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Committee for Medicinal Products for Human Use (CHMP)

Enbrel

etanercept

Procedure No. EMEA/H/C/000262/A46/145

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

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

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Rapporteur's Assessment Report for Post-Authorisation Commitments (PACs)

Submission of study in accordance with Article 46 of Regulation No 1901/2006 as amended

Enbrel
etanercept

EMEA/H/C/262
P46 145

Marketing Authorisation Holder: Wyeth

Rapporteur:	Robert Hemmings
Start of the procedure:	21 February 2010
Date of the report:	25 March 2010
Deadline for CHMP member's comments:	9 April 2010
Date of the updated report (if applicable):	14th April 2010

I. ASSESSMENT

Introduction

The final report for Amgen study 20021618 submitted in accordance with Article 46 of the Regulation (EC) No 1901/2006.

1. Background

Study 20021618 (open label extension treatment with Etanercept for subjects with DMARD-refractory rheumatoid arthritis participating in etanercept clinical trials) is part of the paediatric development programme (PIP EMEA-000299-PIP-01-08).

Previous annual updates, including that submitted in January 2009, have presented safety information from the following two juvenile idiopathic arthritis (JIA) studies:

- Amgen study 20021626 (formerly study 16.0026) – a 36 month phase 4 open-label registry study of etanercept versus methotrexate in children with polyarticular and systemic onset JIA.

- Amgen Study 20021618 (formerly study 16.0018) – an open label extension treatment with etanercept for participating patients in etanercept JIA clinical trials.

Study 20021626 completed in 2008 and its CSR was presented with the January 2009 update for this follow-up measure. Therefore this year's update consists of the CSR 79728 abbreviated report for study 20021618 plus a brief clinical overview.

LINE LISTING OF ALL THE STUDIES INCLUDED IN THE DEVELOPMENT PROGRAM

Clinical studies

Product Name: Enbrel **Active substance: Etanercept**

Study title	Study number	Date of completion	Estimated date of submission of final study report
A 36-month phase 4 open-label registry study of etanercept versus methotrexate in children with polyarticular and systemic onset JIA	20021626	Complete	January 2009
An open-label extension treatment with etanercept for participating patients in etanercept JIA clinical trials	20021618	Complete	January 2010
Phase 3 multicenter, open-label extension study for patients who participated in study 20030111	20050111	June 2012	December 2013
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	0881A1-3338-WW	Part 1: June 2011 Part 2: March 2013	Part 1: October 2011 Part 2: September 2013
8-Year active surveillance for malignancy for study 0881A1-3338-WW participants	TBD	March 2021	September 2021
A Long-Term, Prospective, Observational Cohort Study of the Safety and Effectiveness of Etanercept in the Treatment of Paediatric Psoriasis Patients in a Naturalistic Setting: A Post-Authorisation Safety Study (PASS)	0881X1 4654	2017	2018

2. SECTION 2 – DATA FROM STUDY 20021618 ONLY WITH FOCUS ON PAEDIATRIC DATA

Etanercept was first approved for use in pediatric patients in May 1999 in the United States and in February 2000 in the European Union for the indication of polyarticular juvenile idiopathic arthritis (JIA) in children 4 to 17 years of age. Subsequently, etanercept has more recently been approved for use in pediatric patients with severe plaque psoriasis from the age of 8 years in the EU.

Per the approval of etanercept for the treatment of polyarticular JIA in the European Union, the Marketing Authorisation Holder (MAH) was committed to present the results from future studies in pediatric subjects (Commitment 16). Updates on the progress of the pediatric studies were to be provided on an annual basis and final study reports were to be submitted.

Study 16.0016 established the safety, population pharmacokinetics, and efficacy of 0.4 mg/kg etanercept twice weekly (BIW) in subjects aged 4 to 17 years who were refractory or intolerant to methotrexate, and was the basis for the approval for the treatment of polyarticular JIA.
Study 20021618 was an open-label study of long-term etanercept treatment through 10 years, which included pediatric subjects who had previously participated in study 16.0016 as well as adult subjects who had previously participated in double-blind rheumatoid arthritis studies. Pediatric subjects who entered study 20021618 with well-controlled arthritis symptoms 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 study was conducted at 36 sites in the United States and 2 sites in Canada. Study 20021618 was completed in December 2008, and the final clinical study report (CSR-79728) summarizing approximately 10 years of cumulative safety and efficacy results from study 20021618 is included in this post-approval commitment.

Study Design, Methodology, and Study Population
All subjects from the initial etanercept study 16.0016 were eligible to enrol in study 20021618. Although pediatric 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 subcutaneous (SC) injections either on the same day or 3 to 4 days apart, or as a single 0.8-mg/kg injection once weekly.

Fifty-eight (58, 84%) of the 69 pediatric subjects from study 16.0016 received etanercept in study 20021618 (Table 14-1.1.1B).

Table 14-1.1.B Subject Disposition

	Total Adults N=581	Pediatric Subjects N=58	All Subjects N=639
Subjects enrolled	581	58	639
Subjects enrolled and received at least 1 dose of etanercept	581	58	639
Subjects who discontinue at year 1[a]	62 (10.7)	8 (13.8)	70 (11.0)
Subjects who discontinue at year 2	40 (6.9)	4 (6.9)	44 (6.9)
Subjects who discontinue at year 3	34 (5.9)	6 (10.3)	40 (6.3)
Subjects who discontinue at year 4	29 (5.0)	3 (5.2)	32 (5.0)
Subjects who discontinue at year 5	37 (6.4)	2 (3.4)	39 (6.1)
Subjects who discontinue at year 6	31 (5.3)	3 (5.2)	34 (5.3)
Subjects who discontinue at year 7	35 (6.0)	5 (8.6)	40 (6.3)
Subjects who discontinue at year 8	18 (3.1)	7 (12.1)	25 (3.9)
Subjects who discontinue at year 9	31 (5.3)	1 (1.7)	32 (5.0)
Subjects who discontinue at year 10	21 (3.6)	2 (3.4)	23 (3.6)
Subjects who discontinue at year 11	22 (3.8)	1 (1.7)	23 (3.6)
Subjects who discontinue at year 12	3 (0.5)	1 (1.7)	4 (0.6)
Subjects who completed the study to closure[b]	218 (37.5)	15 (25.9)	233 (36.5)
Subjects who discontinued before study closure	363 (62.5)	43 (74.1)	406 (63.5)
Adverse Event	87 (15.0)	4 (6.9)	91 (14.2)
Completed Month 12 Only	0 (0.0)	1 (1.7)	1 (0.2)
Death	33 (5.7)	0 (0.0)	33 (5.2)
Lost To Follow-Up	23 (4.0)	4 (6.9)	27 (4.2)
Other	49 (8.4)	10 (17.2)	59 (9.2)
Physician Decision	39 (6.7)	5 (8.6)	44 (6.9)
Protocol Issues	14 (2.4)	3 (5.2)	17 (2.7)
Refusal-Subject	57 (9.8)	7 (12.1)	64 (10.0)
Response Status	61 (10.5)	9 (15.5)	70 (11.0)

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First subject enrolled: 31JUL1997. Last subject completed follow-up: 16DEC2008
Note: Percentages are based on the number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618
[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 10December 2008

Fifteen (15) of the 58 pediatric subjects who enrolled in study 20021618 completed the study and 43 discontinued treatment.

