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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Enbrel

etanercept

Procedure No.: EMEA/H/C/000262/II/0145

Note

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

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1. Scientific discussion

1.1. Introduction

About the product

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 2 to 17 years, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis in adults and paediatric plaque psoriasis in children and adolescents from the age of 6 years.

Problem statement

Etanercept is authorized in the European Union (EU) for use in the treatment of active polyarticular juvenile idiopathic arthritis (JIA) in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate (MTX).

The 2 studies contributing data to this variation include study 0881A1-3338-WW (referred to at study 3338; also known as study B1801014) and study 20021618. The Part 1 (Week 12) results from study 3338 for children and adolescents with extended oligoarticular JIA (eoJIA) from the age of 2 years, children and adolescents with enthesitis-related arthritis (ERA) from the age of 12 years and children and adolescents with psoriatic arthritis (PsA) from the age of 12 years are presented in the Part 1 (Week 12) clinical study report (CSR). Part 2 of study 3338 (96 weeks) is currently ongoing.

The final 10-year results from study 20021618 for subjects with polyarticular-course JIA (polyarticular, pauciarticular-, or systemic-onset) aged 4 to 17 years are presented in the Final CSR. If the International League of Associations for Rheumatology (ILAR) criteria are retrospectively applied to study 20021618 then there would be minimal overlap between the JIA populations in the 2 studies. There were no subjects in study 20021618 who would appear to have met the ILAR criteria for ERA or PsA; however, the subjects with pauciarticular-onset JIA (n=5) in study 20021618 would likely be classified as eoJIA patients. Due to the lack of data in these 3 additional JIA subtypes, study 3338 was conducted to further characterize them.

Scope of the variation

The purpose of this variation application is to extend the JIA indication for etanercept to include children and adolescents with extended oligoarticular JIA from the age of 2 years, children and adolescents with enthesitis-related arthritis (ERA) from the age of 12 years and children and adolescents with psoriatic arthritis (PsA) from the age of 12 years, together with reclassification of the licensed indication of polyarticular JIA into the ILAR classification of polyarthritis (rheumatoid factor positive) and polyarthritis (rheumatoid factor negative). Furthermore, an additional etanercept dosage regimen of 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly (QW) is being proposed in addition to the current approved JIA dosage of 0.4 mg/kg (up to a maximum of 25 mg per dose) BIW for the treatment of JIA. An etanercept dosage of 0.8 mg/kg (up to a maximum of 50 mg per dose)

QW is currently approved in children and adolescents with plaque psoriasis. No changes will be made to the etanercept formulation for the treatment of JIA.

The subdivision of the JIA subtypes on the basis of the revised ILAR criteria overcomes the limitation of the old classification where a subject with e.g. polyarticular course JIA could have had a different classification for the onset of the disease; e.g. systemic onset polyarticular course JIA which differed in terms of AE profile and response to etanercept compared with those who had either oligo articular or polyarticular onset. The sensitivity analysis for efficacy done by the MAH in support of the previous extension of age range for JIA from 4 years down to 2 years (variation II/126 approved in August 2011) excluded subjects who had systemic onset polyarticular course JIA. The revised classification removes this possible source of confusion and the principle of this classification is that all categories of JIA are mutually exclusive and based on the disease characteristics in the first six months.

The older studies were performed before the revised ILAR classification and the MAH provided long term safety data in subjects with polyarticular JIA (now classifiable as Polyarthritis (RF positive) and Polyarthritis (RF negative)). In addition the MAH conducted a new study in the JIA subtypes of Psoriatic arthritis, Enthesitis-related arthritis and Oligoarthritis (extended subtype).

Below is the ILAR classification list of subtypes of JIA.

- Systemic arthritis
- Oligoarthritis (presistent subtype/ extended subtype)
- Polyarthritis (RF negative)(already licensed)
- Polyarthritis (RF positive) (already licensed)
- Psoriatic arthritis
- Enthesitis related arthritis
- Undifferentiated arthritis

As the majority of patients from older trials could be re-classified as predominantly polyarthritis (RF neg or RF pos) then these subtypes are already licensed from the age of 2 years.

Enbrel is licensed for psoriatic arthritis and ankylosing spondylitis (AS) in adults. The main focus of this variation is to assess the evidence provided in support of efficacy in the following subtypes and age groups:

- Extended oligoarthiris (from the age of 2 years)
- Enthesitis related arthritis (from the age of 12 -18 years)
- Psoriatic arthritis (from the age of 12-18 years)

The originally proposed SmPC changes to 4.1 and 4.2 are in underlined text below and proposed deletions from the MAH are in ~~strikethrough~~

~~Polyarticular j~~Juvenile idiopathic arthritis Treatment of rheumatoid factor positive or negative polyarthritis ~~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.

Treatment of extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in children and adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Treatment of psoriatic arthritis in children and adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Further proposed changes to the SmPC include the posology in section 4.2.

Paediatric population

~~Polyarticular j~~Juvenile idiopathic arthritis ~~(age 2 years and above)~~
The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose) ~~after reconstitution of Enbrel in 1 ml of solvent~~, given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly.
Discontinuation of treatment should be considered in patients who show no response after 4 months.

Further changes in section 5.1 to update the SmPC with the results of the 12 week data from Study 3338 and the final 10 year data from Study 20021618 provided in support of this variation are also included.

The following variation application is made in this submission:

Clinical:

Variation requested		**Type**
C.I.6.a	Addition of a new therapeutic indication or modification of an approved one	II

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006 as amended the application included an EMA decision (P/241/2011) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/241/2011) was completed.

The PDCO issued an opinion on compliance for the PIP (P/241/2011).

Information on Scientific advice

The MAH did not seek scientific advice at the CHMP.

1.2. Clinical aspects

1.2.1. Introduction

In support of this variation the MAH provided:

- The Clinical Study Report (CSR) for Part 1 (Week-12 Analysis) of study 0881A1-3338-WW (also known as B1801014) - A 2-Part Open-Label Study to Assess the Clinical Benefit and Long-Term Safety of Etanercept in Children and Adolescents With Extended Oligoarticular Juvenile Idiopathic Arthritis, Enthesitis-Related Arthritis, or Psoriatic Arthritis.
- An updated CSR for study 20021618 - An Open-Label, Long-Term Multicentre Extension Study for Evaluation of Long Term Efficacy and Safety in Patients with RA and JIA Involved in Previous Studies.

1.2.2. GCP

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

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

1.2.3. Pharmacokinetics

The approved dosage forms of etanercept include powder and solvent for solution for injection, solution for injection in a prefilled syringe and solution for injection in a prefilled pen. All etanercept dosage forms are intended for subcutaneous (SC) injection. For the treatment of active polyarticular juvenile idiopathic arthritis (JIA) in children and adolescents from the age of 2 years, the approved dosage of etanercept is 0.4 mg/kg (up to a maximum of 25 mg per dose) twice weekly (BIW).

The formulation of etanercept used in study 0881A1-3338-WW (3338) was identical to the 25 mg powder and solvent for solution for injection that is currently approved in the European Union (EU/1/99/126/003), in which the contents of the vials are reconstituted with sterile water for injection. Study 20021618 was conducted in North America and used the same powder for solution; however, it was reconstituted in bacteriostatic water for injection rather than sterile water for injection. The dosage regimen used in study 3338 was 0.8 mg/kg QW (up to a maximum dose of 50 mg), identical to the approved regimen for the treatment of paediatric psoriasis; each injection contained a maximum of 25 mg of etanercept reconstituted in 1 ml of sterile water. Although paediatric subjects who entered study 20021618 initially continued with the etanercept dose administered in double-blind study 16.0016 (0.4 mg/kg etanercept BIW up to a maximum dose of 25 mg per injection), the 0.8-mg/kg weekly dose (maximum dose of 50 mg per week) could be administered as two 0.4-mg/kg SC injections either on the same day or 3 to 4 days apart, or as a single 0.8-mg/kg injection QW.

It should also be noted that the dosage regimen used in registry 20021626 was 0.8 mg/kg QW, up to a maximum dose of 50 mg. This 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. This was the basis to extend the lower age range for the approved therapeutic indication for polyarticular juvenile idiopathic arthritis (JIA). Furthermore, in the SmPC of Enbrel the following statement is included: "...Patients with paediatric plaque psoriasis (aged 4 to 17 years) were administered 0.8 mg/kg (up to a maximum dose of 50 mg per week) of etanercept once weekly for up to 48 weeks. The mean serum steady-state trough concentrations ranged from 1.6 to 2.1 mcg/ml at weeks 12, 24, and 48. These mean concentrations in patients with paediatric plaque psoriasis were similar to the concentrations observed in patients with juvenile idiopathic arthritis (treated with 0.4 mg/kg etanercept twice weekly, up to maximum dose of 50 mg per week). These mean concentrations were similar to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice-weekly...".

Data in adults have shown that the same total weekly dose provides similar exposure when administered as either QW or BIW doses for both RA and psoriasis.[5] Simulation using data collected in children with JIA shows that QW dosing would be expected to have steady-state peak and trough etanercept concentrations 11% higher and 18% lower, respectively, compared with BIW dosing with a large overlap of concentration profiles at steady state.

A comprehensive population pharmacokinetic analysis of the available data in children has not been performed as was done in adults. Nonetheless, the clinical results of the current studies (3338 and

20021618), in which etanercept was administered at weekly intervals in 0.8 mg/kg doses, along with the available pharmacokinetic and clinical data in children with JIA and paediatric psoriasis, support the approval of the 0.8 mg/kg QW dosage regimen.

Discussion on clinical pharmacology

The 0.8 mg/kg dose once weekly is therefore considered acceptable as the PK data from adults support similar PK profiles comparing 0.4 mg/kg twice weekly and 0.8 mg/kg once weekly; the use of 0.8 mg/kg in paediatric plaque psoriasis is already licensed; the data from Study 20021626 and the current trial 3338 (week 12 data provided in support of this application) was derived with a 0.8 mg/kg once weekly dosing and also from published literature in support of once weekly posology in JIA. In addition the requirement for fewer injections in children is endorsed.

Conclusion on clinical pharmacology

From a pharmacokinetic point of view the introduction of the 0.8 mg/kg dose once weekly dosing scheme is considered acceptable.

1.2.4 Clinical efficacy

Dose-response studies and main clinical studies

Main studies

Study 3338: A 2-Part Open-Label Study to Assess the Clinical Benefit and Long-Term Safety of Etanercept in Children and Adolescents With Extended Oligoarticular Juvenile Idiopathic Arthritis, Enthesitis-Related Arthritis, or Psoriatic Arthritis (Part 1: Week-12 Analysis)

Methods

Study 3338 is a phase 3b, single-treatment, open-label, 2-part, multicenter study of etanercept in children and adolescents with eoJIA from the age of 2 years, children and adolescents with ERA from the age of 12 years, and children and adolescents with PsA from the age of 12 years.

Study Participants

To be eligible for enrollment, subjects had to meet the International League of Associations for Rheumatology (ILAR) criteria for diagnosis of one of the following JIA subtypes before the screening visit and must be within the specified age range at the time of the screening visit:

(1) eoJIA between the ages of 2 and 17 years.

(2) ERA between the ages of 12 and 17 years; or

(3) PsA between the ages of 12 and 17 years.

Subjects with systemic JIA, persistent oligoarticular JIA, rheumatoid factor positive or negative polyarticular JIA, or un-differentiated arthritis per ILAR criteria were excluded.

Treatments

All subjects were receiving etanercept 0.8 mg/kg once weekly (QW) subcutaneously (to a maximum dose of 50 mg QW) throughout the course of their participation in study 3338 unless withdrawal of treatment is warranted.

Objectives

The primary objective of Part 1 (12 weeks) of the study was to assess the clinical benefit of etanercept in subjects with eoJIA, ERA, or PsA. The secondary objective of Part 1 (12 weeks) was to assess the effect of etanercept on safety and physical functioning in subjects with eoJIA, ERA, or PsA.

The primary objective of Part 2 (96 weeks) will be to assess the long-term safety of etanercept. All subjects who receive at least 1 dose of investigational product, including those who prematurely withdraw from investigational product, will be followed for 96 weeks in this study. Once subjects complete 96 weeks of investigational product and/or follow-up in study 3338, they will be asked to participate in the long-term extension study (B1801023).

Outcomes/endpoints

The main (primary) endpoint for evaluation of clinical benefit in the combined population in study 3338 was the proportion of subjects meeting the American College of Rheumatology (ACR) Paediatric 30 (Pedi 30) criteria at week 12, defined as ≥30% improvement from baseline in at least 3 of 6 of the following variables, with worsening >30% in no more than 1 of these variables:

1. Physician's Global Assessment (PGA) of disease activity on a 21-circle Visual Analogue Scale (VAS)

2. Parent/Patient Global Assessment on a 21-circle VAS

3. Childhood Health Assessment Questionnaire (CHAQ)

4. Number of active joints, defined as joints with swelling or, in the absence of swelling, joints with limitation of motion (LOM) with pain and/or tenderness

5. Number of joints with LOM

6. Laboratory measure of inflammation (C-reactive protein [CRP])

Additional assessments of clinical benefit in the combined population included:

- ACR Pedi 30 at all time points other than week 12
- ACR Pedi 50, 70, 90, and 100
- PGA of disease activity on a 21-circle VAS
- Parent/Patient Global Assessment
- Number of active joints, defined as joints with swelling or, in the absence of swelling, joints with limitation of motion with pain and/or tenderness
- Number of joints with Limitation of Motion
- Laboratory measure of inflammation (CRP)
- Pain assessment on a 21-circle VAS

- Duration of morning stiffness
- Disease status, where inactive disease is defined as no joints with active arthritis, a normal CRP, and a PGA of Disease Activity of 0 on a 21-circle VAS
- Health outcomes assessment: physical functioning as evaluated by the CHAQ

The above assessments of clinical benefit were also performed in each of the eoJIA, ERA, and PsA subpopulations. The following additional disease-specific endpoints were assessed in the ERA and PsA subpopulations:

- For subjects with ERA: Tender Entheseal Assessment; Overall Back Pain and Nocturnal Back Pain; and Modified Schober's test.
- For subjects with PsA: body surface area (BSA) affected by psoriasis; and PGA of psoriasis.

Sample size

The sample size was not based on any statistical hypothesis testing or power calculations. It was anticipated that approximately 100 subjects overall would be enrolled in this study. With this sample size, the half-width of the 95% CI would be no more than 10% for estimation of the ACR Pedi 30 response rate.

Approximately 100 subjects were to be enrolled as follows:

Extended oligoarticular JIA: minimum of 35 subjects. 2 to 4 years of age: minimum of 2 subjects 5 to 11 years of age: minimum of 18 subjects 12 to 17 years of age: minimum of 15 subjects

ERA: 12 to 17 years of age: minimum of 20 subjects

PsA: 12 to 17 years of age: minimum of 20 subjects

No more than 10% of the overall study population was to be enrolled at a single site.

Randomisation

This was a non-randomized study.

Blinding (masking)

This was an open-label study.

Statistical methods

The primary population for efficacy analysis was the modified intent to treat (mITT) population, which is defined as all subjects who received at least 1 dose of investigational product. The secondary population for efficacy analysis was the per-protocol population (valid for efficacy [VFE] population). The VFE population is a subset of the mITT population, excluding subjects who had major protocol deviations that were determined by the sponsor's clinical team to be likely to have a substantial impact on efficacy at any time point in Part 1 of the study.

For the ACR Pedi 30, 50, 70, 90, and 100 response rates at each time point in Part 1 of the study, sensitivity analyses were also performed using the following imputation methods for missing data:

- Last observation carried forward (LOCF) imputation for missing ACR Pedi values. This approach was applied to all visits missing ACR Pedi data. Baseline values, however, were not

carried forward. For the LOCF analysis, imputation was applied to the 6 components separately before assigning the ACR Pedi response status.

- Non-responder imputation (NRI)

The study 0881A1-3338 ACR Pedi 30 response rates at Week 12 were compared as follows with the prospectively selected historical placebo control data.

An odds ratio and corresponding 95% CI was computed for the overall population as well as for each of the 3 JIA subtypes versus the historical placebo mean composite endpoint response rate from the meta-analysis of 6 JIA studies by Ruperto et al.

Two (2) methods were used for the comparison of ACR Pedi 30 response rates to the historical placebo control data: the 6 studies included in the meta-analysis were treated individually in the logistic regression model (adjusted) and were pooled as one (unadjusted).

For the ERA subtype, an additional analysis was conducted in a similar manner using the ACR Pedi 30 placebo response rate from the Burgos-Vargas study of juvenile-onset spondyloarthropathies.

The initial 12-week open-label period ACR Pedi 30 response rate from the etanercept study 16.0016 of polyarticular-course JIA subjects was used as an active historical control. The response rate from the overall population as well as each of the 3 JIA subtypes was compared with the etanercept response rate from study 16.0016, adjusting for selected baseline characteristics in a logistic regression model. The logistic regression analyses included the following factors: baseline age, sex, duration of disease at study entry, age of disease onset, the baseline values of all 6 ACR Pedi 30 components. The odds ratios and corresponding 95% CIs were provided.

All safety analyses were based on the safety population, which was the same as the mITT population, defined as all subjects who received at least 1 dose of investigational product.

Results

Participant flow

A total of 127 subjects were enrolled and received at least 1 dose of investigational product. The mITT and safety populations include these 127 subjects: 60 subjects with extended oligoarticular JIA, 38 subjects with ERA, and 29 subjects with PsA. The mITT and safety population for subjects with eoJIA consisted of 15 subjects in the 2- to 4-year age group, 23 subjects in the 5- to 11-year age group, and 22 subjects in the 12- to 17-year age group.

Table 1. Number of Subjects in Each Analysis Population

	JIA Subtype			
Population	eoJIA (n)	ERA (n)	PsA (n)	Total (n)
mITT and Safety[a]	60	38	29	127
VFE	50	31	28	109

Abbreviations: eoJIA = extended oligoarticular juvenile idiopathic arthritis; ERA = enthesitis-related arthritis; mITT = modified intent to treat; PsA = psoriatic arthritis; VFE = valid for efficacy.
a. The safety population is the same as the mITT population in this study.
Source: 0881A1-3338 DEMO4 - 26AUG11 08:52; 0881A1-3338 DEMO4_VFE - 16AUG11 13:25

Five (5) subjects (3.9%) were withdrawn from investigational product prior to completion of Part 1 (Week 12) of the study; 4 subjects were withdrawn due to AEs and 1 subject was withdrawn due to a protocol violation.

Table 2. Summary of Subject Participation Status for Part 1

Conclusion Status Reason[a]	JIA Subtype eoJIA (N=60) n (%)	ERA (N=38) n (%)	PsA (N=29) n (%)	Total (N=127) n (%)
Total	60 (100)	38 (100)	29 (100)	127 (100)
Completed Part 1	58 (96.7)	36 (94.7)	28 (96.6)	122 (96.1)
Discontinued[a,b]	2 (3.3)	2 (5.3)	1 (3.4)	5 (3.9)
Adverse event including infections	1 (1.7)	2 (5.3)	1 (3.4)	4 (3.1)
Protocol violation	1 (1.7)	0	0	1 (0.8)

Abbreviations: eoJIA = extended oligoarticular juvenile idiopathic arthritis; ERA = enthesitis-related arthritis; PsA = psoriatic arthritis.
a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.
b. All subjects who discontinued investigational product continued to be monitored for safety in the study.
Source: 0881A1-3338 CPP4_PH1 - 02AUG11 - 15:38

Recruitment

The study was conducted at 38 centers in 19 countries in Europe, Latin America, and Australia. Twelve (12) centers in 6 countries received investigational product but did not enroll any subjects. The First Subject First Visit (FSFV) was 23 November 2009. The date of the last subject last visit for the Part 1 Week-12 analysis was 15 June 2011.

Conduct of the study

Prior to the last subject last visit (LSLV) for Part 1 of the study, 2 protocol amendments were finalized and approved for use at study sites. Amendment 1 was a global amendment and Amendment 2 was a site-specific amendment. Protocol Amendment 1 (dated 16 November 2009) included revisions based on updates to the Wyeth protocol template as well as the following key study-specific changes (among other):

- Clarified that the ≥2 active joints must be peripheral joints

- Revised the criteria relating to positive HLA-B27 and IgM RF tests to match the ILAR diagnosis criteria for JIA

- Removed the exclusion for subjects with guttate psoriasis

- Clarified that immunosuppressive drugs included cyclosporine and azothioprine

- Revised the exclusion for receipt of live (attenuated) vaccines to 2 months before the Baseline visit

- Revised the exclusion for receipt of combinations of non-biologic DMARDs and DMARDs which would not be continued during the study to 4 weeks before the Baseline visit.

Protocol Amendment 2 (dated 01 Dec 2009), which was specific to site 008, repeated the changes made to the original protocol in Protocol Amendment 1. In addition, at the request of the site's IRB, the eligibility criterion for the subjects with extended oligoarticular JIA subtype was revised, so that the lower age limit was increased from 2 years to 4 years at site 008.

Three (3) changes were made to the planned analyses in the SAP:

- The ACR Pedi response definition used for the reports contained in the CSR was revised after finalization of the SAP. This changed the ACR Pedi 30 response definition from requiring a >30% improvement in 3 of the 6 variables to requiring ≥30% improvement in 3 of the 6 variables. The change was also applied to the definitions for the ACR Pedi 50, 70, 90, and 100 responses. The change was made for consistency with the definition in the literature and the

active historical control study 16.0016. The SAP was not updated prior to release of the final tables for the CSR.

- The following data were summarized by age group for the extended oligoarticular JIA subtype: demography and baseline disease characteristics, ACR Pedi response rates, TEAEs excluding infections and ISRs, treatment-emergent infections, Tanner stage scores, and z-scores for height, weight, and BMI.

- Mean percent change from baseline was calculated at each visit for the following continuous efficacy variables: PGA of Disease Activity, Patient/Parent Global Assessment, CHAQ, number of active joints, number of joints with limitation of motion, CRP, pain assessment, duration of morning stiffness, tender entheseal score, overall and nocturnal back pain, modified Schober's Assessment, percent BSA affected by psoriasis, and PGA of Psoriasis score.

Baseline data

The mean (SD) age was 11.70 (4.51) years with a range of 2 to 17 years for the overall JIA population in study 3338:

8.60 (4.63) years with a range of 2 to 16 years for the eoJIA subtype;

14.50 (1.61) years with a range of 12 to 17 years for the ERA subtype; and

14.45 (1.99) years with a range of 12 to 17 years for the PsA subtype.

Fifteen (15) subjects with eoJIA (11.81%) were 2 to 4 years of age, 23 subjects with eoJIA (18.11%) were 5 to 11 years of age, and 89 subjects in the overall population (70.08%) were 12 to 17 years of age at baseline (table 3).

Overall, the majority of subjects in study 3338 were female (56.69%) and white (90.55%); however, in the ERA subtype, the majority of subjects were male (78.95%) which is expected.

Overall, the mean (SD) disease duration was 26.79 (26.44) months with a range of 0.49 to 139.10 months. Prior to the study, all subjects had received at least 1 DMARD except for 2 subjects with ERA who had not received prior DMARDs, and 109 subjects (85.83%) were taking a DMARD at baseline.

