11 January 2013
EMA/20003/2013
Committee for Medicinal Products for Human Use (CHMP)

Enbrel

etanercept

Procedure No. EMEA/H/C/000262/A46/134

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 paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

P46 134

Enbrel

EMEA/H/C/262

Marketing Authorisation Holder: Pfizer Limited

Rapporteur:	Robert Hemmings
Start of the procedure:	22.07.2012
Date of this report:	21.08.2012
Deadline for Rapporteur's AR:	21.08.2012
Deadline for CHMP member's comments:	05.09.2012

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Enbrel
INN (or common name) of the active substance(s):	Etanercept
MAH:	Pfizer Limited
Currently approved Indication(s)	Rheumatoid arthritis Polyarticular juvenile idiopathic arthritis Psoriatic arthritis Ankylosing spondylitis Plaque psoriasis Paediatric plaque psoriasis
Pharmaco-therapeutic group (ATC Code):	Immunosuppressants, Tumour necrosis factor alpha (TNF-α) inhibitors (L04AB01)
Pharmaceutical form(s) and strength(s):	25mg powder for solution for injection 25mg powder and solvent for solution for injection 50mg powder for solution for injection 50mg powder and solvent for solution for injection 25mg/ml powder and solvent for solution for injection for paediatric use 25 mg solution for injection in pre-filled syringe 50 mg solution for injection in pre-filled syringe

LIST OF ABBREVIATIONS

ANA	antinuclear antibody
AS	ankylosing spondylitis
BSA	body surface area
CDLQI	Children's Dermatology Life Quality Index
CRF	case report form
CRO	contract research organizations
CTC	Common Toxicity Criteria Version 2.0
CTCAE	Common Terminology Criteria for Adverse Events
DMARD	disease-modifying antirheumatic drug
GCP	Good Clinical Practice
HRQOL	health-related quality of life
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	interactive voice response system
JRA	juvenile rheumatoid arthritis
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PASI	Psoriasis Area and Severity Index
PASI 50	A 50% or greater improvement (ie, decrease) in PASI score compared to baseline
PASI 75	A 75% or greater improvement (ie, decrease) in PASI score compared to baseline
PASI 90	A 90% or greater improvement (ie, decrease) in PASI score compared to baseline
PPD	Pharmaceutical Product Development
sPGA	Static Physician Global Assessment (of psoriasis)
Q1 (Q3)	first quartile (third quartile)
QW	once weekly
RA	rheumatoid arthritis
SC	subcutaneous
SD	standard deviation
SE	standard error
TNF	tumor necrosis factor
TNFR	tumor necrosis factor receptor
TNFR:Fc	tumor necrosis factor receptor
USP	United States Pharmacopeia
VZV	aricella zoster virus

I. INTRODUCTION

Follow-up Measure:

Area	Description	Due Date
Clinical	FUM 134: The MAH should submit the results of the multicentre, open-label long term safety trial (study 20050111)	6 months after the completion of the study

The MAH states that the data does not require an update of the Product Information and this is agreed.

II. SCIENTIFIC DISCUSSION

Background

The original approval in pediatric psoriasis for subjects aged 8 to 17 years (Type II Variation EMEA/H/C/262/II/94 approved December 2008) was based on study 20030211. Study 20030211 was a randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and pharmacokinetics of etanercept 0.8 mg/kg (up to a maximum dose of 50 mg) once weekly (QW) versus placebo in children (aged 4 to 11 years) and adolescents (aged 12 to 17 years) with moderate to severe plaque psoriasis for up to 48 weeks. Per the Letter of Undertaking for Variation EMEA/H/C/262/II/94, the Marketing Authorisation Holder (MAH) agreed to submit the results of open-label study 20050111 within 6 months after completion of the study as a Post-Authorisation Commitment.

Study 20050111 is a multicenter, open-label extension study for up to 264 weeks (or until the quarterly visit after the subject's 18th birthday, whichever comes last) for pediatric subjects who participated in study 20030211. Data from the first 96 weeks of study 20050111 were provided to support the extension of the pediatric psoriasis indication to include patients from the age of 6 years (Type II Variation EMEA/H/C/262/II/134). Data through week 264 of study 20050111 are provided herein to fulfil the Post-Authorisation Commitment for Variation EMEA/H/C/262/II/94. There are 28 subjects who are continuing in study 20050111 until they reach 18 years of age; serious adverse events (SAEs) and static Physician's Global Assessment of psoriasis (sPGA) scores will be collected in these subjects and appended to the 264-week clinical study report.

II.1 Information on the pharmaceutical formulation used in the study

The pharmaceutical formulation used in this study was a sterile, lyophilized powder containing 25 mg etanercept, 40 mg mannitol, 10 mg sucrose and 1.2 mg tromethamine. The powder was reconstituted with 1 ml of sterile bacteriostatic water for injection (containing benzyl alcohol). This same formulation is approved in the EU; however, it is being replaced by a new low-strength, preservative-free lyophilized powder containing 10 mg etanercept for pediatric use. The new 10 mg strength of etanercept powder is reconstituted with plain sterile water for injection.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Subjects received 0.8 mg/kg (up to a maximum dose of 50 mg) of etanercept administered QW by SC injection using a maximum of 2 vials per dose. Lot numbers used in the study were : 0010008070, 0010035402, 916A070342, 916D052831, 916D067637, 916D104842, D044859, D048404, D091967.
Duration of Treatment: Up to 264 weeks

II.2 Clinical aspects

1. Introduction

The Clinical Study Report for 20050111 was provided. This was an open label extension study to evaluate safety of Etanercept in paediatric subjects with plaque psoriasis up to 264 weeks. Report Date: 01 June 2012

This study was designed to evaluate the long-term safety and efficacy of etanercept in pediatric subjects with moderate to severe plaque psoriasis for subjects who participated in controlled Study 20030211. This study was conducted at 38 sites in the United States and Canada.

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/ guidelines.

Study Period: 11 August 2005 (first subject enrolled) to 22 February 2012 (data cut-off date for this report). Date of last subject last visit was 19 December 2011, including the 30-day follow-up visit. This report comprises the main comprehensive, integrated analysis of Study 20050111 data. Per protocol amendment 4, 28 subjects are continuing treatment until they reach age 18; however, safety and efficacy assessments for these subjects will include, respectively, only serious adverse events (including serious infectious episodes) and sPGA using observed cases.

2. Clinical study

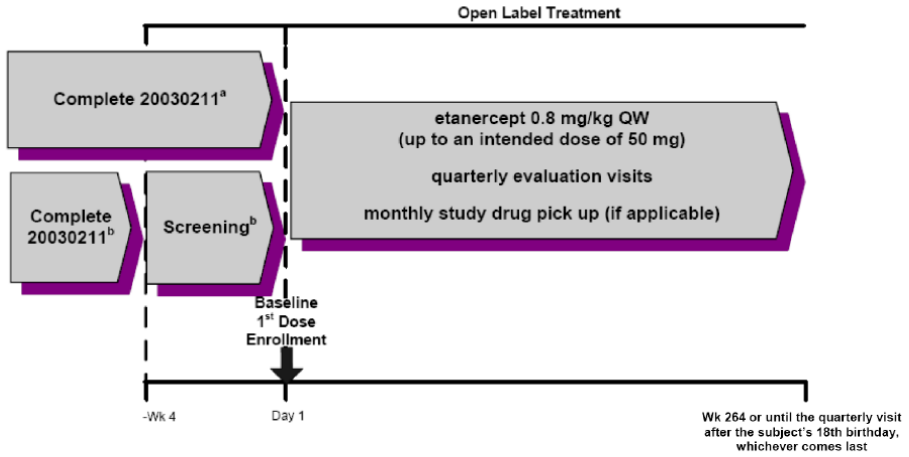
➢ Description

Study 20050111
The primary objective was to evaluate the safety of long-term administration of etanercept in pediatric subjects with moderate to severe plaque psoriasis. The secondary objective was to evaluate the long-term efficacy of etanercept administration in pediatric subjects with moderate to severe plaque psoriasis.

Methodology: This study was a multicenter, open-label extension study for subjects who participated in Study 20030211. Subjects received etanercept 0.8 mg/kg (up to a maximum dose of 50 mg) subcutaneously (SC) once weekly (QW) for 264 weeks. Subjects with a Static Physician Global Assessment (sPGA) score of clear (0) or almost clear (1) were allowed to stop treatment with etanercept at or after week 96. Subjects who temporarily stopped treatment with etanercept at or after week 96 continued with evaluations every 12 weeks. The investigator was allowed to restart treatment with etanercept for the subject at any time. A subject could stop and restart treatment with etanercept more than once.
Number of Subjects Planned: 200
Number of Subjects Enrolled: 182

The study design and treatment schema is provided in Figure 7-1.

Figure 7-1. Study Design and Treatment Schema for Study 20050111



The end of treatment visit for the original study (20030211) could have occurred at the same time as the baseline visit for this study.
[a] Subjects with ≤ 4 weeks investigational product interruption between last dose on Study 20030211 and first dose of this extension study did not require a screening visit.

[b] Subjects with > 4 weeks investigational product interruption between last dose on Study 20030211 and the first dose of this extension study required a screening visit.

Data Monitoring Committee (DMC)
Cumulative safety data were tabulated and reported periodically during the course of the study for review by an independent data monitoring committee (DMC). The DMC, which oversaw the safety and conduct of the original study (20030211), continued to meet and review the safety data of this extension study (20050111) at least twice yearly for the first 5 years of the study.
The first planned analysis for the purpose of evaluating safety and efficacy occurred after all subjects had completed the week 96 assessments and all data through week 96 had been finalized (Abbreviated Interim Clinical Study Report: 20050111, dated 22 April 2009).

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.

Discussion of Study Design
Plaque psoriasis is a chronic disease requiring long-term therapy. Therefore, there is a medical need to provide long-term safety as well as efficacy data of etanercept in this patient population. The preceding study (20030211) treated subjects with etanercept for up to 48 weeks. This open-label extension study succeeded in its designed purpose to provide up to 5 years of additional safety and efficacy data.
The Harter's Self-Perception Profile in Children and Adolescents was used in the parent study (20030211) as an exploratory endpoint to measure patient-reported outcomes of treatment. To simplify the current Study 20050111 and based on the lack of significant results in this exploratory endpoint in the first 12 weeks of Study 20030211, the Harter's Profile data were not collected after week 168 per protocol Amendment 3 (see Table 7-2). It was determined that discontinuing the Harter's assessment would not have an impact on the overall interpretation of study results.

Comment: The lack of continued collection of the Harter's assessment in the long-term study 20050111 and the MAH position that lack of this data would not impact on the overall study results is agreed.

Selection of Study Population
Subjects with moderate to severe plaque psoriasis who completed Study 20030211 or received substantial benefit (achieved a minimum of Psoriasis Area and Severity Index 50% response [PASI 50]) from etanercept on or after week 12 and did not have a serious adverse event or other clinically significant adverse event considered related to investigational product were eligible to participate in the study.