The most common reasons for discontinuation for pediatric subjects enrolled in study 20021618 were as follows: other (not related to safety, 10 subjects), response status (lack of efficacy in 9 subjects and remission in 3 subjects), and subject refusal (7 subjects).

Comment: A higher rate of discontinuation in children (74.1%) compared with adults (62.5%) was seen. Discontinuations due to AEs were less common in children compared with adults

The study 20021618 pediatric population consisted of 39 female and 19 male subjects aged 4 to 17 years (mean age 11.02 years).
CSR-79728 includes cumulative data from both studies 16.0016 and 20021618 (n=69), as well as study-specific data for study 20021618 alone (n=58).

Effectiveness Endpoints

The effectiveness endpoints for paediatric subjects in the study 20021618 database included

1. juvenile rheumatoid arthritis 30% definition of improvement (JRA-DOI 30), JRA-DOI 50, JRA-DOI 70, JRA-DOI 90, and JRA-DOI 100 responses;
2. JRA-DOI components at the effectiveness assessment visit: physician global assessment (PGA) of disease activity, subject global assessment (SGA) of disease activity, number of active joints, Childhood Health Assessment Questionnaire (CHAQ) score, C-reactive protein (CRP), and loss of motion (LOM) joint count;
3. other clinical endpoints at the effectiveness assessment visits: LOM plus tender/painful joint count, JRA-DOI 30, subject's pain visual analog scale (VAS), and duration of morning stiffness;
4. change from baseline in subject's assessment of pain; and
5. change from baseline in morning stiffness.

No imputation or estimation methods were used for missing values during the study (ie, a last-observation-carried-forward approach was not used).

Comment: This approach is endorsed.

Results

Pediatric subjects received up to 7 months of etanercept exposure in study 16.0016 before enrolling in study 20021618. During study 20021618, pediatric subjects maintained clinical improvements in disease activity (total active joints, LOM and pain/tender joints, pain assessment, PGA, patient/parent global assessment, CHAQ, and CRP) relative to baseline (Table 2-4).

The proportion of pediatric subjects achieving JRA-DOI 30, JRA-DOI 50, JRA-DOI 70, JRA-DOI 90, and JRA-DOI 100 remained relatively stable over 10 years (Table 2-4).

Table 2-4. Median Disease Activity Measures Over Time (Pediatric Subjects)

DMARD-refractory RA	Baseline[a] (n = 58)	Year 1 (n = 53)[b]	Year 2 (n = 47)[b]	Year 3 (n = 41)[b]	Year 4 (n = 32)[b]	Year 5 (n = 31)[b]	Year 6 (n = 27)[b]	Year 7 (n = 26)[b]	Year 8 (n = 22)[b]	Year 9 (n = 18)[b]	Year 10 (n = 14)
Total active joints[c]	36.5	16.0	19.5	21.0	16.0	18.0	9.0	11.0	7.0	12.0	3.0
LOM + pain/tender joints[d]	29.0	14.0	19.0	24.0	13.0	18.0	9.5	10.5	7.5	10.5	3.0
Pain Assessment[e]	3.6	0.3	0.8	0.5	0.6	0.6	0.7	0.5	0.1	0.2	0.3
Physician's global assessment[e]	6.5	2.0	1.0	1.0	1.0	1.0	2.0	1.0	1.0	0.5	0.0
Patient/Parent global assessment[e]	5.0	2.0	1.0	1.0	1.0	2.0	2.0	1.5	1.0	0.5	1.0
CRP[f]	3.4	0.3	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1
CHAQ[g]	2.0	1.0	0.9	0.8	0.5	0.8	0.5	0.4	0.3	0.0	0.0
Percentage of subjects achieving:											
JRA-DOI 30 (%)[h]	--	n = 41/52 (78.8)	n = 38/47 (80.9)	n = 28/41 (68.3)	n = 23/32 (71.9)	n = 17/31 (54.8)	n = 19/27 (70.4)	n = 14/22 (63.6)	n = 9/11 (81.8)	n = 5/6 (83.3)	n = 3/3 (100.0)
JRA-DOI 50 (%)[h]	--	n = 39/52 (75.0)	n = 34/47 (72.3)	n = 27/41 (65.9)	n = 21/32 (65.6)	n = 16/31 (51.6)	n = 19/27 (70.4)	n = 14/22 (63.6)	n = 9/11 (81.8)	n = 4/6 (66.7)	n = 3/3 (100.0)
JRA-DOI 70 (%)[h]	--	n = 30/52 (57.7)	n = 27/47 (57.4)	n = 24/41 (58.5)	n = 16/32 (50.0)	n = 13/31 (41.9)	n = 15/27 (55.6)	n = 13/22 (59.1)	n = 9/11 (81.8)	n = 4/6 (66.7)	n = 3/3 (100.0)
JRA-DOI 90 (%)[h]	--	n = 14/52 (26.9)	n = 15/47 (31.9)	n = 14/41 (34.1)	n = 11/32 (34.4)	n = 9/31 (29.0)	n = 6/27 (22.2)	n = 6/22 (27.3)	n = 5/11 (45.5)	n = 4/6 (66.7)	n = 3/3 (100.0)
JRA-DOI 100 (%)[h]	--	n = 10/52 (19.2)	n = 7/47 (14.9)	n = 4/41 (9.8)	n = 5/32 (15.6)	n = 4/31 (12.9)	n = 4/27 (14.8)	n = 2/22 (9.1)	n = 1/11 (9.1)	n = 3/6 (50.0)	n = 2/3 (66.7)

JRA-DOI 30, JRA-DOI 50, JRA-DOI 70, JRA-DOI 90, and JRA-DOI 100 = improvement from baseline of at least 30%, 50%,70%, 90%, or 100%, respectively, in 3 of the 6 core set variables with no more than 1 of the remaining variables worsening by > 30%; CHAQ = Childhood Health Assessment Questionnaire; CRP = C-reactive protein; DMARD-refractory RA = disease-modifying antirheumatic drug-refractory rheumatoid arthritis; ESR = erythrocyte sedimentation rate; LOM = limitation of motion; n = number of subjects

[a] Baseline from Study 016.0016
[b] Values were not available for all subjects at all time points
[c] Scale 0 to 74
[d] Scale 0 to 71
[e] 0 = best, 10 = worst
[f] A lower CRP value indicates lower levels of inflammation (normal range: 0 to 0.79 mg/dL [EIA], 0 to 0.287 mg/dL [NHS])
[g] 0 = best, 3 = worst; in source Table 14-3.10.A, this measure is referred to as HAQ-DI
[h] DOI Responders: per Giannini et al. 1997

Created on 26 May 2009 from Table 14-3.10.A

Comment:

While it is likely that efficacy was maintained in those who remained on etanercept, it is difficult to evaluate long-term efficacy after year 6. The number of subjects for whom there was efficacy data available after year 6 constitutes a progressively smaller percentage of the patients still in the study at those time points.