Table 3. Summary of Demographic and Baseline Characteristics in Study 3338

Characteristic Statistic	JIA Subtype eoJIA (N=60)	ERA (N=38)	PsA (N=29)	Total (N=127)
Age (years)				
N	60	38	29	127
Mean (SD)	8.60 (4.63)	14.50 (1.61)	14.45 (1.99)	11.70 (4.51)
Min, max	2.00, 16.00	12.00, 17.00	12.00, 17.00	2.00, 17.00
Median	8.00	14.00	15.00	13.00
Age group, N (%)				
2-4	15 (25.00)	0	0	15 (11.81)
5-11	23 (38.33)	0	0	23 (18.11)
12-17	22 (36.67)	38 (100)	29 (100)	89 (70.08)
Sex, N (%)				
Female	41 (68.33)	8 (21.05)	23 (79.31)	72 (56.69)
Male	19 (31.67)	30 (78.95)	6 (20.69)	55 (43.31)
Race, N (%)				
White	55 (91.67)	32 (84.21)	28 (96.55)	115 (90.55)
Asian	0	1 (2.63)	0	1 (0.79)
Other	5 (8.33)	5 (13.16)	1 (3.45)	11 (8.66)

Characteristic Statistic	JIA Subtype eoJIA (N=60)	ERA (N=38)	PsA (N=29)	Total (N=127)
Baseline height (cm)				
N	58	38	29	125
Mean (SD)	132.43 (27.81)	166.98 (9.83)	162.52 (10.47)	149.92 (26.05)
Min, max	79.80, 174.00	149.50, 184.70	138.80, 184.30	79.80, 184.70
Median	134.00	167.75	160.00	159.00
Missing	2	0	0	2
Baseline weight (kg)				
N	60	38	29	127
Mean (SD)	34.84 (18.86)	54.41 (8.75)	59.97 (14.23)	46.43 (18.96)
Min, max	10.90, 73.50	34.30, 69.20	41.00, 105.00	10.90, 105.00
Median	29.25	54.40	56.60	50.40
Baseline BMI				
N	58	38	29	125
Mean (SD)	17.92 (3.56)	19.47 (2.41)	22.66 (4.54)	19.49 (3.96)
Min, max	12.50, 27.00	14.60, 25.60	14.90, 33.50	12.50, 33.50
Median	17.50	19.25	21.90	19.40
Missing	2	0	0	2
Disease duration (months)				
N	60	38	29	127
Mean (SD)	31.63 (31.74)	22.96 (19.79)	21.81 (20.24)	26.79 (26.44)
Min, max	0.49, 139.10	0.56, 84.90	2.37, 84.86	0.49, 139.10
Median	21.90	15.71	13.24	16.59
Number of prior DMARDs, N (%)				
0	0	2 (5.26)	0	2 (1.57)
1	44 (73.33)	21 (55.26)	22 (75.86)	87 (68.50)
2	14 (23.33)	15 (39.47)	7 (24.14)	36 (28.35)
3	2 (3.33)			2 (1.57)
Baseline DMARDs, N (%)				
No	6 (10.00)	6 (15.79)	6 (20.69)	18 (14.17)
Yes	54 (90.00)	32 (84.21)	23 (79.31)	109 (85.83)
Baseline MTX, N (%)				
No	11 (18.33)	20 (52.63)	10 (34.48)	41 (32.28)
Yes	49 (81.67)	18 (47.37)	19 (65.52)	86 (67.72)
Baseline HCQ, N (%)				
No	59 (98.33)	36 (94.74)	29 (100)	124 (97.64)
Yes	1 (1.67)	2 (5.26)	0	3 (2.36)
Baseline chloroquine, N (%)				
No	59 (98.33)	38 (100)	29 (100)	126 (99.21)
Yes	1 (1.67)	0	0	1 (0.79)
Baseline SSZ, N (%)				
No	57 (95.00)	26 (68.42)	25 (86.21)	108 (85.04)
Yes	3 (5.00)	12 (31.58)	4 (13.79)	19 (14.96)
Baseline oral corticosteroids, N (%)				
No	53 (88.33)	30 (78.95)	28 (96.55)	111 (87.40)
Yes	7 (11.67)	8 (21.05)	1 (3.45)	16 (12.60)
Baseline oral NSAIDs, N (%)				
No	30 (50.00)	14 (36.84)	15 (51.72)	59 (46.46)
Yes	30 (50.00)	24 (63.16)	14 (48.28)	68 (53.54)

Abbreviations: BMI=body mass index; DMARD=disease-modifying antirheumatic drug; eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; HCQ=hydroxychloroquine; JIA=juvenile idiopathic arthritis; max=maximum; min=minimum; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; PsA=psoriatic arthritis; SD=standard deviation; SSZ=sulfasalazine.

Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 9.

In general, the mean and median baseline values for most disease characteristics were numerically similar across the 3 JIA subtypes in study 3338 except for those noted below (Table 4).

The mean number of active joints was numerically lower in subjects with ERA (5.21 joints) compared to subjects with eoJIA and PsA (7.58 and 7.00 joints, respectively). Similarly, the mean number of swollen joints was numerically lower in subjects with ERA (3.79 joints) compared to subjects with eoJIA and PsA (6.52 and 5.59 joints, respectively). Although some subjects with eoJIA had ≤5 active joints at the Baseline visit, they were still required to have a history arthritis affecting >4 joints in order to meet the ILAR classification criteria. The mean duration of morning stiffness at baseline was numerically longer in subjects with ERA (89.29 minutes) compared to subjects with eoJIA and PsA (72.78 minutes and 54.31 minutes, respectively).

Mean baseline CRP was numerically higher in subjects with ERA (15.27 mg/L) compared to subjects with eoJIA and PsA (6.27 mg/L and 3.19 mg/L, respectively). Median baseline CRP in subjects with the latter 2 JIA subtypes (1.40 mg/L and 1.00 mg/L for subjects with eoJIA and PsA, respectively) was at, below, or near the lowest limit of detection of 1.00 mg/L. As expected, a greater proportion of subjects with ERA were HLA-B27 positive (68.42%) compared to subjects with eoJIA and PsA (15.00% and 10.34%, respectively). The subjects with eoJIA and PsA who were HLA-B27 positive were either males with arthritis starting before the 6th birthday or females. Therefore, they did not meet the ILAR exclusion criteria for these subtypes.

Table 4. Summary of Baseline Disease Characteristics, All Subjects in Study 3338

Characteristic Statistic	JIA Subtype eoJIA (N=60)	ERA (N=38)	PsA (N=29)	Total (N=127)
Patient/Parent Global Assessment[a]				
N	60	38	29	127
Mean (SD)	4.82 (2.44)	5.43 (2.26)	4.62 (2.17)	4.96 (2.33)
Min, max	0.50, 9.00	1.00, 10.00	0.00, 9.00	0.00, 10.00
Median	5.00	5.25	5.00	5.00
Physician Global Assessment[a]				
N	60	38	29	127
Mean (SD)	4.96 (1.76)	5.39 (1.94)	4.66 (1.42)	5.02 (1.75)
Min, max	2.00, 8.50	2.00, 10.00	2.00, 7.50	2.00, 10.00
Median	4.50	5.25	4.50	5.00
Number of active joints[b]				
N	60	38	29	127
Mean (SD)	7.58 (5.09)	5.21 (3.57)	7.00 (4.33)	6.74 (4.59)
Min, max	1.00, 26.00	2.00, 20.00	2.00, 21.00	1.00, 26.00
Median	6.50	4.00	5.00	5.00
Number of joints with LOM[c]				
N	60	38	29	127
Mean (SD)	6.33 (4.37)	4.84 (4.00)	5.62 (4.10)	5.72 (4.22)
Min, max	0.00, 23.00	0.00, 21.00	0.00, 14.00	0.00, 23.00
Median	5.00	4.00	4.00	5.00
Number of painful joints[d]				
N	60	38	29	127
Mean (SD)	5.47 (4.12)	6.74 (4.93)	7.83 (7.04)	6.39 (5.20)
Min, max	0.00, 18.00	1.00, 26.00	1.00, 26.00	0.00, 26.00
Median	5.00	5.00	5.00	5.00
Number of swollen joints[e]				
N	60	38	29	127
Mean (SD)	6.52 (4.79)	3.79 (2.78)	5.59 (3.65)	5.49 (4.16)
Min, max	1.00, 26.00	0.00, 12.00	1.00, 19.00	0.00, 26.00
Median	5.00	3.00	4.00	4.00
Pain assessment[a]				
N	60	38	29	127
Mean (SD)	4.81 (2.56)	5.76 (2.51)	4.64 (2.31)	5.06 (2.52)
Min, max	0.00, 9.00	1.00, 10.00	0.00, 8.50	0.00, 10.00
Median	5.00	6.00	5.00	5.00
Morning stiffness (minutes)				
N	60	38	29	127
Mean (SD)	72.78 (97.24)	89.29 (128.94)	54.31 (54.16)	73.50 (100.61)
Min, max	0.00, 435.00	0.00, 620.00	0.00, 180.00	0.00, 620.00
Median	35.00	52.50	30.00	35.00
CHAQ score				
N	60	38	29	127
Mean (SD)	0.90 (0.68)	0.72 (0.51)	0.68 (0.63)	0.80 (0.63)
Min, max	0.00, 2.50	0.00, 1.88	0.00, 2.00	0.00, 2.50
Median	0.88	0.63	0.38	0.63
CRP (mg/L)				
N	60	38	29	127
Mean (SD)	6.27 (10.59)	15.27 (21.52)	3.19 (4.71)	8.26 (14.70)
Min, max	1.00, 64.80	1.00, 78.90	1.00, 20.40	1.00, 78.90
Median	1.40	6.60	1.00	1.50
HLA-B27, N (%)				
Absence	51 (85.00)	12 (31.58)	26 (89.66)	89 (70.08)
Presence	9 (15.00)	26 (68.42)	3 (10.34)	38 (29.92)

Abbreviations: CHAQ=Childhood Health Assessment Questionnaire; CRP=C-reactive protein; eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; HLA-B27=human leukocyte antigen, subtype B, number 27; JIA=juvenile idiopathic arthritis; LOM=limitation of motion; max=maximum; min=minimum; PsA=psoriatic arthritis; SD=standard deviation; VAS=visual analog scale.

a. Scores could range from 0 to 10 on a 21-circle VAS.
b. Seventy-three (73) joints were assessed for activity.
c. Sixty-nine (69) joints were assessed for limitation of motion.
d. Seventy-five (75) joints were assessed for pain and/or tenderness on motion.
e. Sixty-eight (68) joints were assessed for swelling.

Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 10.

The mean (SD) tender entheseal score at baseline in subjects with ERA was 5.87 (9.42) (Table 5). It should be noted that, although some subjects had no enthesitis at the Baseline visit, this was not required in order to meet the ILAR classification criteria for ERA.

Table 5. Summary of Additional Baseline Disease Characteristics in Subjects with Enthesitis-Related Arthritis in Study 3338

Characteristic Statistic	Subjects with ERA (N=38)
Tender entheseal score	
N	38
Mean (SD)	5.87 (9.42)
Min, max	0.00, 51.00
Median	3.00
Overall back pain VAS (mm)	
N	37
Mean (SD)	25.94 (28.00)
Min, max	0.00, 96.00
Median	18.00
Missing	1
Nocturnal back pain VAS (mm)	
N	38
Mean (SD)	16.37 (27.76)
Min, max	0.00, 96.00
Median	2.25
Modified Schober's test (cm)	
N	37
Mean (SD)	15.03 (1.94)
Min, max	11.80, 22.00
Median	14.60
Missing	1

Abbreviations: ERA=enthesitis-related arthritis; max=maximum; min=minimum; SD=standard deviation; VAS=visual analog scale.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 11.

The mean (SD) percent of BSA affected by psoriasis at baseline in subjects with PsA was 10.41% (13.39) (Table 6). The mean (SD) PGA of Psoriasis score at baseline was 1.83 (1.42). It should be noted that, although some subjects had no psoriasis at the Baseline visit, this was not required in order to meet the ILAR classification criteria for PsA.

Table 6. Summary of Additional Baseline Disease Characteristics in Subjects with Psoriatic Arthritis in Study 3338

Characteristic Statistic	Subjects with PsA (N=29)
Physician's Assessment of Psoriasis, % BSA affected	
N	29
Mean (SD)	10.41 (13.39)
Min, max	0.00, 46.00
Median	5.00
Physician's Global Assessment of Psoriasis	
N	29
Mean (SD)	1.83 (1.42)
Min, max	0.00, 5.00
Median	2.00

Abbreviations: BSA=body surface area; max=maximum; min=minimum; PsA=psoriatic arthritis; SD=standard deviation.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 12.

On the whole, the baseline demographics and disease characteristics are considered to reflect those subtypes of JIA for whom the indication is proposed. The MAH provided the type of psoriasis lesions of the patients recruited in the study 3338. Of the 29 subjects included in study 0881A1-3338 with a diagnosis of PsA:

- 2 had confirmed guttate psoriasis,
- 19 had confirmed plaque psoriasis,
- 6 subjects with no reported history of skin involvement (presence of psoriasis lesions is not required per the ILAR classification criteria for PsA diagnosis), and
- 2 had an unknown type of psoriasis lesions

In the original protocol, Patients with guttate, pustular, or erythrodermic psoriasis were excluded. However in Protocol Amendment 1, the exclusion of guttate psoriasis was removed. This was because, for subjects with psoriatic arthritis, the skin psoriasis assessments are only secondary measures of clinical benefit. Therefore, the inclusion of subjects with guttate psoriasis would not impact the primary variables of clinical benefit (i.e. ACR PEDI 30 response rate). A total of two subjects with guttate

psoriasis were included and appeared to have a similar response to treatment as those with plaque psoriasis and all PsA subjects.

Numbers analysed

The mITT and safety populations include these 127 subjects: 60 subjects with eoJIA, 38 subjects with ERA, and 29 subjects with PsA. The mITT and safety population for subjects with eoJIA consisted of 15 subjects in the 2 to 4-year age group, 23 subjects in the 5 to 11-year age group, and 22 subjects in the 12 to 17-year age group.

Table 7 Summary of Subject Participation Status for Part 1 of Study 3338

	JIA Subtype			
Conclusion Status Reason[a]	eoJIA (N=60) n (%)	ERA (N=38) n (%)	PsA (N=29) n (%)	Total (N=127) n (%)
Total	60 (100)	38 (100)	29 (100)	127 (100)
Completed Part 1	58 (96.7)	36 (94.7)	28 (96.6)	122 (96.1)
Discontinued[a,b]	2 (3.3)	2 (5.3)	1 (3.4)	5 (3.9)
Adverse event including infections	1 (1.7)	2 (5.3)	1 (3.4)	4 (3.1)
Protocol violation	1 (1.7)	0	0	1 (0.8)

Abbreviations: eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; PsA=psoriatic arthritis.
a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.
b. All subjects who discontinued investigational product continued to be monitored for safety in the study.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 7.

Outcomes and estimation

Efficacy Endpoints for JIA

ACR Pedi 30 Response at Week 12 (Primary Endpoint)

In the overall population, 109 subjects (88.6%) achieved an ACR Pedi 30 response at Week 12 of study 3338 (OC data; 95% CI: 81.6%, 93.6%; Table 8). The percentages of subjects with eoJIA, ERA, and PsA who achieved an ACR Pedi 30 response at Week 12 were similar (89.7%, 83.3%, and 93.1%, respectively).

Table 8. Number (%) of Subjects Achieving an ACR Pedi 30 Response at Week 12 of Study 3338 (Observed Cases), mITT Population

	JIA Subtype							
	eoJIA		ERA		PsA		Total	
Time Point	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
Week 12	52/58 (89.7)	(78.8, 96.1)	30/36 (83.3)	(67.2, 93.6)	27/29 (93.1)	(77.2, 99.2)	109/123 (88.6)	(81.6, 93.6)

Abbreviations: ACR Pedi= American College of Rheumatology pediatric response criteria; CI=confidence interval; eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; JIA=juvenile idiopathic arthritis; mITT=modified intent to treat; PsA=psoriatic arthritis.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 14.

Comparison of ACR Pedi 30 Response Rates to Historical Placebo Control Data.

The ACR Pedi 30 response rate at Week 12 for the subjects in this study was compared with the placebo mean composite endpoint response rate from Ruperto et al for the overall population as well as for each of the 3 JIA subtypes (Table 9). The estimates of the treatment effect were similar when the 6 studies included in the meta analysis were pooled and treated as if 1 study (unadjusted) or when the treatment effect was estimated by adjusting for among study differences (adjusted). Generally, the adjusted method is preferred when there are multiple studies in the comparison.

For the ERA subtype, the ACR Pedi 30 response rate at Week 12 was also compared with the placebo response rate from Burgos-Vargas et al (Table 9). All odds ratios and the lower bound of the 95% CI were greater than 1. Thus, the ACR Pedi 30 response rate at Week 12 in study 3338 was significantly higher than that from historical placebo controls.

Table 9. ACR Pedi 30 Response Rates at Week 12 of Study 3338 (Observed Cases) Compared to Historical Placebo Control, mITT Population

	ACR Pedi 30 Response Rate		Odds Ratio (95% CI) Study 3338 vs Historical Placebo Control	
Group	Study 3338 % (95% CI)	Historical Placebo Control % (95% CI)	Individual[c]	Pooled[d]
Overall	88.6% (81.6, 93.6)	28.9% (24.0, 34.2)[a]	23.49 (12.5, 44.3)	21.80 (11.9, 40.1)
eoJIA	89.7% (78.8, 96.1)	28.9% (24.0, 34.2)[a]	26.15 (10.6, 64.2)	24.27 (10.1, 58.5)
ERA	83.3% (67.2, 93.6)	28.9% (24.0, 34.2)[a]	15.09 (6.0, 38.2)	14.00 (5.6, 34.8)
ERA	83.3% (67.2, 93.6)	42.8% (16.9, 68.8)[b]	6.67 (1.7, 26.3)	
PSA	93.1% (77.2, 99.2)	28.9% (24.0, 34.2)[a]	40.73 (9.4, 176.9)	37.80 (8.8, 162.4)

Abbreviations: ACR Pedi= American College of Rheumatology pediatric response criteria; CI=confidence interval; eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; mITT=modified intent to treat; PsA=psoriatic arthritis.

a Meta analysis weighted estimate of placebo response rate in Ruperto et al.
b. Placebo response rate in Burgos-Vargas et al.
c. Six (6) historical studies treated individually in the logistic regression model (adjusted).
d. Pooling 6 historical studies as 1 in the logistic regression model (unadjusted).

Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 15.

Comparison of ACR Pedi 30 Response Rates to Historical Active Control Data.

The initial 12-week open-label period ACR Pedi 30 response rate from etanercept study 16.0016 (Lovell et al) was used as an active historical control for the overall population as well as for each of the 3 JIA subtypes (Table 10). The 95% CI of each of the odds ratios included 1. Therefore, the ACR Pedi 30 response rate at Week 12 in study 3338 was comparable to that from study 16.0016.

Table 10. ACR Pedi 30 Response Rates at Week 12 of Study 3338 (Observed Cases) Compared to Historical Active Control, mITT Population

	ACR Pedi 30 Response Rates		Odds Ratio (95% CI)
Group	Study 3338 % (95% CI)	Historical Active Control[a] % (95% CI)	Study 3338 vs Historical Active Control[b]
Overall	88.6% (81.6, 93.6)	73.9% (63.6, 84.3)	1.97 (0.5, 8.3)
eoJIA	89.7% (78.8, 96.1)	73.9% (63.6, 84.3)	2.00 (0.4, 9.8)
ERA	83.3% (67.2, 93.6)	73.9% (63.6, 84.3)	1.53 (0.2, 10.4)
PSA	93.1% (77.2, 99.2)	73.9% (63.6, 84.3)	2.27 (0.2, 21.3)

Abbreviations: ACR Pedi= American College of Rheumatology pediatric response criteria; CI=confidence interval; eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; mITT=modified intent to treat; PsA=psoriatic arthritis.

a. Etanercept study 16.0016 (Lovell et al).
b. Adjusted for covariates: baseline age, sex, duration of disease at study entry, age of disease onset, the baseline values of all 6 ACR Pedi 30 components.

Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 16.

ACR Pedi 30, ACR Pedi 50, and ACR Pedi 70 Responses at All Timepoints

Clinically meaningful ACR Pedi 30 responses were noted at the first time point (Week 4) and maintained throughout the duration of Part 1 of the study. In the overall population, 81.1% and 61.5% of subjects achieved ACR Pedi 50 and ACR Pedi 70 responses, respectively, at Week 12 (Table 11). Within each ACR Pedi response level, the percentages of subjects with eoJIA, ERA, and PsA who achieved a response at Week 12 were similar.

Table 11. Number (%) of Subjects Achieving ACR Pedi 30, ACR Pedi 50, and ACR Pedi 70 Responses in Study 3338 (Observed Cases), mITT Population

ACR Pedi	Time	eoJIA		ERA		PsA		Total	
Response	Point	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
ACR Pedi 30	Week 4	40/59 (67.8)	(54.4, 79.4)	32/38 (84.2)	(68.7, 94.0)	18/29 (62.1)	(42.3, 79.3)	90/126 (71.4)	(62.7, 79.1)
	Week 8	49/56 (87.5)	(75.9, 94.8)	33/36 (91.7)	(77.5, 98.2)	25/29 (86.2)	(68.3, 96.1)	107/121 (88.4)	(81.3, 93.5)
	Week 12	52/58 (89.7)	(78.8, 96.1)	30/36 (83.3)	(67.2, 93.6)	27/29 (93.1)	(77.2, 99.2)	109/123 (88.6)	(81.6, 93.6)
ACR Pedi 50	Week 4	30/58 (51.7)	(38.2, 65.0)	24/38 (63.2)	(46.0, 78.2)	10/29 (34.5)	(17.9, 54.3)	64/125 (51.2)	(42.1, 60.2)
	Week 8	42/56 (75.0)	(61.6, 85.6)	31/36 (86.1)	(70.5, 95.3)	20/29 (69.0)	(49.2, 84.7)	93/121 (76.9)	(68.3, 84.0)
	Week 12	46/58 (79.3)	(66.6, 88.8)	28/35 (80.0)	(63.1, 91.6)	25/29 (86.2)	(68.3, 96.1)	99/122 (81.1)	(73.1, 87.7)
ACR Pedi 70	Week 4	17/59 (28.8)	(17.8, 42.1)	11/38 (28.9)	(15.4, 45.9)	5/29 (17.2)	(5.8, 35.8)	33/126 (26.2)	(18.8, 34.8)
	Week 8	29/56 (51.8)	(38.0, 65.3)	19/36 (52.8)	(35.5, 69.6)	9/29 (31.0)	(15.3, 50.8)	57/121 (47.1)	(38.0, 56.4)
	Week 12	37/58 (63.8)	(50.1, 76.0)	25/35 (71.4)	(53.7, 85.4)	13/29 (44.8)	(26.4, 64.3)	75/122 (61.5)	(52.2, 70.1)

Abbreviations: ACR Pedi= American College of Rheumatology pediatric response criteria; CI=confidence interval; eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; mITT=modified intent to treat; PsA=psoriatic arthritis

Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Section 14, Table 14.2.3.

ACR Pedi 30 (Except Week 12), ACR Pedi 50, ACR Pedi 70, ACR Pedi 90, and ACR Pedi 100 Response

In the overall population, the percentages of subjects who achieved ACR Pedi 50, ACR Pedi 70, ACR Pedi 90, and ACR Pedi 100 responses (OC data) at Week 12 were 81.1%, 61.5%, 29.8%, and 23.0% (Table 12). Within each ACR Pedi response level, the percentages of subjects with extended oligoarticular JIA, ERA, and PsA who achieved a response (OC data) at Week 12 were similar. The results were also similar in the VFE population using OC data.

