3).

Table 3 Percentage Improvement of Paediatric Total Joint Assessment Over Time - Joint Assessment Variable: Number of Active Joints

Visit		Methotrexate Only (N = 197)	Etanercept Only (N = 103)	Etanercept + Methotrexate (N = 294)
Month 12 (Year 1)	N	68	35	97
	Mean	62.96	53.94	36.24
	SD	51.60	50.13	106.88
	SE	6.26	8.47	10.85
	95% CI Mean	50.47, 75.45	36.72, 71.16	14.70, 57.78
	Median	100.00	75.00	66.67
	Min, Max	-100.0, 100.0	-100.0, 100.0	-700.0, 100.0
Month 24 (Year 2)	N	46	20	72
	Mean	71.58	32.31	67.77
	SD	56.91	221.91	52.69
	SE	8.39	49.62	6.21
	95% CI Mean	54.68, 88.48	-71.55, 136.17	55.39, 80.15
	Median	100.00	100.00	87.75
	Min, Max	-225.0, 100.0	-900.0, 100.0	-200.0, 100.0
Month 36 (Year 3)	N	65	46	128
	Mean	57.01	63.22	58.86
	SD	93.61	56.24	75.80
	SE	11.61	8.29	6.70
	95% CI Mean	33.82, 80.21	46.52, 79.92	45.60, 72.12
	Median	100.00	94.84	91.29
	Min, Max	-550.0, 100.0	-100.0, 100.0	-366.7, 100.0

N = Number of subjects enrolling into the registry and completing at least 1 evaluation while on methotrexate or etanercept

At year 3, the mean (SD) percentage improvement in the Physician Global Assessment of Disease Activity was 61% (45.0) for the methotrexate only arm, 61% (44.1) for the etanercept only arm, and 55% (53.3) for the etanercept + methotrexate arm (Table 4).

Table 4. Percentage Improvement of Physician Global Assessment of Disease Activity

Visit		Methotrexate Only (N = 197)	Etanercept Only (N = 103)	Etanercept + Methotrexate (N = 294)
Month 12 (Year 1)	n	113	68	203
	Mean	55.7	44.2	53.8
	SD	57.8	73.5	47.0
	SE	5.4	8.9	3.3
	95% CI Mean	44.9, 66.4	26.4, 62.0	47.3, 60.3
	Median	71.4	66.7	66.7
	Min, Max	-250, 100	-400, 100	-100, 100
Month 24 (Year 2)	n	83	49	141
	Mean	63.6	59.6	51.0
	SD	62.4	42.3	67.8
	SE	6.9	6.0	5.7
	95% CI Mean	50.0, 77.3	47.4, 71.7	39.7, 62.3
	Median	77.8	75.0	71.4
	Min, Max	-400, 100	-50, 100	-300, 100
Month 36 (Year 3)	n	64	46	119
	Mean	60.7	60.9	55.4
	SD	45.0	44.1	53.3
	SE	5.6	6.5	4.9
	95% CI Mean	49.4, 71.9	47.8, 74.0	45.8, 65.1
	Median	73.2	71.4	66.7
	Min, Max	-100, 100	-50, 100	-200, 100

N = Number of subjects enrolling into the registry and completing at least 1 evaluation while on methotrexate or etanercept

Patient-reported Outcomes:

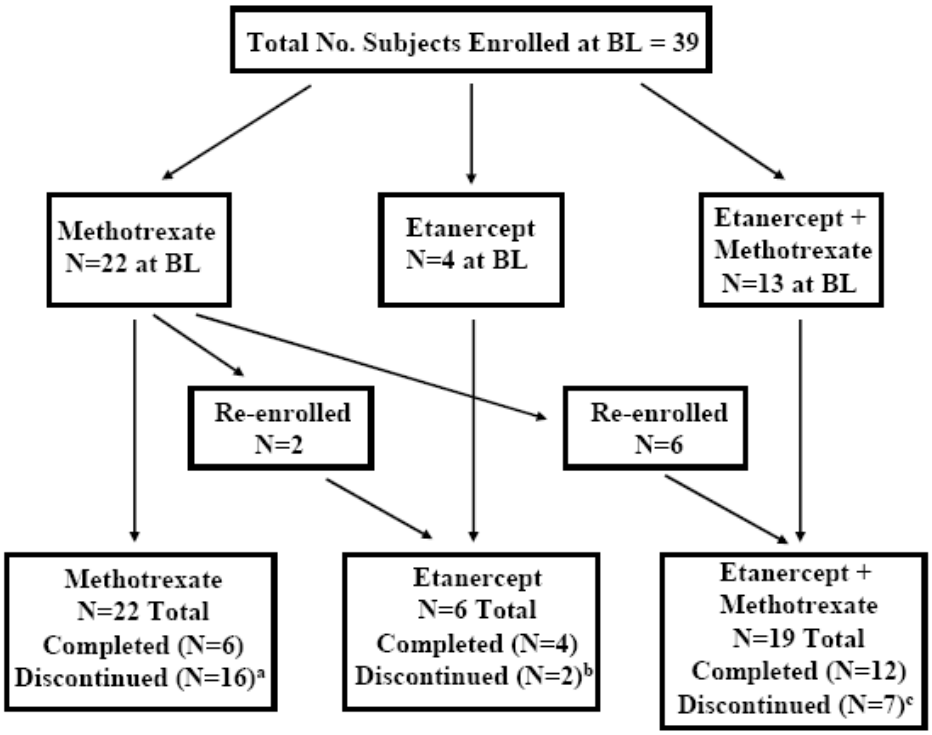
Following treatment, subjects in all 3 treatment arms had improvement on all domains including physical, psychosocial, emotional, social and school as well as pain and hurt, daily activities, treatment, worry, and communication at each visit.

Ancillary analyses

In support of the current variation, the MAH analysed the data in the subjects who were 2 to <4 years old with polyarticular JIA. The restriction to polyarticular JIA is in line with the currently approved indication in JIA which is restricted to the polyarticular subtype.

The subgroup analysis included subjects with polyarticular JIA who were between the ages of 2 and <4 years at the time of enrolment in registry 20021626 and who were included in the final safety analysis in CSR-75813. Subjects with either systemic-onset or systemic-course JIA were not included in the subgroup analysis. Forty-seven (47) subjects were included in the subgroup analysis: 22 subjects received MTX only, 6 subjects received etanercept only, and 19 subjects received etanercept + MTX. Although data were collected on 47 subjects across the 3 treatment groups, there were 39 unique subjects included in this subgroup analysis because there were 8 subjects in the MTX only arm who re-enrolled in the etanercept only or etanercept + MTX arm (figure 4).

Figure 4: Flowchart of Subjects Aged 2 to <4 Years in Registry 20021626



Abbreviation: BL=baseline.

a. Eight (8) out of 16 subjects who discontinued from the methotrexate arm re-enrolled in the etanercept only arm or etanercept + methotrexate arm. The remaining 8 subjects permanently discontinued from the registry.
b. Following discontinuation from the methotrexate only arm, none of the patients who re-enrolled in the etanercept only arm discontinued from the registry.
c. Following discontinuation from the methotrexate only arm, 2 of the patients who re-enrolled in the etanercept + methotrexate arm discontinued from the registry.

Demographics and Baseline Disease Characteristics

Gender and race were consistent across the 3 treatment groups, with a higher percentage of females and Caucasians observed in the subpopulation aged 2 to <4 years (table 5).

Table 5: Demographic Characteristics for Polyarticular JIA Subjects Aged 2 to <4 Years in Registry 20021626

	Methotrexate Only (N=22)[a]	Etanercept Only (N=6)[b]	Etanercept + Methotrexate (N=19)[b]
Sex - n (%)			
Male	4 (18.2)	1 (16.7)	3 (15.8)
Female	18 (81.8)	5 (83.3)	16 (84.2)
Race - n (%)			
Asian	0 (0.0)	0 (0.0)	0 (0.0)
African American	0 (0.0)	0 (0.0)	0 (0.0)
Caucasian	18 (81.8)	5 (83.3)	17 (89.5)
Hispanic	3 (13.6)	1 (16.7)	2 (10.5)
Native American	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (4.5)	0 (0.0)	0 (0.0)
Age (Years)			
n	22	6	19
Mean	2.36	2.83	2.63
SD	0.49	0.75	0.60
SE	0.10	0.31	0.14
95% CI Mean	2.15, 2.58	2.04, 3.62	2.34, 2.92
Median	2.00	3.00	3.00
Min, Max	2.0, 3.0	2.0, 4.0	2.0, 4.0
JIA Disease Duration (Months)			
n	22	5	16
Mean	7.51	13.94	13.32
SD	6.60	6.83	9.05
SE	1.41	3.05	2.26
95% CI Mean	4.58, 10.44	5.46, 22.42	8.49, 18.14
Median	5.80	10.40	10.35
Min, Max	0.9, 23.9	8.2, 25.1	1.4, 33.7
Height (cm)			
n	22	6	19
Mean	91.28	92.27	92.68
SD	6.44	5.37	6.17
SE	1.37	2.19	1.42
95% CI Mean	88.42, 94.14	86.63, 97.91	89.71, 95.66
Median	91.25	91.25	92.20
Min, Max	78.0, 100.2	85.6, 99.1	80.0, 106.2
Weight (kg)			
n	22	6	19
Mean	13.73	13.07	13.74
SD	2.30	1.33	2.54
SE	0.49	0.54	0.58
95% CI Mean	12.71, 14.75	11.67, 14.47	12.51, 14.96
Median	13.50	13.25	13.60
Min, Max	9.4, 17.7	10.9, 14.7	9.5, 18.0
BMI (kg/m^2)			
n	22	6	19
Mean	16.42	15.34	15.91
SD	1.70	0.74	1.98
SE	0.36	0.30	0.45
95% CI Mean	15.66, 17.17	14.57, 16.11	14.96, 16.86
Median	16.30	15.25	15.43
Min, Max	13.6, 21.0	14.4, 16.3	13.6, 20.6

Abbreviations: BMI=body mass index; CI=confidence interval; JIA=juvenile idiopathic arthritis; SD=standard deviation; SE=standard error.

a. N=number of subjects assigned to methotrexate only arm at original baseline.

b. N=number of subjects receiving the respective treatment at any time during the registry (ie, includes re-enrolled subjects).

The mean duration of JIA was approximately 2 times longer for subjects receiving etanercept only and etanercept + MTX compared with those receiving MTX only. The mean number of active joints at baseline for subjects aged 2 to <4 years was consistent with that of the overall population (Table 6).

Table 6: Baseline Paediatric Total Joint Assessment (All Sites) for Polyarticular JIA Subjects Aged 2 to <4 Years in Registry 20021626

	Methotrexate Only (N=22)[a]	Etanercept Only (N=6)[b]	Etanercept + Methotrexate (N=19)[b]
Number of Active Joints			
n	22	6	19
Mean	13.7	5.3	10.4
SD	9.7	6.7	9.5
SE	2.1	2.7	2.2
95% CI Mean	9.4, 18.0	-1.6, 12.3	5.8, 15.0
Median	12.0	4.0	6.0
Min, Max	2, 30	0, 18	1, 28
Limitation of Motion			
n	22	6	19
Mean	6.0	3.2	6.2
SD	5.0	3.3	5.6
SE	1.1	1.3	1.3
95% CI Mean	3.8, 8.2	-0.2, 6.6	3.5, 8.9
Median	5.0	2.5	5.0
Min, Max	0, 19	0, 8	0, 18
Limitation of Motion With Pain			
n	22	6	19
Mean	2.8	0.7	3.1
SD	4.5	1.2	4.8
SE	1.0	0.5	1.1
95% CI Mean	0.8, 4.8	-0.6, 1.9	0.8, 5.3
Median	1.0	0.0	1.0
Min, Max	0, 17	0, 3	0, 14

Abbreviations: CI=confidence interval; JIA=juvenile idiopathic arthritis; SD=standard deviation; SE=standard error.

a. N=number of subjects assigned to methotrexate only arm at original baseline.

b. N=number of subjects receiving the respective treatment at any time during the registry (ie, includes re-enrolled subjects).

Gender and race across the 3 treatment groups were consistent with a higher percentage of females (83% and 74% of the subpopulation and overall population, respectively) and Caucasians (85% and 75% of the subpopulation and overall population, respectively) observed in both populations.

Duration of disease activity for the subpopulation was considerably less than that for the overall population because of the young age of this group. The mean ± standard deviation (SD) duration of JIA for subjects aged 2 to <4 years was 7.51 ± 6.60 months, 13.94 ± 6.83 months, and 13.32 ± 9.05 months for the MTX only, etanercept only, and etanercept + MTX treatment arms, respectively.

This is consistent with the overall population for whom the disease duration was approximately 2 times longer for subjects receiving etanercept only and etanercept + MTX compared with those receiving MTX only.