At year 6, 27/27 were evaluable; year 7, 22/26; year 8, 11/22; year 9, 6/18 and for year 10 only 3/14 cases had efficacy data available. Therefore while the statement that the proportion of paediatric subjects achieving JRA-DOI 30, JRA-DOI 50, JRA-DOI 70, JRA-DOI 90, and JRA-DOI 100 remained relatively

stable over 10 years is correct in terms of percentages, the absolute numbers evaluable make the data less definitive. The MAH is requested to explain why such little efficacy data was available in the later years of the study.

Safety

The safety endpoints for the study-specific database (20021618) included exposure to etanercept, vital signs and physical examinations, adverse events, hematology profile, chemistry profile, urinalysis, premature discontinuations, deaths, serious adverse events (SAEs), anti-etanercept antibodies, and autoimmune features checklist. Throughout the initial study 16.0016 and the first year of study 20021618, adverse events (serious and nonserious) were collected and analyzed. After the first year of study 20021618, data were collected 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).

SAEs were classified using a modified version of the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) dictionary. In previous reports of long-term etanercept use, serious infections were defined as those requiring hospitalization or intravenous (IV) antibiotics. Because the only informational source for serious infections after the first year of study 20021618 was SAE reports, nonserious infections treated with IV antibiotics, but not requiring hospitalization, were not collected.

Opportunistic infections were defined based on the Centers for Disease Control (CDC) and Prevention definition of opportunistic infections, as described for patients with human immunodeficiency virus (CDC Wonder On-line Database, 1992). Exposure-adjusted rates of events per subject-year were calculated as total number of events reported, divided by total etanercept exposure (summed over subjects), excluding time elapsed between studies.

Safety Results

Fifty-eight (58, 84%) of the 69 pediatric subjects from study 16.0016 received etanercept in study 20021618. The total etanercept exposure for the 58 pediatric subjects in study 20021618 was **341.98 patient-years** (Table 14-6.4.1B).

Table 14-6.4.1.B Enbrel Annual Safety Summary - Exposure Adjusted

Year Event Type	Total Adults N=581 n (r)	Pediatric Subjects N=58 n (r)	All Subjects N=639 n (r)
Year 1			
Number of Subjects with At Least 1 Dose of ETN (N_1)	581	58	639
Total Number of Patient-Years on ETN with Gaps (E)	546.86	53.10	599.96
Serious Adverse Events	97 (17.74)	10 (18.83)	107 (17.83)
Malignancy (Including Lymphoma)	6 (1.10)	0 (0.0)	6 (1.00)
Lymphoma	2 (0.37)	0 (0.0)	2 (0.33)
Serious Infectious Events	32 (5.85)	3 (5.65)	35 (5.83)
Death	5 (0.91)	0 (0.0)	5 (0.83)
Year 2			
Number of Subjects with At Least 1 Dose of ETN (N_1)	516	50	566
Total Number of Patient-Years on ETN with Gaps (E)	496.27	48.15	544.42
Serious Adverse Events	92 (18.54)	16 (33.23)	108 (19.84)
Malignancy (Including Lymphoma)	3 (0.60)	0 (0.0)	3 (0.55)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)
Serious Infectious Events	26 (5.24)	6 (12.46)	32 (5.88)
Death	3 (0.60)	0 (0.0)	3 (0.55)
Year 3			
Number of Subjects with At Least 1 Dose of ETN (N_1)	477	46	523
Total Number of Patient-Years on ETN with Gaps (E)	459.26	42.89	502.15
Serious Adverse Events	67 (14.59)	3 (6.99)	70 (13.94)
Malignancy (Including Lymphoma)	8 (1.74)	0 (0.0)	8 (1.59)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)
Serious Infectious Events	19 (4.14)	0 (0.0)	19 (3.78)
Death	3 (0.65)	0 (0.0)	3 (0.60)
Year 4			
Number of Subjects with At Least 1 Dose of ETN (N_1)	443	40	483
Total Number of Patient-Years on ETN with Gaps (E)	429.68	38.36	468.04
Serious Adverse Events	71 (16.52)	4 (10.43)	75 (16.02)
Malignancy (Including Lymphoma)	8 (1.86)	0 (0.0)	8 (1.71)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)
Serious Infectious Events	24 (5.59)	1 (2.61)	25 (5.34)
Death	1 (0.23)	0 (0.0)	1 (0.21)
Year 5			
Number of Subjects with At Least 1 Dose of ETN (N_1)	413	37	450

N_1 = Number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618
E = patient-years
n = number of events
r = Exposure-adjusted event rate per 100 patient-years (n/E*100)
Only includes events within 30 days of last dose, including events with outcome of death. Includes recurrent malignancies (including lymphomas)
Death events include death dates only within 30 days of the last dose

Table 14-6.4.1.B Enbrel Annual Safety Summary - Exposure Adjusted

Year Event Type	Total Adults N=581 n (r)	Pediatric Subjects N=58 n (r)	All Subjects N=639 n (r)
Year 5			
Total Number of Patient-Years on ETN with Gaps (E)	394.19	34.69	428.88
Serious Adverse Events	66 (16.74)	2 (5.76)	68 (15.86)
Malignancy (Including Lymphoma)	9 (2.28)	0 (0.0)	9 (2.10)
Lymphoma	3 (0.76)	0 (0.0)	3 (0.70)
Serious Infectious Events	17 (4.31)	0 (0.0)	17 (3.96)
Death	2 (0.51)	0 (0.0)	2 (0.47)
Year 6			
Number of Subjects with At Least 1 Dose of ETN (N_1)	377	34	411
Total Number of Patient-Years on ETN with Gaps (E)	363.35	31.59	394.94
Serious Adverse Events	87 (23.94)	2 (6.33)	89 (22.53)
Malignancy (Including Lymphoma)	1 (0.28)	0 (0.0)	1 (0.25)
Lymphoma	1 (0.28)	0 (0.0)	1 (0.25)
Serious Infectious Events	14 (3.85)	0 (0.0)	14 (3.54)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Year 7			
Number of Subjects with At Least 1 Dose of ETN (N_1)	346	29	375
Total Number of Patient-Years on ETN with Gaps (E)	330.30	27.04	357.34
Serious Adverse Events	93 (28.16)	3 (11.09)	96 (26.86)
Malignancy (Including Lymphoma)	6 (1.82)	0 (0.0)	6 (1.68)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)
Serious Infectious Events	15 (4.54)	1 (3.70)	16 (4.48)
Death	2 (0.61)	0 (0.0)	2 (0.56)
Year 8			
Number of Subjects with At Least 1 Dose of ETN (N_1)	312	26	338
Total Number of Patient-Years on ETN with Gaps (E)	302.14	22.64	324.78
Serious Adverse Events	98 (32.43)	2 (8.83)	100 (30.79)
Malignancy (Including Lymphoma)	4 (1.32)	0 (0.0)	4 (1.23)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)
Serious Infectious Events	22 (7.28)	0 (0.0)	22 (6.77)
Death	3 (0.99)	0 (0.0)	3 (0.92)
Year 9			
Number of Subjects with At Least 1 Dose of ETN (N_1)	294	18	312