Table 12. Number (%) of Subjects Achieving ACR Pedi 50, ACR Pedi 70, ACR Pedi 90, and ACR Pedi 100 Responses at Week 12 (Observed Cases), mITT Population

ACR Pedi		JIA Subtype						Total	
		eoJIA		ERA		PsA			
Response	Time Point	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
ACR Pedi 50	Week 12	46/58 (79.3)	(66.6, 88.8)	28/35 (80.0)	(63.1, 91.6)	25/29 (86.2)	(68.3, 96.1)	99/122 (81.1)	(73.1, 87.7)
ACR Pedi 70	Week 12	37/58 (63.8)	(50.1, 76.0)	25/35 (71.4)	(53.7, 85.4)	13/29 (44.8)	(26.4, 64.3)	75/122 (61.5)	(52.2, 70.1)
ACR Pedi 90	Week 12	16/58 (27.6)	(16.7, 40.9)	16/35 (45.7)	(28.8, 63.4)	4/28 (14.3)	(4.0, 32.7)	36/121 (29.8)	(21.8, 38.7)
ACR Pedi 100	Week 12	12/58 (20.7)	(11.2, 33.4)	12/35 (34.3)	(19.1, 52.2)	4/29 (13.8)	(3.9, 31.7)	28/122 (23.0)	(15.8, 31.4)

Abbreviations: ACR = American College of Rheumatology; CI = confidence interval; eoJIA = extended oligoarticular juvenile idiopathic arthritis; ERA = enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; mITT = modified intent to treat; Pedi = pediatric; PsA = psoriatic arthritis.

Source: 0881-3338 eff_pedi_oc - 10AUG11 10:49

Figure 1 ACR Pedi Response Rates Over Time (Observed Cases), All Subjects, mITT Population

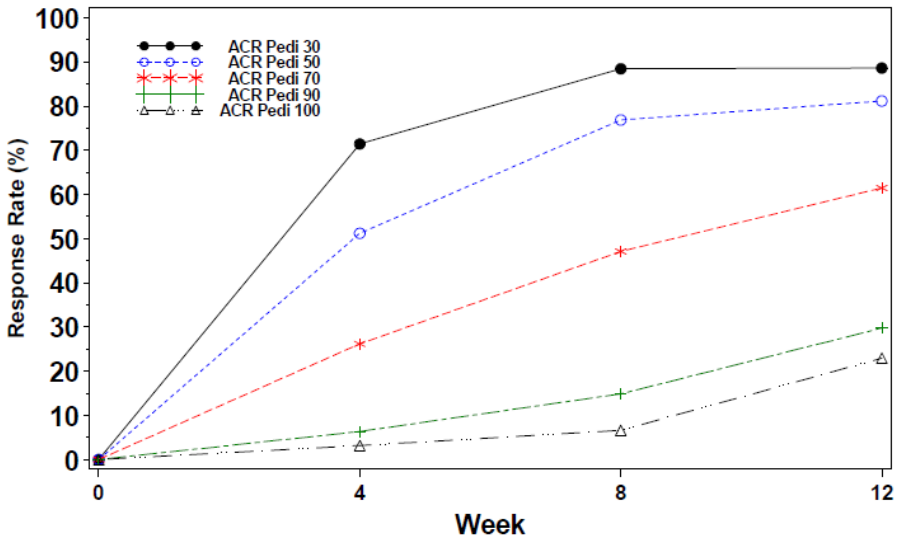

Table 13. Number (%) of Subjects with Extended Oligoarticular Juvenile Idiopathic Arthritis who Achieved ACR Pedi 30, ACR Pedi 50, ACR Pedi 70, ACR Pedi 90, and ACR Pedi 100 Responses at Week 12 (Observed Cases), by Age Group, mITT Population

		Age Group							
ACR Pedi		2 to ≤4 Years		5 to ≤11 Years		12 to ≤17 Years		Total	
Response	Time Point	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
ACR Pedi 30	Week 12	14/15 (93.3)	(68.1, 99.8)	20/22 (90.9)	(70.8, 98.9)	18/21 (85.7)	(63.7, 97.0)	52/58 (89.7)	(78.8, 96.1)
ACR Pedi 50	Week 12	13/15 (86.7)	(59.5, 98.3)	18/22 (81.8)	(59.7, 94.8)	15/21 (71.4)	(47.8, 88.7)	46/58 (79.3)	(66.6, 88.8)
ACR Pedi 70	Week 12	11/15 (73.3)	(44.9, 92.2)	15/22 (68.2)	(45.1, 86.1)	11/21 (52.4)	(29.8, 74.3)	37/58 (63.8)	(50.1, 76.0)
ACR Pedi 90	Week 12	5/15 (33.3)	(11.8, 61.6)	8/22 (36.4)	(17.2, 59.3)	3/21 (14.3)	(3.0, 36.3)	16/58 (27.6)	(16.7, 40.9)
ACR Pedi 100	Week 12	2/15 (13.3)	(1.7, 40.5)	7/22 (31.8)	(13.9, 54.9)	3/21 (14.3)	(3.0, 36.3)	12/58 (20.7)	(11.2, 33.4)

Abbreviations: ACR = American College of Rheumatology; CI = confidence interval; mITT = modified intent to treat; Pedi = pediatric.
Note: Age is based on age at the Baseline visit.
Source: 0881-3338 eff_pedi_age_oc - 10AUG11 10:49

Table 14. Change from Baseline for the Individual Components of the ACR Pedi Response at Week 12 of Study 3338 (Observed Cases), mITT Population

		Change from Baseline			
Time Point	Statistic	eoJIA	ERA	PsA	Total
Physician's Global Assessment of Disease Activity[a]					
Week 12	N	58	36	29	123
	Mean (%)	-3.52 (-73.2%)	-3.94 (-70.9%)	-2.97 (-65.0%)	-3.51 (-70.6%)
	95% CI of mean	(-3.92, -3.11)	(-4.63, -3.26)	(-3.48, -2.45)	(-3.81, -3.21)
Patient/Parent Global Assessment[a]					
Week 12	N	58	36	29	123
	Mean (%)	-2.82 (-53.1%)	-2.82 (-47.6%)	-2.36 (-47.7%)	-2.71 (-50.2%)
	95% CI of mean	(-3.46, -2.17)	(-3.74, -1.89)	(-3.11, -1.61)	(-3.14, -2.28)
Childhood Health Assessment Questionnaire					
Week 12	N	58	36	29	123
	Mean (%)	-0.52 (-52.2%)	-0.48 (-57.8%)	-0.39 (-51.3%)	-0.48 (-53.6%)
	95% CI of mean	(-0.65, -0.39)	(-0.65, -0.31)	(-0.58, -0.20)	(-0.57, -0.39)
Number of Active Joints[b]					
Week 12	N	58	36	29	123
	Mean (%)	-5.46 (-69.8%)	-4.25 (-77.7%)	-5.21 (-73.8%)	-5.05 (-73.0%)
	95% CI of mean	(-6.74, -4.19)	(-5.44, -3.06)	(-6.83, -3.58)	(-5.83, -4.27)
Number of Joints with Limitation of Motion[c]					
Week 12	N	58	36	29	123
	Mean (%)	-4.48 (-64.1%)	-3.36 (-67.4%)	-4.28 (-71.7%)	-4.10 (-66.9%)
	95% CI of mean	(-5.63, -3.33)	(-4.11, -2.61)	(-5.68, -2.87)	(-4.77, -3.44)
C-Reactive Protein (mg/L)					
Week 12	N	58	34	28	120
	Mean (%)	-2.78 (-18.9%)	-13.15 (-36.8%)	-1.32 (-11.0%)	-5.38 (-22.1%)
	95% CI of mean	(-4.91, -0.65)	(-20.46, -5.83)	(-2.83, 0.20)	(-7.81, -2.94)

Abbreviations: ACR Pedi= American College of Rheumatology pediatric response criteria; CI=confidence interval; eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; mITT=modified intent to treat; PsA=psoriatic arthritis.
a. Scores could range from 0 to 10 on a 21-circle VAS.
b. Seventy-three (73) joints were assessed for activity.
c. Sixty-nine (69) joints were assessed for limitation of motion.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 19.

The breakdown of the individual components of the composite score supports the primary efficacy endpoint for study 3338, as no worsening of any of the components was seen.

Pain Assessment

There was a mean improvement of 51.9% from baseline in pain assessment scores across all JIA subtypes at Week 12 of study 3338 (Table 15). Mean pain assessment scores at Week 4 and Week 8 were also improved from baseline for all JIA subtypes.

Table 15. Change from Baseline in Pain Assessment at Week 12 of Study 3338 (Observed Cases), mITT Population

		Change from Baseline			
Time Point	Statistic	eoJIA	ERA	PsA	Total
Week 12	N	58	36	29	123
	Mean (%)	-3.15 (-58.9%)	-3.21 (-44.9%)	-2.60 (-46.6%)	-3.04 (-51.9%)
	95% CI of mean	(-3.79, -2.51)	(-4.17, -2.24)	(-3.40, -1.80)	(-3.48, -2.59)

Abbreviations: CI=confidence interval; eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; mITT=modified intent to treat; PsA=psoriatic arthritis.
Note: Scores could range from 0 to 10.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 20.

Duration of Morning Stiffness

Table 16. Mean Change (95% CI) from Baseline in Duration of Morning Stiffness at Week 12 (Observed Cases), mITT Population

		Change from Baseline			
Time Point	Statistic	eoJIA	ERA	PsA	Total
Week 12	N	58	36	29	123
	Mean (%)	-60.29 (-61.5%)	-65.61 (-64.1%)	-47.93 (-77.2%)	-58.93 (-66.0%)
	95% CI of mean	(-83.58, -37.01)	(-97.60, -33.62)	(-67.28, -28.58)	(-73.73, -44.14)

Abbreviations: CI = confidence interval; eoJIA = extended oligoarticular juvenile idiopathic arthritis; ERA = enthesitis-related arthritis; mITT = modified intent to treat; PsA = psoriatic arthritis.
Source: 0881-3338 eff_stiff - 08AUG11 16:05

Inactive Disease Status

Inactive disease status was defined as no joints with active arthritis (ie, no pain, swelling, or limitation of motion), a CRP result within normal limits, and a PGA of Disease Activity score of 0 on a 21-circle VAS. 15 subjects (12.1%) in the overall population had inactive disease status at Week 12 (Table 17). The percentages of subjects with extended oligoarticular JIA, ERA, and PsA who had inactive disease status at Week 12 were11.9%, 6.9%, and 16.7%, respectively.

Table 17. Number (%) of Subjects with Inactive Disease Status at Week 12 (Observed Cases), mITT Population

	JIA Subtype							
	eoJIA		ERA		PsA		Total	
Time Point	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
Week 12	7/59 (11.9)	(4.9, 22.9)	2/29 (6.9)	(0.8, 22.8)	6/36 (16.7)	(6.4, 32.8)	15/124 (12.1)	(6.9, 19.2)

Abbreviations: CI = confidence interval; eoJIA = extended oligoarticular juvenile idiopathic arthritis; ERA = enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; mITT = modified intent to treat; PsA = psoriatic arthritis.
Note: Inactive disease is defined as no joints with active arthritis (ie, no pain, swelling, or limitation of motion), a CRP result within normal limits, and a Physician Global Assessment of disease activity score of 0.
Source: 0881-3338 EFF_DISEASE - 08AUG11 16:05

Tender Entheseal Score

In subjects with ERA, there was a mean improvement of 57.8% from baseline in tender entheseal score at Week 12 of study 3338 (Table 18).

Table 18. Change from Baseline in Tender Entheseal Score at Week 12 of Study 3338 (Observed Cases), mITT Population, Subjects with Enthesitis-Related Arthritis

Time Point	Statistic	Change from Baseline
Week 12	N	36
	Mean (%)	-4.36 (-57.8%)
	95% CI of mean	(-6.34, -2.39)

Abbreviations: CI=confidence interval; mITT=modified intent to treat.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 23.

Back Pain

In subjects with ERA, there was a mean improvement of 21.2% from baseline in overall back pain VAS score at Week 12 of study 3338 (Table 19). Additionally, the mean nocturnal back pain VAS score at Week 12 was improved from baseline.

Table 19. Change from Baseline in Overall Back Pain VAS (100-mm Scale) at Week 12 of Study 3338 (Observed Cases), mITT Population, Subjects with Enthesitis-Related Arthritis

Time Point	Statistic	Change from Baseline
Week 12	N	36
	Mean (%), mm	-12.47 (-21.2%)
	95% CI of mean	(-21.25, -3.69)

Abbreviations: CI=confidence interval; mITT=modified intent to treat; VAS=visual analog scale.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 24.

Table 20. Change from Baseline in Nocturnal Back Pain VAS (100-mm Scale) at Week 12 of Study 3338 (Observed Cases), mITT Population, Subjects with Enthesitis-Related Arthritis

Time Point	Statistic	Change from Baseline
Week 12	N	36
	Mean (%), mm	-8.94 (-6.8%)
	95% CI of mean	(-16.67, -1.22)

Abbreviations: CI=confidence interval; mITT=modified intent to treat; VAS=visual analog scale.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 25.

Modified Schober's Test

In subjects with ERA, there was a mean improvement of 9.7% from baseline in modified Schober's test at Week 12 of study 3338 (Table 21).

Table 21. Change from Baseline in Modified Schober's Test at Week 12 of Study 3338 (Observed Cases), mITT Population, Subjects with Enthesitis-Related Arthritis

Time Point	Statistic	Change from Baseline
Week 12	N	35
	Mean (%), cm	0.35 (9.7%)
	95% CI of mean	(-0.02, 0.72)

Abbreviations: CI=confidence interval; mITT=modified intent to treat.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 26.

Percent Body Surface Area Affected by Psoriasis

In subjects with PsA, there was a mean improvement of 48.2% from baseline in BSA affected by psoriasis at Week 12 of study 3338 (Table 22).

Table 22. Change from Baseline in Percent Body Surface Area Affected by Psoriasis at Week 12 of Study 3338 (Observed Cases), mITT Population, Subjects with Psoriatic Arthritis

Time Point	Statistic	Change from Baseline
Week 12	N	29
	Mean (%)	-6.72 (-48.2%)
	95% CI of mean	(-10.58, -2.85)

Abbreviations: CI=confidence interval; mITT=modified intent to treat.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 27.

Physician's Global Assessment of Psoriasis

In subjects with PsA, there was a mean improvement of 39.6% from baseline in PGA of Psoriasis score at Week 12 of study 3338 (Table 23).

Table 23. Change from Baseline in Physician's Global Assessment of Psoriasis Score at Week 12 (Observed Cases), mITT Population, Subjects with Psoriatic Arthritis

Time Point	Statistic	Change from Baseline
Week 12	N	28
	Mean (%)	-0.96 (-39.6%)
	95% CI of mean	(-1.37, -0.56)

Abbreviations: CI=confidence interval; mITT=modified intent to treat.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 28.

Comparison of Results in Subpopulations

ACR Pedi response rates were summarized by age group (2 to 4 years, 5 to 11 years, and 12 to 17 years) for subjects with eoJIA in study 3338. Within each ACR Pedi response level for ACR Pedi 30, ACR Pedi 50, and ACR Pedi 70, the percentages of subjects in each age group who achieved responses at Week 12 were generally similar (Table 24).

Table 24. Number (%) of Subjects with Extended Oligoarticular Juvenile Idiopathic Arthritis in Study 3338 who Achieved ACR Pedi 30, ACR Pedi 50, and ACR Pedi 70 Responses (Observed Cases), by Age Group, mITT Population

		Age Group							
ACR Pedi Response	Time Point	2 to ≤4 Years		5 to ≤11 Years		12 to ≤17 Years		Total	
		n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
ACR Pedi 30	Week 4	11/15 (73.3)	(44.9, 92.2)	17/23 (73.9)	(51.6, 89.8)	12/21 (57.1)	(34.0, 78.2)	40/59 (67.8)	(54.4, 79.4)
	Week 8	14/14 (100)	(76.8, 100)	17/21 (81.0)	(58.1, 94.6)	18/21 (85.7)	(63.7, 97.0)	49/56 (87.5)	(75.9, 94.8)
	Week 12	14/15 (93.3)	(68.1, 99.8)	20/22 (90.9)	(70.8, 98.9)	18/21 (85.7)	(63.7, 97.0)	52/58 (89.7)	(78.8, 96.1)
ACR Pedi 50	Week 4	7/14 (50.0)	(23.0, 77.0)	14/23 (60.9)	(38.5, 80.3)	9/21 (42.9)	(21.8, 66.0)	30/58 (51.7)	(38.2, 65.0)
	Week 8	12/14 (85.7)	(57.2, 98.2)	16/21 (76.2)	(52.8, 91.8)	14/21 (66.7)	(43.0, 85.4)	42/56 (75.0)	(61.6, 85.6)
	Week 12	13/15 (86.7)	(59.5, 98.3)	18/22 (81.8)	(59.7, 94.8)	15/21 (71.4)	(47.8, 88.7)	46/58 (79.3)	(66.6, 88.8)
ACR Pedi 70	Week 4	3/15 (20.0)	(4.3, 48.1)	10/23 (43.5)	(23.2, 65.5)	4/21 (19.0)	(5.4, 41.9)	17/59 (28.8)	(17.8, 42.1)
	Week 8	7/14 (50.0)	(23.0, 77.0)	12/21 (57.1)	(34.0, 78.2)	10/21 (47.6)	(25.7, 70.2)	29/56 (51.8)	(38.0, 65.3)
	Week 12	11/15 (73.3)	(44.9, 92.2)	15/22 (68.2)	(45.1, 86.1)	11/21 (52.4)	(29.8, 74.3)	37/58 (63.8)	(50.1, 76.0)

Note: Age is based on age at the baseline visit.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Section 14, Table 14.2.13.

Study 20021618: Open-label Extension Treatment with TNFR:Fc for Participating Patients in TNFR:Fc Clinical Trials

Methods

Study 20021618 was an open-label study of long-term etanercept treatment through 10 years, which included paediatric subjects who had previously participated in study 16.0016 as well as adult subjects who had previously participated in double-blind rheumatoid arthritis studies.

In the below text only data from the paediatric subjects with JIA are presented.

Study Participants

All paediatric subjects with DMARD-refractory, polyarticular-course JIA (polyarticular-, pauciarticular-, or systemic-onset) who had been enrolled in the initial etanercept study 16.0016, had not had any clinically significant adverse events thought to be due to etanercept, and who met the inclusion/exclusion criteria per the protocol were eligible to enrol in study 20021618. Per the inclusion criteria for the initial study 16.0016, patients were to be between 4 and 17 years of age at the time of enrollment. Furthermore, the inclusion criteria for entry into the study 16.0016 required a diagnosis of

JIA by the American College of Rheumatology (ACR) criteria; disease onset may have been systemic, polyarticular, or pauciarticular but disease course had to be polyarticular.

Treatments

Although paediatric subjects who entered study 20021618 initially continued with the etanercept dose administered in study 16.0016 (0.4 mg/kg etanercept BIW up to a maximum dose of 25 mg per injection), the 0.8-mg/kg weekly dose (maximum dose of 50 mg per week) could be administered as two 0.4-mg/kg SC injections either on the same day or 3 to 4 days apart, or as a single 0.8-mg/kg injection QW.

Objectives

The primary objectives of study 20021618 were:

1. to evaluate the long-term safety of etanercept in subjects with disease-modifying antirheumatic drug (DMARD)-refractory JIA; and
2. to evaluate improvement in physical function/disability and quality of life.

The secondary objective was to evaluate long-term efficacy of etanercept.

Outcomes/endpoints

In terms of efficacy evaluation, the primary endpoint in paediatric subjects is ACR Pedi 30 (referred to in the CSR as the juvenile rheumatoid arthritis 30% definition of improvement [JRA-DOI 30]) at month 3, and is defined as an improvement of at least 30% from baseline in at least 3 of the 6 criteria of the JIA Core Set of Response Criteria, and a worsening of greater than 30% in not more than 1 of the following 6 criteria from baseline:

1. PGA of disease activity on the 0 to 10 VAS scale
2. Subject's/Parent's Global Assessment of disease activity on the 0 to 10 VAS scale
3. CHAQ
4. Number of active joints
5. Number of joints with LOM
6. Erythrocyte sedimentation factor (ESR).

With the exception of the use of ESR, these criteria are the same as that used in study 3338. However, the acute phase reactant was changed to CRP after year 1 in study 20021618. The terminology for the assessment of response in patients with JIA that was current at the time the protocol for study 20021618 was prepared was JRA-DOI; however, the newer terminology (i.e., ACR Pedi) is used herein for consistency. The change in terminology from JRA-DOI to ACR Pedi resulted from the variable being renamed and not due to changes in any of the components that make up the composite index.

Additional efficacy endpoints for paediatric subjects in the study 20021618 database included:

- ACR Pedi 30, ACR Pedi 50, ACR Pedi 70, ACR Pedi 90, and ACR Pedi 100 responses;
- ACR Pedi components: PGA of disease activity, Subject/Parent's Global Assessment of disease activity, number of active joints, CHAQ score, CRP (after first year), and number of joints with LOM

- Number of joints with LOM plus tender/painful
- Subject's pain visual analog scale (VAS)
- Duration of morning stiffness
- Articular severity score
- Complete response (0 swollen joints, 0 tender joints).

Sample size

Study 20021618 enrolled subjects who had been enrolled in previous etanercept studies. No sample size calculations were carried out.

Randomisation

This was a non-randomized study.

Blinding (masking)

This was an open-label study.

Statistical methods

No hypothesis was tested. The primary objective was to examine safety parameters, which were assessed descriptively and summarized for all subjects enrolled in the study.

No statistical analyses were planned for the study 20021618 from an efficacy point of view.

Results

Participant flow

Fifty-eight (58, 84%) of the 69 paediatric subjects from study 16.0016 received etanercept in study 20021618. Fifteen (15) of the 58 paediatric subjects who enrolled in study 20021618 completed the 10-year study and 43 discontinued treatment. In general, the withdrawal rate was highest in the first 3 years and then relatively stable for the remainder of the study. The most common reasons for discontinuation for paediatric subjects enrolled in study 20021618 were as follows: other (not related to safety, 10 subjects), response status (9 subjects), and subject refusal (7 subjects). The reasons that were grouped under the term 'other' for paediatric subjects include withdrew consent, to increase dose, to reduce dose, pregnancy, subject non-compliance, lack of efficacy, and subject moving from the area.

Recruitment

The study was conducted at 38 North American study centers (2 Canada, 36 United States). It was initiated on 31 July 1997 and the last subject visit occurred on 10 December 2008. The study period for the cumulative dataset ranges from 16 August 1993 (first date of etanercept administration in the initial etanercept studies) to 10 December 2008.

Conduct of the study

Study 20021618 protocol was amended 8 times. Major changes for each amendment are described in Table 25.

Table 25. Summary of Protocol Amendments

Amendment	Summary of Key Changes
Original Protocol 09 April 1997 (0 subjects enrolled)	Not applicable
Amendment 1 06 June 1997 (263 subjects enrolled)	• Clarified maximum pediatric dose of 25 mg twice weekly. • Decreased washout period of cyclosporine from 6 months to 2 weeks; exclusion criteria was also revised to reflect this. • Clarified that subjects from Study 016.0014 may be on combination MTX and etanercept. • Clarified subject population for which serum bilirubin was required to be ≤ 2X ULN (pediatric subjects from 016.0016 only). • Clarified use of pain medication in pediatric subjects. • Eliminated monthly assessments during tapering of NSAIDS, MTX, or corticosteroids. • Clarified maximum corticosteroid dose to be used during disease flare (40 mg prednisone equivalent/day). • Clarified NSAID usage following disease flare. • Added the following evaluations: hematology and chemistry profile, and UA/micro. • Clarified that chest X-rays would not be required for pediatric subjects in Study 016.0016. • Clarified transfusion procedures for pediatric subjects in Appendix E. • Clarified toxicity scale for reporting low lymphocytes in Appendix F.
Amendment 2 11 December 1997 (371 subjects enrolled)	• Clarified dose for adult and pediatric subjects. • Added autoimmune features checklist to safety evaluations. • Decreased time from receipt of investigational drugs prior to etanercept from 3 months to 1 month. • Clarified baseline for long term evaluation. • Clarified instructions for MTX administration. • Clarified dose escalation of etanercept from 10 mg to 25 mg. • Provided additional criteria for premature discontinuations. • Allowed treatment period of previous study to satisfy the 12-week requirement for change in permissible medication. • Revised reporting of injection site reactions. • Clarified requirements for baseline pregnancy test, and chest, hand, wrists, and forefoot x-rays. • Allowed for a more thorough evaluation of subjects developing signs and symptoms consistent with new connective tissue disease.
Amendment 3 06 July 1998 (4 subjects enrolled)	• Defined study design of extension period. • Added physical/function and quality of life endpoints. • Allowed adjustment of medications after 1 year of etanercept therapy. • Clarified subjects who could waive screening procedures before entering Study 016.0018.