Shorter disease duration in the MTX arm is seen and this is consistent with the data from the overall population**.** Of note, the age group in the MTX only arm is younger than the other treatment arms with a median age of 2 years (range 2-3 years) compared with a median age of 3 years (range 2-4 yrs) in the etanercept containing treatment arms. The MAH has provided a breakdown of the ages in months for all subjects in each of the three treatment arms as well as the age in months of the 8 subjects who switched treatment arms at the time of the switch. Among the etanercept-treated subjects, 10 were below 3 years of age and 13 were aged 3 to <4 years (Table 7)

Table 7. Summary of Age at Time of Enrollment for Polyarticular JIA Subjects Aged 2 to <4 Years (Registry 20021626): Number (%) of Subjects

Age at Time of Enrollment (Months)	MTX Only (N=22)	ETN Only (N=4)	ETN+MTX (N=13)	MTX Only to ETN+MTX (N=6)	MTX Only to ETN Only (N=2)
≥24 to <27	5 (22.7)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)
≥27 to <30	2 (9.1)	0 (0.0)	1 (7.7)	1 (16.7)	0 (0.0)
≥30 to <33	3 (13.6)	1 (25.0)	4 (30.8)	0 (0.0)	0 (0.0)
≥33 to <36	4 (18.2)	1 (25.0)	1 (7.7)	0 (0.0)	0 (0.0)
≥36 to <39	1 (4.5)	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥39 to <42	2 (9.1)	0 (0.0)	2 (15.4)	1 (16.7)	1 (50.0)
≥42 to <45	2 (9.1)	0 (0.0)	1 (7.7)	2 (33.3)	0 (0.0)
≥45 to <48	3 (13.6)	0 (0.0)	3 (23.1)	1 (16.7)	0 (0.0)
≥48	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (50.0)

Most subjects in both the overall population and the subpopulation were already on treatment at baseline of the registry. Of the subjects aged 2 to <4 years, 100% in the MTX only arm were on MTX; 100% in the etanercept only arm were on etanercept; and 100% in the etanercept + MTX arm were on etanercept or MTX, respectively. In addition, 83.3% of subjects in the etanercept only arm had received MTX prior to baseline.

A very high percentage of this subgroup was on treatment prior baseline in this study, as was the case for the overall population and so the interpretation of efficacy is limited. All patients in the etanercept containing arms were on treatment prior to entry into the study for an average time of between approximately 1 to 3 months; the longest duration in one subject was 192 days.

Subjects in the etanercept only and etanercept + MTX arms received MTX for a longer period of time before entering the registry as compared to the MTX only arm (158.80, 273.53, and 63.73 days, respectively). Subjects in the etanercept + MTX arm had the greatest prior MTX exposure. The duration of prior MTX use is consistent with the longer disease duration in the etanercept only and etanercept + MTX arms as compared to the MTX only arm. The mean ± SD number of active joints at baseline for subjects aged 2 to <4 years was 13.7 ± 9.7, 5.3 ± 6.7, and 10.4 ± 9.5 for the MTX only, etanercept only and etanercept + MTX treatment arms, respectively.

This is consistent with the overall population in whom the mean ± SD number of active joints at baseline was 9.1 ± 9.2, 8.4 ± 9.8, and 9.5 ± 9.8 active joint for the MTX only, etanercept only and etanercept + MTX treatment arms, respectively.

Discontinuations

The most common reasons for discontinuation among polyarticular JIA subjects aged 2 to <4 years were "insufficient therapeutic effect" and "other".

Overall, a higher percentage of subjects discontinued from the MTX only arm than from either of the etanercept arms. In addition, according to Kaplan-Meier plots, subjects in the MTX arm withdrew earlier than those in either of the etanercept arms.

A higher percentage of subjects completed the study in the etanercept-containing arms (63.2 – 66.7%) than the MTX only arm (27.3%). Insufficient therapeutic response was commonest single reason for discontinuation in the MTX only group. Although the numbers are small particularly in the etanercept only group (n=4), similar to the overall population there is evidence of "remission" in 9-10.5%.

A Kaplan-Meier plot of study discontinuation for subjects aged 2 to <4 years shows that the rate of discontinuation was greatest for the MTX only arm, and that subjects in the MTX only arm withdrew

earlier in the registry (Figure 5). After 1 year, approximately 35% of the MTX subjects had withdrawn. However, only approximately 15% and 5% of subjects had withdrawn from the etanercept only and etanercept + MTX arms, respectively. At year 3 of the registry, approximately 80% of the MTX subjects, 30% of the etanercept only subjects and 65% of the etanercept + MTX subjects had withdrawn. The Kaplan-Meier plot of study discontinuation for the overall population demonstrates similar results (Figure 6).

Figure 5: Kaplan-Meier Plot for Time to Treatment Discontinuation for Subjects Aged 2 to <4 Years in Registry 20021626 (47 Enrolled Subjects)

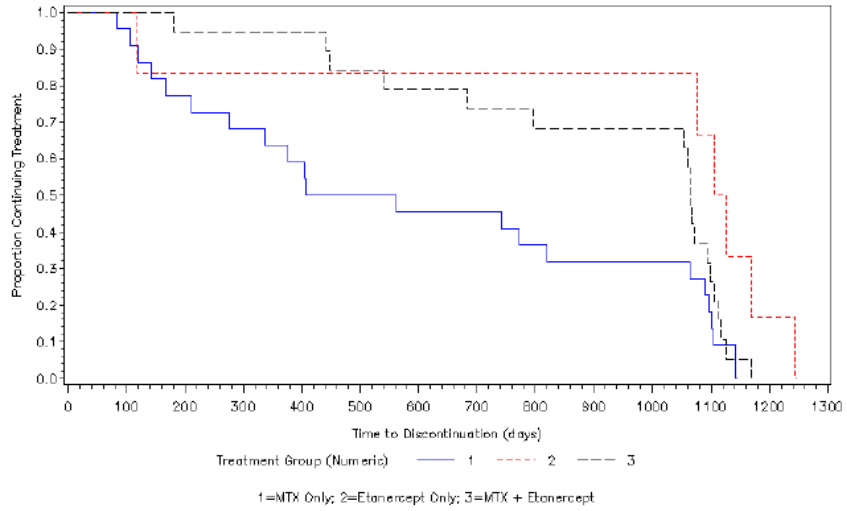
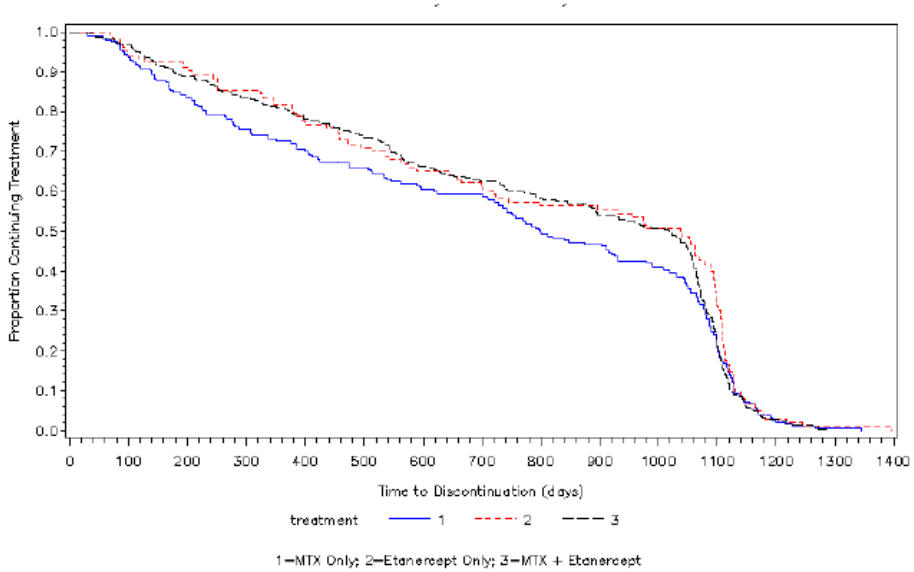


Figure 6 Kaplan-Meier Plot for Time to Treatment Discontinuation for All 594 Enrolled Subjects in Registry 20021626



A similar Kaplan-Meier profile was seen when those subjects who re-enrolled in the etanercept only or etanercept + MTX arm were excluded (Figures 7 and 8).

Figure 7 Kaplan-Meier Plot for Time to Treatment Discontinuation for Subjects Aged 2 to <4 Years in Registry 20026126 (39 Unique Subjects)

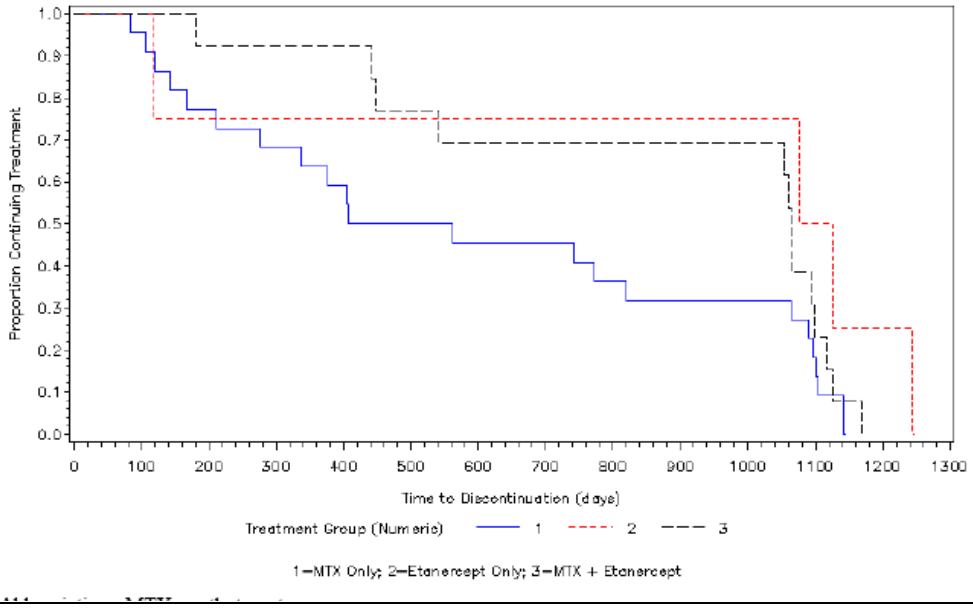
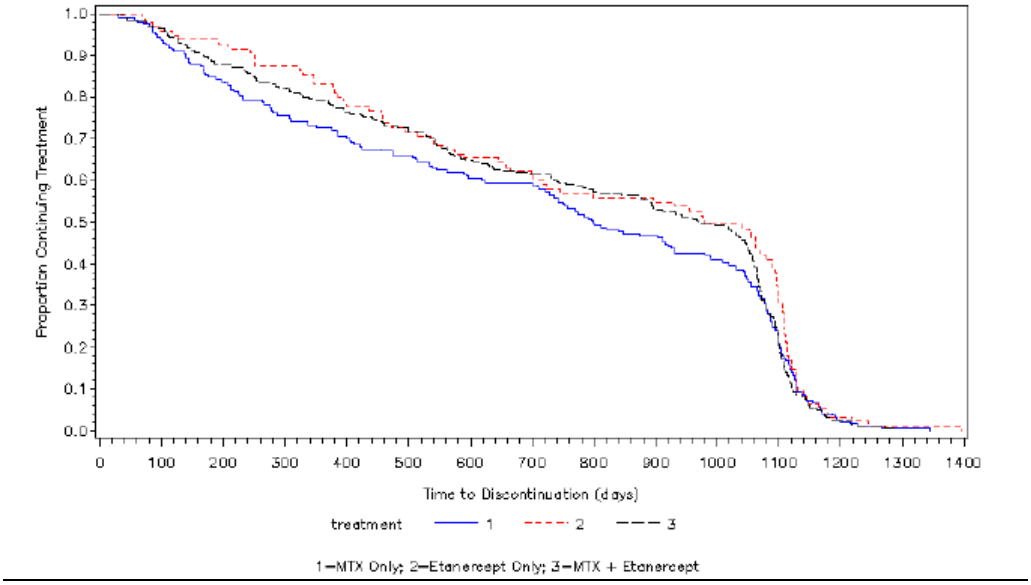


Figure 8 Kaplan-Meier Plot for Time to Treatment Discontinuation for All 562 Unique Subjects in Registry 20021626



EFFICACY RESULTS IN THE 2 TO <4 YEAR SUBGROUP

A limited set of efficacy parameters, including Physician Global Assessment of Disease Activity (PGA) and joint assessment, and health outcomes assessments including Paediatric Quality of Life (PedsQL), were collected and are summarized below for both the subgroup of polyarticular JIA subjects aged 2 to <4 years as well as for the overall population.

Physician Global Assessment of Disease Activity

PGA was collected from all subjects receiving treatment at the time of the evaluation. Because there were a large number of discontinuations by year 3, especially in the MTX group for the reason of insufficient therapeutic response, the number of subjects with available PGA data at year 3 is small. At year 1, when there were more subjects with available PGA data, the mean (SD) percentage

improvement in the PGA was 62.5% (28.5) for the etanercept only arm and 68.5% (34.8) for the etanercept + MTX arm versus 26.0% (85.1) for the MTX only arm. At year 3, the mean (SD) percentage improvement in the PGA for polyarticular JIA subjects aged 2 to <4 years was greater for both etanercept treatment arms compared with the MTX only arm: 91.7% (16.7) for the etanercept only arm and 89.6% (23.4) for the etanercept + MTX arm versus 66.7% (42.5) for the MTX only arm.

The numbers remaining are smaller at 36 months, but the efficacy is consistent with results from the overall population (Table 8).