N_1 = Number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618
E = patient-years
n = number of events
r = Exposure-adjusted event rate per 100 patient-years (n/E*100)
Only includes events within 30 days of last dose, including events with outcome of death. Includes recurrent malignancies (including lymphomas)
Death events include death dates only within 30 days of the last dose

Table 14-6.4.1.B Enbrel Annual Safety Summary - Exposure Adjusted

Year Event Type	Total Adults N=581 n (r)	Pediatric Subjects N=58 n (r)	All Subjects N=639 n (r)
Year 9			
Total Number of Patient-Years on ETN with Gaps (E)	279.85	18.00	297.85
Serious Adverse Events	88 (31.45)	1 (5.56)	89 (29.88)
Malignancy (Including Lymphoma)	7 (2.50)	0 (0.0)	7 (2.35)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)
Serious Infectious Events	18 (6.43)	0 (0.0)	18 (6.04)
Death	2 (0.71)	0 (0.0)	2 (0.67)
Year 10			
Number of Subjects with At Least 1 Dose of ETN (N_1)	261	18	279
Total Number of Patient-Years on ETN with Gaps (E)	252.02	16.93	268.94
Serious Adverse Events	53 (21.03)	1 (5.91)	54 (20.08)
Malignancy (Including Lymphoma)	2 (0.79)	0 (0.0)	2 (0.74)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)
Serious Infectious Events	15 (5.95)	0 (0.0)	15 (5.58)
Death	1 (0.40)	0 (0.0)	1 (0.37)
Year 11			
Number of Subjects with At Least 1 Dose of ETN (N_1)	238	15	253
Total Number of Patient-Years on ETN with Gaps (E)	173.52	8.60	182.12
Serious Adverse Events	33 (19.02)	0 (0.0)	33 (18.12)
Malignancy (Including Lymphoma)	3 (1.73)	0 (0.0)	3 (1.65)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)
Serious Infectious Events	7 (4.03)	0 (0.0)	7 (3.84)
Death	1 (0.58)	0 (0.0)	1 (0.55)
Year 12			
Number of Subjects with At Least 1 Dose of ETN (N_1)	44	0	44
Total Number of Patient-Years on ETN with Gaps (E)	5.63	0	5.63
Serious Adverse Events	0 (0.0)	0 (0.0)	0 (0.0)
Malignancy (Including Lymphoma)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)
Serious Infectious Events	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Total			
Number of Subjects with At Least 1 Dose of ETN (N_1)	581	58	639

N_1 = Number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618
E = patient-years
n = number of events
r = Exposure-adjusted event rate per 100 patient-years (n/E*100)
Only includes events within 30 days of last dose, including events with outcome of death. Includes recurrent malignancies (including lymphomas)
Death events include death dates only within 30 days of the last dose

Table 14-6.4.1.B Enbrel Annual Safety Summary - Exposure Adjusted

Year Event Type	Total Adults N=581 n (r)	Pediatric Subjects N=58 n (r)	All Subjects N=639 n (r)
Total			
Total Number of Patient-Years on ETN with Gaps (E)	4033.07	341.98	4375.05
Serious Adverse Events	845 (20.95)	44 (12.87)	889 (20.32)
Malignancy (Including Lymphoma)	57 (1.41)	0 (0.0)	57 (1.30)
Lymphoma	6 (0.15)	0 (0.0)	6 (0.14)
Serious Infectious Events	209 (5.18)	11 (3.22)	220 (5.03)
Death	23 (0.57)	0 (0.0)	23 (0.53)

N_1 = Number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618
E = patient-years
n = number of events
r = Exposure-adjusted event rate per 100 patient-years (n/E*100)
Only includes events within 30 days of last dose, including events with outcome of death. Includes recurrent malignancies (including lymphomas)
Death events include death dates only within 30 days of the last dose

Comment: This change in the classification of serious infections could lead to a reduction in numbers due to the change in classification after the first year. However from year 2 onwards a comparison of the rates of serious infections is possible. As can be seen from Table 14-6.4.1.B the incidence of serious infections in the paediatric population did not show a trend of increasing over time, although the absolute number of subjects declined each year, and there were no serious infections in the paediatric group after year 8.

The mean paediatric exposure to etanercept was 614.2 doses (mean) over 2153.6 days (mean).

Five (5) pediatric subjects were withdrawn from study 20021618 because of the following adverse events:
JRA flare in 1 subject;
purpura fulminans in 1 subject;
skin disorder and fibro tendon in 1 subject;
infection/infection super in 1 subject; and
diarrhea, vomiting, bone disorder, and meningitis in 1 subject

The rate of SAEs in the pediatric subjects remained relatively constant over time in study 20021618 with the highest rates observed in years 1 and 2 (Table 14-6.4.1B).

A total of 44 SAEs were reported in 16 pediatric subjects (27.6% of subjects; 12.87 events per 100 subject-years) (Tables 14-6.1.1B and 14-6.3.1B).

Table 14-6.3.1.B Exposure-adjusted Rate of Serious Adverse Events by Body System and Preferred Term in Descending Frequency