Amendment	Summary of Key Changes
Amendment 4 30 October 1998 (0 subjects enrolled)	• Defined study design and evaluations scheduled to be performed during the extension period. • Updated the definition for adverse event. • Added sub-study to evaluate concurrent administration of pneumococcal and influenza vaccine with etanercept.
Amendment 5 19 April 1999 (1 subject enrolled)	• Corrected error in units for hemoglobin. • Added Tanner Score to capture growth velocity for pediatric subjects. • Clarified when safety evaluations should be obtained. • Clarified collection of concomitant medications during the extension study.
Amendment 6 10 October 2001 (0 subjects enrolled)	• Revised follow-up requirements.
Amendment 7 12 September 2003 (0 subjects enrolled)	• Clarified the collection of safety data for patients who discontinue study drug. • Updated adverse event section in accordance with IB. • Changed the study drug dosing frequency and offered the option to administer their weekly dose on one day, instead of 2 injections weekly, 3 or 4 days apart. • Clarified the number of missed doses of etanercept, during the study extension phase that would result in discontinuation. • Clarified that Methotrexate (MTX) was the only permissible DMARD during the study. • Added the development of diagnosed cancer and known HIV seropositivity as a reason for prematurely discontinuing.
Amendment 8 09 February 2006 (0 subjects enrolled)	• A 25 mg prefilled syringe was offered as an option. • Updated the definition of adverse event to include the definition from ICH Guideline for GCP and to include the broadened definition of an adverse event as the worsening of any occurrence or pre-existing condition from the time the informed consent is signed to the initiation of the investigational product. • Updated the Reporting Procedures for All Serious Adverse Events, Serious Adverse Events Report, and Subject Informed Consent Template. • Included the Serious Adverse Event Fax Transmittal Form.

Deviations from the protocol-specified analyses included the exclusion of the following tables: Common Toxicity Criteria (CTC) shifts from baseline, current medications for RA, lot numbers for investigational product, and subject listing of investigational product discontinuation.

Analysis of laboratory values, ESR and CRP, corticosteroid use, and methotrexate use were approximated to fit visit windows. In addition, the SAPs specified in the statistical analysis plan that reporting of all serious adverse events and deaths would be limited to ≤30 days of the last dose of etanercept in the tables; however, all serious adverse events and deaths (as of database lock on 12 December 2008) were reported in the listings and the tables included events within 30 days of the last dose of etanercept.

Protocol amendment 1 clarified that the ≥2 active joints must be peripheral joints. This revision was made primarily to ensure that subjects with only back pain were not enrolled in the study.

Baseline data

The mean (SD) age of the JIA population in study 20021618 was 10.52 (3.74) years with a range of 4 to 17 years at the baseline of the initial study 16.0016, the study subjects participated in before entering study 20021618 (Table 26). One (1) of the paediatric subjects in study 20021618 (1.7%) was 4 years of age, 28 subjects (48.3%) were 5 to 11 years of age, and 29 subjects (50.0%) were 12 to 17 years of age at baseline of the initial study 16.0016. Although all subjects had polyarticular-course JIA, 34 of the paediatric subjects in study 20021618 (58.6%) had polyarticular-onset JIA, 19 (32.8%) had systemic-onset JIA, and 5 (8.6%) had pauciarticular onset JIA. The majority of paediatric subjects in study 20021618 were female (67.2%) and White (74.1%).

The mean (SD) disease duration of JIA at the entry of the initial study 16.0016 was 5.96 (3.19) years with a range of 0.7 to 12.4 years. Approximately half of the subjects in study 20021618 had had JIA for greater than 5 years at the time they entered study 16.0016. Approximately half of the subjects in study 20021618 had had JIA for greater than 5 years at the time they entered study 16.0016.

At the baseline of study 16.0016, all of the subjects had received DMARDs: 84% of the subjects were nonresponsive to previous MTX therapy and 22% were intolerant to previous MTX therapy.

Table 26. Subject Demographics and Baseline Characteristics for Paediatric Subjects in Study 20021618 at Analysis Baseline

Characteristic[a] Statistic	Pediatric Subjects (N=58)
Age (Years)	
n	58
Mean	10.52
SD	3.74
SE	0.49
Median	11.00
Min, Max	4.0, 17.0
Age Group - n (%)	
2-4 Years[b]	1 (1.72)
5-11 Years	28 (48.28)
12-17 Years	29 (50.00)
Sex - n (%)	
Female	39 (67.2)
Male	19 (32.8)
Race - n (%)	
American Indian or Alaska Native	1 (1.7)
Asian	1 (1.7)
Black or African American	4 (6.9)
Hispanic or Latino	9 (15.5)
Other	0 (0.0)
White or Caucasian	43 (74.1)
Height (cm)	
n	58
Mean	134.82
SD	21.87
SE	2.87
Median	133.25
Min, Max	88.0, 178.5
Weight (kg)	
n	58
Mean	35.88
SD	19.48
SE	2.56
Median	30.95
Min, Max	13.5, 124.7

Characteristic[a] Statistic	Pediatric Subjects (N=58)
BMI (kg/m^2)	
n	58
Mean	18.55
SD	5.72
SE	0.75
Median	17.21
Min, Max	11.4, 50.9
BSA (m^2)	
n	58
Mean	1.14
SD	0.38
SE	0.05
Median	1.07
Min, Max	0.6, 2.4
JIA Onset Type- n (%)	
Pauciarticular	5 (8.62)
Polyarticular	34 (58.62)
Systemic	19 (32.76)
Rheumatoid Factor (≥20 IU/mL)	
N/A	2 (3.4)
Negative	37 (63.8)
Positive	19 (32.8)
n	58
Mean	4.53
SD	3.78
SE	0.50
Median	3.50
Min, Max	0.0, 15.0
JIA Disease Duration (Years)	
n	58
Mean	5.96
SD	3.19
SE	0.42
Median	5.63
Min, Max	0.7, 12.4
Duration of JIA - n (%)	
<2 Years	4 (6.9)
2-5 Years	22 (37.9)
>5 Years	32 (55.2)

Characteristic[a] Statistic	Pediatric Subjects (N=58)
Use of DMARDs - n (%)	
No	0 (0.0)
Yes	58 (100.0)
Number of DMARDs Used	
n	58
Mean	2.57
SD	1.39
SE	0.18
Median	2.00
Min, Max	1.0, 7.0
Use of Corticosteroids - n (%)	
No	36 (62.1)
Yes	22 (37.9)
Use of NSAIDs - n (%)	
No	2 (3.4)
Yes	56 (96.6)

Abbreviations: BMI=body mass index; BSA=body surface area; DMARD=disease modifying antirheumatic drug; JIA=juvenile idiopathic arthritis; NSAID=nonsteroidal anti-inflammatory drug; SD=standard deviation; SE=standard error.

a. Based on effectiveness analysis baseline.

b. Per the inclusion criteria for study 16.0016, subjects were to be ≥4 years of age.

Source: 5.3.5.2, Final CSR for study 20021618, Table 14-2.1.2.B.

The paediatric subjects in study 20021618 had mean of 39.4 active joints and a mean of 27.5 joints with LOM at the baseline of the initial study 16.0016 (Table 27). The mean PGA at the baseline of study 16.0016 was 6.4. The mean CRP value at the baseline of study 16.0016 was 6.7 mg/dL (67 mg/L).

Table 27. Baseline Disease Characteristics in Study 20021618 (Based on Baseline of Initial Study 16.0016)

Characteristic[a] Statistic	Pediatric Subjects (N=58)
Subject Global Assessment	
n	58
Mean	4.8
SD	2.4
SE	0.3
Median	5.0
Min, Max	0.0, 10.0
Physician Global Assessment	
n	58
Mean	6.4
SD	2.0
SE	0.3
Median	6.5
Min, Max	1.0, 10.0
No. Active Joints	
n	58
Mean	39.4
SD	15.0
SE	2.0
Median	36.5
Min, Max	10.0, 70.0
No. LOM Joints	
n	58
Mean	27.5
SD	15.1
SE	2.0
Median	23.5
Min, Max	0.0, 60.0
Pain VAS	
n	58
Mean	3.7
SD	2.5
SE	0.3
Median	3.6
Min, Max	0.0, 10.0
No. Tender Joints	
n	57
Mean	9.7
SD	10.6
SE	1.4
Median	7.0
Min, Max	0.0, 46.0
No. Swollen Joints	
n	58
Mean	25.4
SD	12.8
SE	1.7
Median	26.0
Min, Max	6.0, 57.0

Characteristic[a] Statistic	Pediatric Subjects (N=58)
Morning Stiffness (minutes)	
n	58
Mean	87.2
SD	102.4
SE	13.5
Median	52.5
Min, Max	0.0, 540.0
CHAQ[b]	
n	58
Mean	1.9
SD	0.8
SE	0.1
Median	2.0
Min, Max	0.0, 3.3
ESR	
n	57
Mean	42.4
SD	27.8
SE	3.7
Median	34.0
Min, Max	4.0, 112.0
C-Reactive Protein (mg/dL)	
n	58
Mean	6.7
SD	8.1
SE	1.1
Median	3.4
Min, Max	0.1, 30.6

Abbreviations: CHAQ=Childhood Health Assessment Questionnaire; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; LOM=limitation of motion; max=maximum; min=minimum; SD=standard deviation; SE=standard error; VAS=visual analog scale.
a. Value at baseline of initial study 16.0016.
b. Also referred to as HAQ-DI in the clinical study report.
Source: 5.3.5.2, Final CSR for study 20021618, Table 14-3.10.A.

Numbers analysed

Fifty-eight (58, 84%) of the 69 paediatric subjects from study 16.0016 received etanercept in study 20021618 (Table 28). Fifteen (15) of the 58 paediatric subjects who enrolled in study 20021618 completed the 10-year study and 43 discontinued treatment.

Table 28. Subject Disposition in Study 20021618

Conclusion Status Reason	Pediatric Subjects (N=58)
Subjects enrolled, n	58
Subjects enrolled and received at least 1 dose of etanercept, n	58
Subjects who discontinued at year 1[a], n (%)	8 (13.8)
Subjects who discontinued at year 2, n (%)	4 (6.9)
Subjects who discontinued at year 3, n (%)	6 (10.3)
Subjects who discontinued at year 4, n (%)	3 (5.2)
Subjects who discontinued at year 5, n (%)	2 (3.4)
Subjects who discontinued at year 6, n (%)	3 (5.2)
Subjects who discontinued at year 7, n (%)	5 (8.6)
Subjects who discontinued at year 8, n (%)	7 (12.1)
Subjects who discontinued at year 9, n (%)	1 (1.7)
Subjects who discontinued at year 10, n (%)	2 (3.4)
Subjects who discontinued at year 11, n (%)	1 (1.7)
Subjects who discontinued at year 12, n (%)	1 (1.7)
Subjects who completed the study to closure[b], n (%)	15 (25.9)
Subjects who discontinued before study closure, n (%)	43 (74.1)
Adverse Event, n (%)	4 (6.9)[c]
Completed Month 12 Only, n (%)	1 (1.7)
Lost to Follow-up, n (%)	4 (6.9)
Other, n (%)	10 (17.2)
Physician Decision, n (%)	5 (8.6)
Protocol Issues, n (%)	3 (5.2)
Refusal-Subject, n (%)	7 (12.1)
Response Status, n (%)	9 (15.5)

a. Per protocol, patients will be considered to have completed the study when they complete a minimum of one year of continuous treatment.
b. Study closed on 10 December 2008.
c. One additional subject discontinued treatment due to adverse events (fibro tendon and skin disorder) but the end of study form indicated discontinuation due to physician decision and thus is captured here under 'Physician Decision'.

Source: 5.3.5.2, Final CSR for study 20021618, Table 14-1.1.B.

Outcomes and estimation

ACR Pedi 30 Response at Month 3 (Primary Endpoint)

At month 3 of study 20021618, 42 paediatric subjects (79.2%) achieved an ACR Pedi 30 response (Table 29).

Table 29. Number (%) of Paediatric Subjects Achieving ACR Pedi 30 Response at Month 3 of Study 20021618 (Observed Cases)

Timepoint	Pediatric Subjects (N=58) n/N1 (%)
Month 3	42/53 (79.2)

Abbreviations: ACR Pedi= American College of Rheumatology pediatric response criteria; N=number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618; N1=number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618, and were available at the assessed visit.
Note: DOI Responders: per Giannini et al, 1997.
Note: ESR included as component in calculation of response through year 1.
Source: 5.3.5.2, Final CSR for study 20021618, Table 14-4.5.14.B.

ACR Pedi 30, ACR Pedi 50, and ACR Pedi 70 Responses at Yearly Timepoints Through 10 Years

The proportion of paediatric subjects in study 20021618 achieving ACR Pedi 30, ACR Pedi 50, and ACR Pedi 70 responses remained relatively stable over 10 years (Table 30). Similar results were observed for ACR Pedi 90 and ACR Pedi 100.

Table 30. ACR Pedi 30, ACR Pedi 50, and ACR Pedi 70 Responses over Time for Paediatric Subjects in Study 20021618 (Observed Cases): n/N1 (%) of Subjects

ACR Pedi Response	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
ACR Pedi 30	40/50 (80.0)	36/47 (76.6)	26/40 (65.0)	23/32 (71.9)	16/31 (51.6)	17/27 (63.0)	14/22 (63.6)	7/9 (77.8)	5/6 (83.3)	3/3 (100.0)
ACR Pedi 50	36/50 (72.0)	29/47 (61.7)	25/40 (62.5)	20/32 (62.5)	15/31 (48.4)	16/27 (59.3)	13/22 (59.1)	7/9 (77.8)	4/6 (66.7)	3/3 (100.0)
ACR Pedi 70	26/50 (52.0)	23/47 (48.9)	21/40 (52.5)	15/32 (46.9)	11/31 (35.5)	12/27 (44.4)	12/22 (54.5)	7/9 (77.8)	4/6 (66.7)	3/3 (100.0)

Abbreviations: ACR Pedi= American College of Rheumatology pediatric response criteria; N1=number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618, and were available at the assessed visit.
Note: DOI Responders: per Giannini et al, 1997.
Note: CRP included as component in calculation of response after year 1.
Source: 5.3.5.2, Final CSR for study 20021618, Table 14-4.5.14.B.

Individual Components of the ACR Pedi Response Variable

As was observed for the ACR Pedi response rates, the individual components of the ACR Pedi response remained relatively stable over time through 10 years (Table 31). However, there was some fluctuation in the mean % improvement in CRP in the later years of the study because of outlier data and the limited number of patients contributing data (18 or less after year 7). As expected, the median % change showed much less fluctuation over the 10-year duration of the study.

Table 31. Percent Improvement from Baseline for the Individual Components of the ACR Pedi Response Over Time for Paediatric Subjects in Study 20021618 (Observed Cases)

Component	Statistic	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Physician Global Assessment	n	46	42	31	21	17	13	10	5	4	3
	Mean	60.34	60.90	66.14	74.54	75.25	74.59	65.64	82.38	88.10	95.24
	SD	46.00	39.27	33.80	28.50	26.92	20.13	37.00	15.58	15.79	8.25
	Median	73.21	73.21	75.00	83.33	83.33	77.78	75.00	85.71	92.86	100.00
Subject Global Assessment	n	45	41	30	20	15	13	9	5	4	3
	Mean	50.71	55.43	46.67	60.80	49.48	39.08	56.90	65.29	65.18	48.81
	SD	63.11	60.45	74.13	35.62	37.18	69.68	61.57	36.77	44.64	42.31
	Median	71.43	70.00	75.00	67.50	62.50	66.67	75.00	80.00	80.36	71.43
CHAQ	n	46	42	32	21	17	13	14	15	16	13
	Mean	48.40	51.15	51.53	61.61	56.32	68.57	65.79	73.34	76.07	71.78
	SD	38.72	40.21	48.16	39.94	47.76	35.59	40.05	35.83	38.09	39.44
	Median	48.08	53.39	56.87	76.47	65.00	76.47	79.50	81.82	100.00	90.91
No. of Active Joints	n	49	44	32	25	27	21	18	9	4	2
	Mean	48.19	43.93	36.87	44.68	47.54	58.79	59.04	61.39	61.56	88.04
	SD	40.41	42.23	54.01	50.47	46.22	37.55	38.96	30.59	24.33	11.37
	Median	54.55	52.80	50.83	60.00	55.56	73.68	73.65	65.00	56.88	88.04
No. of Joints with LOM	n	50	47	38	31	31	25	21	9	6	3
	Mean	41.66	39.89	39.09	45.32	48.06	56.57	58.73	52.90	66.94	88.72
	SD	47.15	54.32	58.68	58.40	46.06	51.10	46.50	43.69	35.03	15.21
	Median	48.17	42.86	47.31	76.47	50.00	77.14	77.14	57.14	73.31	94.74
CRP	n	48	45	37	32	30	26	26	18	18	13
	Mean	42.89	59.85	74.67	80.28	73.45	84.61	-179.11	78.72	56.85	39.11
	SD	133.85	87.81	47.39	30.65	45.45	21.47	1113.65	28.14	138.16	163.49
	Median	87.33	92.11	92.38	93.33	93.79	93.99	96.09	94.88	96.21	95.00

Abbreviations: ACR Pedi= American College of Rheumatology pediatric response criteria; CHAQ= Childhood Health Assessment Questionnaire; CRP=C-reactive protein; LOM=limitation of motion; SD=standard deviation.
Source: 5.3.5.2, Final CSR for study 20021618, Tables 14-4.6.1.B, 14-4.6.2.B, 14-4.6.4.B, 14-4.6.8.B, 14-4.6.9.B, 14-4.6.10.B.

Pain Assessment on Visual Analog Scale

The change from baseline in pain assessment remained relatively stable over time, although there was some fluctuation because of outlier data and the limited number of subjects contributing data in the later years (Table 32). Although there was a large amount of variability in the mean changes from baseline due to outliers, the median changes from baseline were relatively stable through year 7 after which time there was also fluctuation in the median percent improvement most likely due to the small number of subjects assessed in year 8 (n=4), year 9 (n=2), and year 10 (n=1).

Table 32. Percent Improvement from Baseline for Pain Assessment Over Time in Study 20021618 (Observed Cases)

Timepoint	Statistic	Pediatric Subjects (N=58)
Year 1	n	44
	Mean	55.81
	SD	68.31
	Median	84.75
Year 2	n	40
	Mean	26.44
	SD	165.73
	Median	75.00
Year 3	n	29
	Mean	-27.58
	SD	321.15
	Median	72.00

Timepoint	Statistic	Pediatric Subjects (N=58)
Year 4	n	19
	Mean	49.42
	SD	71.22
	Median	82.35
Year 5	n	13
	Mean	22.67
	SD	120.60
	Median	80.00
Year 6	n	11
	Mean	10.28
	SD	165.34
	Median	79.59
Year 7	n	7
	Mean	12.90
	SD	150.71
	Median	90.00
Year 8	n	4
	Mean	28.21
	SD	87.57
	Median	48.08
Year 9	n	2
	Mean	62.50
	SD	53.03
	Median	62.50
Year 10	n	1
	Mean	38.89
	SD	--
	Median	38.89

Abbreviations: N=number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618; SD=standard deviation.
Source: 5.3.5.2, Final CSR for study 20021618, Table 14-4.6.3.B.

Persistence of Efficacy and/or Tolerance Effects

The 10-years efficacy results from the long-term extension study 20021618 in subjects with JIA presented in the preceding sections demonstrate persistence of efficacy over time, through 10 years of treatment. There was no evidence of tolerance (i.e., loss of therapeutic effect over time) from long-term treatment with etanercept in study 20021618. Withdrawal of etanercept was not studied in either study 3338 or 20021618.

Analysis performed across trials (pooled analyses and meta-analysis)

In view of the fact that rheumatoid factor positive and rheumatoid factor negative polyarthritis will now replace polyarticular JIA in section 4.1 of the SmPC, the MAH provided an overview of efficacy results from previous JIA trials; study 16.0016 part 1 and part 2. study 20021618 and registry 20021626

for all RF positive and RF negative polyarthritis subjects.