Table 8. Percentage Improvement of Physician Global Assessment of Disease Activity for Polyarticular JIA Subjects Aged 2 to <4 Years in Registry 20021626

Visit		Methotrexate Only (N=22)[a]	Etanercept Only (N=6)[b]	Etanercept + Methotrexate (N=19)[b]
Month 3	n	16	5	16
	Mean	31.6	48.3	27.7
	SD	83.6	30.3	52.9
	SE	20.9	13.5	13.2
	95% CI Mean	-12.9, 76.2	10.7, 85.9	-0.5, 55.9
	Median	45.0	33.3	29.2
	Min, Max	-250, 100	25, 100	-75, 100
Month 6	n	14	4	18
	Mean	63.9	50.0	46.1
	SD	31.9	43.0	56.3
	SE	8.5	21.5	13.3
	95% CI Mean	45.5, 82.3	-18.5, 118.5	18.0, 74.1
	Median	64.6	50.0	50.0
	Min, Max	-17, 100	0, 100	-133, 100
Month 9	n	13	5	15
	Mean	64.8	60.0	66.4
	SD	36.4	30.3	38.5
	SE	10.1	13.5	9.9
	95% CI Mean	42.9, 86.8	22.4, 97.6	45.1, 87.7
	Median	75.0	50.0	80.0
	Min, Max	0, 100	33, 100	-33, 100
Month 12	n	11	4	16
	Mean	26.0	62.5	68.5
	SD	85.1	28.5	34.8
	SE	25.7	14.2	8.7
	95% CI Mean	-31.2, 83.1	17.2, 107.8	49.9, 87.1
	Median	66.7	58.3	81.7
	Min, Max	-200, 100	33, 100	0, 100
Month 18	n	9	5	15
	Mean	21.8	35.0	46.0
	SD	125.8	93.6	88.6
	SE	41.9	41.9	22.9
	95% CI Mean	-74.9, 118.5	-81.2, 151.2	-3.0, 95.1
	Median	66.7	66.7	85.7
	Min, Max	-300, 100	-125, 100	-167, 100
Month 24	n	5	4	13
	Mean	69.0	83.3	64.9
	SD	35.5	33.3	64.0
	SE	15.9	16.7	17.7
	95% CI Mean	25.0, 113.1	30.3, 136.4	26.2, 103.5
	Median	83.3	100.0	83.3
	Min, Max	29, 100	33, 100	-133, 100
Month 30	n	5	5	13
	Mean	35.0	35.0	74.7
	SD	74.2	93.6	36.2
	SE	33.2	41.9	10.0
	95% CI Mean	-57.1, 127.1	-81.2, 151.2	52.8, 96.5
	Median	50.0	66.7	80.0
	Min, Max	-75, 100	-125, 100	-33, 100
Month 36	n	5	4	12
	Mean	66.7	91.7	89.6
	SD	42.5	16.7	23.4
	SE	19.0	8.3	6.8
	95% CI Mean	13.9, 119.4	65.1, 118.2	74.7, 104.5
	Median	83.3	100.0	100.0
	Min, Max	0, 100	67, 100	25, 100
Early Discontinuation	n	14	1	4
	Mean	12.1	0.0	-10.4
	SD	72.7		111.7
	SE	19.4		55.8
	95% CI Mean	-29.8, 54.1		-188.1, 167.3
	Median	22.9	0.0	-4.2
	Min, Max	-200, 100	0, 0	-133, 100

Abbreviations: CI=confidence interval; JIA=juvenile idiopathic arthritis; SD=standard deviation; SE=standard error.

a. N=number of subjects assigned to methotrexate only arm at original baseline.

b. N=number of subjects receiving the respective treatment at any time during the registry (ie, includes re-enrolled subjects).

A comparable result was observed at year 3 for the overall population: 61% for the MTX only arm, 61% for the etanercept only arm and 55% for the etanercept + MTX arm (Table 9).

Table 9. Percentage Improvement of Physician Global Assessment of Disease Activity

Visit		Methotrexate Only (N = 197)	Etanercept Only (N = 103)	Etanercept + Methotrexate (N = 294)
Month 12 (Year 1)	n	113	68	203
	Mean	55.7	44.2	53.8
	SD	57.8	73.5	47.0
	SE	5.4	8.9	3.3
	95% CI Mean	44.9, 66.4	26.4, 62.0	47.3, 60.3
	Median	71.4	66.7	66.7
	Min, Max	-250, 100	-400, 100	-100, 100
Month 24 (Year 2)	n	83	49	141
	Mean	63.6	59.6	51.0
	SD	62.4	42.3	67.8
	SE	6.9	6.0	5.7
	95% CI Mean	50.0, 77.3	47.4, 71.7	39.7, 62.3
	Median	77.8	75.0	71.4
	Min, Max	-400, 100	-50, 100	-300, 100
Month 36 (Year 3)	n	64	46	119
	Mean	60.7	60.9	55.4
	SD	45.0	44.1	53.3
	SE	5.6	6.5	4.9
	95% CI Mean	49.4, 71.9	47.8, 74.0	45.8, 65.1
	Median	73.2	71.4	66.7
	Min, Max	-100, 100	-50, 100	-200, 100

N = Number of subjects enrolling into the registry and completing at least 1 evaluation while on methotrexate or etanercept

Paediatric Quality of Life

The PedsQL Arthritis Module scores were summarized by subdomain (daily activities, pain and hurt, and treatment) for the toddler age group of 2 to <4 years old. Following 3 years of treatment, polyarticular JIA subjects aged 2 to <4 years in all treatment arms had similar improvements in the 3 subdomains (Tables 10, 11 and 12).

Table 10. Paediatric Quality of Life, Arthritis Module - Part II - Toddler Report for Polyarticular JIA Subjects Aged 2 to <4 Years in Registry 20021626 - Subdomain: Daily Activities

Visit		Methotrexate Only (N=22)[a]	Etanercept Only (N=6)[b]	Etanercept + Methotrexate (N=19)[b]
Baseline	n	20	6	18
	Mean	73.50	83.33	73.89
	SD	27.91	20.41	27.58
	SE	6.24	8.33	6.50
	95% CI Mean	60.44, 86.56	61.91, 104.75	60.18, 87.60
	Median	85.00	87.50	82.50
	Min, Max	15.0, 100.0	45.0, 100.0	15.0, 100.0
Month 3	n	15	6	17
	Mean	85.08	88.33	77.94
	SD	17.09	14.38	23.32
	SE	4.41	5.87	5.66
	95% CI Mean	75.62, 94.55	73.25, 103.42	65.95, 89.93
	Median	90.00	95.00	85.00
	Min, Max	45.0, 100.0	70.0, 100.0	40.0, 100.0
Month 6	n	13	3	18
	Mean	84.62	83.33	85.28
	SD	18.76	20.82	14.60
	SE	5.20	12.02	3.44
	95% CI Mean	73.28, 95.95	31.62, 135.04	78.02, 92.54
	Median	100.00	90.00	87.50
	Min, Max	55.0, 100.0	60.0, 100.0	55.0, 100.0
Month 9	n	13	4	13
	Mean	85.38	83.75	90.00
	SD	20.46	17.02	12.42
	SE	5.67	8.51	3.44
	95% CI Mean	73.02, 97.75	56.67, 110.83	82.50, 97.50
	Median	100.00	87.50	95.00
	Min, Max	40.0, 100.0	60.0, 100.0	65.0, 100.0
Month 12	n	10	2	14
	Mean	90.00	82.50	89.64
	SD	11.55	17.68	15.38
	SE	3.65	12.50	4.11
	95% CI Mean	81.74, 98.26	-76.33, 241.33	80.77, 98.52
	Median	95.00	82.50	100.00
	Min, Max	75.0, 100.0	70.0, 95.0	50.0, 100.0
Month 18	n	9	5	12
	Mean	87.78	89.00	95.52
	SD	15.83	11.40	6.65
	SE	5.28	5.10	1.92
	95% CI Mean	75.61, 99.95	74.84, 103.16	91.30, 99.74
	Median	100.00	90.00	100.00
	Min, Max	60.0, 100.0	75.0, 100.0	81.3, 100.0
Month 24	n	6	3	10
	Mean	85.00	91.67	94.50
	SD	16.73	7.64	8.32
	SE	6.83	4.41	2.63
	95% CI Mean	67.44, 102.56	72.69, 110.64	88.55, 100.45
	Median	87.50	90.00	97.50
	Min, Max	65.0, 100.0	85.0, 100.0	75.0, 100.0
Month 30	n	5	4	11
	Mean	92.00	76.25	95.91
	SD	13.04	16.01	6.64
	SE	5.83	8.00	2.00
	95% CI Mean	75.81, 108.19	50.78, 101.72	91.45, 100.37
	Median	100.00	70.00	100.00
	Min, Max	70.0, 100.0	65.0, 100.0	80.0, 100.0
Month 36	n	6	3	11
	Mean	94.17	93.33	95.45
	SD	10.21	11.55	7.89
	SE	4.17	6.67	2.38
	95% CI Mean	83.46, 104.88	64.65, 122.02	90.15, 100.76
	Median	100.00	100.00	100.00
	Min, Max	75.0, 100.0	80.0, 100.0	80.0, 100.0
Early Discontinuation	n	12	1	4
	Mean	86.67	100.00	83.75
	SD	17.49		26.26
	SE	5.05		13.13
	95% CI Mean	75.55, 97.78		41.96, 125.54
	Median	95.00	100.00	95.00
	Min, Max	40.0, 100.0	100.0, 100.0	45.0, 100.0

Abbreviations: CI=confidence interval; JIA=juvenile idiopathic arthritis; SD=standard deviation; SE=standard error.

a. N=number of subjects assigned to methotrexate only arm at original baseline.

b. N=number of subjects receiving the respective treatment at any time during the registry (ie, includes re-enrolled subjects).

Table 11. Paediatric Quality of Life, Arthritis Module - Part II - Toddler Report for Polyarticular JIA Subjects Aged 2 to <4 Years in Registry 20021626 - Subdomain: Pain and Hurt

Visit		Methotrexate Only (N=22)[a]	Etanercept Only (N=6)[b]	Etanercept + Methotrexate (N=19)[b]
Baseline	n	20	6	18
	Mean	39.69	57.29	50.69
	SD	28.84	34.10	28.67
	SE	6.45	13.92	6.76
	95% CI Mean	26.19, 53.18	21.51, 93.08	36.44, 64.95
	Median	31.25	62.50	43.75
	Min, Max	0.0, 100.0	6.3, 100.0	6.3, 100.0
Month 3	n	15	6	17
	Mean	73.75	78.13	70.59
	SD	23.65	18.85	21.85
	SE	6.11	7.70	5.30
	95% CI Mean	60.66, 86.84	58.34, 97.91	59.35, 81.82
	Median	68.75	81.25	68.75
	Min, Max	18.8, 100.0	43.8, 100.0	12.5, 100.0
Month 6	n	13	3	18
	Mean	77.88	64.58	73.61
	SD	26.84	37.67	22.64
	SE	7.44	21.75	5.34
	95% CI Mean	61.67, 94.10	-29.00, 158.17	62.35, 84.87
	Median	87.50	68.75	68.75
	Min, Max	6.3, 100.0	25.0, 100.0	18.8, 100.0
Month 9	n	13	4	14
	Mean	80.29	76.56	83.04
	SD	19.07	21.88	19.06
	SE	5.29	10.94	5.09
	95% CI Mean	68.77, 91.81	41.75, 111.37	72.03, 94.04
	Median	75.00	78.13	90.63
	Min, Max	50.0, 100.0	50.0, 100.0	50.0, 100.0
Month 12	n	10	2	14
	Mean	73.13	75.00	80.80
	SD	30.48	8.84	18.42
	SE	9.64	6.25	4.92
	95% CI Mean	51.32, 94.93	-4.41, 154.41	70.17, 91.44
	Median	84.38	75.00	84.38
	Min, Max	0.0, 100.0	68.8, 81.3	50.0, 100.0
Month 18	n	9	5	12
	Mean	90.28	71.25	74.48
	SD	16.27	27.81	26.17
	SE	5.42	12.44	7.56
	95% CI Mean	77.77, 102.79	36.72, 105.78	57.85, 91.11
	Median	100.00	62.50	78.13
	Min, Max	56.3, 100.0	37.5, 100.0	18.8, 100.0
Month 24	n	6	3	10
	Mean	91.67	79.17	76.88
	SD	9.41	18.04	14.75
	SE	3.84	10.42	4.66
	95% CI Mean	81.79, 101.54	34.35, 123.99	66.33, 87.42
	Median	93.75	68.75	75.00
	Min, Max	75.0, 100.0	68.8, 100.0	50.0, 100.0
Month 30	n	5	4	11
	Mean	72.50	65.63	79.55
	SD	22.79	34.80	13.14
	SE	10.19	17.40	3.96
	95% CI Mean	44.20, 100.80	10.25, 121.00	70.72, 88.37
	Median	75.00	71.88	81.25
	Min, Max	43.8, 100.0	18.8, 100.0	56.3, 100.0
Month 36	n	6	3	11
	Mean	88.54	77.08	81.82
	SD	16.96	15.73	14.10
	SE	6.93	9.08	4.25
	95% CI Mean	70.74, 106.34	38.01, 116.16	72.34, 91.29
	Median	93.75	75.00	81.25
	Min, Max	56.3, 100.0	62.5, 93.8	62.5, 100.0
Early Discontinuation	n	12	1	4
	Mean	67.19	81.25	62.50
	SD	34.66		37.85
	SE	10.00		18.92
	95% CI Mean	45.17, 89.21		2.28, 122.72
	Median	84.38	81.25	65.63
	Min, Max	6.3, 100.0	81.3, 81.3	18.8, 100.0

Abbreviations: CI=confidence interval; JIA=juvenile idiopathic arthritis; SD=standard deviation; SE=standard error.

a. N=number of subjects assigned to methotrexate only arm at original baseline.

b. N=number of subjects receiving the respective treatment at any time during the registry (ie, includes re-enrolled subjects).