Body System Preferred Term	Total Adults n (r)	Pediatric Subjects n (r)	All Subjects n (r)
Number of subjects with at least 1 dose of ETN	N=581	N=58	N=639
Total number of patient-years on ETN with gaps	E=4033.07	E=341.98	E=4375.05
Number of Serious Adverse Events	845 (20.95)	44 (12.87)	889 (20.32)
Body as a Whole	241 (5.98)	17 (4.97)	258 (5.90)
React Aggrav	32 (0.79)	3 (0.88)	35 (0.80)
Cellulitis	33 (0.82)	0 (0.0)	33 (0.75)
Infect	25 (0.62)	2 (0.58)	27 (0.62)
Injury Accid	18 (0.45)	0 (0.0)	18 (0.41)
Sepsis	17 (0.42)	1 (0.29)	18 (0.41)
Pain Chest	17 (0.42)	0 (0.0)	17 (0.39)
Infect Bact	10 (0.25)	1 (0.29)	11 (0.25)
Abscess	10 (0.25)	0 (0.0)	10 (0.23)
Surgical Procedure	10 (0.25)	0 (0.0)	10 (0.23)
Carcinoma	7 (0.17)	0 (0.0)	7 (0.16)
Pain Abdo	3 (0.07)	4 (1.17)	7 (0.16)
Pain Back	7 (0.17)	0 (0.0)	7 (0.16)
Device Malfunction	6 (0.15)	0 (0.0)	6 (0.14)
Fever	5 (0.12)	1 (0.29)	6 (0.14)
Asthenia	4 (0.10)	0 (0.0)	4 (0.09)
Death	4 (0.10)	0 (0.0)	4 (0.09)
Pain	4 (0.10)	0 (0.0)	4 (0.09)
Anaphyl	3 (0.07)	0 (0.0)	3 (0.07)
Infect Viral	2 (0.05)	1 (0.29)	3 (0.07)
Malignant Melanoma	3 (0.07)	0 (0.0)	3 (0.07)
Cyst	2 (0.05)	0 (0.0)	2 (0.05)
Disease Progression	1 (0.02)	1 (0.29)	2 (0.05)
Flu Synd	2 (0.05)	0 (0.0)	2 (0.05)
Headache	2 (0.05)	0 (0.0)	2 (0.05)
Hem Retroperit	2 (0.05)	0 (0.0)	2 (0.05)
Hernia	2 (0.05)	0 (0.0)	2 (0.05)
Peritonitis	1 (0.02)	1 (0.29)	2 (0.05)
Sarcoidosis	2 (0.05)	0 (0.0)	2 (0.05)
Allerg React	0 (0.0)	1 (0.29)	1 (0.02)
Blood Cult Positive	1 (0.02)	0 (0.0)	1 (0.02)
Infect Fung	1 (0.02)	0 (0.0)	1 (0.02)

N = Number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618
E = patient-years
n = number of events
r = Exposure-adjusted event rate per 100 patient-years (n/E*100)
Only includes events within 30 days of last dose, including events with outcome of death

Table 14-6.3.1.B Exposure-adjusted Rate of Serious Adverse Events by Body System and Preferred Term in Descending Frequency

Body System Preferred Term	Total Adults n (r)	Pediatric Subjects n (r)	All Subjects n (r)
Body as a Whole (Cont)			
Malaise	1 (0.02)	0 (0.0)	1 (0.02)
Necro	1 (0.02)	0 (0.0)	1 (0.02)
Neopl	1 (0.02)	0 (0.0)	1 (0.02)
Pain Neck	1 (0.02)	0 (0.0)	1 (0.02)
Shock	0 (0.0)	1 (0.29)	1 (0.02)
Sudden Death	1 (0.02)	0 (0.0)	1 (0.02)
Musculoskeletal System	166 (4.12)	17 (4.97)	183 (4.18)
Arthritis Rheumat	41 (1.02)	12 (3.51)	53 (1.21)
Bone Fract Spontan	36 (0.89)	0 (0.0)	36 (0.82)
Arthritis	19 (0.47)	2 (0.58)	21 (0.48)
Bone Dis	16 (0.40)	1 (0.29)	17 (0.39)
Joint Dis	17 (0.42)	0 (0.0)	17 (0.39)
Arthritis Pyogen	9 (0.22)	0 (0.0)	9 (0.21)
Arthralgia	6 (0.15)	2 (0.58)	8 (0.18)
Arthrosis	3 (0.07)	0 (0.0)	3 (0.07)
Bursa Pyogen	3 (0.07)	0 (0.0)	3 (0.07)
Herniated Disc	3 (0.07)	0 (0.0)	3 (0.07)
Osteomyelitis	3 (0.07)	0 (0.0)	3 (0.07)
Synovitis	3 (0.07)	0 (0.0)	3 (0.07)
Bursitis	2 (0.05)	0 (0.0)	2 (0.05)
Hem Muscle	1 (0.02)	0 (0.0)	1 (0.02)
Joint Effusion	1 (0.02)	0 (0.0)	1 (0.02)
Myalgia	1 (0.02)	0 (0.0)	1 (0.02)
Myopathy	1 (0.02)	0 (0.0)	1 (0.02)
Myositis	1 (0.02)	0 (0.0)	1 (0.02)
Cardiovascular System	145 (3.60)	1 (0.29)	146 (3.34)
Infarct Myocard	25 (0.62)	0 (0.0)	25 (0.57)
Heart Fail	18 (0.45)	0 (0.0)	18 (0.41)
Coronary Art Dis	13 (0.32)	0 (0.0)	13 (0.30)
Cerebrovasc Accid	11 (0.27)	0 (0.0)	11 (0.25)
Fibrillat Atr	8 (0.20)	0 (0.0)	8 (0.18)
Emb Pulm	6 (0.15)	0 (0.0)	6 (0.14)
Heart Arrest	6 (0.15)	0 (0.0)	6 (0.14)
Syncope	4 (0.10)	1 (0.29)	5 (0.11)
Arrhythmia	4 (0.10)	0 (0.0)	4 (0.09)

N = Number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618
E = patient-years
n = number of events
r = Exposure-adjusted event rate per 100 patient-years (n/E*100)
Only includes events within 30 days of last dose, including events with outcome of death

Table 14-6.3.1.B Exposure-adjusted Rate of Serious Adverse Events by Body System and Preferred Term in Descending Frequency

Body System Preferred Term	Total Adults n (r)	Pediatric Subjects n (r)	All Subjects n (r)
Cardiovascular System (Cont)			
Cardiovasc Dis	4 (0.10)	0 (0.0)	4 (0.09)
Chf Aggravated	4 (0.10)	0 (0.0)	4 (0.09)
Hypotens	4 (0.10)	0 (0.0)	4 (0.09)
Thrombophleb Deep	4 (0.10)	0 (0.0)	4 (0.09)
Ischemia Cerebr	3 (0.07)	0 (0.0)	3 (0.07)
Angina Pectoris	2 (0.05)	0 (0.0)	2 (0.05)
Anomaly Vascul	2 (0.05)	0 (0.0)	2 (0.05)
Hem	2 (0.05)	0 (0.0)	2 (0.05)
Hypertens	2 (0.05)	0 (0.0)	2 (0.05)
Myocarditis	2 (0.05)	0 (0.0)	2 (0.05)
Occlus	2 (0.05)	0 (0.0)	2 (0.05)
Pericarditis	2 (0.05)	0 (0.0)	2 (0.05)
Tachycardia	2 (0.05)	0 (0.0)	2 (0.05)
Aneurysm Intracran	1 (0.02)	0 (0.0)	1 (0.02)
Arrhythmia Atr	1 (0.02)	0 (0.0)	1 (0.02)
Arrhythmia Nod	1 (0.02)	0 (0.0)	1 (0.02)
Cardiomyopathy	1 (0.02)	0 (0.0)	1 (0.02)
Fibrillat Vent	1 (0.02)	0 (0.0)	1 (0.02)
Flutter Atr	1 (0.02)	0 (0.0)	1 (0.02)
Hypertens Pulm	1 (0.02)	0 (0.0)	1 (0.02)
Ischemia Myocard	1 (0.02)	0 (0.0)	1 (0.02)
Purpura Vasc	1 (0.02)	0 (0.0)	1 (0.02)
Tachycardia Supvent	1 (0.02)	0 (0.0)	1 (0.02)
Tachycardia Vent	1 (0.02)	0 (0.0)	1 (0.02)
Throm	1 (0.02)	0 (0.0)	1 (0.02)
Throm Art	1 (0.02)	0 (0.0)	1 (0.02)
Throm Cerebr	1 (0.02)	0 (0.0)	1 (0.02)
Vasc Dis Periph	1 (0.02)	0 (0.0)	1 (0.02)
Respiratory System	90 (2.23)	1 (0.29)	91 (2.08)
Pneumonia	45 (1.12)	0 (0.0)	45 (1.03)
Carcinoma Lung	10 (0.25)	0 (0.0)	10 (0.23)
Dyspnea	6 (0.15)	0 (0.0)	6 (0.14)
Bronchitis	5 (0.12)	0 (0.0)	5 (0.11)
Respirat Dis	4 (0.10)	0 (0.0)	4 (0.09)
Upper Resp Infect	4 (0.10)	0 (0.0)	4 (0.09)
Resp Dis Syndrome	2 (0.05)	1 (0.29)	3 (0.07)