<u>Inclusion Criteria</u>

Subjects must have met one of the following conditions on the original study 20030211:

- Complete the week 48 visit on the original study 20030211.
- Complete at least the week 12 visit on the original study 20030211 and have received benefit from the investigational product therapy as demonstrated by achieving ≥ PASI 50 on or after week 12.
- Heterosexually active male and female subjects must practice a method of birth control (considered effective and medically acceptable by the investigator) during the study, including screening.
- An adult must be available to assist with administering SC injections of etanercept and/or subjects must be capable of performing self-injection technique, in the judgment of the investigator.
- Before any study-specific procedure, the appropriate written informed consent and assent must be obtained (see Section 12.1).
- Subjects entering the study following an interruption of investigation product administration > 4 weeks between the last dose on the original study 20030211 and the first dose on this extension study 20050111, must meet the following additional criteria:
- No active guttate, erythrodermic, or pustular psoriasis during the screening period.
- No presence of a grade 3 or 4 infection ≤ 30 days before the first screening visit or during the screening period.
- ALT or AST ≤ 2.0 times the upper limit of normal for the age range.
- Creatinine ≤ 1.5 times the upper limit of normal for the age range.
- White blood cell count ≥ 2.0 x 109/L.
- Hemoglobin ≥ 8.5 g/dL.
- Platelet count ≥ 150 x 109/L.
- Female subjects of childbearing potential must have negative serum pregnancy test at screening and a urine pregnancy test at day 1. A female subject of childbearing potential is defined as a female who has had at least one menstrual period, regardless of age.

Exclusion Criteria

Subjects who had a serious adverse event considered related to study drug during their participation in Study 20030211 were excluded from participating in this study (20050111). Subjects who had a grade 3 or 4 adverse event (Common Terminology Criteria for Adverse Events [CTCAE] criteria) during Study 20030211 considered related to study drug may have been allowed to enrol in the current study after discussion between Amgen and the investigator.

Full exclusion Criteria are listed below.

- Any serious adverse event reported during the original study 20030211 and considered to be related to investigational product.
- Any grade 3 or 4 adverse event reported during the original study 20030211 and considered related to study drug must be discussed between Amgen and the investigator.
- Receipt of PUVA, UVB, UVA, systemic psoriasis therapy other than etanercept (eg, Methotrexate, cyclosporine), parenteral corticosteroids, oral corticosteroids, or potent topical steroids ≤ 14 days before the first dose on this extension study 20050111. Potent topical steroids are defined as greater than moderate strength according to the package insert.
- Receipt of systemic biologics or investigational product(s) other than etanercept (eg, Raptiva, Amevive) ≤ 30 days before the first dose on this extension study 20050111.
- Receipt of live attenuated vaccines ≤ 12 weeks prior to the first dose on this extension study 20050111 (eg, MMR, Varicella, or intranasal influenza vaccine [FluMist®]).

Treatments

Subjects received SC etanercept 0.8 mg/kg (up to a maximum dose of 50 mg) QW in 1 or 2 injections. Subjects who weighed or approached ≥62 kg received as close as possible to 0.8 mg/kg dose (up to a maximum dose of 50 mg) using a maximum of 2 vials of etanercept. The dose of etanercept was based on each subject's body weight at baseline and subsequently their weight at each quarterly evaluation visit. Each injection contained a maximum of 25 mg of etanercept in 1 mL of bacteriostatic water. Therefore, subjects with the body weight >31 kg received 2 injections per dose, and subjects weighing ≤ 31 kg received 1 injection per dose. When 2 syringes were required, each syringe was injected at different locations. The site for the injections was rotated with each successive dose.
The injection was either self-administered or given by a designated caregiver. The individual administering the SC injection had to demonstrate to the site staff competency in being able to correctly administer the SC dose.

Rationale for Selection of Dosages in the Study
The dosage selected for this study is the same as the recommended dose of etanercept for pediatric patients with JIA: 0.8 mg/kg per week, up to a maximum of 50 mg per week.

Proscribed Therapy During Study Period
In order to prevent interference with study assessments, subjects should not receive the following therapies throughout the duration of the study:
• PUVA therapy
• UVA therapy
• UVB therapy
• Any systemic psoriasis therapy
• Oral or parenteral corticosteroids including intramuscular or intraarticular administration (the use of otic, nasal, or inhaled corticosteroids within recommended doses is allowed)
• Topical steroids of higher than moderate potency per the package insert
• Kineret® (anakinra)
• Any investigational products other than etanercept provided in this study
• In investigator's opinion, excessive sunbathing or use of tanning salons
• Live attenuated vaccines (eg, MMR, Varicella, intranasal influenza vaccine [FluMist®])

Subjects were allowed to use topical standard of care therapy during the study. Some examples of topical standard of care therapies were vitamin A and D analogs, anthralin, calcineurin inhibitors and corticosteroids (mild or moderate potency per package inserts). Topical anesthetic agents (eg, Elamax and Emla cream) were encouraged to be used for local analgesia about 30 minutes prior to SC injections of etanercept or prior to venipuncture for blood sampling.
In the event the subject was exposed to or infected with varicella zoster virus (VZV) during the study, the subject was to be treated according to the standard of care for those at high risk for developing severe disease (eg, varicella zoster immunoglobulin [VZIG] and/or appropriate antiviral treatment).
All concomitant medications, including over-the-counter and antipsoriatic medications, administered at each study visit and through the End of Treatment visit were recorded on the case report form and reviewed along with adverse events.

Assessment of Treatment Compliance
When etanercept was dispensed for administration to the subject during a study, the investigator or responsible person determined the level of compliance with the administration of etanercept. The subject's etanercept compliance (eg, amount used/amount expected to be used in interval between visits) was recorded on the investigational product administration case report form. This may have required the review of subject diaries, subject interviews, or other methods.

Removal of Subjects From Therapy or Assessment
Subjects had the right to withdraw fully or partially from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

Subjects were discontinued from study treatment if any of the following occurred:

• Became pregnant
• Had a systemic infection that required IV antibiotics or hospitalization
• Had a grade 3 systemic adverse event that recurred after treatment and/or dosing suspension
• Had a grade 4 adverse event thought to be related to study treatment or any serious adverse event thought to be related to study treatment
• Developed an infection with clinical finding suggestive of impending sepsis syndrome
• Required vaccination with live attenuated vaccines
• Became actively suicidal
• Withdrew consent
• Decision by Investigator
• Termination of the study for any reason

Subjects may have been discontinued from the study if any of the following occurred:
• A significant protocol deviation (ie, any protocol deviation deemed significant enough to put the subject at risk in the study)
• Lack of subject compliance with the protocol

Efficacy and Safety Assessments

Schedule of Study Assessments

Appendix A. Schedule of Assessments

	>4 weeks dose interruption		≤ 4 weeks dose interruption	For all subjects												For subjects who have not reached their 18th birthday by week 264; visits continue until the quarterly evaluation visit after the subject's 18th birthday		For all subjects
Assessment ↓ Visit →	SCR	BL	BL	12	24	36	48	60	72	84	96	108 132 156 180 204 228 252	120	144 168	192 216 240	264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504, 528, 552, 576, 600, 624	276, 300, 324, 348, 372, 396, 420, 444, 468, 492, 516, 540, 564, 588, 612, 636	End of treatment visit
Informed Consent	X		X															
Medical & Medication history	X	X																
Physical examination	X	X	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of TB risk												X	X	X	X	X	X	X
PPD test												X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Vital signs	X	X	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event/ Concomitant Medication Review		X	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X[3]	X[3]	X[3]
PASI		X	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X[4]		X[5]
sPGA		X	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BSA Involvement		X	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X[4]		X[5]

[1] If the Baseline visit for 20050111 is on the same day as the End of Treatment visit for 20030211, this procedure does not need to be repeated.
[2] A PPD test must be performed on all subjects at the first visit after IRB approval of amendment 3. PPD tests must also be performed on any subject who becomes high risk for tuberculosis since his or her last visit.
[3] Concomitant medications at all visits. After week 264, adverse event collection only requires collection of serious adverse events.
[4] Week 264 only.
[5] Only for those subjects with an end of treatment visit at week 264 or an early termination visit prior to week 264.

	>4 weeks dose interruption		≤ 4 weeks dose interruption	For all subjects												For subjects who have not reached their 18th birthday by week 264; visits continue until the quarterly evaluation visit after the subject's 18th birthday		For all subjects
Assessment Visit →	SCR	BL	BL	12	24	36	48	60	72	84	96	108 132 156 180 204 228 252	120	144 168	192 216 240	264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504, 528, 552, 576, 600, 624	276, 300, 324, 348, 372, 396, 420, 444, 468, 492, 516, 540, 564, 588, 612, 636	End of treatment visit
CDLQI		X	X[5]		X		X		X		X		X	X	X	X[4]		X[3]
Harter's Self Perception Profile		X	X[5]		X		X		X		X		X	X				
Joint pain[6]		X	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[4]		X[3]
Hematology/ chemistry	X		X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X		X[5]		X		X		X		X		X	X	X	X		X
Serum Pregnancy test	X																	
Urine Pregnancy test[7]		X																
Antinuclear Antibodies	X		X[5]				X				X			X		X[4]		X
Anti-etanercept antibodies	X		X[5]				X				X			X		X[4]		X
Serum sample for vaccination or VZV exposure[8]																		

[4] Only for those subjects with an end of study visit at week 264 or an early termination visit prior to week 264.
[5] If these evaluations are incomplete or missing at the End of Treatment visit for 20030211, this procedure must be done
[6] If assessed for the subject in 20030211
[7] Urine pregnancy test should be done during the study if suspicious of pregnancy
[4] Week 264 only.
[5] Follow up sample will be collected at ≥ 4 weeks following any inactivated vaccine and/or VZV infection that occur during the study.

Efficacy Assessments

Psoriasis Area and Severity Index (PASI) Assessment

PASI assessments were performed by a dermatologist (or a dermatologist in training) who was certified as trained with the standard PASI training material provided by Amgen. It was suggested that at each visit the same assessor perform the PASI assessment for a subject.

Static Physician Global Assessment (sPGA)

Static physician global assessment (sPGA) was used to assess overall lesions of psoriasis. The sPGA is a static measurement based on induration, erythema, and scaling.

Body Surface Area (BSA) Involvement

Physicians used the body surface area (BSA) assessment to measure the subject's total body surface area involvement of psoriasis.

Children's Dermatology Life Quality Index (CDLQI)

The Children's Dermatology Life Quality Index (CDLQI) was used to assess the impact of psoriasis on subject health-related quality of life. The CDLQI has 10 items assessing health-related quality of life (HRQOL) in subjects with skin disease. The total score ranges from 0 to 30, with lower scores indicating better quality of life. If subjects were ≥ 13 years old, the text instrument was completed by the subjects themselves. If subjects were ≥ 8 but < 13 years old, the cartoon version of the instrument was completed by the subject. Subjects ≤ 7 years old had the cartoon version of the instrument completed with help from the parents or caregivers. It was suggested that the same person complete or assist with the instrument throughout the study. The subject filled out the same age group form completed on the original study (20030211) regardless of their current age. It was suggested that CDLQI be completed prior to performing any other study procedures and that it should be consistent with respect to the order of assessment throughout the study visits.

Joint Pain

Joint pain severity was assessed by a visual analog scale completed by the subject. The subject was asked to cross a line to indicate how much pain they experienced in the last 7 days with no pain on the left end of the line and severe pain on the right side of the line. This assessment was performed only for subjects who completed the joint pain assessment on the original study (20030211).

Harter's Self Perception Profile for Children and Adolescents

The impact of psoriasis on a subject's self esteem was evaluated as an exploratory endpoint using the Harter's Self Perception Profile for Children and Adolescents. Higher scores indicated better quality of life. This assessment was performed only in children ≥ 7 years old. If subjects were 7 to 12 years old, a child version of the instrument was administered. If subjects were age 13 or older, an adolescent version of the instrument was administered. The subject was to fill out the same age group form completed on the original study (20030211) regardless of their current age. This instrument was completed by the subject without the assistance of a caregiver.

The lack of significant results in this exploratory measurement observed during the first 12 weeks of Study 20030211 led to its removal with protocol amendment 3 and the data were not collected after week 168.