Tab 33 Mean and Median Percent Improvement from Baseline in Disease Activity Measures at Day 90 for Subjects with Polyarthritis by RF Status in Study 16.0016, Part 1

Efficacy Assessment	Statistic	RF-negative Polyarthritis	RF-positive Polyarthritis
Total Active Joints	Mean (SD)	47 (36)	54 (31)
	Median	48	63
	Min - Max	-61 – 100	-17 – 92
	N	29	11
LOM Joints + Pain/Tenderness	Mean (SD)	32 (127)	66 (35)
	Median	80	75
	Min - Max	-400 – 100	0 – 100
	N	26	11
LOM Joints	Mean (SD)	34 (33)	32 (34)
	Median	23	40
	Min - Max	-48 – 100	-40 – 70
	N	29	11
Physicians Global Assessment	Mean (SD)	55 (31)	59 (36)
	Median	67	71
	Min - Max	-17 – 100	-17 – 100
	N	29	11
Patients/Parents Global Assessment	Mean (SD)	41 (56)	33 (85)
	Median	50	71
	Min - Max	-200 – 100	-150 – 100
	N	29	11
CHAQ	Mean (SD)	45 (34)	44 (68)
	Median	37	78
	Min - Max	-5 – 100	-89 – 100
	N	28	11
ESR	Mean (SD)	42 (51)	25 (45)
	Median	60	35
	Min - Max	-135 – 92	-90 – 66
	N	29	11
C-Reactive Protein	Mean (SD)	34 (133)	36 (42)
	Median	70	39
	Min - Max	-609 – 98	-18 – 93
	N	29	11

Abbreviations: CHAQ=Childhood Health Assessment Questionnaire; ESR=erythrocyte sedimentation rate; LOM=limitation of motion; RF=rheumatoid factor.
Source: Compounds/PF-05/PF-05208752/Clinical/Summary/Tables and Figures/PIP EMA 201204 RF polyarthritis Amgen Study 160016/ t-jra1616-d90imp-rf

Table 34 ummary of Subjects Experiencing Disease Flare in Study 16.0016, Part 2

	RF-negative Polyarthritis		RF-positive Polyarthritis	
	Placebo (N=11)	Etanercept (N=11)	Placebo (N=6)	Etanercept N=3)
Disease Flare	7 (64%)	3 (27%)	6 (100%)	0
Median Time to Flare (days)	30.0	116.0	18.5	116.0

Abbreviation: RF=rheumatoid factor.
Source: Compounds/PF-05/PF-05208752/Clinical/Summary/Tables and Figures/PIP EMA 201204 RF polyarthritis Amgen Study 160016/ t-flare1616

Tab 35 Number (%) of Subjects Achieving 30%, 50%, and 70% ACR Pedi Response at Day 210 Compared With Day 90 in Study 16.0016, Part 2

	RF-negative Polyarthritis				RF-positive Polyarthritis			
	Day 90		Day 210		Day 90		Day 210	
ACR-Pedi, n (%)	Placebo (N=11)	Etanercept (N=11)	Placebo (N=11)	Etanercept (N=11)	Placebo (N=6)	Etanercept (N=3)	Placebo (N=6)	Etanercept (N=3)
ACR Pedi 30	11 (100)	11 (100)	5 (45)	10 (91)	6 (100)	3 (100)	0	3 (100)
ACR Pedi 50	10 (91)	9 (82)	4 (36)	9 (82)	6 (100)	3 (100)	0	3 (100)
ACR Pedi 70	6 (55)	3 (27)	3 (27)	5 (45)	5 (83)	1 (33)	0	1 (33)

Abbreviations: ACR=American College of Rheumatology; RF=rheumatoid factor.
Source: Compounds/PF-05/PF-05208752/Clinical/Summary/Tables and Figures/PIP EMA 201204 RF polyarthritis Amgen Study 160016/ t-jra1616-d210-rf

Table 36 Percentage of Subjects Achieving ACR Pedi Response Over Time in Pediatric Subjects with RF-negative Polyarthritis JIA and RF-positive Polyarthritis JIA in Study 20021618

	Year 1 n/N (%)	Year 2 n/N (%)	Year 3 n/N (%)	Year 4 n/N (%)	Year 5 n/N (%)	Year 6 n/N (%)	Year 7 n/N (%)	Year 8 n/N (%)	Year 9 n/N (%)	Year 10 n/N (%)
RF-negative Polyarthritis (n=20)	n=19	n=18	n=18	n=14	n=11	n=11	n=10	n=3	n=1	n=0
ACR Pedi 30	15/19 (78.9)	15/18 (83.3)	14/18 (77.8)	11/14 (78.6)	7/11 (63.6)	7/11 (63.6)	5/10 (50.0)	2/3 (66.7)	1/1 (100)	--
ACR Pedi 50	13/19 (68.4)	13/18 (72.2)	14/18 (77.8)	10/14 (71.4)	6/11 (54.5)	7/11 (63.6)	4/10 (40.0)	2/3 (66.7)	1/1 (100)	--
ACR Pedi 70	10/19 (52.6)	10/18 (55.6)	13/18 (72.2)	8/14 (57.1)	4/11 (36.4)	6/11 (54.5)	4/10 (40.0)	2/3 (66.7)	1/1 (100)	--
RF-positive Polyarthritis (n=9)	n=9	n=8	n=5	n=5	n=4	n=5	n=3	n=1	n=0	n=0
ACR Pedi 30	6/9 (66.7)	5/8 (62.5)	3/5 (60.0)	3/5 (60.0)	1/4 (25.0)	2/5 (40.0)	2/3 (66.7)	0/1 (0.0)	--	--
ACR Pedi 50	5/9 (55.6)	3/8 (37.5)	3/5 (60.0)	2/5 (40.0)	1/4 (25.0)	2/5 (40.0)	2/3 (66.7)	0/1 (0.0)	--	--
ACR Pedi 70	4/9 (44.4)	2/8 (25.0)	3/5 (60.0)	2/5 (40.0)	1/4 (25.0)	1/5 (20.0)	1/3 (33.3)	0/1 (0.0)	--	--

Abbreviations: ACR=American College of Rheumatology; JIA=juvenile idiopathic arthritis; RF=rheumatoid factor.
Sources: Compounds/PF-05/PF-05208752/Clinical/Summary/Tables and Figures/PIP EMA 201204 RF polyarthritis Amgen Study 20021618/ t_14_04_05_014_g_adoi_rsp_rfneg; t_14_04_05_014_g_adoi_rsp_rfpos

Table 37 Mean and Median Percentage Improvement of Disease Activity Measures Over Time in Registry 20021626

	RF-negative Polyarthritis			RF-positive Polyarthritis		
Assessment	Methotrexate Only N=97	Etanercept Only N=43	Etanercept + Methotrexate N=116	Methotrexate Only N=27	Etanercept Only N=10	Etanercept + Methotrexate N=58
Number of Active Joints (% Improvement)						
Year 1	n=39	n=11	n=44	n=8	n=5	n=17
Mean (SD)	23.71 (182.54)	31.85 (118.19)	22.34 (218.76)	69.71 (56.35)	70.93 (24.91)	43.85 (61.07)
Median	100.00	87.50	82.84	87.98	66.67	73.91
Year 2	n=24	n=7	n=32	n=7	n=3	n=10
Mean (SD)	49.70 (121.70)	63.10 (56.08)	78.50 (31.05)	89.25 (13.79)	93.33 (11.55)	59.14 (60.37)
Median	93.20	100.00	94.24	100.00	100.00	85.29
Year 3	n=37	n=16	n=65	n=6	n=5	n=20
Mean (SD)	40.23 (145.87)	94.32 (9.71)	44.25 (131.31)	49.60 (67.24)	66.67 (47.14)	50.36 (83.79)
Median	95.65	100.00	92.86	81.14	100.00	97.37
Physician's Global Assessment (% Improvement)						
Year 1	n=55	n=24	n=83	n=14	n=9	n=40
Mean (SD)	54.9 (53.6)	53.8 (37.0)	62.7 (38.1)	46.2 (54.9)	40.8 (46.2)	39.7 (47.6)
Median	71.4	58.3	66.7	58.3	40.0	50.0
Year 2	n=43	n=18	n=58	n=9	n=6	n=26
Mean (SD)	64.0 (40.9)	55.6 (45.3)	56.9 (66.5)	76.7 (25.6)	59.8 (34.0)	52.6 (63.4)
Median	75.0	66.7	75.0	80.0	75.0	66.7

Tab 38 Mean and Median Percentage Improvement of Disease Activity Measures Over Time in Registry 20021626

	RF-negative Polyarthritis			RF-positive Polyarthritis		
Assessment	Methotrexate Only N=97	Etanercept Only N=43	Etanercept + Methotrexate N=116	Methotrexate Only N=27	Etanercept Only N=10	Etanercept + Methotrexate N=58
Year 3	n=36	n=18	n=58	n=6	n=6	n=18
Mean (SD)	58.6 (49.9)	68.4 (33.5)	59.1 (43.2)	58.3 (49.2)	54.5 (35.8)	66.4 (25.7)
Median	75.7	69.0	63.3	75.0	69.0	69.0
Limitation of Motion (% Improvement)						
Year 1	n=37	n=10	n=41	n=8	n=5	n=14
Mean (SD)	32.0 (197.2)	22.2 (203.4)	-8.4 (163.5)	64.3 (45.0)	-300.0 (839.6)	41.0 (64.0)
Median	87.5	100.0	50.0	81.1	100.0	59.6
Year 2	n=23	n=5	n=29	n=7	n=3	n=10
Mean (SD)	70.0 (41.5)	100.0	45.3 (75.7)	80.3 (37.0)	50.0 (86.6)	-33.2 (348.3)
Median	100.0	0.0	77.8	100.0	100.0	87.5
Year 3	n=35	n=16	n=63	n=6	n=5	n=20
Mean (SD)	64.4 (60.8)	58.8 (62.0)	29.9 (131.7)	-30.3 (168.9)	30.9 (107.7)	30.2 (204.6)
Median	100	93.2	80.0	45.5	100.0	99.0
Limitation of Motion With Pain (% Improvement)						
Year 1	n=39	n=11	n=41	n=8	n=5	n=15
Mean (SD)	41.0 (49.8)	54.6 (52.2)	24.8 (100.6)	86.6 (35.1)	-40.0 (260.8)	51.5 (46.0)
Median	0.0	100.0	0.00	100.0	100.0	69.2

Table 39 ean and Median Percentage Improvement of Disease Activity Measures Over Time in Registry 0021626

	RF-negative Polyarthritis			RF-positive Polyarthritis		
Assessment	Methotrexate Only N=97	Etanercept Only N=43	Etanercept + Methotrexate N=116	Methotrexate Only N=27	Etanercept Only N=10	Etanercept + Methotrexate N=58
Year 2	n=25	n=6	n=32	n=7	n=3	n=10
Mean (SD)	45.9 (49.2)	66.7 (51.6)	47.4 (49.2)	81.0 (37.8)	100.0 (0.0)	71.2 (41.7)
Median	0.0	100.0	25.0	100.0	100.0	100.0
Year 3	n=37	n=17	n=62	n=6	n=5	n=20
Mean (SD)	46.0 (50.5)	47.1 (51.5)	39.7 (48.5)	16.1 (136.2)	70.0 (44.7)	79.2 (40.8)
Median	0.0	0.0	0.0	73.2	100.0	100.0

Abbreviations: RF=rheumatoid factor; SD=standard deviation.

Sources: Compounds/PF-05/PF-05208752/Clinical/Summary/Tables and Figures/PIP EMA 201204 RF polyarthritis Amgen Study 20021626/
t_04_002_001_jtotpc_tactjnt_rfneg; t_04_002_001_jtotpc_tactjnt_rfpos
t_04_003_mdga_by_visit_rfneg; t_04_003_mdga_by_visit_rfpos
t_04_002_002_jtotpc_lom_rfneg; t_04_002_002_jtotpc_lom_rfpos
t_04_002_003_jtotpc_lompt_rfneg; t_04_002_003_jtotpc_lompt_rfpos

Table 40 Summary of Subjects with Total Active Joints = 0 and Physician Global Assessment = 0 and Over Time in Registry 20021626

	RF-negative Polyarthritis			RF-positive Polyarthritis		
	Methotrexate Only	Etanercept Only	Etanercept + Methotrexate	Methotrexate Only	Etanercept Only	Etanercept + Methotrexate
	N=97	N=39	N=104	N=27	N=9	N=54
Assessment	n/N1 (%)	n/N1 (%)	n/N1 (%)	n/N1 (%)	n/N1 (%)	n/N1 (%)
Number of Subjects with Active Joints = 0						
Baseline	15/97 (15.5)	6/39 (15.4)	9/104 (8.7)	2/27 (7.4)	1/9 (11.1)	4/54 (7.4)
Year 1	28/39 (71.8)	6/13 (46.2)	13/37 (35.1)	3/8 (37.5)	0/5 (0.0)	2/15 (13.3)
Year 2	13/27 (48.1)	5/7 (71.4)	11/26 (42.3)	4/7 (57.1)	1/3 (33.3)	3/8 (37.5)
Year 3	25/37 (67.6)	10/18 (55.6)	29/58 (50.0)	2/6 (33.3)	2/5 (40.0)	8/16 (50.0)
Number of Subjects with Physician Global Assessment = 0						
Baseline	10/97 (10.3)	4/39 (10.3)	5/104 (4.8)	0/27 (0.0)	0/9 (0.0)	2/54 (3.7)
Year 1	19/62 (30.6)	7/25 (28.0)	19/83 (22.9)	5/15 (33.3)	0/8 (0.0)	7/40 (17.5)
Year 2	21/49 (42.9)	7/18 (38.9)	17/60 (28.3)	4/9 (44.4)	0/5 (0.0)	7/26 (26.9)
Year 3	19/38 (50.0)	8/18 (44.4)	18/58 (31.0)	3/6 (50.0)	0/5 (0.0)	3/16 (18.8)

Abbreviation: RF=rheumatoid factor.
Sources: Compounds/PF-05/PF-05208752/Clinical/Summary/Tables and Figures/PIP EMA 201204 RF polyarthritis Amgen Study 20021626/ t_04_019_002_jtotzero_by_visit_5col_rfneg; t_04_019_002_jtotzero_by_visit_5col_rfpos t_04_020_002_mdgazero_by_visit_5col_rfneg; t_04_020_002_mdgazero_by_visit_5col_rfpos

Subjects meeting the ILAR classification of RF-negative polyarthritis and RF-positive polyarthritis JIA were identified based on a retrospective application of the ILAR assessment criteria and using only one assessment of the presence or absence of RF. In general, both subtypes demonstrated efficacy that were consistent with that reported in the original study reports for the overall polyarticular-course JIA population, thereby supporting the inclusion of the indication for RF-negative polyarthritis JIA and RF-positive polyarthritis JIA in the SmPC.

Discussion on clinical efficacy

The MAH has provided an open label study 3338 in support of efficacy for the subtypes of JIA namely: eoJIA (from the age of 2 years), ERA and PsA (both from the age of 12 years). In addition the final CSR from the open label study 20021618 where patients with polyarticular course JIA were analysed was also provided. The majority of subjects in study 20021618 reflect the ILAR classification of polyarticular JIA (RF positive and RF negative).

Study 3338

The overall study plan for the open-label study 3338 is acceptable. While a double-blind randomised controlled study is the standard design to show efficacy, the comparison with placebo for the same subtypes using historical control can be accepted to support efficacy of etanercept in the subtypes of JIA studies namely eoJIA, ERA and PSA.

The open-label etanercept period of study 16.0016 in JIA subjects reported by Lovell *et al* paper referred to polyarticular-course JRA regardless of subtype. The MAH retrospectively reviewed the reported medical histories, JRA onset type, gender, age at disease onset, screening RF status, and screening efficacy results for joint assessment and morning stiffness in the inclusion criteria for study 16.0016, all subjects had polyarticular-course JRA.

5 subjects would meet the ILAR classification for eoJIA based on the available data but none would meet the ILAR classification for ERA pr PsA based on the available data.

Given the rarity of the ILAR subtypes and the fact that a placebo-controlled study may be difficult to conduct and may raise ethical concerns, one way to address these concerns, while still retaining the ability to assess the clinical benefit in the combined population as well as in each of the JIA subtypes under study (i.e., eoJIA, ERA, and PsA), would be to utilize appropriate historical control data.

Ideally, the historical control group(s) for study 3338 would have assessed subjects with eoJIA, ERA, and PsA based on the ILAR classification criteria separately. However, the MAH was not able to identify reports of studies conducted in meaningful numbers of subjects with well-defined eoJIA or PsA.

The intent of using the etanercept response rate from study 16.0016 as an active historical control was to help establish comparability of clinical response and this is acceptable. In addition, published reports of treatment response in eoJIA, ERA, and PSA indicate that the ACR Pedi 30 response rates of eoJIA, ERA, and PsA may be similar to the response of the overall JIA population [14, 15, 16] This is not unexpected since they all are tumor necrosis factor (TNF)-mediated diseases and the response to treatment may be similar to that observed with polyarticular disease.

In view of the above considerations, the use of study 16.0016 as an active historical control, together with the 2 historical placebo controls is considered appropriate.

The failure of previous DMARD treatment in the majority of subjects is noted. The proposed indication is restricted to those who have failed or have a contraindication to MTX or (in the case of ERA) conventional therapy. The latter is endorsed in the case of ERA as there is no standard of therapy in this subtype.

The ACR Pedi 30, a clinically relevant endpoint, is high in all three subtypes in study 3338 at week 12. For the overall population, 109 subjects (88.6%; 95% CI: 81.6%, 93.6%) achieved an ACR Pedi 30 response. The percentages of subjects with extended oligoarticular JIA, ERA, and PsA who achieved an ACR Pedi 30 response at Week 12 were similar (89.7%, 83.3%, and 93.1%, respectively). For the disease-specific variables in subjects with ERA and PsA, improvements were noted at Week 12. In subjects with ERA, the mean tender entheseal score, the mean overall back pain VAS score, the mean nocturnal back pain VAS score, and the mean modified Schober's test were improved from baseline at Week 12. In subjects with PsA, the mean percent BSA affected by psoriasis and the mean PGA of Psoriasis score were improved from baseline at Week 12.

The response rate continues to increase from week 4 to week 12 and this is clear with the ACR Pedi 50 and 70 and is evident for all subtypes. This similarity in response in terms of absolute response and increase in the more stringent efficacy measure of ACR Pedi 50 and 70 over a similar time frame supports inclusion of all three subtypes specifically.

The breakdown of the individual components of the composite score supports the primary efficacy endpoint for study 3338, as no worsening of any of the components was seen.

Regarding the ERA-specific endpoints, the more than 50% reduction in mean tender entheseal score is considered to be very clinically relevant. However it has to be borne in mind that this was an open study which may have had an effect on patient perception.

Regarding the PsA-specific efficacy endpoint, the improvement in the percentage BSA affected by psoriasis is expected as Enbrel is licensed for plaque psoriasis in children aged 6 years and above.

The comparison of the results in subpopulations showed that within each ACR Pedi response level for ACR Pedi 30, ACR Pedi 50, and ACR Pedi 70, the percentages of subjects in each age group who achieved responses at Week 12 were generally similar. This important information on ACR Pedi scores by age group is supportive of the entire data from 3338 and shows that response to etanercept is similar across the different age categories presented.

Study 20021618

The use of the newer terminology of ACR Pedi is accepted in view of the minor differences between the older scoring technique of JRA-DOI (VAS scales and CRP versus ESR). With the introduction of the CRP in study 20021618 the MAH plan to use ACR Pedi is acceptable.

100% of patients in study 20021618 with JIA were on DMARDs as compared with 80-90% of subjects in study 3338. This difference is likely to reflect the lack of well established DMARDs for use in specific subtypes of JIA which are not polyarticular and the higher severity of disease in JIA subjects enrolled into study 20021618.

The proportion of paediatric subjects in study 20021618 achieving ACR Pedi 30, ACR Pedi 50, and ACR Pedi 70 responses remained relatively stable over 10 years. Similar results were observed for ACR Pedi 90 and ACR Pedi 100. It is difficult to draw conclusions for maintenance of efficacy out to 10 years in view of the very small numbers at this time and the loss of subjects over time due to various reasons including lack of efficacy. In addition those who remain with some response and lack of SAEs necessitating cessation of therapy are the most likely to have long-term continuation of treatment. However even with these caveats, by year 7 where number are in double figures, efficacy remains similar to that at year 1.

As was observed for the ACR Pedi response rates, the individual components of the ACR Pedi response remained relatively stable over time through 10 years. At the later time points when the numbers are small (years 8, 9 and 10) the data are difficult to interpret as there are a higher number of active joints at these time points compared with year 1. However it is likely that only those subjects with severe disease who showed some response to treatment continued for many years.

One of the primary objectives of study 20021618 was to evaluate improvement in physical function/disability and quality of life. The mean percent improvement in the CHAQ at year 1 was 48%. The mean percent improvement in the CHAQ score was relatively stable up to 5 years and increased slightly over the last 5 years. Thus, the physical function and quality of life improvements in these paediatric subjects were maintained for up to 10 years in the study.

The change from baseline in pain assessment remained relatively stable over time. The only time point (year 3) where there was an increase in pain score is explained by outliers and a high standard deviation. All other time points show a mean improvement in pain score compared with baseline.

Little is known about when or how to discontinue etanercept treatment in patients with JIA after a good clinical response has been achieved, nor are there guidelines from recognized bodies to define criteria for discontinuing treatment of etanercept. The criteria for clinically inactive disease (CID) in oligoarticular (persistent and extended), polyarticular (RF positive and negative), and systemic JIA have recently been revised by Wallace et al (2011)[25]. CID is defined as the absence of joints with active arthritis, fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level within normal limits; Physician Global Assessment of disease activity score of best possible on scale used; duration of morning stiffness of ≤15 minutes; and no active uveitis.

The MAH has attempted to address this lack of information by interaction with the two European biological registries which include children with JIA; in Germany and in the UK. Since 2009, the German JIA registry has collected data on disease activity specifically the set of criteria for inactive disease and remission as defined by Wallace et al. The MAH will explore the possibility to collect additional safety data, and in addition, efficacy data in order to optimize the management of JIA

patients following the achievement of clinical remission with etanercept treatment (as described in the RMP).

In addition the planned ongoing long-term study B1801023 (described in the RMP), provides a further opportunity to collect data on clinically inactive disease/remission rates in the different ILAR subtypes of JIA. This information could lead to further understanding about the length of time treatment should be given as many patients with JIA become clinically quiescent over time. This information is important to ensure that treatment is not administered for extended periods unnecessarily.

Although the purpose of study B1801023 is to monitor long-term (8-year) safety data, due to the lack of information on CID and remission rates, the MAH has substantially amended the protocol to collect data that may inform when treatment with etanercept should be discontinued and the success of re-treatment if relapse occurs. The amendment includes additional efficacy assessments, collection of data on CID/remission rates, and success rate of re-treatment upon disease relapse in subjects with eoJIA, ERA and PsA (described in the RMP).

Although it is not possible to predict how many subjects will contribute data to the new withdrawal/re-treatment period, the addition of a withdrawal/re-treatment period to the B1801023 protocol is endorsed and may provide guidance to prescribers on optimal treatment regimens in pediatric patients with eoJIA, ERA, and PsA. It is acknowledged that interpretation of the data may be limited by the relatively small number of patients who contribute data to the new withdrawal/re-treatment period of the study. However, the study is expected to provide useful information on CID/remission rates and the success rate of re-treatment upon disease relapse while still preserving the primary objective of study (as described in the RMP) .

Conclusion on clinical efficacy

In view of the rarity of JIA subtypes and the well established use of etanercept in polyarticular JIA, the open-label single arm design of study 3338 is considered acceptable and in terms of assessment of effect, the comparison with historical controls for placebo is accepted. It is of note that during the procedure for variation II/126 (which approved the extension of the lower age range for polyarticular JIA from 4 years to 2 years) was accepted on the basis of an open label study (20021626) and ancillary analysis of the subgroup aged 2 to <4 years.

As JIA has been re-classified by ILAR into 8 clear mutually exclusive subtypes, and already etanercept has been licensed from the age of 2 years in polyarticular course JIA; this additional information is beneficial and an update to the SmPC with the results from study 3338 and the long-term extension of study 20021618 is endorsed. Efficacy in 5 out of 8 of the subtypes of JIA is considered to have been shown and as such these patients, if they fail conventional therapy and are severe enough to require significant immunosuppression, are likely to benefit from etanercept treatment.

While the MAH position that persistence of efficacy through 10 years has been shown, it is considered difficult to draw any firm conclusions from the efficacy data presented from 8 years onwards in view of the small numbers treated at those time points. While withdrawal of etanercept was not studied in either study presented in this variation procedure, when and how to withdraw etanercept from patients who have responded and have no active disease remains an important area of missing information. In order to address this issue the MAH has amended the long-term safety study B1801023 to include the collection of data on CID/remission rates, and success rate of re-treatment upon disease relapse in subjects with eoJIA, ERA and PsA subtypes. Further data on efficacy and remission is planned to be collected from registries, as described in the RMP.

1.2.5 Clinical safety

Patient exposure

A total of 127 paediatric subjects received at least 1 dose of etanercept in study 3338: 60 subjects with eoJIA, 38 subjects with ERA, and 29 subjects with PsA. The 60 subjects with eoJIA consisted of 15 subjects in the 2- to 4-year age group, 23 subjects in the 5- to 11-year age group, and 22 subjects in the 12- to 17-year age group. The mean (SD) duration of etanercept treatment was 12.61 (1.61) weeks, with a range of 1 to 15 weeks and was similar across the 3 JIA subtypes. The etanercept exposure in the overall population was 29.16 subject-years (Table 33). The mean (SD) weekly etanercept dose was 34.97 (13.12) mg, and ranged from 8.0 to 56.0 mg. No clinically meaningful differences were observed across JIA subtypes. Consistent with the lower mean baseline age and weight for subjects with eoJIA, the mean etanercept dose was also lower for this subtype than the ERA and PsA subtypes.

Of the 69 paediatric subjects who participated in the double-blind study 16.0016, 58 subjects received at least 1 dose of etanercept in the extension study 20021618. The total etanercept exposure for the 58 paediatric subjects in study 20021618 was 341.98 subject-years (Table 33). The mean exposure to etanercept was 614.2 doses (mean) over 2153.6 days (mean).