N = Number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618
E = patient-years
n = number of events
r = Exposure-adjusted event rate per 100 patient-years (n/E*100)
Only includes events within 30 days of last dose, including events with outcome of death

Table 14-6.3.1.B Exposure-adjusted Rate of Serious Adverse Events by Body System and Preferred Term in Descending Frequency

Body System Preferred Term	Total Adults n (r)	Pediatric Subjects n (r)	All Subjects n (r)
Respiratory System (Cont)			
Apnea	2 (0.05)	0 (0.0)	2 (0.05)
Lung Dis	2 (0.05)	0 (0.0)	2 (0.05)
Sinusitis	2 (0.05)	0 (0.0)	2 (0.05)
Asthma	1 (0.02)	0 (0.0)	1 (0.02)
Carcinoma Larynx	1 (0.02)	0 (0.0)	1 (0.02)
Edema Lung	1 (0.02)	0 (0.0)	1 (0.02)
Effus Pleural	1 (0.02)	0 (0.0)	1 (0.02)
Epistaxis	1 (0.02)	0 (0.0)	1 (0.02)
Hemoptysis	1 (0.02)	0 (0.0)	1 (0.02)
Pleural Dis	1 (0.02)	0 (0.0)	1 (0.02)
Pneumonia Aspir	1 (0.02)	0 (0.0)	1 (0.02)
Digestive System	76 (1.88)	2 (0.58)	78 (1.78)
Hem Gi	9 (0.22)	0 (0.0)	9 (0.21)
Carcinoma Gi	7 (0.17)	0 (0.0)	7 (0.16)
Cholelith	6 (0.15)	0 (0.0)	6 (0.14)
Colitis	6 (0.15)	0 (0.0)	6 (0.14)
Cholecyst	5 (0.12)	0 (0.0)	5 (0.11)
Gastritis	4 (0.10)	0 (0.0)	4 (0.09)
Obstruct Intest	4 (0.10)	0 (0.0)	4 (0.09)
Ulcer Esoph	4 (0.10)	0 (0.0)	4 (0.09)
Gi Dis	3 (0.07)	0 (0.0)	3 (0.07)
Hepatitis	3 (0.07)	0 (0.0)	3 (0.07)
Appendicitis	1 (0.02)	1 (0.29)	2 (0.05)
Colitis Pseudomem	2 (0.05)	0 (0.0)	2 (0.05)
Colitis Ulcer	2 (0.05)	0 (0.0)	2 (0.05)
Constip	2 (0.05)	0 (0.0)	2 (0.05)
Diarrhea	2 (0.05)	0 (0.0)	2 (0.05)
Gastroenteritis	2 (0.05)	0 (0.0)	2 (0.05)
Intest Large Per	2 (0.05)	0 (0.0)	2 (0.05)
Liver Fail	2 (0.05)	0 (0.0)	2 (0.05)
Abscess Periodont	0 (0.0)	1 (0.29)	1 (0.02)
Anomaly Gi	1 (0.02)	0 (0.0)	1 (0.02)
Carcinoma Liver	1 (0.02)	0 (0.0)	1 (0.02)
Dysphagia	1 (0.02)	0 (0.0)	1 (0.02)
Gastritis Hem	1 (0.02)	0 (0.0)	1 (0.02)
Hem Rectal	1 (0.02)	0 (0.0)	1 (0.02)

N = Number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618
E = patient-years
n = number of events
r = Exposure-adjusted event rate per 100 patient-years (n/E*100)
Only includes events within 30 days of last dose, including events with outcome of death

Table 14-6.3.1.B Exposure-adjusted Rate of Serious Adverse Events by Body System and Preferred Term in Descending Frequency

Body System Preferred Term	Total Adults n (r)	Pediatric Subjects n (r)	All Subjects n (r)
Digestive System (Cont)			
Pancreatitis	1 (0.02)	0 (0.0)	1 (0.02)
Rectal Dis	1 (0.02)	0 (0.0)	1 (0.02)
Steno Esoph	1 (0.02)	0 (0.0)	1 (0.02)
Ulcer Stomach Hem	1 (0.02)	0 (0.0)	1 (0.02)
Vomit	1 (0.02)	0 (0.0)	1 (0.02)
Urogenital System	44 (1.09)	1 (0.29)	45 (1.03)
Carcinoma Breast	8 (0.20)	0 (0.0)	8 (0.18)
Pyelonephritis	7 (0.17)	1 (0.29)	8 (0.18)
Carcinoma Prostate	6 (0.15)	0 (0.0)	6 (0.14)
Infect Urin Tract	4 (0.10)	0 (0.0)	4 (0.09)
Kidney Fail Acute	4 (0.10)	0 (0.0)	4 (0.09)
Kidney Fail	3 (0.07)	0 (0.0)	3 (0.07)
Carcinoma Bladder	2 (0.05)	0 (0.0)	2 (0.05)
Kidney Calculus	2 (0.05)	0 (0.0)	2 (0.05)
Kidney Func Abnorm	2 (0.05)	0 (0.0)	2 (0.05)
Carcinoma Cervix	1 (0.02)	0 (0.0)	1 (0.02)
Carcinoma Cervix Situ	1 (0.02)	0 (0.0)	1 (0.02)
Endometr Dis	1 (0.02)	0 (0.0)	1 (0.02)
Hem Vaginal	1 (0.02)	0 (0.0)	1 (0.02)
Pain Kidney	1 (0.02)	0 (0.0)	1 (0.02)
Vaginitis	1 (0.02)	0 (0.0)	1 (0.02)
Hemic & Lymphatic System	26 (0.64)	2 (0.58)	28 (0.64)
Anemia	6 (0.15)	0 (0.0)	6 (0.14)
Lymphoma	6 (0.15)	0 (0.0)	6 (0.14)
Coagul Dis	1 (0.02)	1 (0.29)	2 (0.05)
Leukemia Chron Lympho	2 (0.05)	0 (0.0)	2 (0.05)
Pancytopenia	2 (0.05)	0 (0.0)	2 (0.05)
Blood Dyscrasia	0 (0.0)	1 (0.29)	1 (0.02)
Cyanosis	1 (0.02)	0 (0.0)	1 (0.02)
Hypovolem	1 (0.02)	0 (0.0)	1 (0.02)
Leukemia Acute Myelo	1 (0.02)	0 (0.0)	1 (0.02)
Leukopenia	1 (0.02)	0 (0.0)	1 (0.02)
Myeloprolif Dis	1 (0.02)	0 (0.0)	1 (0.02)
Neutropenia	1 (0.02)	0 (0.0)	1 (0.02)
Purpura	1 (0.02)	0 (0.0)	1 (0.02)