Anti-etanercept Antibody Assessments

Anti-etanercept antibody assessments were conducted by PPD (Pharmaceutical Product Development). Binding antibodies to etanercept were detected using an anti-etanercept immunoassay. The positive samples in the immunoassay were further analyzed for the presence of neutralizing antibodies using a bioassay.

C**omment:** The assays are considered adequate and are briefly summarised below

Methods

The standard testing strategy for Enbrel studies was to screen all post-dose samples for the development of anti-etanercept antibodies relative to a drug naïve pre-dose sample in a validated enzyme-linked immunosorbent assay (ELISA). Samples that screened positive were further evaluated for the level of antibody in a validated titration ELISA. Subsequently, screening assay positive and outlier samples were analyzed in a validated neutralizing antibody detection ELISA.

Safety Assessments

Subjects were evaluated for adverse events at each study visit through the End of Treatment visit. Adverse events were recorded on the case report form beginning after the first dose of etanercept. During the 30-day follow-up, only serious adverse events discovered during the 30-day follow up period were to be recorded on the case report form.

Comment: The collection of SAEs only for 30 day follow-up period is acceptable

Laboratory specimens, physical examinations, and vital signs were collected/performed per the schedule of assessments in Appendix A of the protocol. An exploratory analysis of growth (height and weight data) was done on all 181 subjects who received at least 1 dose of investigational product during Study 20050111 for the week 96 analysis. After week 96, subjects were allowed to withdraw from study drug and then restart at any time after they withdrew.

Because of the lack of treatment consistency among subjects after week 96, no growth analyses were done after this time point. Growth analysis results are reported in Section 9.3.2 and in Appendix 23, as well as in the Abbreviated Interim Clinical Study Report: 20050111 dated 22 April 2009.

Appropriateness of Assessments

The efficacy and safety assessments used in this study are generally recognized as reliable, accurate, and relevant for this therapeutic indication and are consistent with those used in previous studies in the etanercept psoriasis program. The Harter's Self Perception Profile for Children and Adolescents was found not to be appropriate for the study population and its use was discontinued.

Data Quality Assurance

Comment: The Safety monitoring, standardisation of laboratory procedures investigator responsibilities and clinical data management were described and all were satisfactory.

Statistical Hypothesis
A formal hypothesis was not tested in this study.
Due to the nature of the eligibility criteria, the sample size was dependent on the number of subjects who participated in Study 20030211 and elected to continue etanercept treatment in this study.

Study Endpoints, Subsets, and Covariates
Study Endpoints
The primary endpoint was the subject incidence of adverse events, including infectious episodes, serious adverse events, and serious infectious episodes. After week 264, only serious adverse events (including serious infectious episodes) and sPGA will be assessed for the 28 subjects who are continuing in the study.
The secondary safety endpoints were:
• Injection site reactions
• Exposure-adjusted event rates for adverse events, infections, and injection site reactions
• Changes in physical characteristics as measured by physical examination including height and weight
• Vital signs (blood pressure, pulse, temperature)
• Laboratory toxicity based on the CTC (version 2.0)
• Anti-etanercept antibody formation
The secondary efficacy endpoints were:
• PASI 50, PASI 75, and PASI 90
• Percent improvement from baseline in PASI score
• sPGA
• Clear or almost clear status of sPGA
• Percent improvement from baseline in CDLQI
• Percent improvement from baseline in CDLQI subscales
• Improvement from baseline in joint pain for those subjects who completed the joint pain assessment on the original study (20030211)

The exploratory endpoint was the improvement from baseline in Harter's Self-perception Profile for Children and Adolescents total scores and subscales, which was evaluated only through week 168.

Subsets
All subjects who received at least 1 dose of etanercept in this study were evaluated for all safety and efficacy endpoints.
Covariates that were collected included the baseline value of the parameter of interest, the baseline PASI score, BSA, prior systemic therapy, or photo-therapy for psoriasis before enrollment into the original study (20030211), PASI response at week 12 of the double-blind period of the original study (20030211), and the time between the last dose in the original study (20030211) and this extension study (20050111).
Interim Analysis and Early Stopping Guidelines
Ongoing results for safety were tabulated and reported periodically during the course of this study for the purposes of monitoring safety by an independent DMC in this study. The DMC, which oversaw the safety and conduct of the original study (20030211), continued to meet and review the safety data of this extension study (20050111) at least twice yearly for the first 5 years of the study.
The first planned interim analysis for the purpose of evaluating safety and efficacy occurred after all subjects had completed the week 96 assessments and all data through week 96 had been finalized. This necessitated a snapshot of all data up to week 96. All safety and efficacy analyses were done using descriptive statistics. Anti-etanercept antibody formation was not summarized in the interim analysis.
The main analysis of safety and efficacy occurred after all subjects had completed the week 264 assessments and all data through week 264 had been finalized. All safety and efficacy analyses were done using descriptive statistics.
For the 28 subjects who are continuing treatment until they reach age 18, safety and efficacy assessments will include, respectively, only serious adverse events (including serious infectious episodes) and only sPGA using observed cases.

Comment: The MAH is requested to provide the results of these 28 subjects when available.

Planned Methods of Analysis
The general approach of the statistical analyses focuses on the estimation of long-term effects of etanercept therapy on safety by assessing the subject incidence and exposure-adjusted event rates of adverse events, infections, and injection site reactions up to week 264.
All analyses were done using descriptive statistics on the as-observed data. Of note, as-observed data may yield inflated results given the decreased denominators at the end of 5 years. Descriptive statistics provided for continuous data include the number of subjects, mean, standard deviation, standard error, median, first quartile (Q1), third quartile (Q3), minimum and maximum. Categorical data include the number and percent of subjects. No formal statistical testing was done.
Baseline values for safety endpoints, including anti-etanercept antibodies, were those values obtained immediately before the first dose of etanercept in this study, whereas baseline values for efficacy endpoints were the baseline values from the original study (20030211).

Efficacy Analyses
Efficacy data were tabulated for all subjects combined, using descriptive statistics. All binary or ordinal endpoints were summarized using the number and percent of subjects. All continuous endpoints were summarized using descriptive statistics including the number of subjects, mean, standard deviation (SD), standard error (SE), median, Q1, Q3, minimum, and maximum.
Up to week 96, missing post-baseline efficacy data were imputed using 2 different approaches: (1) treatment failure imputation and (2) last observation carried forward (LOCF) imputation. For analyses using treatment failure imputation, missing values were imputed as non-responders for binary endpoints including PASI 50 response, PASI 75 response, PASI 90 response, and the clear and clear/almost clear status of sPGA. For continuous endpoints, like the percent improvement in CDLQI, missing values were imputed as a 0% improvement from the baseline of Study 20030211. For analyses using LOCF imputation, missing post-baseline efficacy data were carried forward from the last non-missing post-baseline value for that endpoint. Baseline efficacy data were not carried forward to any missing post-baseline values.
Because subjects could stop treatment with investigational product at or after week 96 per requirements in Section 7.1, missing efficacy data after week 96 were not imputed but were summarized using as-observed data only.

Safety Analyses
Changes in laboratory, physical examination (only at week 96), and vital sign values, and the presence or absence of an antibody response were evaluated for safety. Subject incidence and exposure-adjusted event rates were used to summarize adverse events, infections, and injection site reactions through week 264.
Adverse events, serious adverse events, grades 3 and 4 adverse events, infections, serious infections, and grade 3 and 4 infections were tabulated by system organ class and preferred term. Tables and/or narratives of deaths, serious and significant adverse events, including early withdrawals due to adverse events that occurred during the study, were also provided as follows:
• Subject incidence tables include the 5 subjects who temporarily stopped receiving etanercept at or after week 96
• Exposure adjusted tables based on person-time-of-exposure include only events that occurred while the subject was receiving etanercept
• Exposure adjusted tables based on person-time-of-observation include all events that occurred during the course of the study, including events occurring while the subject was not receiving etanercept
Laboratory parameters (haematology, serum chemistry and urinalysis) were descriptively tabulated by time point.
Vital signs were summarized by study visit and for all subjects combined, based on the safety evaluable subset.
The presence or absence of antibodies to etanercept was tabulated for all subjects combined. If an antibody sample was deemed unusable, the sample was not analyzed and the appropriate documentation was produced.
Safety data were examined for differences in age groups, sex, race/ethnicity, and the time between the last dose in the original study (20030211) and this extension study (20050111).

Changes in Study Conduct

There were 4 amendments to the protocol at the time this report was completed. Key points of each amendment are described in Table 7-2.

Table 7-2. Protocol Amendments

Protocol Amendment	Summary of Key Changes
Original Protocol 09 May 2005 (All subjects were enrolled from this date to the date of the first amendment)	• Not applicable
Amendment 1 19 July 2005	• Per US Food and Drug Administration request, the discontinuation and dose adjustment criteria were amended to require that subjects with a systemic infection that required intravenous antibiotic use or hospitalization be removed from the study. • Etanercept dose wording was changed to correctly reflect that an exact 0.8 mg/kg dose is not always possible using 2 vials of lyophilized investigational product as the subject's body weight approaches 62 kg.
Amendment 2 19 October 2006	• Extended length of study for an additional 18 months • Included the option for investigators to stop treatment with investigational product for subjects with a Static Physician Global Assessment score of clear (0) or almost clear (1) at week 96, 108, 120, 132, 144, or 156
Amendment 3 10 September 2008	• Extended length of the study to 5 years • Subjects were no longer required to permanently discontinue treatment if therapy was temporarily withheld more than once because of clearing of psoriasis or if more than 3 consecutive doses were withheld because of an adverse event or surgical procedure • Removed 30 day follow-up visit • Removed collection of Harter's Self-Perception Profile in Children and Adolescents
Amendment 4 26 July 2010	• Allowed for the collection of additional safety data (assessments of adverse events and concomitant medication use) on subjects who were under the age of 18. After week 264, only serious adverse events were to be collected. • Subjects were allowed to continue on this study until they reached 18 years of age. • Added a second planned interim analysis (a "week 264 analysis") after all subjects remaining in the study completed the week 264 assessments. This comprises the main comprehensive, integrated analysis of Study 20050111 data.

Changes in Statistical Methods

There were 2 amendments to the statistical analysis plan. Changes to the statistical analyses plan were made based on the protocol amendments as follows:

Table 7-3. Statistical Analysis Plan Amendments

Amendment 1 17 October 2008	• Extension of study to 5 years in accordance with the amended protocol dated 10 September 2008. • Subjects with an sPGA score of 0 or 1 were allowed to stop treatment at or after week 96. • Addition of sensitivity analyses for efficacy endpoints using last observation carried forward (LOCF) imputation for missing data • Restriction of growth analyses to summaries of age- and sex-adjusted percentiles and height standard deviation scores
Amendment 2 20 May 2011	• Allowed for the evaluation of subject data until the quarterly visit after the subject's 18th birthday, whichever comes last, following their completion of study 20030211. • Provided for a second planned interim analysis (a "week 264 analysis") for the purpose of evaluating safety and efficacy after all subjects have completed the week 264 assessments and all data through week 264 have been finalized. The presence of anti-etanercept antibodies will be summarized at this analysis. • After week 264, only serious adverse events (including serious infectious episodes) were to be assessed for safety. • After week 264, only sPGA was to be assessed for efficacy.