Table 12. Paediatric Quality of Life, Arthritis Module - Part II - Toddler Report for Polyarticular JIA Subjects Aged 2 to <4 Years in Registry 20021626 - Subdomain: Treatment

Visit		Methotrexate Only (N=22)[a]	Etanercept Only (N=6)[b]	Etanercept + Methotrexate (N=19)[b]
Baseline	n	20	6	18
	Mean	60.35	49.17	59.79
	SD	27.32	25.18	24.44
	SE	6.11	10.28	5.76
	95% CI Mean	47.57, 73.14	22.74, 75.59	47.64, 71.94
	Median	64.17	47.50	65.00
	Min, Max	10.0, 100.0	15.0, 90.0	20.0, 100.0
Month 3	n	14	6	17
	Mean	67.50	66.67	65.59
	SD	26.51	26.01	19.36
	SE	7.09	10.62	4.69
	95% CI Mean	52.19, 82.81	39.37, 93.97	55.64, 75.54
	Median	72.50	70.00	65.00
	Min, Max	15.0, 100.0	35.0, 100.0	35.0, 100.0
Month 6	n	13	3	18
	Mean	67.69	81.67	68.33
	SD	24.46	16.07	17.06
	SE	6.78	9.28	4.02
	95% CI Mean	52.91, 82.47	41.74, 121.59	59.85, 76.82
	Median	75.00	75.00	65.00
	Min, Max	25.0, 100.0	70.0, 100.0	45.0, 100.0
Month 9	n	13	4	14
	Mean	67.31	71.25	78.93
	SD	22.32	31.46	14.83
	SE	6.19	15.73	3.96
	95% CI Mean	53.82, 80.80	21.19, 121.31	70.37, 87.49
	Median	70.00	82.50	77.50
	Min, Max	35.0, 100.0	25.0, 95.0	60.0, 100.0
Month 12	n	10	2	14
	Mean	70.00	82.50	77.86
	SD	24.49	3.54	17.18
	SE	7.75	2.50	4.59
	95% CI Mean	52.48, 87.52	50.73, 114.27	67.94, 87.77
	Median	70.00	82.50	77.50
	Min, Max	30.0, 100.0	80.0, 85.0	40.0, 100.0
Month 18	n	9	5	12
	Mean	83.33	67.00	80.83
	SD	21.51	20.49	17.69
	SE	7.17	9.17	5.11
	95% CI Mean	66.80, 99.86	41.55, 92.45	69.59, 92.07
	Median	90.00	60.00	82.50
	Min, Max	40.0, 100.0	40.0, 90.0	45.0, 100.0
Month 24	n	6	3	9
	Mean	75.83	68.33	87.22
	SD	24.78	24.66	10.34
	SE	10.12	14.24	3.45
	95% CI Mean	49.83, 101.84	7.06, 129.60	79.27, 95.17
	Median	82.50	80.00	90.00
	Min, Max	40.0, 100.0	40.0, 85.0	70.0, 100.0
Month 30	n	5	4	11
	Mean	82.00	62.81	83.64
	SD	20.49	13.01	12.67
	SE	9.17	6.50	3.82
	95% CI Mean	56.55, 107.45	42.12, 83.51	75.13, 92.15
	Median	90.00	60.63	85.00
	Min, Max	60.0, 100.0	50.0, 80.0	70.0, 100.0
Month 36	n	6	3	11
	Mean	89.17	93.33	81.25
	SD	20.10	5.77	20.24
	SE	8.21	3.33	6.10
	95% CI Mean	68.07, 110.26	78.99, 107.68	67.65, 94.85
	Median	100.00	90.00	90.00
	Min, Max	50.0, 100.0	90.0, 100.0	43.8, 100.0
Early Discontinuation	n	12	1	4
	Mean	62.08	60.00	81.25
	SD	29.03		14.36
	SE	8.38		7.18
	95% CI Mean	43.64, 80.53		58.40, 104.10
	Median	67.50	60.00	80.00
	Min, Max	15.0, 100.0	60.0, 60.0	65.0, 100.0

Abbreviations: CI=confidence interval; JIA=juvenile idiopathic arthritis; SD=standard deviation; SE=standard error.

a. N=number of subjects assigned to methotrexate only arm at original baseline.

b. N=number of subjects receiving the respective treatment at any time during the registry (ie, includes re-enrolled subjects).

A comparable result was observed for the overall population where subjects in all treatment arms had similar improvements in these 3 subdomains at year 3.

Patient Quality of Life Assessments

The PedsQL Core Module and PedsQL Arthritis Module scores were summarized for the following age groups: toddler (≤4 years old), young children (5 to 7 years old), children (8 to 12 years old), and

teens (13 to 18 years old). An overall summary of these 2 quality of life assessments was also performed.

At baseline for the PedsQL Core Module, subjects in the 3 treatment arms had comparable scores. Following treatment, subjects in all treatment arms had improvement on all domains including physical, psychosocial, emotional, social and school at each visit. Results of additional analysis by age and treatment arm were consistent with the overall findings.

At baseline for the PedsQL Arthritis Module, subjects in 3 treatment arms had comparable scores on all domains (pain and hurt, daily activities, treatment, worry, and communication). Following treatment, subjects in all treatment arms had improvement on all domains at each visit. Results of additional analysis by age and treatment arm were consistent with the overall findings.

Efficacy Analysis of 8 subjects who switched treatment and re-enrolled

Eight of the 22 polyarticular JIA subjects aged 2 to <4 years who were receiving MTX at baseline were allowed to discontinue from the MTX only arm and to re-enroll into the etanercept only or etanercept + MTX arm.

The results show that at year 3, the mean percentage improvement in the PGA for the subjects who re-enrolled in the etanercept only or etanercept + MTX arm (100% and 97.5%, respectively) was similar to that for the subjects who were originally assigned to the etanercept only or etanercept + MTX arm (83.3% and 85.6%, respectively) (Table13).

Table 13. Percentage Improvement of Physician Global Assessment of Disease Activity for Polyarticular JIA Subjects Aged 2 to <4 Years in Registry 20021626, With Re-enrolled Subjects Presented Separately

Visit		Methotrexate Only (N=22) n/N1 (%)	Etanercept Only (N=4) n/N1 (%)	Etanercept + Methotrexate (N=13) n/N1 (%)	MTX Only to ETN Only (N=2) n/N1 (%)	MTX Only to ETN+MTX (N=6) n/N1 (%)
Month 3	n	16	3	10	2	6
	Mean	31.6	52.8	14.6	41.7	49.5
	SD	83.6	41.1	51.1	11.8	52.7
	SE	20.9	23.7	16.2	8.3	21.5
	95% CI Mean	-12.9, 76.2	-49.3, 154.9	-22.0, 51.1	-64.2, 147.6	-5.8, 104.8
	Median	45.0	33.3	19.6	41.7	69.0
	Min, Max	-250, 100	25, 100	-75, 100	33, 50	-50, 90
Month 6	n	14	2	12	2	6
	Mean	63.9	50.0	32.0	50.0	74.1
	SD	31.9	70.7	62.8	23.6	26.2
	SE	8.5	50.0	18.1	16.7	10.7
	95% CI Mean	45.5, 82.3	-585.3, 685.3	-7.9, 71.9	-161.8, 261.8	46.6, 101.6
	Median	64.6	50.0	50.0	50.0	85.7
	Min, Max	-17, 100	0, 100	-133, 100	33, 67	33, 100
Month 9	n	13	3	10	2	5
	Mean	64.8	61.1	55.4	58.3	88.5
	SD	36.4	34.7	42.6	35.4	13.7
	SE	10.1	20.0	13.5	25.0	6.1
	95% CI Mean	42.9, 86.8	-25.1, 147.3	24.9, 85.9	-259.3, 376.0	71.5, 105.5
	Median	75.0	50.0	53.6	58.3	90.0
	Min, Max	0, 100	33, 100	-33, 100	33, 83	67, 100
Month 12	n	11	3	10	1	6
	Mean	26.0	61.1	68.7	66.7	68.2
	SD	85.1	34.7	35.3		37.4
	SE	25.7	20.0	11.2		15.3
	95% CI Mean	-31.2, 83.1	-25.1, 147.3	43.5, 93.9		28.9, 107.5
	Median	66.7	50.0	77.5	66.7	84.5
	Min, Max	-200, 100	33, 100	0, 100	67, 67	0, 100
Month 18	n	9	3	10	2	5
	Mean	21.8	2.8	47.4	83.3	43.3
	SD	125.8	115.6	83.1	23.6	109.0
	SE	41.9	66.7	26.3	16.7	48.8
	95% CI Mean	-74.9, 118.5	-284.3, 289.9	-12.1, 106.9	-128.4, 295.1	-92.1, 178.7
	Median	66.7	33.3	82.9	83.3	100.0
	Min, Max	-300, 100	-125, 100	-167, 100	67, 100	-150, 100
Month 24	n	5	2	8	2	5
	Mean	69.0	66.7	52.7	100.0	84.3
	SD	35.5	47.1	80.2	0.0	15.6
	SE	15.9	33.3	28.4	0.0	7.0
	95% CI Mean	25.0, 113.1	-356.9, 490.2	-14.4, 119.8	100.0, 100.0	64.9, 103.6
	Median	83.3	66.7	90.0	100.0	83.3
	Min, Max	29, 100	33, 100	-133, 100	100, 100	67, 100

Visit		Methotrexate Only (N=22) n/N1 (%)	Etanercept Only (N=4) n/N1 (%)	Etanercept + Methotrexate (N=13) n/N1 (%)	MTX Only to ETN Only (N=2) n/N1 (%)	MTX Only to ETN+MTX (N=6) n/N1 (%)
Month 30	n	5	3	9	2	4
	Mean	35.0	-8.3	70.3	100.0	84.5
	SD	74.2	102.4	42.1	0.0	18.0
	SE	33.2	59.1	14.0	0.0	9.0
	95% CI Mean	-57.1, 127.1	-262.7, 246.0	37.9, 102.6	100.0, 100.0	55.9, 113.1
	Median	50.0	33.3	80.0	100.0	85.7
	Min, Max	-75, 100	-125, 67	-33, 100	100, 100	67, 100
Month 36	n	5	2	8	2	4
	Mean	66.7	83.3	85.6	100.0	97.5
	SD	42.5	23.6	28.2	0.0	5.0
	SE	19.0	16.7	10.0	0.0	2.5
	95% CI Mean	13.9, 119.4	-128.4, 295.1	62.0, 109.2	100.0, 100.0	89.5, 105.5
	Median	83.3	83.3	100.0	100.0	100.0
	Min, Max	0, 100	67, 100	25, 100	100, 100	90, 100
Early Discontinuation						
	n	14	1	2		2
	Mean	12.1	0.0	-104.2		83.3
	SD	72.7		41.2		23.6
	SE	19.4		29.2		16.7
	95% CI Mean	-29.8, 54.1		-474.8, 266.4		-128.4, 295.1
	Median	22.9	0.0	-104.2		83.3
	Min, Max	-200, 100	0, 0	-133, -75		67, 100

Abbreviations: ETN=etanercept; JIA=juvenile idiopathic arthritis; MTX=methotrexate; N=number of subjects enrolling into the registry and completing at least 1 evaluation while on methotrexate or etanercept; N1=number of subjects enrolling into the registry, completing at least 1 evaluation while on methotrexate or etanercept and having data available at each visit.

As was done with percentage improvement in mean PGA, an analysis was done in which the 8 polyarticular JIA subjects aged 2 to <4 years who discontinued from the MTX only arm and re-enrolled into the etanercept only or etanercept + MTX arm were summarized as separate treatment arms according to whether they had a PGA of zero over time. The results showed that subjects who switched from MTX to etanercept or etanercept + MTX had a similar treatment response as those who received etanercept or etanercept + MTX throughout the entire registry. Overall, between 50% and 100% of the subjects aged 2 to <4 years in each treatment arm had a PGA score of zero by year 3 (Table 14).

Table 14. Subjects With Total Physician Global Assessment = 0 Over Time for Polyarticular JIA Subjects Aged 2 to <4 Years in Registry 20021626, With Re-enrolled Subjects Presented Separately

Visit	Methotrexate Only (N=22) n/N1 (%)	Etanercept Only (N=4) n/N1 (%)	Etanercept + Methotrexate (N=13) n/N1 (%)	MTX Only to ETN Only (N=2) n/N1 (%)	MTX Only to ETN+MTX (N=6) n/N1 (%)
Baseline	1/22 (4.5)	1/4 (25.0)	1/13 (7.7)	0/2 (0.0)	0/6 (0.0)
Month 3	3/18 (16.7)	1/4 (25.0)	1/12 (8.3)	0/2 (0.0)	0/6 (0.0)
Month 6	3/16 (18.8)	1/2 (50.0)	1/13 (7.7)	0/2 (0.0)	1/6 (16.7)
Month 9	5/14 (35.7)	1/3 (33.3)	3/11 (27.3)	0/2 (0.0)	2/5 (40.0)
Month 12	2/12 (16.7)	1/3 (33.3)	4/11 (36.4)	0/1 (0.0)	1/6 (16.7)
Month 18	2/11 (18.2)	1/3 (33.3)	4/10 (40.0)	1/2 (50.0)	3/5 (60.0)
Month 24	2/7 (28.6)	1/2 (50.0)	4/8 (50.0)	2/2 (100.0)	2/5 (40.0)
Month 30	2/7 (28.6)	0/3 (0.0)	3/9 (33.3)	2/2 (100.0)	2/4 (50.0)
Month 36	3/6 (50.0)	1/2 (50.0)	6/8 (75.0)	2/2 (100.0)	3/4 (75.0)
Early Discontinuation	2/14 (14.3)	1/1 (100.0)	0/3 (0.0)		1/2 (50.0)

Abbreviations: ETN=etanercept; JIA=juvenile idiopathic arthritis; MTX=methotrexate; N=number of subjects enrolling into the registry and completing at least 1 evaluation while on methotrexate or etanercept; N1=number of subjects enrolling into the registry, completing at least 1 evaluation while on methotrexate or etanercept and having data available at each visit.