Table 33. Etanercept Exposure in JIA Studies

Study	Population	Treatment Period	Number of Subjects	Etanercept Exposure (Subject-years)
3338	Overall	Up to 12 weeks	127[a]	29.16
	eoJIA subjects aged 2 to 17 years	Up to 12 weeks	60[a]	13.71
	ERA subjects aged 12 to 17 years	Up to 12 weeks	38[a]	8.75
	PsA subjects aged 12 to 17 years	Up to 12 weeks	29[a]	6.70
20021618	Polyarticular-course[b] JIA subjects aged 4 to 17 years	Up to 10 years	58[c]	341.98

Abbreviations: eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA= enthesitis-related arthritis; PsA=psoriatic arthritis.

a. All subjects received etanercept 0.8 mg/kg once weekly.
b. Polyarticular-, pauciarticular-, or systemic-onset.
c. Subjects received etanercept either as 0.4 mg/kg twice weekly or 0.8 mg/kg once weekly.

Table 34. Overview of Demographic and Disease Characteristics for Paediatric Subjects in Studies 3338 and 20021618

	Study 3338				Study 20021618
Characteristics	eoJIA (N=60)	ERA (N=38)	PsA (N=29)	Total (N=127)	Polyarticular-course JIA (N=58)
Sex, % Male	31.7	79.0	20.7	43.3	32.8[a]
Race, % White	91.7	84.2	96.6	90.6	74.1[a]
Age (years), mean	8.6	14.5	14.5	11.7	10.5[a]
Height (cm), mean	132.4	167.0	162.5	149.9	134.8[a]
Weight (kg), mean	34.8	54.4	60.0	46.4	35.9[a]
Disease duration (months), mean	31.6	23.0	21.8	26.8	71.5[a]
Baseline DMARDs, % Yes	90.0	84.2	79.3	85.8	100[a]
Physician Global Assessment, mean	5.0	5.4	4.7	5.0	6.4[a]
Patient/Parent Global Assessment, mean	4.8	5.4	4.6	5.0	4.8[a]
CHAQ score, mean	0.9	0.7	0.7	0.8	1.9[a]
Number of active joints, mean	7.6	5.2	7.0	6.7	39.4[a]
Number of joints with LOM, mean	6.3	4.8	5.6	5.7	27.5
CRP (mg/L), mean	6.3	15.3	3.2	8.3	67
Pain assessment (VAS), mean	4.8	5.8	4.6	5.1	3.7[a]
Tender entheseal score, mean	N/A	5.9	N/A	N/A	N/A
Psoriasis % BSA, mean	N/A	N/A	10.4	N/A	N/A

Abbreviations: BSA=body surface area; CHAQ=Childhood Health Assessment Questionnaire; CRP=C-reactive protein; DMARD=disease-modifying antirheumatic drug; eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; JIA=juvenile idiopathic arthritis; LOM=limitation of motion; N/A=not applicable; PsA=psoriatic arthritis; VAS=visual analog scale.

a. Based on baseline of initial study 16.0016.

Adverse events

Analysis of Adverse Events

No combined/integrated analyses across studies 3338 and 20021618 were performed because of the large difference in the study durations (12 weeks for Part 1 of study 3338 versus 10 years for study 20021618). Furthermore, as discussed below, nonserious adverse events were only collected during year 1 of study 20021618. Therefore, the safety results are presented below by study.

Both nonserious and serious adverse events were collected and analyzed during year 1 of study 20021618. After the first year of study 20021618, nonserious adverse events were not intended to be collected, although data for all SAEs and predefined events of interest (including hospitalization, deaths, serious infections, development of malignancies, and new signs or symptoms of other connective tissue disease) continued to be collected after year 1. However, there were some nonserious adverse events that were reported by investigators after year 1.

Adverse events in study 3338 are primarily presented below as proportion of subjects with events due to the short period of treatment (12 weeks), and adverse events in study 20021618 are primarily presented below adjusted for exposure due to the longer-term treatment (10 years).

Treatment-Emergent Adverse Events

Treatment-Emergent Adverse Events, Excluding Infections and Injection Site Reactions, in Study 3338

Forty-five (45) subjects (35.4%) reported at least 1 treatment-emergent adverse event (TEAE), excluding infections and ISRs, in study 3338 through 12 weeks (Table 35). The most common TEAEs reported in the overall population were headache (7 subjects, 5.5%), followed by fatigue, pyrexia, abdominal pain, and diarrhea (4 subjects each, 3.1%). No large differences were observed across JIA subtypes although a higher rate of abdominal pain and diarrhoea was seen in the ERA subtype but the numbers were small and at present there is no evidence of a JIA subtype-related safety signal. However further safety data will become available with Part 2 of study 3338. The overall exposure-adjusted rate of TEAEs, excluding infections and ISRs, across all 3 JIA subtypes was 3.74 events per subject-year: 2.77 events per subject-year for eoJIA, 5.48 events per subject-year for ERA, and 3.43 events per subject-year for PsA.

Table 35. Number (%) of Subjects with Treatment-Emergent Adverse Events Occurring in ≥3% of Subjects with eoJIA, ERA, or PsA in Study 3338 Through 12 Weeks, Excluding Infections and Injection Site Reactions

System Organ Class[a] Preferred Term	JIA Subtype eoJIA (N=60) n (%)	ERA (N=38) n (%)	PsA (N=29) n (%)	Total (N=127) n (%)
Any TEAE	21 (35.0)	16 (42.1)	8 (27.6)	45 (35.4)
Blood and lymphatic system disorders	2 (3.3)	0	1 (3.4)	3 (2.4)
Eosinophilia	0	0	1 (3.4)	1 (0.8)
Neutropenia	2 (3.3)	0	0	2 (1.6)
Ear and labyrinth disorders	0	2 (5.3)	1 (3.4)	3 (2.4)
Ear pain	0	0	1 (3.4)	1 (0.8)
Gastrointestinal disorders	3 (5.0)	6 (15.8)	0	9 (7.1)
Abdominal pain	0	4 (10.5)	0	4 (3.1)
Diarrhoea	1 (1.7)	3 (7.9)	0	4 (3.1)
General disorders and administration site conditions	4 (6.7)	5 (13.2)	0	9 (7.1)
Fatigue	0	4 (10.5)	0	4 (3.1)
Pyrexia	3 (5.0)	1 (2.6)	0	4 (3.1)
Injury, poisoning and procedural complications	6 (10.0)	2 (5.3)	1 (3.4)	9 (7.1)
Arthropod bite	1 (1.7)	0	1 (3.4)	2 (1.6)
Investigations	5 (8.3)	3 (7.9)	1 (3.4)	9 (7.1)
Alanine aminotransferase increased	2 (3.3)	1 (2.6)	0	3 (2.4)
Aspartate aminotransferase increased	3 (5.0)	0	0	3 (2.4)
Transaminases increased	0	0	1 (3.4)	1 (0.8)
Metabolism and nutrition disorders	0	2 (5.3)	0	2 (1.6)
Decreased appetite	0	2 (5.3)	0	2 (1.6)
Musculoskeletal and connective tissue disorders	1 (1.7)	4 (10.5)	3 (10.3)	8 (6.3)
Arthralgia	0	1 (2.6)	1 (3.4)	2 (1.6)
Back pain	0	0	2 (6.9)	2 (1.6)
Myalgia	0	3 (7.9)	0	3 (2.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.7)	0	1 (3.4)	2 (1.6)
Skin papilloma	1 (1.7)	0	1 (3.4)	2 (1.6)
Nervous system disorders	2 (3.3)	3 (7.9)	4 (13.8)	9 (7.1)
Dizziness postural	0	0	1 (3.4)	1 (0.8)
Headache	2 (3.3)	2 (5.3)	3 (10.3)	7 (5.5)
Renal and urinary disorders	0	1 (2.6)	1 (3.4)	2 (1.6)
Renal cyst	0	0	1 (3.4)	1 (0.8)
Reproductive system and breast disorders	0	0	2 (6.9)	2 (1.6)
Dysmenorrhoea	0	0	1 (3.4)	1 (0.8)
Menstrual disorder	0	0	1 (3.4)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	2 (3.3)	6 (15.8)	2 (6.9)	10 (7.9)
Epistaxis	0	2 (5.3)	0	2 (1.6)
Respiratory disorder	0	0	2 (6.9)	2 (1.6)
Rhinitis allergic	0	2 (5.3)	0	2 (1.6)
Wheezing	0	2 (5.3)	0	2 (1.6)
Skin and subcutaneous tissue disorders	2 (3.3)	1 (2.6)	1 (3.4)	4 (3.1)
Psoriasis	0	0	1 (3.4)	1 (0.8)
Vascular disorders	0	2 (5.3)	1 (3.4)	3 (2.4)
Haematoma	0	0	1 (3.4)	1 (0.8)

Abbreviations: eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; JIA=juvenile idiopathic arthritis; PsA=psoriatic arthritis.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different adverse events within the higher level category.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 31.

All Treatment-Emergent Adverse Events in Study 20021618

Per the protocol for study 20021618, nonserious adverse events were to be collected only during year 1 of the 10-year study.

The exposure-adjusted rate of TEAEs during year 1 of study 20021618 (the primary safety endpoint), including infections and ISRs, was 798.50 events per 100 subject-years (Table 36). The most common TEAEs reported were injection site reaction (112 events, 210.93 events per 100 subject-years), upper respiratory infection (68 events, 128.06 events per 100 subject years), headache (44 events, 82.86 events per 100 subject-years), and abdominal pain (20 events, 37.67 events per 100 subject-years). Fifty (50) paediatric subjects (86.2%) reported at least 1 TEAE during year 1 of the study.

Table 36. Exposure-adjusted Rate of All Treatment-Emergent Adverse Events During Year 1 of Study 20021618, by Body System and Preferred Term in Descending Frequency

Body System Preferred Term	Pediatric Subjects n (r)
Number of subjects with at least 1 dose of etanercept	N=58
Total number of subject-years on etanercept - Year 1	E=53.10
Number of TEAEs - Year 1	424 (798.50)
Body as a Whole	217 (408.67)
Inject Site React	112 (210.93)
Headache	44 (82.86)
Pain Abdo	20 (37.67)
Flu Synd	9 (16.95)
Injury Accid	6 (11.30)
Fever	6 (11.30)
Pain	3 (5.65)
Infect	3 (5.65)
Pain Chest	2 (3.77)
Edema Face	2 (3.77)
Pain Neck	2 (3.77)
Infect Bact	2 (3.77)
Asthenia	1 (1.88)
Abscess	1 (1.88)
Cyst	1 (1.88)
Infect Viral	1 (1.88)
Malaise	1 (1.88)
Peritonitis	1 (1.88)
Respiratory System	103 (193.98)
Upper Resp Infect	68 (128.06)
Rhinitis	9 (16.95)
Pharyngitis	9 (16.95)
Sinusitis	6 (11.30)
Cough Inc	3 (5.65)
Epistaxis	3 (5.65)
Throat Irritation	2 (3.77)
Bronchitis	2 (3.77)
Respirat Dis	1 (1.88)
Digestive System	27 (50.85)
Nausea	8 (15.07)
Diarrhea	4 (7.53)
Dyspepsia	3 (5.65)
Vomit	3 (5.65)
Gastroenteritis	2 (3.77)
Ulcer Mouth	2 (3.77)
Esophagitis	1 (1.88)
Anorexia	1 (1.88)
Flatul	1 (1.88)
Hem GI	1 (1.88)
Appendicitis	1 (1.88)
Skin & Appendages	26 (48.96)
Rash	6 (11.30)
Nail Dis	4 (7.53)
Alopecia	2 (3.77)
Herpes Zoster	2 (3.77)
Eczema	2 (3.77)
Derm Exfol	2 (3.77)
Derm Contact	2 (3.77)
Rash Mac Pap	1 (1.88)
Derm Fung	1 (1.88)
Rash Vesic Bull	1 (1.88)
Acne	1 (1.88)
Rash Pust	1 (1.88)
Skin Discolor	1 (1.88)
Musculoskeletal System	11 (20.72)
Arthritis Rheumat	3 (5.65)
Bone Fract Spontan	2 (3.77)
Spasm General	2 (3.77)
Joint Effusion	2 (3.77)
Myalgia	1 (1.88)
Bone Dis	1 (1.88)
Nervous System	9 (16.95)
Dizziness	3 (5.65)
Nervousness	3 (5.65)
Agitation	1 (1.88)
Meningitis	1 (1.88)
Somnolence	1 (1.88)
Urogenital System	4 (7.53)
Dysmenorrhea	3 (5.65)
Infect Urin Tract	1 (1.88)
Special Senses	18 (33.90)
Otitis Med	8 (15.07)
Conjunctivitis	5 (9.42)
Pain Eye	2 (3.77)
Amblyopia	1 (1.88)
Otitis Ext	1 (1.88)
Stye	1 (1.88)
Cardiovascular System	6 (11.30)
Migraine	4 (7.53)
Vasculitis	1 (1.88)
Hem	1 (1.88)
Metabolic & Nutritional Disorders	1 (1.88)
Calcium Dis	1 (1.88)
Hemic & Lymphatic System	2 (3.77)
Ecchymosis	1 (1.88)
Anemia Iron Defic	1 (1.88)

Abbreviations: E=patient-years of exposure; N=number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618; n=number of events; r=exposure-adjusted event rate per 100 subject-years (n/E*100); TEAE=treatment-emergent adverse event.

Only includes events within 30 days of last dose, including events with outcome of death.

Source: 5.3.5.2, Final CSR for study 20021618, Table 14-6.3.8.C.

Treatment-Emergent Infections

Study 3338

Fifty-eight (58) subjects (45.7%) reported treatment-emergent infections in study 3338 through 12 weeks (Table 37). The most common treatment-emergent infections were upper respiratory tract infection (18 subjects, 14.2%), followed by pharyngitis (15 subjects, 11.8%), rhinitis (8 subjects, 6.3%), gastroenteritis (5 subjects, 3.9%), and bronchitis (4 subjects, 3.1%). No clinically meaningful differences were observed across JIA subtypes. The overall exposure-adjusted rate of treatment-emergent infections across all 3 JIA subtypes was 3.33 events per subject-year: 4.09 events per subject-year for eoJIA, 2.29 events per subject year for ERA, and 3.13 events per subject-year for PsA. It is noted that the small numbers involved preclude any firm conclusions and further data on infection rate in each subtypes will become available with part 2 of the study.

Table 37. Number (%) of Subjects with Treatment-Emergent Infections (MedDRA Classification) Occurring in ≥3% of Subjects in any JIA Subtype in Study 3338 Through 12 Weeks

	JIA Subtype			
System Organ Class[a] Preferred Term	eoJIA (N=60) n (%)	ERA (N=38) n (%)	PsA (N=29) n (%)	Total (N=127) n (%)
Any treatment-emergent infection	31 (51.7)	15 (39.5)	12 (41.4)	58 (45.7)
Blood and lymphatic system disorders	0	0	1 (3.4)	1 (0.8)
Lymphadenopathy	0	0	1 (3.4)	1 (0.8)
Gastrointestinal disorders	0	0	1 (3.4)	1 (0.8)
Gastritis	0	0	1 (3.4)	1 (0.8)
Infections and infestations	30 (50.0)	15 (39.5)	11 (37.9)	56 (44.1)
Bronchitis	1 (1.7)	3 (7.9)	0	4 (3.1)
Campylobacter infection	0	0	1 (3.4)	1 (0.8)
Ear infection	2 (3.3)	0	0	2 (1.6)
Fungal skin infection	0	0	1 (3.4)	1 (0.8)
Gastroenteritis	3 (5.0)	1 (2.6)	1 (3.4)	5 (3.9)
Nasopharyngitis	2 (3.3)	0	0	2 (1.6)
Pharyngitis	9 (15.0)	4 (10.5)	2 (6.9)	15 (11.8)
Pyelocystitis	0	0	1 (3.4)	1 (0.8)
Respiratory tract infection	1 (1.7)	0	1 (3.4)	2 (1.6)
Rhinitis	4 (6.7)	2 (5.3)	2 (6.9)	8 (6.3)
Sinusitis	3 (5.0)	0	0	3 (2.4)
Upper respiratory tract infection	9 (15.0)	4 (10.5)	5 (17.2)	18 (14.2)
Urinary tract infection	1 (1.7)	1 (2.6)	1 (3.4)	3 (2.4)

Abbreviations: eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; JIA=juvenile idiopathic arthritis; PsA=psoriatic arthritis.
Classifications of infections are based on the Medical Dictionary for Regulatory Activities (MedDRA).
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different infections within the higher level category.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 33.

Study 20021618

Per the protocol for study 20021618, nonserious infections were to be collected only during year 1 of the 10-year study.

The exposure-adjusted rate of treatment-emergent infections in paediatric subjects during year 1 of study 20021618 was 237.29 events per 100 subject-years (Table 38). The most common treatment-emergent infections reported were upper respiratory infection (68 events, 128.06 events per 100 subject-years), pharyngitis (9 events, 16.95 events per 100 subject years), and flu syndrome (9 events, 16.95 events per 100 subject-years). Forty-four (44) paediatric subjects (75.9%) reported at least 1 treatment-emergent infection during year 1 of the study.

Table 38. Exposure-adjusted Rate of Treatment-Emergent Infections During Year 1 of Study 20021618, by Body System and Preferred Term in Descending Frequency

Body System Preferred Term	Pediatric Subjects n (r)
Number of subjects with at least 1 dose of etanercept	N=58
Total number of subject-years on etanercept - Year 1	E=53.10
Number of treatment-emergent infections - Year 1	126 (237.29)
Respiratory System	83 (156.31)
Upper Resp Infect	68 (128.06)
Pharyngitis	9 (16.95)
Sinusitis	4 (7.53)
Bronchitis	2 (3.77)
Body as a Whole	17 (32.02)
Flu Synd	9 (16.95)
Infect	3 (5.65)
Infect Bact	2 (3.77)
Abscess	1 (1.88)
Infect Viral	1 (1.88)
Peritonitis	1 (1.88)
Urogenital System	1 (1.88)
Infect Urin Tract	1 (1.88)
Digestive System	3 (5.65)
Gastroenteritis	2 (3.77)
Appendicitis	1 (1.88)
Skin & Appendages	7 (13.18)
Herpes Zoster	2 (3.77)
Nail Dis	2 (3.77)
Derm Fung	1 (1.88)
Rash Pust	1 (1.88)
Acne	1 (1.88)
Special Senses	14 (26.37)
Otitis Med	8 (15.07)
Conjunctivitis	4 (7.53)
Otitis Ext	1 (1.88)
Stye	1 (1.88)
Nervous System	1 (1.88)
Meningitis	1 (1.88)

Abbreviations: E=patient-years of exposure; N=number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618; n=number of events; r=exposure-adjusted event rate per 100 subject-years (n/E*100).
Only includes events within 30 days of last dose, including events with outcome of death.
Source: 5.3.5.2, Final CSR for study 20021618, Table 14-6.3.4.C.

Treatment-Emergent Injection Site Reactions

Study 3338

Of the 127 subjects, 10 (7.9%) reported at least 1 treatment-emergent ISR in study 3338 through 12 weeks (Table 39). The overall exposure-adjusted rate of ISRs across all 3 JIA subtypes was 0.79 events per subject-year: 0.37 events per subject-year for eoJIA, 0.80 events per subject-year for ERA, and 1.64 events per subject-year for PsA.

Table 39. Number (%) of Subjects with Treatment-Emergent Injection Site Reactions in Study 3338 Through 12 Weeks

	JIA Subtype			
Characteristic	eoJIA (N=60) n (%)	ERA (N=38) n (%)	PsA (N=29) n (%)	Total (N=127) n (%)
At least 1 treatment-emergent ISR	4 (6.67)	4 (10.53)	2 (6.90)	10 (7.87)

Abbreviations: eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; ISR=injection site reaction; JIA=juvenile idiopathic arthritis; PsA=psoriatic arthritis.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 32.

Study 20021618

The exposure-adjusted rate of ISRs in paediatric subjects during year 1 of study 20021618 was 210.93 events per 100 subject-years. Eleven (11) paediatric subjects (19.0%) reported at least 1 ISR during study 20021618.

Serious adverse events and deaths

Deaths

No deaths occurred in paediatric subjects during the first 12 weeks of study 3338 or up to 10 years of exposure in study 20021618.

Serious Adverse Events

Study 3338

Four (4) subjects (3.1%) reported SAEs, including serious infections (Table 40). No serious ISRs were reported. All SAEs and serious infections were treatment emergent.

One (1) subject had a non-infectious SAE: This was a 16-year-old female with ERA, experienced abdominal pain on Day 13. The event led to hospitalization. Investigational product was continued and the event resolved 9 days later without sequelae, and was considered by the investigator to be moderate and unrelated to investigational product.

The overall exposure-adjusted rate of non-infectious SAEs across all 3 JIA subtypes was 0.034 events per subject-year (0.114 events per subject-year for ERA).

Three (3) subjects had serious infections. A 6 year-old female with eoJIA experienced bronchopneumonia on Day 38. The event led to withdrawal from investigational product, hospitalization, and treatment with anti-infectives. The event resolved after 7 days without sequelae, and was considered by the investigator to be mild and unrelated to investigational product.

A 17-year-old female with PsA had pyelocystitis on Day 52. The event led to withdrawal from investigational product, hospitalization, and treatment with antiinfectives. The event resolved 7 days later without sequelae, and was considered by the investigator to be mild and unrelated to investigational product.

A 5-year-old female with eoJIA experienced gastroenteritis on Day 10. The event led to hospitalization and use of supportive treatment. The subject did not receive antibiotics for the infection. Investigational product was continued and the event resolved 2 days later without sequelae, and was considered by the investigator to be severe and unrelated to investigational product.

Table 40. Number (%) of Subjects Reporting Treatment-Emergent Serious Adverse Events and Serious Infections in Study 3338 Through 12 Weeks

	JIA Subtype			
System Organ Class[a] Preferred Term	eoJIA (N=60) n (%)	ERA (N=38) n (%)	PsA (N=29) n (%)	Total (N=127) n (%)
Any treatment-emergent SAE or serious infection	2 (3.3)	1 (2.6)	1 (3.4)	4 (3.1)
Any treatment-emergent SAE	0	1 (2.6)	0	1 (0.8)
Gastrointestinal disorders	0	1 (2.6)	0	1 (0.8)
Abdominal pain	0	1 (2.6)	0	1 (0.8)
Any treatment-emergent serious infection	2 (3.3)	0	1 (3.4)	3 (2.4)
Infections and infestations	2 (3.3)	0	1 (3.4)	3 (2.4)
Bronchopneumonia	1 (1.7)	0	0	1 (0.8)
Gastroenteritis	1 (1.7)	0	0	1 (0.8)
Pyelocystitis	0	0	1 (3.4)	1 (0.8)

Abbreviations: eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; JIA=juvenile idiopathic arthritis; PsA=psoriatic arthritis; SAE=serious adverse event.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Note: All SAEs were treatment emergent.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different adverse events within the higher level category.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 36.

Study 20021618

Throughout the 10-year study, 44 SAEs were reported in 16 paediatric subjects (27.6%). The exposure-adjusted rate of SAEs, including infections, in paediatric subjects through 10 years in study 20021618 was 12.87 events per 100 subject-years (Table 41). The only SAE preferred terms occurring

in more than 1 subject each were rheumatoid arthritis which occurred in 6 (10.3%) paediatric subjects, and aggravated reaction, infection, abdominal pain, and arthralgia which occurred in 2 (3.4%) subjects each.

Of the 16 subjects with SAEs, 8 had serious infections.