Outcomes/endpoints

Safety Endpoints: The primary endpoint was the subject incidence of adverse events, including infectious episodes, serious adverse events, and serious infectious episodes.
The secondary safety endpoints were:
• Injection site reactions
• Exposure-adjusted event rates for adverse events, infections, and injection site reactions
• Changes in physical characteristics as measured by physical examination including height and weight
• Vital signs (blood pressure, pulse, respiration rate, temperature)
• Laboratory toxicity based on the Common Toxicity Criteria (CTC)
• Anti-etanercept antibody formation

Efficacy Endpoints: The secondary efficacy endpoints were:
• PASI 50, PASI 75, and PASI 90
• Percent improvement from study 20030211 baseline in PASI score
• sPGA
• Clear and clear/almost clear status of sPGA
• Percent improvement from Study 20030211 baseline in Children's Dermatology Life Quality Index (CDLQI; through week 264 only)
• Percent improvement from Study 20030211 baseline in CDLQI subscales
• Improvement from Study 20030211 baseline in joint pain for those subjects who completed the joint pain assessment on the original study (20030211)

➢ Results

Recruitment/ Number analysed
Enrollment and Disposition of Subjects
Of the 182 subjects enrolled in the study, 181 received investigational product, 63 subjects (34.6%) completed week 264; 28 subjects (15.4%) are continuing treatment until they reach age 18. The most common reason for study discontinuation was consent withdrawn in 42 subjects (23.1%). Reasons for study discontinuation are provided in Table 8-1.
For the subset of 28 subjects who are continuing treatment until they reach age 18, safety and efficacy assessments will include, respectively, only serious adverse events (including serious infectious episodes) and sPGA using observed cases.

Table 8-1. Subject Disposition

	Study 20030211 Placebo	Study 20030211 Etanercept 0.8 mg/kg QW	Total
Subjects randomized in study 20030211	105	106	211
Subjects who completed study 20030211	96	98	194
Subjects enrolled in study 20050111	92	90	182
Dosed with investigational product - n (%)			
No	1 (1.1)	0 (0.0)	1 (0.5)
Yes	91 (98.9)	90 (100.0)	181 (99.5)
Completed week 48 of study 20050111 - n (%)			
No	10 (10.9)	4 (4.4)	14 (7.7)
Yes	82 (89.1)	86 (95.6)	168 (92.3)
Completed week 96 of study 20050111 - n (%)			
No	24 (26.1)	18 (20.0)	42 (23.1)
Yes	68 (73.9)	72 (80.0)	140 (76.9)
Completed week 264 of study 20050111 - n (%)			
No	62 (67.4)	57 (63.3)	119 (65.4)
Yes	30 (32.6)	33 (36.7)	63 (34.6)
Subject status - n (%)			
Remain on study	13 (14.1)	15 (16.7)	28 (15.4)
Completed study	19 (20.7)	22 (24.4)	41 (22.5)
Subject discontinuations – n (%)			
Consent withdrawn	17 (18.5)	25 (27.8)	42 (23.1)
Lost to follow-up	14 (15.2)	5 (5.6)	19 (10.4)
Noncompliance	10 (10.9)	7 (7.8)	17 (9.3)
Disease progression	2 (2.2)	5 (5.6)	7 (3.8)
Protocol deviation	3 (3.3)	4 (4.4)	7 (3.8)
Adverse event	3 (3.3)	2 (2.2)	5 (2.7)
Pregnancy	4 (4.3)	0 (0.0)	4 (2.2)
Administrative decision	2 (2.2)	0 (0.0)	2 (1.1)
Ineligibility determined	1 (1.1)	1 (1.1)	2 (1.1)
Other	4 (4.3)	4 (4.4)	8 (4.4)

Treatment groups represent original randomized treatment from study 20030211.
QW = each week

Source: Table 14-1.1.1 (19APR12:09:05:48)

Subjects with an sPGA score of clear (0) or almost clear (1) were allowed to stop treatment with etanercept at or after week 96. The investigator could restart treatment with etanercept for the subject at any time thereafter and could elect to stop and restart treatment for a subject more than once. As shown in Table 8-2, a total of 5 subjects elected to discontinue etanercept at or after week 96, and of these, 2 subjects reinstated treatment at week 109 and 1 reinstated treatment at week 124. In addition, 1 subject missed a dose at week 169 due to an adverse event and reinstated treatment at week 170, and 1 subject stopped treatment at week 94 and reinstated treatment at week 103.

Table 8-2. Summary of Subjects Who Discontinued Investigational Product at or After Week 96

	Etanercept 0.8 mg/kg QW (N = 181)
Subjects who discontinued IP at or after week 96	
Week 96	2/131 (1.5)
Week 98	1/120 (0.8)
Week 116	1/121 (0.8)
Week 135	1/115 (0.9)
Subjects who reinstated IP after initial discontinuation	
Week 103	1/123 (0.8)
Week 109	2/112 (1.8)
Week 124	1/118 (0.8)
Week 170	1/ 88 (1.1)

N = Number of subjects who received at least one dose of investigational product.
IP = investigational product; QW = each week

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-dr-sum-ipdisc-p.sas
Output: t14-03-003-dr-sum-ipdisc-w96-p.rtf (Date generated: 09MAR2012:12:26) Source data: crt.ptinfo, crt.drgadmin

Protocol Deviations and Treatment Compliance

Eighty-five of the 181 (47.0%) subjects who received investigational product had an important protocol deviation (IPD). The most common IPDs included subjects who received an excluded concomitant treatment (41 subjects [22.7%]) (Table 14-3.1).

Table 14-3.1. Summary of Important Protocol Deviations in Descending Frequency

Category Subcategory	Etanercept 0.8 mg/kg QW (N = 181) n (%)
Number of subjects with at least one important protocol deviation	85 (47.0)
PD-XM: Received an excluded concomitant treatment	41 (22.7)
Use of above moderate topical steroid	32 (17.7)
Use of parenteral corticosteroid	5 (2.8)
Received live attenuated vaccine	3 (1.7)
Use of Systemic Therapy	2 (1.1)
Use of UVB	2 (1.1)
PD-TA: Received the wrong treatment or incorrect dose	26 (14.4)
Missed at least 6 consecutive doses of IP	17 (9.4)
Received IP outside stability range	8 (4.4)
Received 2 times allowed weekly dosage	1 (0.6)
PD-OT: Other	25 (13.8)
Did not meet revised consent or PPD criteria	25 (13.8)
PD-EN: Entered study even though entry criteria was not satisfied	7 (3.9)
Did not meet criteria after 4wk gap from 20030211	4 (2.2)
Did not meet criteria from 20030211	2 (1.1)
Proscribed therapies within 14 days of first dose	1 (0.6)
PD-MD: Missing data (other than TA or TC)	2 (1.1)
Missed at least 3 consecutive visits	2 (1.1)
PD-NW: Developed withdrawal criteria but were not withdrawn	2 (1.1)
Pregnancy	2 (1.1)

N = Number of subjects who received at least one dose of investigational product.
n = Number of subjects with protocol deviation.

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-pd-sum-p.sas
Output: t14-03-001-pd-sum-p.rtf (Date Generated: 09MAR12:12:14:36) Source Data: raw.deviations_eclin, crt.ptinfo

A complete list of IPDs that occurred during the study is provided by subject number in Listing 14-3.1 (Appendix 19) and the IPDs identified were not expected to have an impact on subject safety and/or interpretation of safety or efficacy data.

Comment: It is agreed that the IPDs were not expected to have an impact on safety or overall efficacy.

Demographic and Other Baseline Characteristics

Similar numbers of females and males (49.5% and 50.5%, respectively) enrolled in this study, 181 of 182 enrolled subjects (99.5%) received investigational product (Table 8-1). The majority of subjects were white (138 [75.8%]); the mean age was 12.8 years and ranged from 4 to 17 years (Table 8-3). Treatment groups in Table 8-3 represent the original randomized treatment in Study 20030211. The mean duration of psoriasis at baseline was 6.1 years, and 107 subjects (58.8%) had previously used systemic or phototherapies (Table 14-2.2.1).

Table 8-3. Baseline Demographics (Based on Study 20030211 Baseline)

	Study 20030211 Placebo (N = 92)	Study 20030211 Etanercept 0.8 mg/kg QW (N = 90)	Total (N = 182)
Sex - n (%)			
Male	45 (48.9)	47 (52.2)	92 (50.5)
Female	47 (51.1)	43 (47.8)	90 (49.5)
Race - n (%)			
White or Caucasian	67 (72.8)	71 (78.9)	138 (75.8)
Black or African American	8 (8.7)	2 (2.2)	10 (5.5)
Hispanic or Latino	9 (9.8)	8 (8.9)	17 (9.3)
Asian	5 (5.4)	8 (8.9)	13 (7.1)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (1.1)	1 (0.5)
Other	3 (3.3)	0 (0.0)	3 (1.6)
Age (years) at randomization			
n	92	90	182
Mean	12.7	12.9	12.8
SD	3.4	3.7	3.5
Min, Max	5, 17	4, 17	4, 17
Age group			
4 - 11 years	32 (34.8)	31 (34.4)	63 (34.6)
12 - 17 years	60 (65.2)	59 (65.6)	119 (65.4)
Weight (kg)			
n	92	90	182
Mean	60.994	63.694	62.329
SD	24.938	29.569	27.284
Min, Max	18.00, 123.00	17.70, 168.30	17.70, 168.30
Height (cm)			
n	92	89	181
Mean	155.638	156.253	155.940
SD	17.629	19.662	18.607
Min, Max	112.00, 190.50	104.20, 188.00	104.20, 190.50

Treatment groups represent original randomized treatment from study 20030211.
N = Number of subjects who were enrolled.
Min, Max = minimum, maximum; QW = each week; SD = standard deviation.

Source: Table 14-2.1 (09MAR12:12:01:59)

Baseline disease characteristics for this report were analyzed based on both Study 20030211 subject baseline (Table 14-2.2.1) and Study 20050111 subject baseline (Table 8-4).

Table 14-2.2.1. Summary of Baseline Disease Characteristics (Based on Study 20030211 Baseline)

	Study 20030211 Placebo (N = 92)	Study 20030211 Etanercept 0.8 mg/kg QW (N = 90)	Total (N = 182)
Psoriasis BSA (%)			
n	92	90	182
Mean	24.982	26.801	25.881
SD	14.615	16.590	15.606
SE	1.524	1.749	1.157
Median	22.000	21.550	21.800
Q1, Q3	13.950, 33.500	16.000, 33.000	14.300, 33.000
Min, Max	10.00, 95.00	10.00, 90.00	10.00, 95.00
Duration of psoriasis (years)			
n	92	90	182
Mean	6.0	6.3	6.1
SD	3.8	4.3	4.0
SE	0.4	0.5	0.3
Median	5.8	6.7	6.1
Q1, Q3	2.7, 8.7	2.0, 9.5	2.5, 9.0
Min, Max	0, 16	0, 18	0, 18
Prior use of systemic or photo therapies - n (%)			
No	36 (39.1)	39 (43.3)	75 (41.2)
Yes	56 (60.9)	51 (56.7)	107 (58.8)
Psoriatic arthritis - n (%)			
No	79 (85.9)	86 (95.6)	165 (90.7)
Yes	13 (14.1)	4 (4.4)	17 (9.3)

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

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-cv-sum-bldis-p.sas
Output: t14-02-002-001-cv-sum-bldis-211-p.rtf (Date Generated: 09MAR12:12:07:03) Source Data: crt.ptinfo, crt.covar, crt.hartersa

	Study 20030211 Placebo (N = 92)	Study 20030211 Etanercept 0.8 mg/kg QW (N = 90)	Total (N = 182)
Psoriasis Area and Severity Index (PASI)			
n	92	90	182
Mean	18.715	18.750	18.732
SD	6.821	7.028	6.905
SE	0.711	0.741	0.512
Median	16.450	16.950	16.600
Q1, Q3	13.950, 21.350	13.900, 21.500	13.900, 21.500
Min, Max	12.00, 56.70	12.00, 51.60	12.00, 56.70
Static Physician Global Assessment of psoriasis (sPGA) - n (%)			
0	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)
2	0 (0.0)	1 (1.1)	1 (0.5)
3	62 (67.4)	59 (65.6)	121 (66.5)
4	29 (31.5)	27 (30.0)	56 (30.8)
5	1 (1.1)	3 (3.3)	4 (2.2)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Total Children's Dermatology Life Quality Index (CDLQI)			
n	89	85	174
Mean	9.7	9.1	9.4
SD	6.2	6.1	6.2
SE	0.7	0.7	0.5
Median	9.0	8.0	8.5
Q1, Q3	5.0, 14.0	4.0, 14.0	4.0, 14.0
Min, Max	0, 29	0, 26	0, 29