N = Number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618
E = patient-years
n = number of events
r = Exposure-adjusted event rate per 100 patient-years (n/E*100)
Only includes events within 30 days of last dose, including events with outcome of death

Table 14-6.3.1.B Exposure-adjusted Rate of Serious Adverse Events by Body System and Preferred Term in Descending Frequency

Body System Preferred Term	Total Adults n (r)	Pediatric Subjects n (r)	All Subjects n (r)
Hemic & Lymphatic System (Cont)			
Spleen Dis	1 (0.02)	0 (0.0)	1 (0.02)
Thrombocytopenia	1 (0.02)	0 (0.0)	1 (0.02)
Metabolic & Nutritional Disorders	21 (0.52)	0 (0.0)	21 (0.48)
Dehydrat	8 (0.20)	0 (0.0)	8 (0.18)
Hypoglycem	3 (0.07)	0 (0.0)	3 (0.07)
Hypokalem	3 (0.07)	0 (0.0)	3 (0.07)
Healing Abnorm	2 (0.05)	0 (0.0)	2 (0.05)
Hyponatrem	2 (0.05)	0 (0.0)	2 (0.05)
Edema	1 (0.02)	0 (0.0)	1 (0.02)
Edema Periph	1 (0.02)	0 (0.0)	1 (0.02)
Hypoglycem React	1 (0.02)	0 (0.0)	1 (0.02)
Skin & Appendages	19 (0.47)	1 (0.29)	20 (0.46)
Carcinoma Skin	7 (0.17)	0 (0.0)	7 (0.16)
Ulcer Skin	6 (0.15)	0 (0.0)	6 (0.14)
Herpes Zoster	3 (0.07)	1 (0.29)	4 (0.09)
Angioedema	2 (0.05)	0 (0.0)	2 (0.05)
Skin Dis	1 (0.02)	0 (0.0)	1 (0.02)
Nervous System	14 (0.35)	1 (0.29)	15 (0.34)
Confus	2 (0.05)	0 (0.0)	2 (0.05)
Dizziness	2 (0.05)	0 (0.0)	2 (0.05)
Manic Depress React	2 (0.05)	0 (0.0)	2 (0.05)
Meningitis	1 (0.02)	1 (0.29)	2 (0.05)
Neopl Cns	2 (0.05)	0 (0.0)	2 (0.05)
Neuropathy	2 (0.05)	0 (0.0)	2 (0.05)
Depression	1 (0.02)	0 (0.0)	1 (0.02)
Paresthesia	1 (0.02)	0 (0.0)	1 (0.02)
Sclerosis Mult	1 (0.02)	0 (0.0)	1 (0.02)
Endocrine System	3 (0.07)	1 (0.29)	4 (0.09)
Adren Insuffic	2 (0.05)	0 (0.0)	2 (0.05)
Diabetes Mell	0 (0.0)	1 (0.29)	1 (0.02)
Neopl Thyr	1 (0.02)	0 (0.0)	1 (0.02)

N = Number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618
E = patient-years
n = number of events
r = Exposure-adjusted event rate per 100 patient-years (n/E*100)
Only includes events within 30 days of last dose, including events with outcome of death

Most of the SAEs occurred in only 1 pediatric subject each, with the exception of rheumatoid arthritis which occurred in 6 (10.3%) pediatric subjects, and aggravated reaction, infection, abdominal pain, and arthralgia which occurred in 2 (3.4%) subjects each.

The rate of serious infections in the pediatric subjects remained relatively constant over time with increasing exposure to etanercept (Table 14-6.4.1B).

A total of 11 serious infections were reported in 8 pediatric subjects (13.8% of subjects; 3.22 events per 100 subject-years) (Tables 14-6.1.2B and 14-6.3.2B).

Table 14-6.1.2.B Subject Incidence of Serious Infectious Events by Body System and Preferred Term in Descending Frequency

BODY SYSTEM Preferred Term	Total Adults (N = 581) n (%)	Pediatric Subjects (N = 58) n (%)	All Subjects (N = 639) n (%)
Number of Subjects Reporting Serious Infections	114 (19.6)	8 (13.8)	122 (19.1)
BODY AS A WHOLE	62 (10.7)	5 (8.6)	67 (10.5)
Cellulitis	21 (3.6)	0 (0)	21 (3.3)
Infect	18 (3.1)	2 (3.4)	20 (3.1)
Sepsis	16 (2.8)	1 (1.7)	17 (2.7)
Infect Bact	9 (1.5)	1 (1.7)	10 (1.6)
Abscess	8 (1.4)	0 (0)	8 (1.3)
Fever	4 (0.7)	0 (0)	4 (0.6)
Infect Viral	2 (0.3)	1 (1.7)	3 (0.5)
Flu Synd	2 (0.3)	0 (0)	2 (0.3)
Peritonitis	1 (0.2)	1 (1.7)	2 (0.3)
Blood Cult Positive	1 (0.2)	0 (0)	1 (0.2)
Infect Fung	1 (0.2)	0 (0)	1 (0.2)

N = Number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618
Only includes events within 30 days of last dose, including events with outcome of death

Table 14-6.1.2.B Subject Incidence of Serious Infectious Events by Body System and Preferred Term in Descending Frequency