Table 41. Exposure-adjusted Rate of Serious Adverse Events, Including Serious Infections, in Study 20021618 Through 10 Years, by Body System and Preferred Term in Descending Frequency

Body System Preferred Term	Pediatric Subjects n (r)
Number of subjects with at least 1 dose of etanercept	N=58
Total number of subject-years on etanercept	E=341.98
Number of Serious Adverse Events	44 (12.87)
Body as a Whole	17 (4.97)
Pain Abdo	4 (1.17)
React Aggrav	3 (0.88)
Infect	2 (0.58)
Sepsis	1 (0.29)
Infect Bact	1 (0.29)
Fever	1 (0.29)
Infect Viral	1 (0.29)
Disease Progression	1 (0.29)[a]
Peritonitis	1 (0.29)
Allerg React	1 (0.29)
Shock	1 (0.29)
Musculoskeletal System	17 (4.97)
Arthritis Rheumat	12 (3.51)
Arthritis	2 (0.58)
Arthralgia	2 (0.58)
Bone Dis	1 (0.29)
Cardiovascular System	1 (0.29)
Syncope	1 (0.29)
Respiratory System	1 (0.29)
Resp Dis Syndrome	1 (0.29)
Digestive System	2 (0.58)
Appendicitis	1 (0.29)
Abscess Periodont	1 (0.29)
Urogenital System	1 (0.29)
Pyelonephritis	1 (0.29)
Hemic & Lymphatic System	2 (0.58)
Coagul Dis	1 (0.29)
Blood Dyscrasia	1 (0.29)
Skin & Appendages	1 (0.29)
Herpes Zoster	1 (0.29)
Nervous System	1 (0.29)
Meningitis	1 (0.29)
Endocrine System	1 (0.29)
Diabetes Mell	1 (0.29)

Abbreviations: E=patient-years of exposure; N=number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618; n=number of events; r=exposure-adjusted event rate per 100 subject-years (n/E*100).
Only includes events within 30 days of last dose, including events with outcome of death.
a. The verbatim term mapped to the preferred term of 'Disease progression' was 'macrophage activation syndrome'.
Source: 5.3.5.2, Final CSR for study 20021618, Table 14-6.3.1.B.

The exposure-adjusted rate of SAEs in the paediatric subjects remained relatively constant over time in study 20021618 with the highest rates observed in years 1 and 2 (Table 42).

Table 42. Rates of All Serious Adverse Events, Including Serious Infections, at Yearly Timepoints Throughout Study 20021618

Timepoint	N1	Exposure-adjusted Rate (Events per 100 Subject-years)
Year 1	58	18.83
Year 2	50	33.23
Year 3	46	6.99
Year 4	40	10.43
Year 5	37	5.76
Year 6	34	6.33
Year 7	29	11.09
Year 8	26	8.83
Year 9	18	5.56
Year 10	18	5.91

Abbreviation: N1=number of subjects with at least 1 dose of etanercept.
Source: 5.3.5.2, Final CSR for study 20021618, Table 14-6.4.1.B.

Serious Infections

Study 3338

There were 3 serious infections reported during Part 1 of study 3338: 1 eoJIA subject with bronchopneumonia, 1 eoJIA subject with gastroenteritis, and 1 PsA subject with pyelocystitis.

Study 20021618

Throughout the 10-year study, 11 serious infections were reported in 8 paediatric subjects (13.8%). The exposure-adjusted rate of serious infections in paediatric subjects through 10 years in study 20021618 was 3.22 events per 100 subject-years (Table 43). All of the serious infection terms occurred in only 1 paediatric subject each, with the exception of the preferred term of infection (verbatim terms of soft tissue infection and post operative wound infection) which occurred in 2 subjects (3.4%).

Table 43. Exposure-adjusted Rate of Serious Infections in Study 20021618 Through 10 Years, by Body System and Preferred Term in Descending Frequency

Body System Preferred Term	Pediatric Subjects n (r)
Number of subjects with at least 1 dose of etanercept	N=58
Total number of subject-years on etanercept	E=341.98
Number of Serious Infections	11 (3.22)
Body as a Whole	6 (1.75)
Infect	2 (0.58)
Sepsis	1 (0.29)
Infect Bact	1 (0.29)
Infect Viral	1 (0.29)
Peritonitis	1 (0.29)
Digestive System	2 (0.58)
Appendicitis	1 (0.29)
Abscess Periodont	1 (0.29)
Urogenital System	1 (0.29)
Pyelonephritis	1 (0.29)
Skin & Appendages	1 (0.29)
Herpes Zoster	1 (0.29)
Nervous System	1 (0.29)
Meningitis	1 (0.29)

Abbreviations: E=patient-years of exposure; N=number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618; n=number of events; r=exposure-adjusted event rate per 100 subject-years (n/E*100).
Only includes events within 30 days of last dose, including events with outcome of death.
Source: 5.3.5.2, Final CSR for study 20021618, Table 14-6.3.2.B.

Other Significant Adverse Events

Safety-Related Discontinuations

Study 3338

Four (4) subjects were withdrawn from investigational product due to adverse events including infections. Two (2) subjects were withdrawn from investigational product due to non-infectious TEAEs.

Two (2) subjects were withdrawn from investigational product due to treatment-emergent infections, both of which met seriousness criteria:

1. A 6-year-old female with eoJIA, was withdrawn from investigational product due to bronchopneumonia on Day 38. The subject was hospitalized and received antiinfectives. The treatment-emergent infection resolved without sequelae, and was considered by the investigator to be mild and unrelated to investigational product.

2. A 17-year-old female with PsA was withdrawn from investigational product due to pyelocystitis on Day 52. She was hospitalized and received anti-infectives. The treatment-emergent infection resolved within 7 days without sequelae, and was considered by the investigator to be mild and unrelated to investigational product.

The overall exposure-adjusted rate of treatment-emergent infections leading to withdrawal across all 3 JIA subtypes was 0.069 events per subject-year: 0.073 events per subject-year for eoJIA and 0.149 events per subject-year for PsA.

Table 44. Number (%) of Subjects Reporting TEAEs (Excluding Infections and ISRs) Causing Withdrawal from Study 3338 Through 12 Weeks, Including Primary and Secondary Reasons for Withdrawal

	JIA Subtype			
System Organ Class[a] Preferred Term	eoJIA (N=60) n (%)	ERA (N=38) n (%)	PsA (N=29) n (%)	Total (N=127) n (%)
Any TEAE (excluding infections and ISRs) leading to withdrawal	0	2 (5.3)	0	2 (1.6)
General disorders and administration site conditions	0	2 (5.3)	0	2 (1.6)
Asthenia	0	1 (2.6)	0	1 (0.8)
Fatigue	0	1 (2.6)	0	1 (0.8)
Pyrexia	0	1 (2.6)	0	1 (0.8)
Nervous system disorders	0	1 (2.6)	0	1 (0.8)
Dizziness	0	1 (2.6)	0	1 (0.8)
Respiratory, thoracic and mediastinal disorders	0	1 (2.6)	0	1 (0.8)
Wheezing	0	1 (2.6)	0	1 (0.8)

Abbreviations: eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; ISR=injection site reaction; JIA=juvenile idiopathic arthritis; TEAE=treatment-emergent adverse event; PsA=psoriatic arthritis.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different adverse events within the higher level category.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 34.

Table 45. Number (%) of Subjects Reporting Treatment-Emergent Infections Causing Withdrawal from Study 3338 Through 12 Weeks, Including Primary and Secondary Reasons for Withdrawal

	JIA Subtype			
System Organ Class[a] Preferred Term	eoJIA (N=60) n (%)	ERA (N=38) n (%)	PsA (N=29) n (%)	Total (N=127) n (%)
Any treatment-emergent infection causing withdrawal	1 (1.7)	0	1 (3.4)	2 (1.6)
Infections and infestations	1 (1.7)	0	1 (3.4)	2 (1.6)
Bronchopneumonia	1 (1.7)	0	0	1 (0.8)
Pyelocystitis	0	0	1 (3.4)	1 (0.8)

Abbreviations: eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; JIA=juvenile idiopathic arthritis; PsA=psoriatic arthritis.
Classifications of infections are based on the Medical Dictionary for Regulatory Activities (MedDRA).
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different infections within the higher level category.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 35.

Study 20021618

The exposure-adjusted rate of adverse events leading to withdrawal in paediatric subjects through 10 years in study 20021618 was 2.05 events per 100 subject-years (Table 46). Throughout the 10-year study, 7 adverse events leading to withdrawal were reported in 3 paediatric subjects (5.2%). However, there were 2 additional paediatric subjects who were noted to have withdrawn from the study for adverse events that were not captured in the above-noted table in the CSR: JRA flare in 1 subject, and

infection and infection super in 1 subject. These 2 additional subjects were identified in the end of study case report form as having discontinued for an adverse event. If the 3 events from these 2 additional subjects are included, then the rate of adverse events leading to withdrawal is 2.09 events per 100 subject-years.

Therefore, overall, 5 paediatric subjects were withdrawn from study 20021618 for reasons related to adverse events: (1) JRA flare in 1 subject; (2) purpura fulminans (associated with SAEs of sepsis, shock, coagulation disorder, respiratory distress) in 1 subject; (3) skin disorder and fibro tendon in 1 subject (reported as physician decision on the end of study case report form); (4) infection and infection super in 1 subject; and (5) diarrhoea, vomiting, bone disorder, and meningitis in 1 subject.

Table 46. Exposure-adjusted Rate of Adverse Events Leading to Withdrawal from Study 20021618, by Body System and Preferred Term in Descending Frequency

Body System Preferred Term	Pediatric Subjects n (r)
Number of subjects with at least 1 dose of etanercept	N=58
Total number of subject-years on etanercept with gaps	E=341.98
Number of Adverse Events Leading to Withdrawal	7 (2.05)
Skin & Appendages	1 (0.29)
Skin Dis	1 (0.29)
Digestive System	2 (0.58)
Diarrhea	1 (0.29)
Vomit	1 (0.29)
Hemic & Lymphatic System	1 (0.29)
Purpura Fulminans	1 (0.29)
Musculoskeletal System	2 (0.58)
Bone Dis	1 (0.29)
Fibro Tendon	1 (0.29)
Nervous System	1 (0.29)
Meningitis	1 (0.29)

Body System Preferred Term	Pediatric Subjects n (r)

Abbreviations: E=patient-years of exposure; N=number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618; n=number of events; r=exposure-adjusted event rate per 100 subject-years (n/E*100).
Only includes events within 30 days of last dose, including events with outcome of death.
Source: 5.3.5.2, Final CSR for study 20021618, Table 14-6.3.9.B.

Adverse Events of Special Interest

Adverse events of special interest generally identified for close clinical monitoring in subjects receiving therapy with TNF inhibitors include lymphoma, malignancy, demyelinating disease, blood dyscrasias related to bone marrow suppression, autoimmune disorders, opportunistic infections, and tuberculosis.

No cases of lymphoma, malignancy, demyelinating disease, blood dyscrasias, autoimmune disorders, or tuberculosis were reported in study 3338. All medically important infections met the criteria for a serious infection. Three (3) subjects had medically-important infections; all were treatment emergent. No subject who had a history of vaccination experienced an infection considered preventable by vaccination. Two (2) subjects with no history of vaccination experienced an infection considered preventable by vaccination. There were 2 cases of varicella-zoster infection, one of which was reported as herpes zoster.

No cases of lymphoma, malignancy, demyelinating disease, opportunistic infection, or tuberculosis were reported in paediatric subjects in study 20021618. Three (3) cases of autoimmune disorders were reported in paediatric subjects in study 20021618: 2 subjects with scleroderma (1 subject with morphea and 1 subject with scleroderma of the left leg) and 1 subject with uveitis.

None of the 3 cases were SAEs and each of the subjects remained in the study for at least 3 more years. Although 4 subjects (2 with systemic-onset JIA) experienced a varicella-zoster infection in study 20021618, they were not considered to be opportunistic infections. Two (2) of the 4 cases were SAEs, and 2 were reported during year 1 of the study. One (1) of the SAEs was reported as herpes zoster affecting the leg. At least 3 of the 4 subjects had not been vaccinated against varicella.

Study 3338

No cases of lymphoma, malignancy, demyelinating disease, blood dyscrasias, autoimmune disorders, or tuberculosis were reported in study 3338. All medically important infections met the criteria for a serious infection. Three (3) subjects had medically-important infections; all were treatment emergent. (see above).

No subject who had a history of vaccination experienced an infection considered preventable by vaccination. Two (2) subjects with no history of vaccination experienced an infection considered preventable by vaccination:

1. A 6-year-old female with eoJIA, experienced varicella infection that was treated with an anti-infective and resolved. One (1) day after the start date of the varicella infection, the subject was hospitalized for bronchopneumonia. It is unknown whether the bronchopneumonia was related to the varicella infection. The varicella infection was considered by the investigator to be mild and unrelated to investigational product.
2. A 13-year-old female with ERA, experienced herpes zoster affecting 2 dermatomes on Day 16. No treatment was given, investigational product was continued, and the event resolved after 12 days without sequelae. The infection was considered by the investigator to be mild and unrelated to investigational product. It should be noted that this study was conducted primarily in countries in which varicella vaccination was not considered standard of care.

There were 2 cases of varicella-zoster infection, one of which was reported as herpes zoster. The case of herpes zoster was also considered to be an opportunistic infection per the definition noted above. No other cases of herpes zoster were reported.

Study 20021618

No cases of lymphoma, malignancy, demyelinating disease, opportunistic infection, or tuberculosis were reported in paediatric subjects in study 20021618 .

Three (3) cases of autoimmune disorders were reported in paediatric subjects in study 20021618: 2 subjects with scleroderma (1 subject with morphea and 1 subject with scleroderma of the left leg) and 1 subject with uveitis. The 2 subjects with scleroderma were both females with polyarticular-onset JIA, 7 and 11 years of age. The 1 case of uveitis occurred in a 10-year old female with pauciarticular-onset JIA. The event of uveitis was reported after approximately 2 years in the study and was mild in severity. None of the 3 cases were SAEs and each of the subjects remained in the study for at least 3 more years.

Although 4 subjects (2 with systemic-onset JIA) experienced a varicella-zoster infection in study 20021618, they were not considered to be opportunistic infections. Two (2) of the 4 cases were SAEs, and 2 were reported during year 1 of the study. One (1) of the SAEs was reported as herpes zoster affecting the leg. At least 3 of the 4 subjects had not been vaccinated against varicella.

Laboratory findings

Grades 3 and 4 Laboratory Toxicities

Study 3338

No subject had a Grade 4 laboratory test result. Five (5) subjects had Grade 3 laboratory test results (Table 47): 3 subjects had Grade 3 (decreased) neutrophil values, 1 subject had Grade 3 (increased) bilirubin values, and 1 subject had Grade 3 (increased) alkaline phosphatase values. All subjects with Grade 3 laboratory tests continued into Part 2 of the study.

Table 47. Number (%) of Subjects with Grade 3 or 4 Laboratory Test Results in Study 3338 Through 12 Weeks

	JIA Subtype			
Analyte, units Grade	**eoJIA n/N (%)**	**ERA n/N (%)**	**PsA n/N (%)**	**Total n/N (%)**
Total	4/59 (6.8)	1/38 (2.6)	0/29	5/126 (4.0)
Total bilirubin, µmol/L				
Grade 3[a]	0/59	1/38 (2.6)	0/29	1/126 (0.8)
Alkaline phosphatase, U/L				
Grade 3[b]	1/59 (1.7)	0/38	0/29	1/126 (0.8)
Neutrophils, 10^9/L				
Grade 3[c]	3/59 (5.1)	0/38	0/29	3/126 (2.4)

Abbreviations: eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; JIA=juvenile idiopathic arthritis; PsA=psoriatic arthritis; ULN=upper limit of normal.
For each test only the maximum grade per subject was counted.
Note: There were no Grade 4 laboratory test results.
a. Grade 3 = >1.5 - 3.0 x ULN
b. Grade 3 = >5 - 20 x ULN
c. Grade 3 = 0.5 - 1.0 x 10^9 cells/L
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 39.

Study 20021618

No grade 4 laboratory toxicities were reported. Three (3) paediatric subjects experienced a Grade 3 decrease in hemoglobin throughout the 10 years of study 20021618. None of these subjects had any additional grade 3 hemoglobin results during the study.

Subjects with Liver Function Test Abnormalities

Study 3338

A total of 12 subjects (9.5%) had increased liver function test (LFT) values, with 9 subjects (7.1%) reporting >2x to ≤3x upper limit of normal (ULN) LFT values and 3 subjects (2.4%) reporting >3x ULN LFT values (Table 48). No clinically meaningful differences were observed across JIA subtypes.

Table 48. Number (%) of Subjects with Liver Function Tests Increased >2x and ≤3x ULN, or >3x ULN During Treatment in Study 3338 Through 12 Weeks

	JIA Subtype			
Analyte, units Degree of Increase	**eoJIA n/N (%)**	**ERA n/N (%)**	**PsA n/N (%)**	**Total n/N (%)**
Total	**7/ 59 (11.9)**	**3/ 38 (7.9)**	**2/ 29 (6.9)**	**12/126 (9.5)**
Total bilirubin, µmol/L	**0/ 59**	**1/ 38 (2.6)**	**0/ 29**	**1/126 (0.8)**
>2x and ≤3x ULN	0/ 59	1/ 38 (2.6)	0/ 29	1/126 (0.8)
AST, U/L	**1/ 59 (1.7)**	**0/ 38**	**0/ 29**	**1/126 (0.8)**
>2x and ≤3x ULN	1/ 59 (1.7)	0/ 38	0/ 29	1/126 (0.8)
ALT, U/L	**5/ 59 (8.5)**	**2/ 38 (5.3)**	**2/ 29 (6.9)**	**9/126 (7.1)**
>3x ULN	1/ 59 (1.7)	0/ 38	1/ 29 (3.4)	2/126 (1.6)
>2x and ≤3x ULN	4/ 59 (6.8)	2/ 38 (5.3)	1/ 29 (3.4)	7/126 (5.6)
Alkaline phosphatase, U/L	**1/ 59 (1.7)**	**0/ 38**	**0/ 29**	**1/126 (0.8)**
>3x ULN	1/ 59 (1.7)	0/ 38	0/ 29	1/126 (0.8)

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; JIA=juvenile idiopathic arthritis; PsA=psoriatic arthritis; ULN=upper limit of normal.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 40.

Study 20021618

During study 20021618, samples for clinical laboratory analyses were to be collected at screening, baseline, and every 3 months for the first 12 months, every 4 months from month 12 to month 48, and then every 6 months thereafter. However, samples were only reported up to month 52 as the data became sparse after this timepoint. No grade 4 laboratory toxicities were reported. Three (3) paediatric subjects experienced a Grade 3 decrease in haemoglobin throughout the 10 years of study 20021618.

Table 49. Number (%) of Subjects with Grades 3 and 4 Laboratory Toxicities in Study 20021618 Through 10 Years

Laboratory Toxicity	Grade	Pediatric Subjects (N=58) n (%)
Hemoglobin	Grade 3	3 (5.2)

Abbreviation: N=number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618.
Source: 5.3.5.2, Final CSR for study 20021618, Table 14-7.2.B.

There were no reports of grade 3 or 4 ALT or AST in paediatric subjects (Table 50). ALT and AST were reported through 52 months in study 20021618. Mean AST and ALT remained relatively stable through 48 months. Only 3 subjects had values reported at month 52.

Table 50. Summary of ALT/AST Values Over Time in Study 20021618

Parameter	Baseline	Month 12	Month 24	Month 36	Month 48	Month 52
ALT, U/L						
n	58	50	47	38	15	3
Mean	16.83	16.08	15.81	20.26	16.80	19.33
SD	11.28	6.53	6.64	16.83	5.00	18.15
Median	13.00	15.00	14.00	17.00	16.00	12.00
Min, max	5.00, 73.00	6.00, 38.00	8.00, 43.00	8.00, 106.00	7.00, 26.00	6.00, 40.00
AST, U/L						
n	58	50	47	38	15	3
Mean	22.72	22.86	21.74	24.45	23.60	21.67
SD	9.50	6.81	9.47	7.88	6.19	6.43
Median	20.00	21.00	19.00	23.00	22.00	19.00
Min, max	8.00, 50.00	12.00, 41.00	9.00, 70.00	15.00, 51.00	16.00, 39.00	17.00, 29.00

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; SD=standard deviation.
Source: 5.3.5.2, Final CSR for study 20021618, Table 14-7.1.2.B and Table 14-7.1.3.B.

Immunological events

Anti-etanercept Antibodies

Study 3338

Seven (7) subjects tested positive for anti-etanercept antibodies at either Week 12 or upon early withdrawal: 5 subjects had ERA and 2 had PsA (Table 51). None of the subjects who were positive for anti-etanercept antibodies tested positive for neutralizing antibodies. Three (3) subjects were missing either the baseline or Week-12 anti-etanercept antibody sample; therefore, no results are presented for these subjects. The presence of anti-etanercept antibodies did not adversely affect efficacy at Week 12. Of the 7 subjects with anti-etanercept antibodies, 6 met ACR Pedi 30 response criteria at Week 12. Six (6) of the 7 subjects who tested positive for anti-etanercept antibodies experienced TEAEs, including infections and ISRs. One (1) of these subjects experienced an SAE of abdominal pain. No serious infections were reported in the subjects who tested positive for anti-etanercept antibodies.

Table 51. Number (%) of Subjects with Positive Anti-Etanercept Antibody and Neutralizing Anti-Etanercept Antibody Test Results at Week 12 or Early Withdrawal of Study 3338

	JIA Subtype			
Week 12	eoJIA (N=56) n (%)	ERA (N=36) n (%)	PsA (N=27) n (%)	Total (N=119) n (%)
Antibody				
Negative	56 (100)	32 (88.89)	25 (92.59)	113 (94.96)
Positive	0	4 (11.11)	2 (7.41)	6 (5.04)
Neutralizing Antibody[a], N (%)				
Negative	0	4 (100)	2 (100)	6 (100)
Early Withdrawal	**eoJIA (N=2) n (%)**	**ERA (N=2) n (%)**	**PsA (N=1) n (%)**	**Total (N=5) n (%)**
Antibody				
Negative	2 (100)	1 (50.00)	1 (100)	4 (80.00)
Positive	0	1 (50.00)	0	1 (20.00)
Neutralizing Antibody[a], N (%)				
Negative	0	1 (100)	0	1 (100)

Abbreviations: eoJIA = extended oligoarticular juvenile idiopathic arthritis; ERA = enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; PsA = psoriatic arthritis.
a. Neutralizing antibody testing was only conducted for subjects who were anti-etanercept antibody-positive.
Source: 5.3.5.2, Part 1 (Week 12) CSR for study 0881A1-3338, Table 41.

Study 20021618

Although the measurement of anti-etanercept antibodies was included as a safety endpoint in the protocol for study 20021618, no anti-etanercept antibody analysis was done. As testing for ADA requires comparison between samples and the baseline level, this will not be possible due to lack of samples/insufficient evidence of sample stability for the baseline samples taken more than 10 years ago.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Subgroup analyses were only performed for the intrinsic factor of age for the eoJIA population in study 3338. TEAEs, infections, and Tanner stage scores were analyzed for the subgroups of eoJIA subjects aged 2 to 4 years, 5 to 11 years, and 12 to 17 years. For subjects with eoJIA, the number (%) of subjects with TEAEs in each of the age groups of 2 to 4 years, 5 to 11 years, and 12 to 17 years, was 5 (33.3%), 10 (43.5%), and 6 (27.3%), respectively. No clinically meaningful differences in the incidence of TEAEs were observed across the 3 age groups of subjects with eoJIA. The number (%) of subjects with eoJIA by age group who had treatment-emergent infections was 11 (73.3%), 12 (52.2%), and 8 (36.4%), for subjects aged 2 to 4 years, 5 to 11 years, and 12 to 17 years, respectively. The incidence of infections in subjects aged 2 to ≤4 years was numerically higher than that of the other 2 age groups. For all 3 eoJIA age subgroups, there was no was no evidence of a decline in growth velocity in height, weight, or BMI from baseline to Week 12 of study 3338. Overall, there was no change in mean Tanner stage score at Week 12 compared with baseline of study 3338 for the 3 eoJIA age subgroups.