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

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-cv-sum-bldis-p.sas
Output: t14-02-002-001-cv-sum-bldis-211-p.rtf (Date Generated: 09MAR12:12:07:03) Source Data: crt.ptinfo, crt.covar, crt.hartersa

	Study 20030211 Placebo (N = 92)	Study 20030211 Etanercept 0.8 mg/kg QW (N = 90)	Total (N = 182)
Total Harter's Self-perception Profile for Children			
n	36	30	66
Mean	2.894	2.853	2.876
SD	0.473	0.530	0.496
SE	0.079	0.097	0.061
Median	2.900	2.950	2.900
Q1, Q3	2.550, 3.250	2.500, 3.300	2.500, 3.300
Min, Max	2.00, 3.80	1.40, 3.70	1.40, 3.80
Total Harter's Self-perception Profile for Adolescents			
n	47	52	99
Mean	2.885	2.863	2.874
SD	0.365	0.366	0.364
SE	0.053	0.051	0.037
Median	2.900	2.850	2.900
Q1, Q3	2.600, 3.100	2.700, 3.100	2.600, 3.100
Min, Max	2.10, 3.60	1.90, 3.80	1.90, 3.80
Patient assessment of joint pain			
n	25	17	42
Mean	3.2	1.9	2.7
SD	3.0	2.9	3.0
SE	0.6	0.7	0.5
Median	3.0	0.0	1.0
Q1, Q3	0.0, 6.0	0.0, 2.0	0.0, 5.0
Min, Max	0, 8	0, 9	0, 9

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

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-cv-sum-bldis-p.sas
Output: t14-02-002-001-cv-sum-bldis-211-p.rtf (Date Generated: 09MAR12:12:07:03) Source Data: crt.ptinfo, crt.covar, crt.hartersa

Changes in disease characteristics from Study 20030211 baseline to Study 20050111 baseline were expected as subjects had already been on treatment for up to 1 year.

Table 8-4. Baseline Disease Summary (Based on Study 20050111 Baseline)

	Study 20030211 Placebo (N = 92)	Study 20030211 Etanercept 0.8 mg/kg QW (N = 90)	Total (N = 182)
Psoriasis BSA (%)			
n	91	89	180
Mean	7.979	6.360	7.178
SD	12.156	7.686	10.198
SE	1.274	0.815	0.760
Median	3.000	4.000	3.000
Q1, Q3	1.000, 10.000	1.000, 9.000	1.000, 9.000
Min, Max	0.00, 68.00	0.00, 37.00	0.00, 68.00
Newly diagnosed psoriatic arthritis - n (%)			
No	92 (100.0)	90 (100.0)	182 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Psoriasis Area and Severity Index (PASI)			
n	91	89	180
Mean	5.270	4.391	4.836
SD	5.656	3.822	4.843
SE	0.593	0.405	0.361
Median	3.400	3.400	3.400
Q1, Q3	1.500, 7.000	1.800, 6.500	1.500, 6.750
Min, Max	0.00, 26.90	0.00, 18.60	0.00, 26.90
Static Physician Global Assessment of Psoriasis (sPGA) - n (%)			
0	7 (7.6)	9 (10.0)	16 (8.8)
1	37 (40.2)	28 (31.1)	65 (35.7)
2	30 (32.6)	39 (43.3)	69 (37.9)
3	15 (16.3)	12 (13.3)	27 (14.8)
4	2 (2.2)	1 (1.1)	3 (1.6)
5	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	1 (1.1)	1 (1.1)	2 (1.1)

Treatment groups represent original randomized treatment from study 20030211.
N= Number of subjects who were enrolled.
BSA = body surface area; Min, Max = minimum, maximum; Q1 = first quartile; Q3 = third quartile; QW = each week; SD = standard deviation; SE = standard error.

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-cv-sum-bldis-p.sas
Output: t14-02-002-002-cv-sum-bldis-111-p.rtf (Date Generated: 09MAR12:12:10:01) Source Data: crt.ptinfo, crt.covar, crt.hartersa

Table 8-4. Baseline Disease Summary (Based on Study 20050111 Baseline) (Cont'd)

	Study 20030211 Placebo (N = 92)	Study 20030211 Etanercept 0.8 mg/kg QW (N = 90)	Total (N = 182)
Total Children's Dermatology Life Quality Index (CDLQI)			
n	88	84	172
Mean	2.3	2.9	2.6
SD	3.1	3.5	3.3
SE	0.3	0.4	0.3
Median	1.0	2.0	1.0
Q1, Q3	0.0, 3.0	1.0, 4.0	0.0, 3.0
Min, Max	0, 15	0, 17	0, 17
Total Harter's Self-perception Profile for Children			
n	37	29	66
Mean	3.143	3.083	3.117
SD	0.539	0.460	0.503
SE	0.089	0.085	0.062
Median	3.100	3.100	3.100
Q1, Q3	2.700, 3.600	2.800, 3.400	2.700, 3.600
Min, Max	2.30, 4.00	2.40, 3.90	2.30, 4.00
Total Harter's Self-perception Profile for Adolescents			
n	46	52	98
Mean	3.072	2.971	3.018
SD	0.442	0.453	0.449
SE	0.065	0.063	0.045
Median	3.050	2.950	3.000
Q1, Q3	2.700, 3.400	2.600, 3.300	2.700, 3.400
Min, Max	2.30, 3.90	1.90, 3.80	1.90, 3.90

Treatment groups represent original randomized treatment from study 20030211.
N= Number of subjects who were enrolled.
BSA = body surface area; Min, Max = minimum, maximum; Q1 = first quartile; Q3 = third quartile; QW = each week; SD = standard deviation; SE = standard error.

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-cv-sum-bldis-p.sas
Output: t14-02-002-002-cv-sum-bldis-111-p.rtf (Date Generated: 09MAR12:12:10:01) Source Data: crt.ptinfo, crt.covar, crt.hartersa

Table 8-4. Baseline Disease Summary (Based on Study 20050111 Baseline) (Cont'd)

	Study 20030211 Placebo (N = 92)	Study 20030211 Etanercept 0.8 mg/kg QW (N = 90)	Total (N = 182)
Patient assessment of joint pain			
n	23	13	36
Mean	2.0	1.6	1.8
SD	2.5	2.3	2.4
SE	0.5	0.6	0.4
Median	1.0	1.0	1.0
Q1, Q3	0.0, 4.0	0.0, 3.0	0.0, 3.0
Min, Max	0, 8	0, 7	0, 8

Treatment groups represent original randomized treatment from study 20030211.
N= Number of subjects who were enrolled.
BSA = body surface area; Min, Max = minimum, maximum; Q1 = first quartile; Q3 = third quartile; QW = each week; SD = standard deviation; SE = standard error.

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-cv-sum-bldis-p.sas
Output: t14-02-002-002-cv-sum-bldis-111-p.rtf (Date Generated: 09MAR12:12:10:01) Source Data: crt.ptinfo, crt.covar, crt.hartersa

Efficacy Results

Psoriasis Area and Severity Index (PASI) 50, 75, and 90 Response Table 9-1 presents PASI responses at weeks 12, 48, 96, 144, 192, 240, and 264.

As shown in Table 9-1, observed responses at week 264 for PASI 50, 75, and 90 were 87.9%, 63.6%, and 28.8%, respectively.

Table 9-1. PASI Response Through Week 264 (Observed Cases) (All Subjects Who Received at Least One Dose of Investigational Product)

		Etanercept 0.8 mg/kg QW
≥50	Week 12	162/181 (89.5%)
	Week 48	150/168 (89.3%)
	Week 96	123/138 (89.1%)
	Week 144	101/114 (88.6%)
	Week 192	80/92 (87.0%)
	Week 240	68/74 (91.9%)
	Week 264	58/66 (87.9%)
≥75	Week 12	122/181 (67.4%)
	Week 48	113/168 (67.3%)
	Week 96	84/138 (60.9%)
	Week 144	71/114 (62.3%)
	Week 192	64/92 (69.6%)
	Week 240	48/74 (64.9%)
	Week 264	42/66 (63.6%)
≥90	Week 12	64/181 (35.4%)
	Week 48	55/168 (32.7%)
	Week 96	41/138 (29.7%)
	Week 144	32/114 (28.1%)
	Week 192	33/92 (35.9%)
	Week 240	27/74 (36.5%)
	Week 264	19/66 (28.8%)

Subjects previously received up to 48 weeks of treatment with etanercept 0.8 mg/kg QW during study 20030211.
QW = each week.

Source: Table 14-4.1.3 (09MAR2012:12:27)

Mean percent improvements from Study 20030211 baseline in PASI scores ranged from approximately 72% to 82% and remained steady in subjects who remained on study through week 264 (Table 14-4.2.6).

Static Physician Global Assessment (sPGA)

The majority of subjects had an sPGA status of 1 (35.7%) or 2 (37.9%) at Study 20050111 baseline indicating minimal to mild induration, erythema, and scaling (Table 8-4).
At week 264, the clear/almost clear (sPGA score of 0 or 1) response rate was 37.9% of subjects in observed cases (Table 9-2). For subjects who remained on the study, observed response rates were similar to those observed in Study 20030211.

Table 9-2. Static Physician Global Assessment of Psoriasis Clear and Clear/Almost Clear Status Through Week 264 (Observed Cases) (All Subjects Who Received at Least One Dose of Investigational Product)

		Etanercept 0.8 mg/kg QW
Clear (0)	Week 12	24/181 (13.3%)
	Week 48	18/168 (10.7%)
	Week 96	16/139 (11.5%)
	Week 144	9/114 (7.9%)
	Week 192	19/92 (20.7%)
	Week 240	13/74 (17.6%)
	Week 264	8/66 (12.1%)
Clear/Almost Clear (0,1)	Week 12	97/181 (53.6%)
	Week 48	82/168 (48.8%)
	Week 96	66/139 (47.5%)
	Week 144	52/114 (45.6%)
	Week 192	44/92 (47.8%)
	Week 240	37/74 (50.0%)
	Week 264	25/66 (37.9%)

Subjects previously received up to 48 weeks of treatment with etanercept 0.8 mg/kg QW during study 20030211.
QW = each week.
Source: Table 14-4.3.3 (09MAR2012:12:52)

Children's Dermatology Life Quality Index (CDLQI)

At week 264, approximately 77% of subjects were considered responders on the CDLQI (≥ 5 point improvement or 0-score) (Table 14-4.5.3).

Table 14-4.5.3. CDLQI Responder [≥ 5 Point Improvement or 0 Score] Through Week 264 (Observed Cases) (All Subjects who Received at Least One Dose of Investigational Product)

		Etanercept 0.8 mg/kg QW
Responder	Week 24	112/157 (71.3%)
	Week 48	109/150 (72.7%)
	Week 72	98/140 (70.0%)
	Week 96	97/131 (74.0%)
	Week 120	78/105 (74.3%)
	Week 144	77/104 (74.0%)
	Week 168	70/94 (74.5%)
	Week 192	61/82 (74.4%)
	Week 216	61/71 (85.9%)
	Week 240	51/65 (78.5%)
	Week 264	43/56 (76.8%)

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

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-cd-inc-resp-p.sas
Output: t14-04-005-003-cd-inc-resp-obs-w264-saf-p.rtf (Date Generated: 09MAR2012:12:59) Source Data: crt.ptinfo, crt.cdlqia

Mean (SE) percent improvements from Study 20030211 baseline in the CDLQI ranged from approximately 55% at week 24 to a high of approximately 76% at week 216 (Table 14-4.7.6) (see CSR).