BODY SYSTEM Preferred Term	Total Adults (N = 581) n (%)	Pediatric Subjects (N = 58) n (%)	All Subjects (N = 639) n (%)
RESPIRATORY SYSTEM	41 (7.1)	0 (0)	41 (6.4)
Pneumonia	37 (6.4)	0 (0)	37 (5.8)
Bronchitis	3 (0.5)	0 (0)	3 (0.5)
Sinusitis	2 (0.3)	0 (0)	2 (0.3)
Upper Resp Infect	2 (0.3)	0 (0)	2 (0.3)
DIGESTIVE SYSTEM	17 (2.9)	2 (3.4)	19 (3.0)
Colitis	6 (1.0)	0 (0)	6 (0.9)
Cholecyst	5 (0.9)	0 (0)	5 (0.8)
Appendicitis	1 (0.2)	1 (1.7)	2 (0.3)
Colitis Pseudomem	2 (0.3)	0 (0)	2 (0.3)
Gastroenteritis	2 (0.3)	0 (0)	2 (0.3)
Abscess Periodont	0 (0)	1 (1.7)	1 (0.2)
Diarrhea	1 (0.2)	0 (0)	1 (0.2)
Hepatitis	1 (0.2)	0 (0)	1 (0.2)

N = Number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618
Only includes events within 30 days of last dose, including events with outcome of death

Table 14-6.1.2.B Subject Incidence of Serious Infectious Events by Body System and Preferred Term in Descending Frequency

BODY SYSTEM Preferred Term	Total Adults (N = 581) n (%)	Pediatric Subjects (N = 58) n (%)	All Subjects (N = 639) n (%)
MUSCULOSKELETAL SYSTEM	12 (2.1)	0 (0)	12 (1.9)
Arthritis Pyogen	7 (1.2)	0 (0)	7 (1.1)
Bursa Pyogen	3 (0.5)	0 (0)	3 (0.5)
Osteomyelitis	3 (0.5)	0 (0)	3 (0.5)
Bursitis	1 (0.2)	0 (0)	1 (0.2)
UROGENITAL SYSTEM	9 (1.5)	1 (1.7)	10 (1.6)
Pyelonephritis	5 (0.9)	1 (1.7)	6 (0.9)
Infect Urin Tract	3 (0.5)	0 (0)	3 (0.5)
Vaginitis	1 (0.2)	0 (0)	1 (0.2)
SKIN & APPENDAGES	3 (0.5)	1 (1.7)	4 (0.6)
Herpes Zoster	3 (0.5)	1 (1.7)	4 (0.6)
CARDIOVASCULAR SYSTEM	2 (0.3)	0 (0)	2 (0.3)
Cerebrovasc Accid	1 (0.2)	0 (0)	1 (0.2)

N = Number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618
Only includes events within 30 days of last dose, including events with outcome of death

Table 14-6.1.2.B Subject Incidence of Serious Infectious Events by Body System and Preferred Term in Descending Frequency

BODY SYSTEM Preferred Term	Total Adults (N = 581) n (%)	Pediatric Subjects (N = 58) n (%)	All Subjects (N = 639) n (%)
CARDIOVASCULAR SYSTEM (Cont'd)			
Myocarditis	1 (0.2)	0 (0)	1 (0.2)
NERVOUS SYSTEM	1 (0.2)	1 (1.7)	2 (0.3)
Meningitis	1 (0.2)	1 (1.7)	2 (0.3)

N = Number of subjects who enrolled and received at least 1 dose of etanercept in Protocol 20021618
Only includes events within 30 days of last dose, including events with outcome of death

No malignancies, including lymphoma, were reported for pediatric subjects in study 20021618 (Table 14-6.4.1B).
No deaths were reported for pediatric subjects in study 20021618 (Table 14-6.4.1B).

Comment: No deaths, no malignancies and no increase in serious infections or SAEs over time were found in the paediatric population.

Several specific adverse events historically have been of increased interest in subjects receiving tumor necrosis factor antagonist therapies. These events include demyelinating diseases, opportunistic infections, cardiovascular events, and sepsis. One (1) case of sepsis was reported in a pediatric subject in study 20021618: an 8-year-old female subject experienced an SAE of sepsis in year 3 of study 20021618, after 810 exposure days to etanercept.

The event of sepsis resolved; however, ischemia of the left foot and distal leg required mid-calf amputation.
No cases of demyelinating disease, opportunistic infection, or cardiovascular disease were reported in pediatric subjects (Table 14-6.7A).

Table 14-6.7.A Subject Incidence of Demyelination Events by Body System and Preferred Term in Descending Frequency

BODY SYSTEM Preferred Term	Total Adults (N = 714) n (%)	Adults not in 160014 (N = 629) n (%)	Adults for 160014 only (N = 85) n (%)	Pediatric Subjects (N = 69) n (%)	All Etanercept (N = 783) n (%)
Number of Subjects Reporting Demyelination Events	1 (0.1)	1 (0.2)	0 (0)	0 (0)	1 (0.1)
NERVOUS SYSTEM	1 (0.1)	1 (0.2)	0 (0)	0 (0)	1 (0.1)
Sclerosis Mult	1 (0.1)	1 (0.2)	0 (0)	0 (0)	1 (0.1)

N = Number of subjects who enrolled and received at least 1 dose of etanercept
Only includes events within 30 days of last dose, including events with outcome of death

MAH CONCLUSIONS

The findings from study 20021618 suggest that long-term treatment with etanercept of pediatric subjects with disease-modifying antirheumatic disease (DMARD)-refractory JIA is associated with a favorable and consistent benefit/risk profile over time. The rates and types of SAEs and serious infections remained relatively constant over approximately 10 years of follow-up. There were no reports of malignancy or death. No previously unknown safety risks were identified as a result of this 10-year analysis. As reflected by the proportion of subjects achieving JRA-DOI 30, JRA-DOI 50, JRA-DOI 70, and JRA-DOI 90, the effectiveness response to etanercept was sustained over time.

In conclusion, these data are consistent with the known safety and efficacy profile of etanercept as described in the Summary of Product Characteristics (SPC) for the treatment of pediatric patients with DMARD-refractory JIA. The MAH considers the SPC to adequately communicate the risks and benefits of etanercept in this population, and therefore no changes to the SPC are proposed at this time.

CHMP's Conclusions on the paediatric safety and efficacy from study 20021618

Limited efficacy is available at later time points after year 6 for the paediatric subjects. The MAH are asked to comment.

However the safety profile of the paediatric data is consistent with what is known for etanercept and highlighted in the SPC. No change to the positive benefit:risk ratio for etanercept follows from this FUM. The data submitted in accordance with Article 46 is considered satisfactory and no changes to the SPC are requested.

II. RAPPORTEUR'S OVERALL CONCLUSION AND FURTHER ACTION IF REQUIRED

Overall Conclusion:

The data from the long-term study 20021618 has shown that the safety profile for paediatric subjects is consistent with what is known for etanercept. The data submitted in accordance with Article 46 is considered satisfactory and no changes to the SPC are requested.

No change to the positive benefit:risk ratio for etanercept follows from this FUM.

☒ PAC fulfilled with one outstanding question.

While it is likely that efficacy was maintained in those who remained on etanercept, it is difficult to evaluate long-term efficacy after year 6 from the paediatric data. The number of subjects for whom there was efficacy data available after year 6 constitutes a progressively smaller percentage of the patients still in the study at those time points.

The MAH is requested to explain why such little efficacy data was available in the later years of the study for the paediatric subjects.