Similarly, in the overall population, between 30% and 80% of subjects in each treatment arm had a PGA score of zero at year 3 (Table 15).

Table 15. Subjects with Physician Global Assessment = 0, Over Time Overall population.

Visit	Methotrexate Only (N = 197) n/N1 (%)	Etanercept Only (N = 95) n/N1 (%)	Etanercept + Methotrexate (N = 270) n/N1 (%)	MTX Only to ETN+MTX (N = 24) n/N1 (%)	MTX Only to ETN Only (N = 8) n/N1 (%)
Baseline	14/197 (7.1%)	7/95 (7.4%)	18/270 (6.7%)	1/24 (4.2%)	0/8 (0.0%)
Month 3	21/175 (12.0%)	16/86 (18.6%)	25/246 (10.2%)	2/24 (8.3%)	0/6 (0.0%)
Month 6	39/145 (26.9%)	18/79 (22.8%)	37/215 (17.2%)	4/23 (17.4%)	1/6 (16.7%)
Month 9	43/131 (32.8%)	20/71 (28.2%)	44/202 (21.8%)	6/22 (27.3%)	1/5 (20.0%)
Month 12	44/124 (35.5%)	18/68 (26.5%)	54/200 (27.0%)	9/23 (39.1%)	3/4 (75.0%)
Month 18	46/114 (40.4%)	25/58 (43.1%)	54/167 (32.3%)	9/18 (50.0%)	3/5 (60.0%)
Month 24	40/93 (43.0%)	16/46 (34.8%)	44/143 (30.8%)	8/16 (50.0%)	4/5 (80.0%)
Month 30	31/74 (41.9%)	16/45 (35.6%)	33/131 (25.2%)	8/16 (50.0%)	4/5 (80.0%)
Month 36	31/67 (46.3%)	17/42 (40.5%)	35/115 (30.4%)	8/17 (47.1%)	4/5 (80.0%)
Early Discontinuation	23/104 (22.1%)	10/42 (23.8%)	16/118 (13.6%)	2/6 (33.3%)	0/3 (0.0%)

MTX = methotrexate
N = Number of subjects enrolling into the registry and completing at least 1 evaluation while on methotrexate or etanercept
N1 = Number of subjects enrolling into the registry, completing at least 1 evaluation while on methotrexate or etanercept and having data available at each visit

Total Joint Assessments

Per the protocol for registry 20021626, joint assessments were collected at baseline and at month 36 from all subjects receiving treatment at the time of the assessment; however, joint assessments were collected more frequently (i.e., at months 6, 12, 18, 24, and 30) from subjects who had previously participated in study 16.0028 (a JIA study that was terminated early because of slow enrollment). Based on the number of subjects who participated in study 16.0028 as well as those remaining on treatment at month 36, the data available for these analyses are extremely limited.

Number of Active Joints

The mean (SD) percentage improvement in the number of active joints at year 1 for polyarticular JIA subjects aged 2 to <4 was 69.86% (36.78) for the MTX only arm, 75% (0.00) for the etanercept only arm, and 87.04% (23.24) for the etanercept + MTX arm. At year 3, the mean (SD) percentage improvement in the number of active joints was 81.11% (31.10) for the MTX only arm, 100% (0.00) for the etanercept only arm, and 90.40% (28.62) for the etanercept + MTX arm (Table 16).

Table 16. Percentage Improvement of Paediatric Total Joint Assessment Over Time for Polyarticular JIA Subjects Aged 2 to <4 Years in Registry 20021626: Number of Active Joints

Visit		Methotrexate Only (N=22)[a]	Etanercept Only (N=6)[b]	Etanercept + Methotrexate (N=19)[b]
Month 6	n	9	1	9
	Mean	72.46	25.00	66.93
	SD	35.34		47.18
	SE	11.78		15.73
	95% CI Mean	45.29, 99.63		30.66, 103.19
	Median	82.14	25.00	100.00
	Min, Max	0.0, 100.0	25.0, 25.0	-33.3, 100.0
Month 12	n	6	1	9
	Mean	69.86	75.00	87.04
	SD	36.78		23.24
	SE	15.02		7.75
	95% CI Mean	31.26, 108.46		69.17, 104.90
	Median	77.40	75.00	100.00
	Min, Max	4.3, 100.0	75.0, 75.0	33.3, 100.0
Month 18	n	5	1	7
	Mean	68.86	75.00	33.33
	SD	30.50		149.07
	SE	13.64		56.34
	95% CI Mean	30.99, 106.72		-104.53, 171.20
	Median	60.00	75.00	100.00
	Min, Max	30.4, 100.0	75.0, 75.0	-300.0, 100.0
Month 24	n	4	1	7
	Mean	70.00	100.00	86.38
	SD	47.61		20.24
	SE	23.80		7.65
	95% CI Mean	-5.76, 145.76		67.67, 105.10
	Median	90.00	100.00	100.00
	Min, Max	0.0, 100.0	100.0, 100.0	50.0, 100.0
Month 30	n	4	1	6
	Mean	51.74	100.00	77.78
	SD	49.87		38.97
	SE	24.94		15.91
	95% CI Mean	-27.62, 131.10		36.88, 118.67
	Median	60.00	100.00	91.67
	Min, Max	-13.0, 100.0	100.0, 100.0	0.0, 100.0
Month 36	n	6	4	12
	Mean	81.11	100.00	90.40
	SD	31.10	0.00	28.62
	SE	12.70	0.00	8.26
	95% CI Mean	48.47, 113.75	100.00, 100.00	72.22, 108.59
	Median	93.33	100.00	100.00
	Min, Max	20.0, 100.0	100.0, 100.0	0.0, 100.0
Early Discontinuation	n	14	1	5
	Mean	37.64	0.00	35.00
	SD	55.65		79.14
	SE	14.87		35.39
	95% CI Mean	5.50, 69.77		-63.27, 133.27
	Median	38.46	0.00	66.67
	Min, Max	-47.4, 100.0	0.0, 0.0	-100.0, 100.0

Abbreviations: CI=confidence interval; JIA=juvenile idiopathic arthritis; SD=standard deviation; SE=standard error.

a. N=number of subjects assigned to methotrexate only arm at original baseline.

b. N=number of subjects receiving the respective treatment at any time during the registry (ie, includes re-enrolled subjects).

A comparable result was observed at year 3 for the overall population: 57%, 63%, and 59%, for the MTX only, etanercept only, and etanercept + MTX arms, respectively (Table 17).

Table 17. Percentage Improvement of Paediatric Total Joint Assessment Over Time - Joint Assessment Variable: Number of Active Joints

Visit		Methotrexate Only (N = 197)	Etanercept Only (N = 103)	Etanercept + Methotrexate (N = 294)
Month 12 (Year 1)	N	68	35	97
	Mean	62.96	53.94	36.24
	SD	51.60	50.13	106.88
	SE	6.26	8.47	10.85
	95% CI Mean	50.47, 75.45	36.72, 71.16	14.70, 57.78
	Median	100.00	75.00	66.67
	Min, Max	-100.0, 100.0	-100.0, 100.0	-700.0, 100.0
Month 24 (Year 2)	N	46	20	72
	Mean	71.58	32.31	67.77
	SD	56.91	221.91	52.69
	SE	8.39	49.62	6.21
	95% CI Mean	54.68, 88.48	-71.55, 136.17	55.39, 80.15
	Median	100.00	100.00	87.75
	Min, Max	-225.0, 100.0	-900.0, 100.0	-200.0, 100.0
Month 36 (Year 3)	N	65	46	128
	Mean	57.01	63.22	58.86
	SD	93.61	56.24	75.80
	SE	11.61	8.29	6.70
	95% CI Mean	33.82, 80.21	46.52, 79.92	45.60, 72.12
	Median	100.00	94.84	91.29
	Min, Max	-550.0, 100.0	-100.0, 100.0	-366.7, 100.0

N = Number of subjects enrolling into the registry and completing at least 1 evaluation while on methotrexate or etanercept

As was done with PGA, an analysis was done in which the 8 polyarticular JIA subjects aged 2 to <4 years who discontinued from the MTX only arm and re-enrolled into the etanercept only or etanercept + MTX arm were summarized as separate treatment arms according to whether they had zero active joints over time. The results showed that subjects who switched from MTX to etanercept or etanercept + MTX had a similar treatment response as those who had received etanercept or etanercept + MTX throughout the entire registry. Overall, 50% to 100% of the polyarticular JIA subjects aged 2 to <4 years in each treatment arm had zero active joints by year 3 (Table 18).

Table 18. Subjects With Total Active Joints = 0 Over Time for Polyarticular JIA Subjects Aged 2 to <4 Years in Registry 20021626, With Re-enrolled Subjects Presented Separately

Visit	Methotrexate Only (N=22) n/N1 (%)	Etanercept Only (N=4) n/N1 (%)	Etanercept + Methotrexate (N=13) n/N1 (%)	MTX Only to ETN Only (N=2) n/N1 (%)	MTX Only to ETN+MTX (N=6) n/N1 (%)
Baseline	0/22 (0.0)	2/4 (50.0)	0/13 (0.0)	0/2 (0.0)	0/6 (0.0)
Month 6	4/9 (44.4)		2/4 (50.0)	0/1 (0.0)	3/5 (60.0)
Month 12	2/6 (33.3)	0/1 (0.0)	3/4 (75.0)	0/1 (0.0)	3/5 (60.0)
Month 18	2/5 (40.0)	0/1 (0.0)	1/2 (50.0)	0/1 (0.0)	4/5 (80.0)
Month 24	2/4 (50.0)		1/2 (50.0)	1/1 (100.0)	3/5 (60.0)
Month 30	1/4 (25.0)	0/1 (0.0)	0/2 (0.0)	1/1 (100.0)	3/4 (75.0)
Month 36	3/6 (50.0)	2/2 (100.0)	6/8 (75.0)	2/2 (100.0)	3/4 (75.0)
Early Discontinuation	3/14 (21.4)	1/1 (100.0)	0/3 (0.0)		1/2 (50.0)

Abbreviations: ETN=etanercept; JIA=juvenile idiopathic arthritis; MTX=methotrexate; N=number of subjects enrolling into the registry and completing at least 1 evaluation while on methotrexate or etanercept; N1=number of subjects enrolling into the registry, completing at least 1 evaluation while on methotrexate or etanercept and having data available at each visit.

Similarly, the results for the overall population showed that 50% to 100% of subjects had zero active joints at year 3 (Table 19).

Table 19. Subjects with Total Active Joints = 0, Over Time. Overall population.

Visit	Methotrexate Only (N = 197) n/N1 (%)	Etanercept Only (N = 95) n/N1 (%)	Etanercept + Methotrexate (N = 270) n/N1 (%)	MTX Only to ETN+MTX (N = 24) n/N1 (%)	MTX Only to ETN Only (N = 8) n/N1 (%)
Baseline	23/197 (11.7%)	17/95 (17.9%)	33/270 (12.2%)	1/24 (4.2%)	0/8 (0.0%)
Month 6	35/79 (44.3%)	12/35 (34.3%)	32/106 (30.2%)	8/16 (50.0%)	0/3 (0.0%)
Month 12	47/68 (69.1%)	14/35 (40.0%)	34/89 (38.2%)	8/14 (57.1%)	2/3 (66.7%)
Month 18	40/59 (67.8%)	14/23 (60.9%)	36/73 (49.3%)	10/13 (76.9%)	2/3 (66.7%)
Month 24	28/50 (56.0%)	11/19 (57.9%)	26/65 (40.0%)	8/13 (61.5%)	3/3 (100.0%)
Month 30	22/39 (56.4%)	13/20 (65.0%)	18/55 (32.7%)	7/12 (58.3%)	2/3 (66.7%)
Month 36	43/66 (65.2%)	24/42 (57.1%)	58/115 (50.4%)	10/18 (55.6%)	5/5 (100.0%)
Early Discontinuation	29/103 (28.2%)	19/42 (45.2%)	34/118 (28.8%)	2/5 (40.0%)	0/3 (0.0%)

MTX = methotrexate
N = Number of subjects enrolling into the registry and completing at least 1 evaluation while on methotrexate or etanercept
N1 = Number of subjects enrolling into the registry, completing at least 1 evaluation while on methotrexate or etanercept and having data available at each visit

Limitation of Motion

The mean (SD) percentage improvement in joints with limitation of motion at year 1 for polyarticular JIA subjects aged 2 to <4 years was 80.00% (33.32) for the MTX only arm, 100% (0.00) for the etanercept only arm, and 58.04% (43.28) for the etanercept + MTX arm. At year 3, the mean (SD) percentage improvement in joints with limitation of motion was 91.11% (14.40) for the MTX only arm, 87.50% (25.00) for the etanercept only arm, and 79.96% (38.55) for the etanercept + MTX arm.

A comparable result was observed at year 3 for the overall population: 57%, 23%, and 43% for the MTX only, etanercept only, and etanercept + MTX arms, respectively (Table 20).