Joint Pain

Severity of joint pain was assessed every 12 weeks during Study 20050111 in subjects who completed the joint pain assessment during Study 20030211. Joint pain assessments are summarized in Tables 14-4.14.3, 14-4.14.7, and 14-4.14.8 (see CSR)

Comment. The summary table of joint pain results through week 264 (observed cases) is summarised by the assessor in the table below. The baseline score for study 20030211 was higher than at any later time-point.

	n	mean	SD
Study 20030211 baseline	41	2.7	3.1
Study 20050111			
baseline	35	1.8	2.4
Wk 12	39	0.9	1.7
Wk 36	30	1.6	2.6
Wk 72	25	0.9	1.9
Wk 96	27	0.7	1.5
Wk 120	19	0.8	1.5
Wk 144	20	1.0	1.7
Wk 168	16	1.3	2.0
Wk 192	15	1.2	1.8
Wk 216	15	0.9	1.1
Wk 240	15	1.1	2.2
Wk 264	16	0.9	1.5

Other Efficacy Results

Harter's Self Perception Profile for Children and Adolescents Mean (SE) improvements from Study 20030211 baseline in the total score in Harter's Self Perception Profile were minimal: 0.248 (0.062) at Study 20050111 baseline and 0.317 (0.073) at week 168 for children (Table 14-4.15.6), and 0.149 (0.032) at Study 20050111 baseline and 0.364 (0.056) at week 168 for adolescents (Table 14-4.16.6).

Based on the lack of significant results in this exploratory endpoint in the first 12 weeks of Study 20030211, the data was not collected after week 168 per protocol Amendment 3 (Table 7-2). Discontinuing its use did not have an impact on the overall interpretation of study results.

Growth Analysis

An exploratory growth analysis of height and weight data was done on all 181 subjects who received at least 1 dose of investigational product during Study 20050111 for the week 96 interim analysis. Results are summarized in **Appendix 23.**

An exploratory growth analysis of height and weight data was done on all 181 subjects who received at least 1 dose of investigational product during Study 20050111. Mean (SE) body mass index percentiles decreased from 80.77% (1.78) at Study 20050111 baseline to 70.65% (2.88) at week 96 (Appendix 23 Table 14-8.6.3).

Table 14-8.6.3. Body Mass Index (BMI) Percentiles by Visit

	Etanercept 0.8 mg/kg QW (N = 181)
Study 20030211 Baseline	
n	180
Mean	75.87
SD	27.51
SE	2.05
Median	88.16
Min, Max	7.4, 100.0
Study 20050111 Baseline	
n	178
Mean	80.77
SD	23.78
SE	1.78
Median	92.14
Min, Max	10.0, 100.0

N = Number of subjects who received at least 1 dose of investigational product
Subjects previously received up to 48 weeks of treatment with Etanercept 0.8 mg/kg QW during Study 20030211.

Program: /stat/amg916/derm/20050111/analysis/week96/tables/t_hwb.sas
Output: t14-08_006_003_hwb_pct_bmi.rtf (Date Generated: 26JAN09:14:37:25) Source Data: physmeas.sas7bdat, covar.sas7bdat

	Etanercept 0.8 mg/kg QW (N = 181)
Week 48	
n	153
Mean	73.73
SD	28.78
SE	2.33
Median	88.24
Min, Max	2.0, 99.7
Week 96	
n	103
Mean	70.65
SD	29.24
SE	2.88
Median	81.35
Min, Max	0.3, 99.8

N = Number of subjects who received at least 1 dose of investigational product
Subjects previously received up to 48 weeks of treatment with Etanercept 0.8 mg/kg QW during Study 20030211.

Program: /stat/amg916/derm/20050111/analysis/week96/tables/t_hwb.sas
Output: t14-08_006_003_hwb_pct_bmi.rtf (Date Generated: 26JAN09:14:37:25) Source Data: physmeas.sas7bdat, covar.sas7bdat

A complete description of the scope of the analysis, the endpoints considered, and the analysis methods are provided in the Statistical Analysis Plan (Appendix 2). Results are summarized in Appendix 23 Tables 14-8.6.1 to 14-8.6.51.

Table 14-8.6.1. Height Percentiles by Visit

	Etanercept 0.8 mg/kg QW (N = 181)
Study 20030211 Baseline	
n	180
Mean	56.96
SD	29.29
SE	2.18
Median	59.40
Min, Max	1.1, 99.4
Study 20050111 Baseline	
n	178
Mean	55.59
SD	30.39
SE	2.28
Median	57.97
Min, Max	0.6, 99.7

N = Number of subjects who received at least 1 dose of investigational product
Subjects previously received up to 48 weeks of treatment with Etanercept 0.8 mg/kg QW during Study 20030211.

Program: /stat/amg916/derm/20050111/analysis/week96/tables/t_hwb.sas
Output: t14-08_006_001_hwb_pct_height.rtf (Date Generated: 26JAN09:14:36:59) Source Data: physmeas.sas7bdat, covar.sas7bdat

	Etanercept 0.8 mg/kg QW (N = 181)
Week 48	
n	153
Mean	52.84
SD	30.84
SE	2.49
Median	53.44
Min, Max	0.0, 99.6
Week 96	
n	103
Mean	57.16
SD	28.96
SE	2.85
Median	58.72
Min, Max	0.8, 99.7

N = Number of subjects who received at least 1 dose of investigational product
Subjects previously received up to 48 weeks of treatment with Etanercept 0.8 mg/kg QW during Study 20030211.

Program: /stat/amg916/derm/20050111/analysis/week96/tables/t_hwb.sas
Output: t14-08_006_001_hwb_pct_height.rtf (Date Generated: 26JAN09:14:36:59) Source Data: physmeas.sas7bdat, covar.sas7bdat

Table 14-8.6.2. Weight Percentiles by Visit

	Etanercept 0.8 mg/kg QW (N = 181)
Study 20030211 Baseline	
n	181
Mean	75.68
SD	26.65
SE	1.98
Median	86.67
Min, Max	3.2, 100.0
Study 20050111 Baseline	
n	179
Mean	75.41
SD	27.08
SE	2.02
Median	86.66
Min, Max	4.2, 100.0

N = Number of subjects who received at least 1 dose of investigational product
Subjects previously received up to 48 weeks of treatment with Etanercept 0.8 mg/kg QW during Study 20030211.

Program: /stat/amg916/derm/20050111/analysis/week96/tables/t_hwb.sas
Output: t14-08_006_002_hwb_pct_weight.rtf (Date Generated: 26JAN09:14:37:12)
Source Data: physmeas.sas7bdat, covar.sas7bdat

	Etanercept 0.8 mg/kg QW (N = 181)
Week 48	
n	154
Mean	73.62
SD	28.74
SE	2.32
Median	83.93
Min, Max	3.3, 99.9
Week 96	
n	104
Mean	71.56
SD	28.32
SE	2.78
Median	80.78
Min, Max	0.3, 99.9

N = Number of subjects who received at least 1 dose of investigational product
Subjects previously received up to 48 weeks of treatment with Etanercept 0.8 mg/kg QW during Study 20030211.

Program: /stat/amg916/derm/20050111/analysis/week96/tables/t_hwb.sas
Output: t14-08_006_002_hwb_pct_weight.rtf (Date Generated: 26JAN09:14:37:12)
Source Data: physmeas.sas7bdat, covar.sas7bdat

Table 14-8.6.3. Body Mass Index (BMI) Percentiles by Visit

	Etanercept 0.8 mg/kg QW (N = 181)
Study 20030211 Baseline	
n	180
Mean	75.87
SD	27.51
SE	2.05
Median	88.16
Min, Max	7.4, 100.0
Study 20050111 Baseline	
n	178
Mean	80.77
SD	23.78
SE	1.78
Median	92.14
Min, Max	10.0, 100.0

N = Number of subjects who received at least 1 dose of investigational product
Subjects previously received up to 48 weeks of treatment with Etanercept 0.8 mg/kg QW during Study 20030211.

Program: /stat/amg916/derm/20050111/analysis/week96/tables/t_hwb.sas
Output: t14-08_006_003_hwb_pct_bmi.rtf (Date Generated: 26JAN09:14:37:25) Source Data: physmeas.sas7bdat, covar.sas7bdat

Table 14-8.6.3. Body Mass Index (BMI) Percentiles by Visit

	Etanercept 0.8 mg/kg QW (N = 181)
Week 48	
n	153
Mean	73.73
SD	28.78
SE	2.33
Median	88.24
Min, Max	2.0, 99.7
Week 96	
n	103
Mean	70.65
SD	29.24
SE	2.88
Median	81.35
Min, Max	0.3, 99.8

N = Number of subjects who received at least 1 dose of investigational product
Subjects previously received up to 48 weeks of treatment with Etanercept 0.8 mg/kg QW during Study 20030211.

Program: /stat/amg916/derm/20050111/analysis/week96/tables/t_hwb.sas
Output: t14-08_006_003_hwb_pct_bmi.rtf (Date Generated: 26JAN09:14:37:25) Source Data: physmeas.sas7bdat, covar.sas7bdat

Table 14-8.6.4. Height Standard Deviation Scores (SDS) by Visit

	Etanercept 0.8 mg/kg QW (N = 181)
Study 20030211 Baseline	
n	180
Mean	0.38
SD	1.04
SE	0.08
Median	0.37
Min, Max	-2.5, 3.6
Study 20050111 Baseline	
n	178
Mean	0.21
SD	1.05
SE	0.08
Median	0.26
Min, Max	-2.6, 2.8

N = Number of subjects who received at least 1 dose of investigational product
Subjects previously received up to 48 weeks of treatment with Etanercept 0.8 mg/kg QW during Study 20030211.

Program: /stat/amg916/derm/20050111/analysis/week96/tables/t_hwb.sas
Output: t14-08_006_004_hwb_sds.rtf (Date Generated: 26JAN09:14:37:38) Source Data: physmeas.sas7bdat, covar.sas7bdat

Table 14-8.6.4. Height Standard Deviation Scores (SDS) by Visit

	Etanercept 0.8 mg/kg QW (N = 181)
Week 48	
n	153
Mean	0.10
SD	1.15
SE	0.09
Median	0.05
Min, Max	-4.0, 2.8
Week 96	
n	103
Mean	0.29
SD	1.05
SE	0.10
Median	0.20
Min, Max	-2.6, 2.6

N = Number of subjects who received at least 1 dose of investigational product
Subjects previously received up to 48 weeks of treatment with Etanercept 0.8 mg/kg QW during Study 20030211.

Program: /stat/amg916/derm/20050111/analysis/week96/tables/t_hwb.sas
Output: t14-08_006_004_hwb_sds.rtf (Date Generated: 26JAN09:14:37:38) Source Data: physmeas.sas7bdat, covar.sas7bdat

Comment: The height SDS scores remain similar throughout the 96 weeks for study 20050111 (table 14.8.6.4 above).

Anti-etanercept Antibody Assays

Serum samples to be collected at screening, baseline, weeks 48, 96, 144, 168, 264, and at the end of the treatment visit.

A total of 169 subjects were tested for the presence (baseline) or development (post-treatment) of anti-etanercept antibodies. All individual data for positive subjects are listed in Table 1.