Subgroup analyses were not performed for intrinsic factors in study 20021618.

Subgroup analyses were not performed for extrinsic factors in either study 3338 or study 20021618.

Measures of Growth

Study 3338

There was no evidence of a decline in growth velocity in height, weight, or BMI from baseline to Week 12 of study 3338.

Study 20021618

Growth measurements were reported through 52 months in study 20021618. As expected, mean height and weight increased for paediatric subjects through 48 months. Mean BMI remained relatively stable through 48 months (Table 52). Only 4 subjects had values reported at month 52.

Table 52. Summary of Height, Weight, and Body Mass Index Over Time in Study 20021618

Parameter	Baseline	Month 12	Month 24	Month 36	Month 48	Month 52
Height (cm)						
n	58	49	46	39	17	4
Mean	136.83	144.19	148.22	151.36	152.08	156.15
SD	21.72	19.83	17.98	16.09	14.55	6.26
Median	135.48	145.50	151.65	153.50	153.00	156.90
Min, max	90.80, 180.20	94.70, 181.90	97.00, 183.10	106.00, 183.70	116.70, 179.00	148.30, 162.50
Weight (kg)						
n	58	49	47	40	17	4
Mean	38.10	44.46	48.81	48.18	50.57	59.30
SD	19.68	23.02	24.36	16.19	14.05	11.62
Median	33.40	41.00	44.50	47.35	54.40	60.85
Min, max	13.10, 124.10	13.60, 144.20	19.80, 166.60	18.40, 86.30	22.80, 69.20	45.20, 70.30
BMI (kg/m^2)						
n	58	48	46	39	17	4
Mean	19.22	20.45	21.26	20.29	21.45	24.38
SD	5.62	6.93	7.50	4.32	4.01	4.91
Median	17.31	18.55	19.20	19.20	20.86	25.11
Min, max	12.85, 50.22	12.53, 55.98	14.34, 62.32	13.63, 30.58	14.01, 27.43	17.74, 29.57

Abbreviations: BMI=body mass index; SD=standard deviation.
Source: 5.3.5.2, Final CSR for study 20021618, Table 14-8.1.1.B, Table 14-8.1.2.B, Table 14-8.1.3.B.

Vital Signs

Study 3338

Six (6) subjects presented with vital signs of potential clinical interest at the Week-4, Week-8, or Week-12 visits, only 1 of which was reported as a TEAE. There was 1 report of a decreased diastolic blood pressure of 40 mm Hg and 5 reports of elevated systolic blood pressures ranging from 141 mm Hg to 150 mm Hg. Per NCI Version 4.03, the elevated systolic blood pressures were Grade 2 in severity. The elevated systolic blood pressures were not accompanied by elevations in diastolic blood pressure. All vital signs of potential clinical interest were isolated to a single visit and returned to normal at the next visit.

Study 20021618

Vital signs were only collected through year 1 of study 20021618. No clinically significant changes in vital signs (body temperature, heart rate, respiratory rate, systolic blood pressure, and diastolic blood pressure) were observed during study 20021618.

Tanner Assessment

Overall, there was no change in mean Tanner stage score at Week 12 compared with baseline of study 3338. Baseline Tanner data were not collected in study 20021618 and therefore the data are not summarized.

Post marketing experience

Postmarketing Experience in Etanercept-treated Patients Under 18 Years of Age

The most frequently reported serious, medically confirmed events in juvenile etanercept users (age 1 to 17 years; all indications) differed when compared with the most frequently reported events for all users combined. Among all juvenile etanercept users, "condition aggravated" (flares or worsening of the indication for use or of a pre-existing condition), pyrexia, uveitis, and injection site reactions were the most frequently reported serious events. Fever and uveitis are often associated with JIA itself and fever often accompanies common childhood illnesses. In addition to condition aggravated, the most frequently reported nonserious, medically confirmed events in this age group included various injection site reactions, drug ineffective, and pyrexia. There have been postmarketing reports of pyrexia, uveitis

and injection site reactions in the general etanercept population. Accordingly, pyrexia, uveitis, and injection site reactions are listed adverse reactions in the etanercept CDS.

Among spontaneous, medically confirmed reports regarding patients under the age of 18 who received etanercept for any indication, there were 23 deaths and 11 malignancies. The malignancies included Hodgkin's disease (4), acute lymphocytic leukemia (2), acute myeloid leukemia (1), leukemia (1), lymphoma (1), renal cancer (1), and colon cancer (1). On 04 June 2008, the FDA issued an Early Communication that described a possible association between use of tumour necrosis factor inhibitors in children and young adults and the development of malignancies. Wyeth, now Pfizer, conducted an analysis of the etanercept experience with malignancies in this population and determined that malignancies occurring after the exposure of juveniles to etanercept merited further investigation. Therefore, the Marketing Authorisation Holder (MAH) initiated several activities to gather further information. Results of an analysis of the background rates of malignancy in paediatric/juvenile patients with inflammatory arthritis suggested that there is a potential increased risk of malignancy in paediatric patients with JIA. The MAH regards the issue of paediatric malignancy as a safety concern and has added information to the warnings and precautions section of the etanercept CDS to include a specific precaution for this population.

There have been reports of inflammatory bowel disease occurring in JIA patients and other paediatric patients who received etanercept at a greater frequency than in the background normal paediatric population, although it is unclear what the frequency of inflammatory bowel disease (IBD) is in the JIA population. Therefore, a precaution regarding reports of IBD in JIA patients being treated with etanercept was added to the CDS, which states that etanercept is not an effective treatment for IBD and that a causal relationship with etanercept is unclear because clinical manifestations of bowel inflammation have also been observed in untreated JIA patients.

To identify potential effects of TNF-alpha inhibition upon the vaccination response in juveniles, the MAH's pharmacovigilance database was searched through 02 February 2011 in patients less than 17 years of age for reports of vaccination failure, vaccine complication, vaccine breakthrough infection and the standardized MedDRA query (SMQ) terms for Lack of efficacy/effect. Two (2) reports with a vaccine as a co-suspect medication were identified; neither described lack of efficacy or reduced efficacy of the vaccine. The etanercept CDS addresses the issue of paediatric immunization in the "Precautions" section, stating, "If possible, bring paediatric patients up to date with immunizations according to current local guidelines before beginning etanercept therapy.

Postmarketing Experience in Etanercept-treated Patients with Juvenile Idiopathic Arthritis

Through 02 February 2011, there were 1,937 spontaneous, medically confirmed events (in 671 cases) reported in patients under the age of 18 who received etanercept for the treatment of JIA. The patients ranged in age from <1 year to 17 years (mean 10.66 years, median 11.0 years). The reported events were similar to those received for the overall etanercept paediatric population. The most frequently reported events were arthritis, injection site reactions, "condition aggravated", and pyrexia. The most frequently reported serious events were "condition aggravated" and pyrexia (20 events each) and uveitis and injection site reactions (16 events each). Uveitis has been shown to resolve with discontinuation of etanercept. Malignancies were reported in 7 patients with JIA. These included Hodgkin's disease (4), acute lymphocytic leukemia (2), and leukemia (1).

The types and reporting proportion of infections in juvenile JIA patients were generally similar to those reported for all etanercept users. Many of the viral infections that were reported in juvenile etanercept patients are common in children in the general population. The comparison of the distribution of adult RA and juvenile JIA infections revealed no unexpected findings.

There have been reports of inflammatory bowel disease occurring in JIA patients and other paediatric patients who received etanercept at a greater frequency than in the background normal paediatric population, although it is unclear what the frequency of IBD is in the JIA population. Therefore, a precaution regarding reports of IBD in JIA patients being treated with etanercept was added to the CDS, which states that etanercept is not an effective treatment for IBD and that a causal relationship with etanercept is unclear because clinical manifestations of bowel inflammation have also been observed in untreated JIA patients.

Safety Concerns Identified During the Postmarketing Period

Several safety concerns were identified during the postmarketing period that resulted in changes to core safety data. These are addressed in the RMP as appropriate. Highlights of these changes (through August 2011) included: Enhancement of special warnings and/or precautions regarding infections including fatal infections, tuberculosis (with recommendations for patient testing, prophylaxis, and monitoring), sepsis, and opportunistic infections (including invasive fungal infections and the possibility of unrecognized fungal infection resulting in death). Information regarding hepatitis B reactivation and worsening of hepatitis C was also added.

Several revisions have been made regarding the occurrence of lymphoma and other malignancies, to reflect the most current information. Included in the CDS is the occurrence of more lymphomas in TNF treated patients in controlled clinical trials than in the placebo groups (though exposure was smaller in placebo groups), and information that postmarketing reports of malignancies have been received. The CDS states that post hoc analyses of rheumatoid arthritis clinical trials with etanercept have neither confirmed nor excluded an increased risk for malignancies. Melanoma, nonmelanoma skin cancer (NMSC), and Merkel cell carcinoma were added as adverse drug reactions with a recommendation for periodic skin examination for patients who are at increased risk for skin cancer. A statement was also added regarding reports of malignancies among children and adolescents who received treatment with TNF-antagonists.

Additional warnings and precautions have been added to the CDS regarding several hematologic reactions (including sometimes fatal aplastic anemia and pancytopenia), neurologic events (central demyelinating disorders and peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome), autoantibody formation, cardiac disorders (worsening congestive heart failure), and the possibility of hypoglycemia in diabetic etanercept users. A precaution regarding reports of IBD in JIA patients being treated with etanercept was added, but states that a causal relationship with etanercept is unclear because clinical manifestations of bowel inflammation have also been observed in untreated JIA patients.

Special warnings are included in the CDS to advise about lack of efficacy and malignancies in patients who received etanercept for Wegener's granulomatosis and about increased mortality and infection rates in patients who received etanercept for treatment of alcoholic hepatitis.

Adverse reactions that have been also been added to the CDS include: autoimmune events (such as development of autoantibodies, lupus-like syndrome, autoimmune hepatitis, systemic vasculitis including anti-neutrophil cytoplasmic antibody [ANCA] positive vasculitis, cutaneous vasculitis [including leukocytoclastic vasculitis]), elevated liver enzymes, interstitial lung disease (including pulmonary fibrosis and pneumonitis), macrophage activation syndrome (MAS), erythema multiforme, psoriasis (all types; new onset, and exacerbations including all subtypes) and psoriasiform rash, pruritus, rash, seizures, Stevens-Johnson syndrome, toxic epidermal necrolysis, and uveitis. Additional CDS updates included information regarding an animal lactation study, the response to pneumococcal polysaccharide vaccine, a warning regarding latex allergy, and revision of instructions for the

preparation and administration of various etanercept presentations. Terms have also been added that provided further description of injection site reactions and allergic reactions.

In the labeling (Summary of Product Characteristics) for the pre-filled syringe and pre-filled pen, dosage information specific to children has been enhanced with recommendations for children less than 62.5 kg to use the powder and solvent for solution for injection for accurate mg/kg dosing. Children weighing 62.5 kg or more may use the fixed-dose pre-filled syringe or pre-filled pen.

Discussion on clinical safety

In regard to the different subtypes of JIA studied in the study 3338, the sample size and the period of study (12 weeks) limits assessment of the safety profile regarding the individual ILAR subtypes. Further information regarding possible difference in safety for the individual subtypes will become available from the second part of the study 3338 (as described in the RMP). As routine pharmacovigilance activities, the MAH will include follow-up questionnaires specifically designed to enable the collection of relevant postmarketing medical data for JIA subtypes in children (as described in the RMP)**.**

In addition, the MAH will provide further updated information which will include JIA subtypes diagnostic descriptions, data on the epidemiology, and important AEs associated with JIA subtypes (as described in the RMP).

In the study 20021618 AEs were only collected in the first year.

Focusing on the study 3338, forty-five (45) subjects (35.4%) reported at least 1 treatment-emergent adverse event (TEAE), excluding infections and ISRs, through 12 weeks. The most common TEAEs reported in the overall population were headache (7 subjects, 5.5%), followed by fatigue, pyrexia, abdominal pain, and diarrhea (4 subjects each, 3.1%). In study 20021618, the most common TEAEs reported were injection site reaction (112 events, 210.93 events per 100 subject-years), upper respiratory infection (68 events, 128.06 events per 100 subject years), headache (44 events, 82.86 events per 100 subject-years), and abdominal pain (20 events, 37.67 events per 100 subject-years). Fifty (50) pediatric subjects (86.2%) reported at least 1 TEAE during year 1 of the study. After the first year of study 20021618, only adverse events that met serious criteria (SAEs) were collected along with predefined events of interest (including hospitalization, deaths, serious infections, development of malignancies, and new signs or symptoms of other connective tissue disease).

Importantly, no deaths occurred in pediatric subjects during the first 12 weeks of study 3338 or up to 10 years of exposure in study 20021618.

Regarding SAEs, four (4) subjects (3.1%) reported SAEs in the study 3338, of them, 3 were serious infections none was related to etanercept according the investigators. In addition, the incidence of infections in extended oligoarticular JIA subjects was numerically higher than that of the other 2 age groups. Moreover, 11 serious infections were reported in 8 paediatric subjects (one case of sepsis was reported) in the study 20021618. Serious infections with etanercept treatment are a risk that is highlighted in the SmPC and also in view of the well known side effect profile, etanercept is restricted for use in children when other treatment options have failed.

No cases of tuberculosis, blood dyscrasias, demyelinating disorders, autoimmune disorders, or malignancies, including lymphomas and skin cancers, were reported in the study 3338. In the paediatric population of the study 20021618 no cases of lymphoma, malignancy, demyelinating disease, opportunistic infection, or tuberculosis were reported.

In study 3338, the higher rate of AEs in the ERA subgroup is noted, particularly gastrointestinal disorders. The details of the cases descried by the MAH do not raise specific concerns regarding a GI AE profile for those with ERA, but further information will become available from the rate of non-infectious AEs related to gastrointestinal disorders that will be reported during Part 2 of the study (as described in the RMP).

In terms of laboratory parameters, the CHMP noted the decrease in neutrophil values (grade 3) in 5.1% of eoJIA subtype. It should also be noted the decrease in neutrophil values (grade 3) in 5.1% of eoJIA subtype. However these decreases were transient and the limited sample size precludes drawing any firm conclusions. Further information will be reported during Part 2 of the study.

5% of patients in the study 3338 developed antibodies; although it is reassuring that none of them were positive for neutralizing antibody. Although the numbers developing ADA are small those with ERA had a higher percentage of ADA positive subjects. The CHMP acknowledges that based on efficacy and safety variables at week 12, those subjects with anti-etanercept antibodies did not show any decrease in the efficacy results compared to the whole population of the study. The same is applicable for safety. However, there seems to be a trend for a higher ADA incidence in the ERA subset. To what extent this fact can affect the efficacy and safety in long-term needs to be discussed with the week 96 data for study 3338**.**

Conclusions on the clinical safety

The safety data provided in the current application has no demonstrated any new or unexpected signals from etanercept in children with eoJIA from the age of 2 years, ERA or PSA. Further data will be available on these JIA subtypes from the 96 week CSR for study 3338. Based on the previous experience in the JIA population, major differences in safety across the ILAR subtypes for which data was provided seem unlikely but assessment for the 96 week data from study 3338 and the long-term extensions study B1801023 (both described in the RMP) will provide further information on this issue.

1.2.6 Risk Management Plan

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

Table 24 Extract from the Summary of the risk management plan including only the changes related:

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities					
Important Missing Information - Specific Indications							
Assessment of spinal mobility (pediatric patients with ERA)	Additional PV Activities by Individual Risks and Indications						
		RA	JIA	AS	PsA	PS	Ped PS
	B1801023		√				
Clinically inactive disease and remission rates and the effectiveness of re-treatment upon disease relapse (pediatric patients with eoJIA, PsA, or ERA)	Additional PV Activities by Individual Risks and Indications						
	B1801023		√				

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
0881A1-3338-WW - A 2-Part Open-Label Study to Assess the Clinical Benefit and Long-Term Safety of Etanercept in Children and Adolescents With Extended Oligoarticular Juvenile Idiopathic Arthritis, Enthesitis-Related Arthritis, or Psoriatic Arthritis	Safety summary report provided annually in the RMP beginning in April 2013
Study B1801023 will monitor long-term (8-year) safety data. The study will include additional efficacy assessments. In addition collection of data on CID/remission rates, effect of withdrawal of therapy in those in CID/remission and success rate of re-treatment upon disease relapse in subjects with eoJIA, ERA and PsA. Study B1801023 will also collect further data including spinal mobility assessments in ERA subjects.	Safety summary report provided annually in the RMP beginning in April 2013. Interim safety and efficacy reports completed every 2 years with the first interim report expected in 4Q2015.
The MAH will develop a specific follow-up questionnaire designed to collect information on JIA subtypes in children for spontaneous reports.	Annually in the RMP beginning in April 2013.
The MAH will provide further updated information which will include JIA subtypes diagnostic descriptions, data on the epidemiology, and important AEs associated with JIA subtypes	Annually in the RMP beginning in April 2013.

1.2.7 User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Enbrel 25 mg solution for injection in pre-filled syringe, Enbrel 50 mg solution for injection in pre-filled syringe and Enbrel 50 mg solution for injection in pre-filled pen. The bridging report submitted by the MAH has been found acceptable.

2. Benefit-Risk Balance

Benefits

Beneficial effects

The beneficial effects of etanercept in 5 subtypes of JIA has been demonstrated in 2 open label single arm trials. Etanercept is already licensed for polyarticular JIA from the age of 2 years (the study group which were included in the submitted clinical data in support of this licensed indication can be classified by the ILAR criteria as polyarthritis (RF positive) and polyarthritis (RF negative)). The data from study 20021618 was assessed in variation II/126 (approved in August 2011), and in this current application the MAH has submitted the final CSR for study 20021618 which now includes 10 years of safety follow-up.

Study 3338 provides evidence for a response at 12 weeks in subjects with eoJIA from the age of 2 years and in subjects with ERA and PSA from the age of 12 years. The response was assessed by ACR Pedi 30, but a beneficial effect was also seen for ACR Pedi 50 and 70 by week 12 and the effect was similar in magnitude in all three subtypes and in all age groups. Comparison with historical placebo data for the same subtypes provides further support for efficacy.

Controlled double-blind trials have not been submitted in this variation application. However as this variation builds on previous well established efficacy in the areas of adult RA, adult ankylosing spondylitis, adult psoriatic arthritis, adult and paediatric plaque psoriasis and JIA (polyarticular) with etanercept and therefore the evidence provided for the extension of indication can be accepted. This is because of the rarity of the individual subtypes, the expected efficacy with etanercept in the subtypes proposed and the difficulty in conducting placebo controlled trials in children with JIA when off-license use of etanercept is available. While long-term efficacy has been supported by clinical data in polyarticular JIA, at present 12 weeks data has been provided for eoJIA, ERA and PsA in children.

Uncertainty in the knowledge about the beneficial effects

An area of uncertainty for those with ERA is whether institution of anti-TNF treatment can prevent progression to axial disease. The MAH has amended the planned long-term study B1801023 to incorporate efficacy evaluations particularly in ERA for effects on spinal disease and this is expected to provide useful additional insight into the effect of early institution of therapy in ERA (as described in the RMP).

Further information on the evidence for maintenance of efficacy will be required, and the final CSR from study 3338 will need to be assessed in order to ensure that maintenance of efficacy in these three subtypes is similar to that for polyarticular JIA (RF positive and RF negative). Further long-term data will be collected for an additional eight years and in addition information on remission rates and on when to withdraw therapy in those who have clinically inactive disease on treatment for each of the three subtypes has been planned for study B1801023 (as described in the RMP).

Risks

Unfavourable effects

The unfavourable effects of etanercept are well established and include infection, opportunistic infection, malignancy, injection site reactions, bone marrow suppression and are in line with the safety profile identified in the trials and are clearly highlighted in the SmPC. The data expected from the ongoing study 3338 should provide further information (as described in the RMP).

Uncertainty in the knowledge about the unfavourable effects

The exposure in the specific subtypes of JIA is limited and further data from the final week 96 CSR from study 3338 should provide more information on the safety profile.

An important area of missing information remains; namely when to cease treatment in a responding subject. While this problem was discussed at length with the MAH during variation II/126 (extension of

polyarticular JIA indication down to the age of 2 years) the difficulty in collecting such information remains an obstacle. However in view of the planned long-term study and 8 year extension study the MAH amended the protocol in order to collect information on this issue as restriction of treatment to the minimum time required is important to minimise unnecessary exposure (as described in the RMP).

Balance

Importance of favourable and unfavourable effects

The importance of alleviating signs and symptoms in children with JIA when they have been unresponsive to methotrexate or conventional therapy (in the case of ERA) means that these patients will have an improved quality of life, less inflammation and pain, better functioning of joints and less need for steroids. The breakdown of the individual components of the composite of ACR Pedi was consistent with the overall results and showed the expected improvement in quality of life, pain score and number of swollen joints and joints with limitation of movement. Such beneficial effects are important for enabling normal development in children.

The important well established adverse effects of etanercept therapy are highlighted in the SmPC and under continual pharmacovigilance review. Infections and serious infections are the commonest adverse event with etanercept. Because of the known risks with etanercept, treatment is limited to subjects with active disease who have not responded to methotrexate and in the case of ERA to conventional therapy. In addition for subjects who do not show a response to etanercept then therapy should be discontinued at 4 months. This ensures that only those who gain benefit from treatment continue to receive etanercept.

Benefit-risk balance

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 polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years; treatment of psoriatic arthritis in adolescents from the age of 12 years; treatment of enthesitis-related arthritis in adolescents from the age of 12 years was positive.

The MAH agreed to include the following wording in section 4.1 of the SmPC:

Juvenile idiopathic arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Discussion on the benefit-risk assessment

In view of the unmet medical need for subjects with the 3 additional subtypes of JIA (eoJIA from age 2 years, ERA from age 12 yrs and PsA from age 12 years) who have active disease unresponsive to methotrexate or conventional therapy, or who are intolerant to methotrexate, the advantages of treatment with etanercept are considered to outweigh the safety concerns. Treatment will only be

continued in such subjects if a response is seen, treatment for such cases is limited to experts in the field of paediatric rheumatology and guidance in the SmPC helps to ensure that the adverse event profile of etanercept is highlighted, thereby enabling a pro-active approach to minimising occurrence of adverse events or, if they occur, that they are rapidly diagnosed and treated appropriately. An ongoing area where information and guidance is lacking is whether early institution of treatment can benefit those with ERA who would go on to develop axial disease. Another important area of missing information is for those who respond to treatment and achieve clinically inactive disease, at what point should be discontinued. The MAH will address both of these issues with the planned study B1801023 (as described in the RMP).

3. Conclusion

On 21 June 2012 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 (P/241/2011) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

4. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

EPAR scope:

Extension to the JIA indication to include the:

- Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

- Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

- Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

together with reclassification of the licensed indication of polyarticular JIA into the ILAR classification of polyarthritis (rheumatoid factor positive) and polyarthritis (rheumatoid factor negative). Furthermore, an additional etanercept dosage regimen of 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly (QW) is proposed in addition to the current approved JIA dosage of 0.4 mg/kg (up to a maximum of 25 mg per dose) BIW for the treatment of JIA.

Consequential changes have been made to section 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the package leaflet. The product information has been brought in line with the latest QRD templates. In addition the list of the local representatives in the PL has been updated.

Scientific discussion:

Please refer to the Scientific Discussion "Enbrel/H/C/262/II/145" for further information.

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