Table 20. Percentage Improvement of Paediatric Total Joint Assessment Over Time for Polyarticular JIA Subjects Aged 2 to <4 Years in Registry 20021626: Limitation of Motion

Visit		Methotrexate Only (N=22)[a]	Etanercept Only (N=6)[b]	Etanercept + Methotrexate (N=19)[b]
Month 6	n	9	1	9
	Mean	48.44	33.33	38.50
	SD	65.54		35.41
	SE	21.85		11.80
	95% CI Mean	-1.94, 98.82		11.28, 65.72
	Median	75.00	33.33	33.33
	Min, Max	-85.7, 100.0	33.3, 33.3	0.0, 92.9
Month 12	n	6	1	9
	Mean	80.00	100.00	58.04
	SD	33.32		43.28
	SE	13.60		14.43
	95% CI Mean	45.03, 114.97		24.78, 91.31
	Median	92.86	100.00	66.67
	Min, Max	14.3, 100.0	100.0, 100.0	0.0, 100.0
Month 18	n	5	1	6
	Mean	82.86	100.00	79.76
	SD	38.33		39.49
	SE	17.14		16.12
	95% CI Mean	35.26, 130.45		38.32, 121.20
	Median	100.00	100.00	96.43
	Min, Max	14.3, 100.0	100.0, 100.0	0.0, 100.0
Month 24	n	4	1	7
	Mean	57.14	100.00	60.20
	SD	85.71		50.15
	SE	42.86		18.95
	95% CI Mean	-79.25, 193.53		13.83, 106.58
	Median	100.00	100.00	100.00
	Min, Max	-71.4, 100.0	100.0, 100.0	0.0, 100.0
Month 30	n	4	1	6
	Mean	-47.86	100.00	60.00
	SD	171.32		48.99
	SE	85.66		20.00
	95% CI Mean	-320.47, 224.76		8.59, 111.41
	Median	14.29	100.00	80.00
	Min, Max	-300.0, 80.0	100.0, 100.0	0.0, 100.0
Month 36	n	6	4	12
	Mean	91.11	87.50	79.96
	SD	14.40	25.00	38.55
	SE	5.88	12.50	11.13
	95% CI Mean	76.00, 106.22	47.72, 127.28	55.47, 104.45
	Median	100.00	100.00	100.00
	Min, Max	66.7, 100.0	50.0, 100.0	0.0, 100.0

Visit		Methotrexate Only (N=22)[a]	Etanercept Only (N=6)[b]	Etanercept + Methotrexate (N=19)[b]
Early Discontinuation	n	13	1	4
	Mean	-58.60	0.00	70.83
	SD	243.77		39.38
	SE	67.61		19.69
	95% CI Mean	-205.91, 88.71		8.17, 133.50
	Median	25.00	0.00	83.33
	Min, Max	-800.0, 100.0	0.0, 0.0	16.7, 100.0

Abbreviations: CI=confidence interval; JIA=juvenile idiopathic arthritis; SD=standard deviation; SE=standard error.

a. N=number of subjects assigned to methotrexate only arm at original baseline.

b. N=number of subjects receiving the respective treatment at any time during the registry (ie, includes re-enrolled subjects).

Discussion on clinical efficacy

The registry baseline is not the true baseline for these patients as the majority were on treatment with either methotrexate or etanercept prior to entry into this open label trial. The indication for JIA is for those who have an inadequate response to, or who have proved intolerant of methotrexate. The fact that the majority of subjects who were in the etanercept-containing arm have received prior methotrexate does support the assumption that these cases responded inadequately to or were intolerant to MTX. Therefore while this trial provides limited evidence of efficacy the included group can be considered to reflect those who in clinical practice will be eligible for etanercept treatment.

Regarding the sample size, the numbers are considered sufficient to pick up a 1.9 increased event rate in the etanercept containing arms. No sample size calculation was done considering efficacy objectives due to the study design.

Less than half of the patients completed the study, the smallest proportion in the MTX arm. Discontinuation rates as a result of adverse events and refusals were similar in all three treatment arms. Discontinuation as a result of insufficient therapeutic response was commonest in the combined etanercept + MTX group. The breakdown of JIA subtypes in those who discontinued in each of the treatment arms as a result of insufficient response demonstrated that those with systemic onset and those with systemic course JIA had the highest rate of discontinuation due to insufficient therapeutic response in each of the three treatment arms.

In the whole population there are around 15% of patients in each group of treatment who discontinued the study due to "other reasons" and the majority of these cases were due to loss of follow-up.

The MAH was asked to discuss the issue on how long treatment should be continued once remission is achieved. The MAH has provided a comprehensive literature review and a post-hoc analysis of data from Study 16.0016 in response to the question. Although the literature does report cases where treatment can be discontinued, there are a high percentage of patients who do relapse. More formal study of this phenomenon should be conducted as this is an important point to address, but it is acknowledged that due to the rarity and heterogeneity of polyarticular JIA that this will be challenging data to collect. The post-hoc review of data from study 16.0016 shows that for those who have a substantial response to treatment (ACR 70), 21% maintain this ACR70 at day 180 following treatment withdrawal. The results are in keeping with the high rate of relapse from the literature. Further information on whether there are particular features in either the disease itself or the response to therapy (including length of and extent of response) that may be of use for further guidance as to when and how to withdraw therapy will be difficult to collect formally in polyarticular JIA in view of the rarity of the condition. However the MAH will contact the JIA registries to examine whether collection of additional efficacy (effectiveness) information to address these questions could be possible as described in the RMP.

The CHMP acknowledges that further guidance from the MAH on discontinuation of etanercept in the event of "remission" in JIA is not possible at this time. To reflect this lack of information the MAH has added the following sentence to section 5.1 of the SmPC:

"Additionally, studies have not been conducted to assess the effects of discontinuing or reducing the recommended dose of Enbrel following its long-term use in patients with JIA".

The MAH was also requested to discuss the length of time a patient with JIA should be treated before concluding that the patient is a non-responder. Bases on a literature review the MAH proposed to consider the discontinuation of the treatment in patients who show no response after 6 months. However the CHMP considered that advising ongoing treatment in non-responders for 6 months is difficult to justify, as etanercept is known to have a rapid onset of action with most cases showing benefit at 12 weeks and has a well described adverse safety profile. Alternative therapy is available for JIA cases that are considered to have failed anti-TNFs and so in line with ACR 2011 guidelines, a trial of etanercept for 4 months should be acceptable in accordance with the ACR guidance. This ensures that ineffective therapy is not continued long-term in children while also increasing slightly the numbers of patients who have a successful response. To reflect this information the MAH has added the following sentence to section 4.2 of the SmPC: *"Discontinuation of treatment should be considered in patients who show no response after 4 months".*

The changes in the paediatric life quality scores over time were minimal and no significant difference between the three treatment arms was evident. As the baseline data was not true baseline as all patients were already on treatment prior to entry, these results show no significant difference between the MTX group and the etanercept containing treatment arms.

Conclusion on clinical efficacy

In view of the open label nature of this trial and the fact that the majority of cases were on treatment prior to the registry study baseline, proof of efficacy cannot be formally demonstrated, as was performed in study 16.0016 and the main objective in the open label study 20021626 is safety. However the efficacy of the 2 to <4 year age group was consistent with the overall population, in whom efficacy has been demonstrated (in those aged 4 years and above with polyarticular JIA). Notably the overall population also included JIA subtype known not to be responsive to etanercept treatment namely systemic JIA and this subgroup accounted for between 6.6 and 11.2%.

The difficulty to carry out an adequate clinical trial in the target population is acknowledged and this is a limitation of the registry. However, considering the possible differences between children below 4 years and those above this age, it is unlikely that etanercept could modify its mechanism of action and consequently its pharmacodynamic effect, on the basis of physiological characteristics of the patients (2-4 years vs. older children). In addition, in the pathology of the disease there does not seem to be big differences with regard to age (at least in this case). Importantly, the efficacy data from the registry appear to confirm these statements.

In summary, despite the study's limitation, it is scientifically justified to conclude that the pathology of the disease, the physiological characteristics and the pharmacodynamics of the drug, should not be significantly different between children aged 2-3 years and those aged 4 years and above. The registry, which has shown efficacy and safety data of Enbrel in the target population, provides an acceptable level of support for this conclusion.

3.2.5 Clinical safety

Patient exposure

Because drug administration information was not collected in this study, the exposure of etanercept or methotrexate are estimated from the reported drug start date and end date under an assumption that the subject received the drug as prescribed. The exposure to investigational product was calculated as (the investigational product stop date - the investigational product start date + 1) / 365.25.

Using this formula, the mean (SD) years of exposure for each arm was as follows:

1.97 years (1.09) for the methotrexate only arm, 2.17 years (1.04) for the etanercept only arm, and 2.16 years (1.02) for the etanercept + methotrexate arm. The median (range) number of years exposed was 2.18 years (0.1 to 3.7) for the methotrexate only arm, 2.84 years (0.2 to 3.8 years) for the etanercept only arm, and 2.79 years (0.1 to 3.5) for the etanercept + methotrexate arm.

Adverse events

OVERALL POPULATION

Overall, the safety profiles of the subjects from the methotrexate, etanercept and etanercept plus methotrexate arm were similar, with no significant difference in exposure-adjusted rates of adverse events between the arms. No cases of lymphoma, tuberculosis, malignancy, or death were reported during the study. There were no cases of demyelinating disorders in the etanercept only arm or etanercept with methotrexate arm, but there was 1 case of optic neuritis in the methotrexate only arm.

All Adverse Events (Non-infectious)

The exposure-adjusted adverse event rate, excluding infectious adverse events, was similar between the methotrexate only arm and the etanercept only arm. The body system with the highest exposure-adjusted adverse event rates was nervous system. The preferred terms of abnormal liver function and increased SGPT (laboratory abnormalities ≥grade 2 were reported as adverse events) had the highest exposure-adjusted adverse event rates (2.06/100 subject-years).

In the whole population, the exposure-adjusted rate of non-infectious AEs was similar among groups, with a higher rate in the combination arm. Some AEs are increased in the etanercept group (nervous system and haemic and lymphatic system). The number of subjects reporting an adverse event was 43 (21.8%) for the methotrexate only arm, 26 (25.2%) for the etanercept only arm, and 78 (26.5%) for the etanercept + methotrexate arm.

Clinically Significant Adverse Events

An overall summary of selected adverse events, including the clinically significant adverse event categories, is presented in Table 21.

Table 21. Summary of Subject Incidence of Selected Adverse Events

	Methotrexate Only (N=197) n (%)	Etanercept Only or Etanercept + Methotrexate (N=397) n (%)	p-value [a]
Number of Subjects Reporting Adverse Events	43 (21.8)	104 (26.2)	0.2242
Infectious Episodes	4 (2.0)	15 (3.8)	0.3004
AEs Leading to Withdrawal from Drug	5 (2.5)	10 (2.5)	0.5794
All Serious Adverse Events	14 (7.1)	37 (9.3)	0.4384
Medically Important Infections	4 (2.0)	15 (3.8)	0.3004
Death	0 (0.0)	0 (0.0)	N/A
Autoimmune Diseases	15 (7.6)	21 (5.3)	0.6750
Grade 3 and 4 Adverse Events	13 (6.6)	40 (10.1)	0.1827
Cancers	0 (0.0)	0 (0.0)	N/A

Page 1 of 1

N = Number of subjects enrolling into the registry and completing at least 1 evaluation while on methotrexate or etanercept

[a] From logistic regression adjusted for age, sex, baseline disease characteristics and treatment crossover

Subpopulation aged 2 to <4 yrs with polyarticular JIA

Safety data were collected for all subjects who received treatment in the registry and are summarized below for both the subgroup of polyarticular JIA subjects aged 2 to <4 years as well as for the overall population. The summary includes noninfectious AEs, serious adverse events (SAEs), medically important infections, safety-related discontinuations, events of interest, and growth data. Unless otherwise stated, the number of subjects in a treatment group refers to the number of subjects receiving the respective treatment at any time during the registry.

Adverse Events

Noninfectious Adverse Events

The exposure-adjusted rate of AEs, excluding infections, for polyarticular JIA subjects aged 2 to <4 years was 22.02 per 100 subject-years for the MTX only arm, 0.0 per 100 subject-years for the etanercept only arm, and 4.22 per 100 subject-years for the etanercept + MTX arm (Table 22).

Table 22. Exposure-adjusted Rates of Adverse Events excluding infection for Polyarticular JIA Subjects Aged 2 to <4 Years in Registry 20021626

Body System Preferred Term	Methotrexate Only (Pt-yr=36.33) (N=22)[a] n (r)	Etanercept Only (Pt-yr=16.00) (N=6)[b] n (r)	Etanercept + Methotrexate (Pt-yr=47.36) (N=19)[b] n (r)
Total Number of Adverse Events	8 (22.02)	0 (0.0)	2 (4.22)
Urogenital System	1 (2.75)	0 (0.0)	1 (2.11)
Albuminuria	0 (0.0)	0 (0.0)	1 (2.11)
Nephrosis	1 (2.75)	0 (0.0)	0 (0.0)
Musculoskeletal System	0 (0.0)	0 (0.0)	1 (2.11)
Arthritis	0 (0.0)	0 (0.0)	1 (2.11)
Metabolic & Nutritional Disorders	5 (13.76)	0 (0.0)	0 (0.0)
LDH Increased	1 (2.75)	0 (0.0)	0 (0.0)
Porphyria	1 (2.75)	0 (0.0)	0 (0.0)
SGOT Increased	1 (2.75)	0 (0.0)	0 (0.0)
SGPT Increased	2 (5.50)	0 (0.0)	0 (0.0)
Hemic & Lymphatic System	1 (2.75)	0 (0.0)	0 (0.0)
ANA	1 (2.75)	0 (0.0)	0 (0.0)
Digestive System	1 (2.75)	0 (0.0)	0 (0.0)
Vomit	1 (2.75)	0 (0.0)	0 (0.0)

Abbreviations: ANA=antinuclear antibody; JIA=juvenile idiopathic arthritis; LDH=lactate dehydrogenase; Pt-yr=total subject years of exposure to investigational product; r=exposure-adjusted event rate per 100 subject-years (n/Pt-yr *100); SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase.

a. N=number of subjects assigned to methotrexate only arm at original baseline.

b. N=number of subjects receiving the respective treatment at any time during the registry (ie, includes re-enrolled subjects).