Table 1. Anti-Etanercept Immunoassay and Bioassay Antibody Results

Subject Number	Time Point	Immunoassay Results	Bioassay Results
501008	BL	Negative	Negative
	UNSCHED	**Positive**	Negative
	ET	**Positive**	Negative
505005	W48	**Positive**	Negative
	W96	Negative	-
	W144	Negative	-
	W168	Negative	-
	W264	**Positive**	Negative
510005	W48	Negative	-
	W96	Negative	-
	W144	Negative	-
	W168	**Positive**	Negative
	ET	Negative	-
513008	W48	Negative	-
	W96	Negative	-
	W144	Negative	-
	W168	**Positive**	Negative
	W264	Negative	-
515005	W48	**Positive**	Negative
	W96	**Positive**	Negative
	W168	**Positive**	Negative
	W264	**Positive**	Negative
520001	W48	Negative	-
	W96	Negative	-
	W144	Negative	-
	ET	**Positive**	Negative
520002	W48	**Positive**	Negative
	W96	**Positive**	Negative
	W144	**Positive**	Negative
	ET	Negative	-
521004	UNSCHED	Negative	-
	W48	Negative	-
	W96	**Positive**	Negative
	W144	**Positive**	Negative
	W168	**Positive**	Negative
	ET	Negative	-
522002	W144	Negative	-
	W168	Negative	-
	W264	**Positive**	Negative

Subject Number	Time Point	Immunoassay Results	Bioassay Results
531001	W48	Negative	-
	W96	**Positive**	Negative
	W144	**Positive**	Negative
	W168	**Positive**	Negative
	ET	**Positive**	Negative
534005	W48	**Positive**	Negative
	W96	Negative	-
535003	W96	**Positive**	Negative
	ET	**Positive**	Negative
537003	W48	**Positive**	Negative
	W144	**Positive**	Negative
	W168	**Positive**	Negative
	UNSCHED	**Positive**	Negative
	W264	**Positive**	Negative
540002	W48	**Positive**	Negative
	W96	Negative	Negative
	W144	**Positive**	Negative
	W168	Negative	-
	W264	Negative	-
552005	W48	Negative	-
	W96	**Positive**	Negative
	W144	Negative	-
	W168	Negative	-
	W264	**Positive**	Negative
554001	ET	**Positive**	Negative
555002	W48	**Positive**	Negative
	W96	**Positive**	Negative
	W144	Negative	-
	W168	Negative	-
	W264	Negative	-
556007	W48	**Positive**	Negative
	W96	**Positive**	Negative
	W144	Negative	-
	ET	Negative	-

Table 2. Summary of Antibody Status

	Etanercept 0.8 mg/kg QW (N = 181)
Subjects with an on-study result[a]	169
Total antibody incidence - n (%)	
Binding antibody positive at anytime	18 (10.7)
Neutralizing antibody positive at anytime	0 (0.0)
Subjects with a result at baseline	0
Pre-existing antibody incidence - n (%)	
Binding antibody positive at or before baseline	0 (0)
Neutralizing antibody positive at or before baseline	0 (0)
Subjects with a post-baseline result	169
Developing antibody incidence - n (%)	
Binding antibody positive post-baseline with a negative or no result at baseline	18 (10.7)
Transient[b]	8 (44.4)
Neutralizing antibody positive post-baseline with a negative or no result at baseline	0 (0.0)
Transient[b]	0 (0)

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

[a] Subjects considered on-study after signing informed consent.

[b] Negative result at the subject's last timepoint tested within the study period.

Note: A total of 10 outlier records were excluded from the analysis.

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-ab-sum-p.sas

Output: t14-07-005-ab-sum-p.rtf (Date Generated: 09MAR12:17:43:29) Source Data: crt.ptinfo, crt.ab

In the study 20050111 "Open-label Extension Study to Evaluate the Safety of Etanercept in Pediatric Subjects with Plaque Psoriasis," 169 subjects were analyzed for antibodies directed against etanercept. Eighteen subjects (10.7%) developed anti-etanercept antibodies during the study, and of these 18 subject, 8 (44.4%) had transient antibodies (ie, these subjects were negative for anti-etanercept antibodies at the last time point tested within the study period). These 8 subjects represent 4.7% of the 169 subjects who had any post baseline result. No subject developed neutralizing antibodies through week 264.

Anti-nuclear Antibody Summary

A summary of anti-nuclear antibody (ANA) titer status is provided in Table 14-7.6.

Table 14-7.6. Summary of Anti-nuclear Antibody (ANA) Titer Status

Visit	Titer Status	Etanercept 0.8 mg/kg QW (N = 181) n (%)
Baseline		
	Negative	147 (81.2)
	Positive	11 (6.1)
Week 48		
	Negative	130 (71.8)
	Positive	0 (0.0)
Week 96		
	Negative	104 (57.5)
	Positive	3 (1.7)
Week 144		
	Negative	76 (42.0)
	Positive	5 (2.8)
Week 168		
	Negative	78 (43.1)
	Positive	6 (3.3)
Week 264		
	Negative	45 (24.9)
	Positive	2 (1.1)

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

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-lb-inc-titer-p.sas
Output: t14-07-006-lb-inc-titer-ana-p.rtf (Date Generated: 09MAR12:17:47:18) Source Data: crt.ptinfo, crt.lab

Eleven subjects (6.1%) had positive ANA at baseline of Study 20050111; most of these subjects also had positive ANA during study 20030211 (subject did not). At week 264, only 2 subjects had positive ANA, 1 who also had positive ANA during Study 20030211 and 1 who had a new case of positive ANA on Study 20050111. Subjects with a positive ANA titer status at any time during Study 20050111 are listed by subject number in Listing 14-7.4 (Appendix 19).

Patient-reported Outcomes

Patient-reported outcomes as measured by the CDLQI and Harter's Self-perception Profile for Children and Adolescents are described in Section 9.

All 181 subjects who received at least 1 dose of etanercept during this study were evaluated for all efficacy endpoints. All efficacy analyses were performed using descriptive statistics on the as-observed data. For subjects who remained in the study, efficacy responses were similar to those observed in study 20030211. Psoriasis Area Severity Index (PASI) 50, 75, and 90 observed responses were 87.9%, 63.6%, and 28.8%, respectively, at week 264. At study 20050111 baseline, the majority of subjects had an sPGA of 1 (36.3%) or 2 (38.5%), indicating minimal to mild in duration, erythema, and scaling. At week 264, the as-observed clear/almost clear (i.e., sPGA score of 0, 1) response rate was 37.9%. At week 264, approximately 77% of subjects were considered responders (i.e., $\geq$ 5 point improvement or 0-score) on the Children's Dermatology Life Quality Index (CDLQI).

MAH Summary of Efficacy Results

All 181 subjects who received at least 1 dose of etanercept during this ongoing study were evaluated for all efficacy endpoints. All efficacy analyses were performed using descriptive statistics on the as-observed data. PASI 50, 75, and 90 observed responses at week 264 were 87.9%, 63.6%, and 28.8%, respectively. The majority of subjects had an sPGA status of 1 (35.7%) or 2 (37.9%) at Study 20050111 baseline, indicating minimal to mild induration, erythema, and scaling. The week 264 clear/almost clear (sPGA score of 0 or 1) response rate was 37.9% of subjects in observed cases. For subjects who remained on the study, observed response rates were similar to those observed in Study 20030211.
At week 264, approximately 77% of subjects were considered responders on the CDLQI ($\geq$ 5 point improvement or 0-score).

Assessor's conclusion on efficacy: The long term maintenance of efficacy has been shown. The MAH summary on efficacy is endorsed.

Safety results

Extent of Exposure

The mean (SD) number of doses of investigational product received during the 264-week period was 84.3 (32.3) for subjects weighing 31 kg or less and 330.6 (164.4) for subjects weighing more than 31 kg. The mean (SD) duration of dosing was 1224.1 (608.1) days (approximately 175 weeks) (Table 14-3.2).

Table 14-3.3. Summary of Subjects who Discontinued Investigational Product (IP) at or After Week 96

	Etanercept 0.8 mg/kg QW (N = 181)
Subjects who discontinued IP at or after week 96	
Week 96	2/131 (1.5)
Week 98	1/120 (0.8)
Week 116	1/121 (0.8)
Week 135	1/115 (0.9)
Subjects who reinstated IP after initial discontinuation	
Week 103	1/123 (0.8)
Week 109	2/112 (1.8)
Week 124	1/118 (0.8)
Week 170	1/ 88 (1.1)

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

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-dr-sum-ipdisc-p.sas
Output: t14-03-003-dr-sum-ipdisc-w96-p.rtf (Date generated: 09MAR2012:12:26) Source data: crt.ptinfo, crt.drgadmin

Summary of Safety Results

A total of 161 subjects (89.0%) reported at least 1 adverse event during the study. Five subjects (2.8%) reported serious non-infectious adverse events (elective abortion, anxiety, intestinal obstruction, osteonecrosis, and thyroid cyst) and 2 subjects (1.1%) reported serious infections (cellulitis and infectious mononucleosis); only the cellulitis was considered by the investigator to be related to treatment. Six (3.3%) adverse events led to study withdrawal (Crohn's disease [2 subjects], glomerulonephritis, psoriasis, sinusitis, and VIIth nerve paralysis [1 subject each]); 1 (0.6%) of these adverse events was infectious (sinusitis) and led to study withdrawal. No serious adverse event led to study withdrawal. No opportunistic infections, malignancies, or deaths occurred during the study.

Most changes in laboratory parameters were mild to moderate (CTC grade 1 or 2);

5 CTC grade 3 and no CTC grade 4 laboratory changes were reported through 264 weeks of the study. All laboratory changes occurred in only 1 subject each, and in all cases laboratory values returned to normal levels. None of the laboratory abnormalities were associated with any clinical reports of serious adverse events.

Table 11-1. Summary of Subject Incidence of Selected Adverse Events Through Week 264

Types of Events	Etanercept 0.8 mg/kg QW (N=181) n (%)
At least 1 event	161 (89.0)
At least 1 non-infectious adverse event	149 (82.3)
At least 1 infection	140 (77.3)
At least 1 grade 3 non-infectious adverse event	14 (7.7)
At least 1 grade 3 infection	5 (2.8)
At least 1 serious non-infectious adverse event	5 (2.8)
At least 1 serious infection	2 (1.1)
At least 1 non-infectious adverse event leading to withdrawal from study	5 (2.8)
At least 1 infection leading to withdrawal from study	1 (0.6)
At least 1 injection site reaction	16 (8.8)
Death	0 (0.0)

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N = Number of subjects who received at least one dose of investigational product.
n = Number of subjects with event.
Coded using MedDRA version 14.1.
MedDRA = Medical Dictionary for Regulatory Activities; QW = each week.

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-ae-inc-select-p.sas
Output: t14-06-003-ae-inc-select-p.rtf (Date Generated: 09MAR2012:15:31) Source Data: crt.ptinfo, crt.ae

Deaths
No deaths occurred during the study.

Withdrawals Due to Adverse Events
Six subjects (3.3%) withdrew from the study due to either an infectious or non-infectious adverse event: 2 subjects withdrew due to Crohn's disease, and 1 subject each withdrew due to glomerulonephritis, psoriasis, sinusitis, and VIIth nerve paralysis (Table 14-6.1.34). Adverse events considered by the investigator to be related to treatment were glomerulonephritis and 1 event of Crohn's disease.