The majority of the AEs occurred in the MTX only arm and most were liver- or gastrointestinal-related, as would be expected with MTX treatment.

The number of polyarticular JIA subjects aged 2 to <4 years who experienced an AE was 6 (27.3%) in the MTX only arm, zero in the etanercept only arm, and 2 (10.5%) in the etanercept + MTX arm.

Table 23. Subject Incidence of Adverse Events excluding infection for Polyarticular JIA Subjects Aged 2 to <4 Years in Registry 20021626

Body System Preferred Term	Methotrexate Only (N=22)[a] n (%)	Etanercept Only (N=6)[b] n (%)	Etanercept + Methotrexate (N=19)[b] n (%)
Number of Subjects Reporting Adverse Events	6 (27.3)	0 (0.0)	2 (10.5)
Urogenital System	1 (4.5)	0 (0.0)	1 (5.3)
Albuminuria	0 (0.0)	0 (0.0)	1 (5.3)
Nephrosis	1 (4.5)	0 (0.0)	0 (0.0)
Musculoskeletal System	0 (0.0)	0 (0.0)	1 (5.3)
Arthritis	0 (0.0)	0 (0.0)	1 (5.3)
Metabolic & Nutritional Disorders	3 (13.6)	0 (0.0)	0 (0.0)
LDH Increased	1 (4.5)	0 (0.0)	0 (0.0)
Porphyria	1 (4.5)	0 (0.0)	0 (0.0)
SGOT Increased	1 (4.5)	0 (0.0)	0 (0.0)
SGPT Increased	2 (9.1)	0 (0.0)	0 (0.0)
Hemic & Lymphatic System	1 (4.5)	0 (0.0)	0 (0.0)
ANA	1 (4.5)	0 (0.0)	0 (0.0)
Digestive System	1 (4.5)	0 (0.0)	0 (0.0)
Vomit	1 (4.5)	0 (0.0)	0 (0.0)

Abbreviations: ANA=antinuclear antibody; JIA=juvenile idiopathic arthritis; LDH=lactate dehydrogenase; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase.

a. N=number of subjects assigned to methotrexate only arm at original baseline.

b. N=number of subjects receiving the respective treatment at any time during the registry (ie, includes re-enrolled subjects).

The number of subjects in the overall population who experienced an AE was 43 (21.8%) in the MTX only arm, 26 (25.2%) in the etanercept only arm, and 78 (26.5%) in the etanercept + MTX arm (Table 23).

Infections

Per the protocol, only medically important infections were collected. Nonserious infections were not collected. No medically important infections were reported in polyarticular JIA subjects aged 2 to <4 years.

By comparison in the overall population, the exposure-adjusted rate of medically important infections was 1.29 per 100 subject-years in the MTX only arm, 1.78 per 100 subject-years in the etanercept only arm and 2.05 per 100 subject-years in the etanercept + MTX arm. One subject (etanercept + methotrexate arm) had an infectious adverse event of sepsis that was considered to be grade 4 (life-threatening). Grade 3 (severe) infectious events were reported by 1 subject in the methotrexate only arm (abscess and sinusitis), 3 subjects in the etanercept only arm (infection, blood culture positive, and viral infection) and 4 subjects in the etanercept + methotrexate arm (abscess, infection, pyelonephritis, colitis, and urinary tract infection).

The safety profiles of both the subpopulation and the overall population are consistent with the known safety profile of etanercept.

Serious adverse events and deaths

There were 2 SAEs reported in polyarticular JIA subjects aged 2 to <4 years:

Nephrotic syndrome in a 2-year-old female subject in the MTX only arm (who subsequently switched to the etanercept + MTX arm) and arthritis flare in a 2-year-old female subject in the etanercept + MTX arm which were considered unrelated to study drug.

The exposure-adjusted rate of all SAEs for subjects aged 2 to <4 years was 2.75 per 100 subject years for the MTX only arm, zero per 100 subject-years for the etanercept only arm and 2.11 per 100 subject-years for the etanercept + MTX arm.

No cases of lymphoma, tuberculosis, malignancy, or death were reported in polyarticular JIA subjects aged 2 to <4 years.

By contrast the exposure-adjusted rate of SAEs for the overall population was 4.64 per 100 subject-years in the MTX only arm, 7.14 per 100 subject-years in the etanercept only arm and 5.98 per 100 subject-years in the etanercept + MTX arm. The body system with the highest exposure-adjusted serious adverse event rate was body as a whole. The serious adverse events with the highest exposure-adjusted rates were viral infection (0.89/100 subject-years for the etanercept only arm), headache and arthritis (both at 0.63/100 subject-years for the etanercept + methotrexate arm).

Fourteen (7.1%) subjects in the methotrexate only arm, 9 (8.7%) subjects in the etanercept only arm and 28 (9.5%) subjects in the etanercept + methotrexate arm reported at least one serious adverse event. Of these, 10 subjects had serious adverse events considered related; 1 subject in the methotrexate only arm, 3 subjects in the etanercept only arm, and 6 subjects in the etanercept + methotrexate arm. One subject in the etanercept + methotrexate arm had a serious adverse event (diabetes mellitus) that was considered probably related.

There were no cases of demyelinating disorders in the etanercept only arm or etanercept with methotrexate arm, but there was 1 case of optic neuritis in the methotrexate only arm.

In the overall population, no deaths occurred during the study.

Laboratory findings

Routine laboratory assessments were not a part of the study protocol. Physicians were to practice the standard of care for monitoring toxicities of methotrexate and other DMARDs.

Grade 2 through Grade 4 laboratory abnormalities that were not part of the symptom complex of another adverse event were recorded as adverse events. Two subjects had laboratory test abnormal as the preferred adverse event term, the verbatim terms were C-reactive protein and ferritin = 8, decreased iron studies. Other preferred terms (verbatim terms) that related to laboratory abnormalities were liver function abnormal (elevated liver enzymes), leukopenia (low white blood cell count), neutropenia (low ANC [absolute neutrophil count]), bilirubinemia (bilirubin total 1.8 mg/dL) and albuminuria (total protein 24 hr – proteinuria <928, normal 10). Other laboratory abnormalities reported were SGOT (serum glutamic oxaloacetic transaminase) increased, SGPT (serum glutamic pyruvic transaminase) increased and LDH (lactate dehydrogenase) increased. Of these, only the decreased ferritin occurred in a subject from the etanercept only arm.

Safety in special populations

As this was a paediatric study additional safety assessment were made on growth and development.

Growth data (height, weight, and body mass index [BMI]) were collected throughout the 3-year study period of registry 20021626. At baseline, subjects were below the expected mean for normal children (based on Centers for Disease Control and Prevention [CDC] reference data). This observation is consistent with previous reports of impaired growth in children with JIA.

Mean percentile and mean percentile change from baseline in height, weight and BMI were assessed for the overall population as well as for the subpopulation of polyarticular JIA subjects aged 2 to <4 years.

In addition, post hoc analyses using standard z-scores were conducted for the overall population, as well as for subjects aged 2 to <4 years, as compared to the general paediatric population.

z-Scores were calculated based on height-for-age, weight-for-age, and BMI-for-age charts provided by the United States CDC website for children from birth to 240 months. Overall, the z-scores demonstrated height, weight and BMI in the overall population, as well as the subpopulation, remained consistent over the 3-year observation period.

At year 3 and the last visit, subjects in the etanercept arms had a significant increase in mean height percentile change from baseline ($p = 0.0385$ and <0.0001 at year 3; and $p = 0.0391$ and 0.0347 at the last visit, Wilcoxon signed rank test). These significant improvements in mean height percentile change from baseline were also observed for each year in the etanercept + methotrexate arm.

Significant increases from 0 in the mean weight percentile change from baseline were observed for each year as well as the last visit ($p<0.008$, Wilcoxon signed rank test). Significant improvements in mean weight percentile change from baseline were also observed for years 2 and 3 for the etanercept only arm compared with the methotrexate only arm; this significant improvement was also observed for the last visit.

Significant increases from 0 in the mean BMI percentile change from baseline were observed for each year as well as the last visit for ($p<0.007$, Wilcoxon signed rank test). Significant improvement in mean BMI percentile change from baseline were also observed for year 3 for the etanercept only arm compared with the methotrexate only arm.

For each age group within the overall population, including 2 to <4 year olds, the z-scores for height, weight and BMI were relatively consistent over time in etanercept-treated subjects.

Tanner Scores

The Tanner Stage Assessment and Pubic Stage Assessment were collected from a subset of study population and tabulated by age group. The absolute difference between the Tanner stage score and

pubic stage score was calculated. No apparent differences in development as assessed by Tanner Scores were noted for any of the treatment arms.

Discontinuation due to AEs

One (1) polyarticular JIA subject aged 2 to <4 years withdrew from registry 20021626 because of an AE of vomiting.

By contrast in the overall population 6 subjects experienced an adverse event that led to study withdrawal; 3 (1.5%) in the methotrexate only arm (rash and 2 cases of elevated liver enzymes), 2 (1.9%) in the etanercept only arm (headaches with each dose and overlap juvenile dermatomyositis), and 1 (0.3%) in the etanercept + methotrexate arm (injection site reaction).

Fifteen (15) subjects experienced an adverse event that led to investigational product withdrawal; 5 (2.5%) in the methotrexate only arm, 1 (1.0%) in the etanercept only arm and 9 (3.1%) in the etanercept + methotrexate arm. The only adverse events reported more than once within a treatment arm were liver function abnormal (2 [1.0%] in the methotrexate only arm) and arthritis (3 [1.0%] in the etanercept + methotrexate arm).

Post marketing experience

Postmarketing Experience in Etanercept Patients Below 4 Years of Age

Through 02 February 2009, relatively few events (n = 121 events in 38 reports) were received regarding children less than 4 years of age who received etanercept. While most events in this group were similar to those reported in all juvenile users, one of the most frequently reported events in this group included accidental overdose (n = 4). These reports included 2 errors on the part of a healthcare professional, 1 receipt of prefilled syringe instead of etanercept paediatric form,and 1 report of a child who took her father's etanercept prefilled pen and injected her right leg. As part of variation II/120 (adopted in January 2011), the MAH improved the information in section 4.2 of the SPC and section 3 of the Package Leaflet to make more clear to the patient that the pre-filled syringe and pre-filled pen presentations are unsuitable for use in patients weighing less than 62.5 kg.

There were 2 deaths in children under 4 with JIA. One (1) occurred in a 2-year-old female with interstitial lung disease who died of sepsis 3 months after etanercept was discontinued. The other death in this age group was attributed to cerebral hemorrhage in a 3-year-old female with a history of infantile convulsions and respiratory tract infection. She was hospitalized for hypoxic-ischemic encephalopathy, secondary cerebral edema, and seizures and experienced a subarachnoid cerebral hemorrhage on the same day. The information provided was insufficient to make a meaningful assessment of the role of etanercept in this complex series of events.

There was 1 report of malignancy in a 3½-year-old male who was diagnosed with acute lymphocytic leukaemia after fewer than 12 doses of etanercept (exact duration of therapy was not provided). The patient was treated with chemotherapy. The outcome of this event is unknown. This report does not provide information regarding the patient’s symptoms leading up to initiation of etanercept. Symptoms of hematopoietic malignancies may be misdiagnosed as JIA. Given the short period of exposure to etanercept, it is possible that the child had leukemia prior to initiation of etanercept therapy.

The MAH was requested to provide a breakdown of post-marketing exposure by country by age and indication, with particular emphasis on JIA subjects under the age of 4 years. The MAH has addressed the question in terms of exposure in JIA using many data sources to provide information for the response. The large exposure in children with JIA (~57,525 patient years under 17 years globally and ~36,040 patient-years under 17years in the US) is expected to include children under the age of

4 years since the licensing of Enbrel for children with polyarticular JIA from the age of 2 years in the US in 2009. Based on prescription information it is estimated that post marketing exposure for patients under the age of 4 years is ~733 patient years in the US. The additional post-marketing safety data since then is reassuring in light of the paucity of reports from children under the age of 4 years in the PSURs. The MAH will collect additional data on JIA patients under the age of 4 years treated with etanercept through the 3 available JIA registries: German JIA registry, Swedish JIA/RA registry (ARTIS), and UK JIA registry (BSPAR) as described in the RMP.

Literature Reports of Etanercept Use Below 4 Years of Age

A subgroup analysis was undertaken utilizing the German JIA registry to examine the safety and efficacy of etanercept in children with JIA below the age of 4 years. Twenty-five (25) patients, 10 with non-systemic JIA, were identified and had a mean etanercept exposure of 19 months. In this subgroup, 2 AEs (varicella zoster virus infection and fever) were reported. No SAEs were reported in these patients and no patients discontinued due to intolerance. Effectiveness parameters from the American College of Rheumatology Paediatric (ACR Pedi) criteria showed improvement from baseline, with statistically significant improvements demonstrated in most of the variables. Nine (9) of the 10 children with non-systemic JIA achieved an ACR Pedi 70 response at last observation. Data were compared with that for older children in the German registry and with data from an open-label multicenter trial with an age range of 4 to 17 years in the United States. No major differences in safety or effectiveness were found. In a published survey of paediatric rheumatologists regarding etanercept use in children <4 years of age, no SAEs were reported.

In addition, there were several publications that reviewed use of etanercept in children with JIA that reported 3 years as the lower age limit for inclusion. No specific information regarding the younger children was provided; however, the conclusions found the results of etanercept use in the stated age range to be favourable.

Discussion on clinical safety

Overall, the safety profiles of the subjects from the methotrexate, etanercept and etanercept plus methotrexate arm were similar, with no significant difference in exposure adjusted rates of adverse events, including autoimmune diseases, between the arms.

The adverse events in the whole study population seem similar between groups. The total number of adverse events was around 18% in the MTX only and etanercept only arm and approximately 21% in the combination arm. The etanercept group had a higher rate of AEs in the category of nervous system (8% versus 4-6%) and in the Hemic and Lymphatic system (3% vs 0.7-1.7%). In the subgroup of children between 2-4 years, the etanercept group (only 9 subjects) barely had AEs.

Regarding infections, no clinically important infections were reported in polyarticular JIA subjects aged 2 to <4 years, whereas in the overall population, the exposure-adjusted rate of clinically important infections was 1.29 per 100 subject-years in the MTX only arm, 1.78 per 100 subject-years in the etanercept only arm and 2.05 per 100 subject-years in the etanercept + MTX arm. The number of subjects in the overall population who experienced a medically important infection was 4 (2.0%) in the MTX only arm, 4 (3.9%) in the etanercept only arm and 11 (3.7%) in the etanercept + MTX arm.

There were 2 SAEs reported in polyarticular JIA subjects aged 2 to <4 years: nephritic syndrome in a 2-year-old female subject in the MTX only arm (who subsequently switched to the etanercept + MTX arm) and arthritis flare in a 2-year-old female subject in the etanercept + MTX arm.

No cases of lymphoma, tuberculosis, malignancy, or death were reported during the study. There were no cases of demyelinating disorders in the etanercept only arm or etanercept with methotrexate arm, but there was 1 case of optic neuritis in the methotrexate only arm.

At year 3, subjects in the etanercept arms had a significant increase in height, weight and BMI percentiles. Significant improvements in mean height, weight, and BMI percentile changes were also observed at year 3 for the etanercept only arm compared with the methotrexate only arm.

Two deaths and two cases of Hodgkin's disease occurred in the follow-up period but none of these cases were on Enbrel at the time of death/lymphoma.

The CHMP noted that the approved 25-mg/mL paediatric presentation utilizes water for injections containing 0.9% benzyl alcohol as the solvent for reconstitution of the powder. A 10 mg benzyl alcohol-free presentation of Enbrel has recently been approved (EMEA/H/C/262/X/127, Commission Decision 29.06.2011). The other benzyl alcohol-containing formulation has a warning in the SmPC. In view of the availability of the new benzyl alcohol-free formulation and the SmPC warning, the potential safety concern relating to the presence of benzyl alcohol is considered to be addressed. In addition the MAH will review as part of the annual PSUR the post-marketing data in JIA patients aged 2 to 3 years on a monthly basis after the approval of JIA in children aged 2 to 3 years, until the new 10 mg formulation is available. The MAH will summarize these data in the PSUR. The reviews will focus on all SAEs with a particular focus on toxic and anaphylactic reactions as described in the RMP.

Conclusions on the clinical safety

The safety profile described in this registry study does not show any special safety concern within the well described safety profile of etanercept. To address general uncertainties of the use of an immunomodulator in this age group 2-<4 years, where the safety database is limited and no data on antibody development was available, the MAH will collect data systematically on the long-term outcomes of JIA patients under the age of 4 years treated with etanercept through the three available JIA registries (German JIA registry, Swedish JIA/RA registry [ARTIS], and UK JIA registry [BSPAR]), with particular emphasis on infection risk, malignancies, and vaccination as described in the RMP.

3.2.6 Risk Management Plan

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

Table 24 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	√		√	√			SPC section 4.4 Special warnings and precautions SPC section 4.8 Undesirable effects
	RABBIT	√						
	ARTIS	√	√	√	√			
	ESC questionnaire	√	√	√	√	√	√	
	BSPAR		√					

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)						
	German JIA registry		√				
	LTE 20040210					√	
	BADBIR					√	
	LTE 20050111						√
	0881X1-4654 (PURPOSE)						√
	B1801023		√				
	0881A1-3338-WW		√				

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

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)						
	LTE 20050111					√	
	B1801023		√				
	0881A1-3338-WW		√				
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		√				
	ESC questionnaire	√	√	√	√	√	√
	RABBIT	√					
							SPC section 4.4 Special warnings and precautions SPC section 4.8 Undesirable effects
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

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

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)						
	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	√	√	√	√	√	√
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		√				

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)							
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					√		SPC section 4.4 Special warnings and precautions
	LTE 20050111						√	
	ESC questionnaire	√	√	√	√	√	√	
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						√	
	B1801023		√					
	0881A1-3338-WW		√					
	ESC questionnaire	√	√	√	√	√	√	

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)						
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
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		√				
Weight Gain	Routine PV Additional PV Activities by Individual Risks and Indications						
		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.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)						
	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 are needed to investigate further some of the safety concerns:

Description	Due date
The MAH will collect data systematically on the long-term outcomes of JIA patients under the age of 4 years treated with etanercept through the 3 available JIA registries (German JIA registry, Swedish JIA/RA registry [ARTIS], and UK JIA registry [BSPAR]), with particular emphasis on infection risk, malignancies, and vaccination. The MAH will discuss with the investigators from each registry: • The possibilities of extending the registries beyond their current ending dates. • The possibilities of extending the age range to enroll patients from the age of 2 years.	31 October 2011

Description	Due date
• The possibilities of collecting data on vaccinations and vaccine preventable illness.	
The MAH will, after discussion with the 3 ongoing JIA registries, provide an update on whether the collection of additional effectiveness data to optimize management of JIA patients following achievement of clinical remission with etanercept information will be possible. This update will be provided in January 2012. If such information can be collected then the MAH will provide information on this every year.	31 January 2012
The MAH will review the post-marketing data in JIA patients aged 2 to 3 years on a monthly basis after the approval of JIA in children aged 2 to 3 years, until the new 10 mg formulation is available. The MAH will summarize these data in the PSUR. The reviews will focus on all SAEs with a particular focus on toxic and anaphylactic reactions.	April 2012 in PSUR

3.2.7 User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable as the changes proposed for the package leaflets as part of the variation to extent the polyarticular juvenile idiopathic arthritis indication to include patients from 2 years of age were minimal.

4. Benefit-Risk Balance

Benefits

Beneficial effects

To support the extension of the indication the MAH has submitted a study (based on data extracted from a registry) whose objective was to determine the long-term safety of etanercept with or without other DMARDs in paediatric subjects aged 2 to 18 years with polyarticular course or systemic JRA compared to a control cohort of subjects with polyarticular course or systemic JRA receiving methotrexate with or without other DMARDs.

The beneficial effects of etanercept in older children from the age of 4 years with polyarticular JIA has previously been formally demonstrated to lead to a reduction in the number of active joints, and improvement in physician global assessment and quality of life leading to licensing of that indication. In study 20021626 the results from the subjects aged 2 to <4 years were similar to the overall population, thereby supporting efficacy in this younger age group.

Although the data are derived from an open label study (based on data extracted from a registry) there is however a clinical need for other treatment options other than methotrexate in the very young children, as a considerable percentage of children may not tolerate MTX. Moreover, it is considered relevant to treat young patients with active arthritis vigorously, to prevent future joint damage. Alternative treatment options of high doses of steroids could cause growth retardation. As no alternative biologicals are available for young children the choice for etanercept may thus be unavoidable in 2- <4 year olds.

Uncertainty in the knowledge about the beneficial effects

The data provided in study 20021626 is supportive of efficacy in the age group 2 to <4 years but because of the open-label nature of the trial, efficacy has not been formally demonstrated. While this is not optimal, recruitment problems have affected other trials in this young age group. As the results of the subpopulation aged 2-<4 years in terms of efficacy were similar to the overall population with polyarticular JIA, these can be considered supportive of efficacy in this group.

An additional area of uncertainty is when to discontinue therapy in non-responders. The MAH has provided an overview of the literature and guidelines available to support discontinuation of treatment in patients who show no response by 4 months of treatment. This additional change in section 4.2 of the SmPC is in line with the evidence provided and the ACR 2011 guidelines.

It is also of interest to explore when and in what manner treatment should be stopped in a patient who has responded well to etanercept. Given the limitations to address this in terms of clinical trial design, the MAH provided literature data and analysis from trials in JIA to show that at present it is not possible to advise on how long a patient should be in a state of low disease activity or remission before deciding on withdrawal of the drug. In addition the high rate of relapse in those who were discontinued was noted, but also it is reassuring that the response to re-treatment in these cases was satisfactory. As unnecessarily long exposure to etanercept should be avoided. The MAH will therefore contact JIA registries to examine whether collection of additional efficacy (effectiveness) information to address this issue is possible as described in the RMP.

Risks

Unfavourable effects

Unfavourable side effects are well documented for etanercept, and 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 scrasias, reduced vaccine responses and demyelination. Also an increased risk for the development of malignancies, including lymphoma cannot be excluded.

Unfavourable effects of benzyl alcohol are seen in children under the age of 3 years and include anaphylactoid reactions and additionally in premature neonates, at high levels can results in infant gasping syndrome. Therefore, a benzyl alcohol-free formulation has been registered for Enbrel. As described in the RMP, the MAH will review as part of the annual PSUR the post-marketing data in JIA patients aged 2 to 3 years on a monthly basis after the approval of JIA in children aged 2 to 3 years, until the new 10 mg formulation is available.

Uncertainty in the knowledge about the unfavourable effects

The unfavourable effects on a younger child may be more serious, in that children below the age of 4 years are often naïve to pathogens including common viruses. This could result in more severe primary viral infections in these children than has been observed in older children. Another area of uncertainty is whether earlier introduction of immunosuppression will lead to an increased risk of malignancy, including virally associated tumour development. The ability to mount an immune response to vaccinations needs to be addressed. The MAH will collect data systematically on the long-term outcomes of JIA patients under the age of 4 years treated with etanercept through the 3 available JIA registries (German JIA registry, Swedish JIA/RA registry [ARTIS], and UK JIA registry [BSPAR]), with particular emphasis on infection risk, malignancies, and vaccination as described in the RMP.

Balance

Importance of favourable and unfavourable effects

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.

The benefits of etanercept treatment in JIA for those aged 2 to <4 years is similar to that of the overall population from the study 20021626. Although formal evidence of efficacy has not been demonstrated as this was an open-label trial, the similarity of outcomes between the overall population and the subgroup aged 2 to <4 years were evident. The benefits of etanercept treatment in 2 to <4 years old with polyarticular JIA unresponsive to conventional therapy, result from disease control. As the underlying disease processes of polyarticular JIA in those aged below and above 4 years are the same, the efficacy demonstrated formally in those over the age of 4 years in terms of reduction in joint inflammation, can be expected to be reflected in those under the age of 4 years. This is confirmed by the registry data submitted by the MAH.

Potential risks associated with initiation of etanercept in children as young as 2 years of age include the known side effect profile of etanercept as described in the SmPC and in addition may lead to a higher risk of severe infection and poor immunisation responses in children under the age of 4 years in view of the immaturity of their immune systems. These risks could be monitored and accepted in severe cases with polyarticular JIA unresponsive to standard DMARD therapy. The long term risks associated with immunosuppression also include development of malignancy, a risk which may be higher in the very young children. In view of this the MAH will collect data systematically on long-term outcomes of JIA patients under the age of 4 years treated with etanercept, through the available JIA registries, with particular emphasis on infection risk, malignancies and vaccination responses as described in the RMP.

Benefit-risk balance

Taken together the available efficacy data and the knowledge about the safety profile, as well as the additional pharmacovigilance measures particularly the long-term safety registry, the benefit risk balance is considered positive.

Discussion on the benefit-risk assessment

The well demonstrated efficacy of etanercept in JIA in those over 4 years led to the approval of etanercept in active polyarticular JIA in children aged 4 years and above. The underlying disease processes are the same for children under the age of 4 years with polyarticular JIA. The registry data provided by the MAH support similar efficacy in those aged 2 to <4 years as was seen in the whole population aged 2-18 years. While high quality trial data is usually required for an extension of indication, the difficulty in recruiting young children into trials for this disease has been demonstrated by the MAH. This is likely to at least in part related to the fact that etanercept is approved in children with polyarticular JIA from the age of 4 years and in the US from the age of 2 years. The benefit of treatment in young children under the age of 4 with active disease, where no alternatives exist is expected to lead to a reduction in joint destruction and improved quality of life. The known risks of etanercept are highlighted in the SmPC and the RMP, but additional concerns relate to its use in those under the age of 4 years. The risks of infection and the possibility that the risk of malignancy will be increased relatively more the younger the age of onset of treatment remain concerns. These concerns will be monitored with long-term active pharmacovigilance activity as described in the RMP. The balance in a subject with active polyarticular JIA is in favour of treatment provided that the warnings in

the SmPC are followed and the subject is followed long-term for assessment of safety, particularly the development of malignancy.

The benefits of earlier introduction of treatment with etanercept in polyarticular JIA patients aged 2 to 4 years who have not tolerated to, have a contra-indication to or do not respond to non-biological DMARD therapy is expected to provide similar benefit as has been formally demonstrated in children aged 4-18 years. Long-term disease associated morbidity is linked to the speed of achieving acute disease control.

Earlier control of resistant disease associated morbidity is expected to lead to less joint destruction and a favourable clinical outcome in terms of joint function, development and quality of life.

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 polyarticular JIA in children from the age of 2 to <4 years was positive.

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

Polyarticular juvenile idiopathic arthritis

Treatment of active polyarticular juvenile idiopathic arthritis in children and adolescents from the age of **2** years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Enbrel has not been studied in children aged less than **2** years.

2. 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.