Table 14-6.1.34. All Events Leading to Withdrawal From Study Through Week 264 by Preferred Term in Descending Frequency

Preferred Term	Etanercept 0.8 mg/kg QW (N = 181) n (%)
Number of subjects reporting events leading to withdrawal from study	6 (3.3)
Crohn's disease	2 (1.1)
Glomerulonephritis	1 (0.6)
Psoriasis	1 (0.6)
Sinusitis	1 (0.6)
VIIth nerve paralysis	1 (0.6)

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N = Number of subjects who received at least one dose of investigational product.
Coded using MedDRA version 14.1.

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-ae-inc-pref-p.sas
Output: t14-06-001-034-ae-inc-pref-all-disc-p.rtf (Date Generated: 09MAR12:15:30:14)
Source Data: crt.ptinfo, crt.ae

Descriptions of events leading to withdrawal from the study are provided in Listing 14-6.9 (Appendix 19).

Comment: The glomerulonephritis was secondary to infection. It is not clear why one case of Crohn's disease AE was considered relate to Enbrel but the other case of Crohn's disease was not considered related and the MAH is asked to comment.

All Adverse Events

One hundred sixty-one of 181 subjects (89.0%) reported at least 1 adverse event. The system organ class most frequently affected was infections and infestations with 137 adverse events (75.7% of subjects) (Table 14-6.2.1).

Among adverse events with a reporting occurrence of at least 5% by preferred term were upper respiratory tract infections (68 subjects, 37.6%), nasopharyngitis (47, 26.0%), headache (39, 21.5%), acne (33, 18.2%), pharyngitis streptococcal (27, 14.9%), sinusitis (24, 13.3%), skin papilloma (24, 13.3%), cough (22, 12.2%), influenza (21, 11.6%), and oropharyngeal pain (20, 11.0%) (Table 11-2).

Serious Adverse Events

Seven subjects (3.9%) reported serious adverse events (Table 14-6.1.31), with each subject reporting a single event: anxiety, cellulitis, infectious mononucleosis, post-operative intestinal obstruction, osteonecrosis, and thyroid cyst; a seventh subject underwent an elective abortion (Appendix 19, Listing 14-6.7 and Listing 14-6.8).

Table 14-6.1.31. All Serious Non-infectious and Infectious Adverse Events Through Week 264 by Preferred Term in Descending Frequency

Preferred Term	Etanercept 0.8 mg/kg QW (N = 181) n (%)
Number of subjects reporting serious adverse events	7 (3.9)
Abortion induced	1 (0.6)
Anxiety	1 (0.6)
Cellulitis	1 (0.6)
Infectious mononucleosis	1 (0.6)
Intestinal obstruction	1 (0.6)
Osteonecrosis	1 (0.6)
Thyroid cyst	1 (0.6)

N = Number of subjects who received at least one dose of investigational product.
Coded using MedDRA version 14.1.

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-ae-inc-pref-p.sas
Output: t14-06-001-031-ae-inc-pref-sae-p.rtf (Date Generated: 09MAR12:15:28:56)
Source Data: crt.ptinfo, crt.ae

Of the 7 serious adverse events, only the cellulitis infection was considered by the investigator to be related to investigational product (Appendix 19, Listing 14-6.7 and Listing 14-6.8). No serious adverse events led to study withdrawal. No opportunistic infections, malignancies, or deaths occurred during the study. None of these events occurred during the off treatment period.

Of the serious adverse events, anxiety, osteonecrosis, cellulitis, elective abortion, and intestinal obstruction were considered to be severe (CTC Grade 3 non-infectious adverse event (Appendix 19, Listing 14-6.3 and Listing 14-6.4). No CTC Grade 4 or Grade 5 serious adverse events were reported.

Subject narratives for all serious adverse events are provided in Appendix 11.

Clinically Significant Adverse Events

One hundred forty of 181 subjects (77.3%) reported an adverse event that was considered infectious. Upper respiratory tract infections (67 subjects, 37.0%), nasopharyngitis (44 subjects, 24.3%), pharyngitis

streptococcal (27 subjects, 14.9%), sinusitis (23 subjects, 12.7%), and influenza (21 subjects, 11.6%) were the most frequently reported infectious adverse events (Table 14-6.1.3). Incidence of infections by age, sex, race, and length of dose interruption are provided in Tables 14-6.1.15 through 14-6.1.22.

Table 14-6.1.3. Infections Through Week 264 by Preferred Term in Descending Frequency

Preferred Term	Etanercept 0.8 mg/kg QW (N = 181) n (%)
Number of subjects reporting infectious adverse events	140 (77.3)
Upper respiratory tract infection	67 (37.0)
Nasopharyngitis	44 (24.3)
Pharyngitis streptococcal	27 (14.9)
Sinusitis	23 (12.7)
Influenza	21 (11.6)
Bronchitis	17 (9.4)
Pharyngitis	15 (8.3)
Ear infection	12 (6.6)
Gastroenteritis	12 (6.6)
Urinary tract infection	12 (6.6)
Gastroenteritis viral	9 (5.0)
Pyrexia	9 (5.0)
Viral upper respiratory tract infection	9 (5.0)
Oropharyngeal pain	8 (4.4)
Otitis media	7 (3.9)
Skin papilloma	6 (3.3)
Cough	4 (2.2)
Folliculitis	4 (2.2)
Infectious mononucleosis	4 (2.2)
Laryngitis	4 (2.2)
Tonsillitis	4 (2.2)
Conjunctivitis	3 (1.7)
Cystitis	3 (1.7)
Diarrhoea	3 (1.7)
Furuncle	3 (1.7)
Influenza like illness	3 (1.7)
Molluscum contagiosum	3 (1.7)
Pneumonia	3 (1.7)

N = Number of subjects who received at least one dose of investigational product.
Coded using MedDRA version 14.1.

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-ae-inc-pref-p.sas
Output: t14-06-001-003-ae-inc-pref-inf-p.rtf (Date Generated: 09MAR12:15:24:22) Source Data: crt.ptinfo, crt.ae

Preferred Term	Etanercept 0.8 mg/kg QW (N = 181) n (%)
Viral infection	3 (1.7)
Wound infection	3 (1.7)
Acne	2 (1.1)
Body tinea	2 (1.1)
Cellulitis	2 (1.1)
Conjunctivitis infective	2 (1.1)
Enterobiasis	2 (1.1)
Fungal skin infection	2 (1.1)
Herpes zoster	2 (1.1)
Impetigo	2 (1.1)
Infection	2 (1.1)
Ingrowing nail	2 (1.1)
Lower respiratory tract infection	2 (1.1)
Nasal congestion	2 (1.1)
Otitis externa	2 (1.1)
Respiratory tract infection	2 (1.1)
Tinea versicolour	2 (1.1)
Upper respiratory tract infection bacterial	2 (1.1)
Viral pharyngitis	2 (1.1)
Viral rash	2 (1.1)
Vulvovaginal candidiasis	2 (1.1)
Abdominal pain upper	1 (0.6)
Abscess limb	1 (0.6)
Acute sinusitis	1 (0.6)
Animal bite	1 (0.6)
Arthropod bite	1 (0.6)
Back pain	1 (0.6)
Bacterial disease carrier	1 (0.6)
Bronchopneumonia	1 (0.6)
Chills	1 (0.6)

N = Number of subjects who received at least one dose of investigational product.
Coded using MedDRA version 14.1.

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-ae-inc-pref-p.sas
Output: t14-06-001-003-ae-inc-pref-inf-p.rtf (Date Generated: 09MAR12:15:24:22) Source Data: crt.ptinfo, crt.ae

Preferred Term	Etanercept 0.8 mg/kg QW (N = 181) n (%)
Clostridial infection	1 (0.6)
Dermal cyst	1 (0.6)
Dermatophytosis	1 (0.6)
Ear infection viral	1 (0.6)
Epididymitis	1 (0.6)
Eye infection	1 (0.6)
Fungal infection	1 (0.6)
Gastritis	1 (0.6)
Gastroenteritis norovirus	1 (0.6)
Genital cyst	1 (0.6)
Gingival infection	1 (0.6)
Goitre	1 (0.6)
H1N1 influenza	1 (0.6)
Hand-foot-and-mouth disease	1 (0.6)
Hordeolum	1 (0.6)
Infected bites	1 (0.6)
Infected cyst	1 (0.6)
Laryngitis bacterial	1 (0.6)
Lice infestation	1 (0.6)
Lip infection	1 (0.6)
Localised infection	1 (0.6)
Lyme disease	1 (0.6)
Lymph node pain	1 (0.6)
Lymphadenitis	1 (0.6)
Lymphadenopathy	1 (0.6)
Myringitis bullous	1 (0.6)
Oral herpes	1 (0.6)
Paronychia	1 (0.6)
Peritonsillar abscess	1 (0.6)
Pitted keratolysis	1 (0.6)

N = Number of subjects who received at least one dose of investigational product.
Coded using MedDRA version 14.1.

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-ae-inc-pref-p.sas
Output: t14-06-001-003-ae-inc-pref-inf-p.rtf (Date Generated: 09MAR12:15:24:22) Source Data: crt.ptinfo, crt.ae

Preferred Term	Etanercept 0.8 mg/kg QW (N = 181) n (%)
Post procedural infection	1 (0.6)
Psoriasis	1 (0.6)
Pyelonephritis	1 (0.6)
Respiratory tract infection viral	1 (0.6)
Rhinitis	1 (0.6)
Rhinitis allergic	1 (0.6)
Sinus congestion	1 (0.6)
Skin mass	1 (0.6)
Splenomegaly	1 (0.6)
Staphylococcal infection	1 (0.6)
Streptococcal infection	1 (0.6)
Subcutaneous abscess	1 (0.6)
Tinea pedis	1 (0.6)
Tonsillitis streptococcal	1 (0.6)
Tooth abscess	1 (0.6)
Tooth infection	1 (0.6)
Vaginitis bacterial	1 (0.6)
Varicella	1 (0.6)
Viral tonsillitis	1 (0.6)
Vomiting	1 (0.6)
Vulvovaginal mycotic infection	1 (0.6)

N = Number of subjects who received at least one dose of investigational product.
Coded using MedDRA version 14.1.

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-ae-inc-pref-p.sas
Output: t14-06-001-003-ae-inc-pref-inf-p.rtf (Date Generated: 09MAR12:15:24:22) Source Data: crt.ptinfo, crt.ae

Injection site reactions were reported by 16 of 181 subjects (8.8%) (Table 14-6.1.4).

Table 14-6.1.4. Injection Site Reactions Through Week 264 by Preferred Term in Descending Frequency

Preferred Term	Etanercept 0.8 mg/kg QW (N = 181) n (%)
Number of subjects reporting injection site reaction adverse events	16 (8.8)
Injection site erythema	6 (3.3)
Injection site reaction	4 (2.2)
Injection site pruritus	3 (1.7)
Injection site haematoma	2 (1.1)
Injection site swelling	2 (1.1)
Injection site discolouration	1 (0.6)
Injection site irritation	1 (0.6)
Injection site pain	1 (0.6)

N = Number of subjects who received at least one dose of investigational product.
Coded using MedDRA version 14.1.

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-ae-inc-pref-p.sas
Output: t14-06-001-004-ae-inc-pref-isr-p.rtf (Date Generated: 09MAR12:15:13:57) Source Data: crt.ptinfo, crt.ae

Incidence of injection site reactions by length of dose interruption is provided in Tables 14-6.1.23 through 14-6.1.30.

Table 14-6.1.30. Injection Site Reactions Through Week 264 by Preferred Term in Descending Frequency (Subjects With Dose Interruption From Study 20030211 ≤ 30 Days)

Preferred Term	Etanercept 0.8 mg/kg QW (N = 166) n (%)
Number of subjects reporting injection site reaction adverse events	16 (9.6)
Injection site erythema	6 (3.6)
Injection site reaction	4 (2.4)
Injection site pruritus	3 (1.8)
Injection site haematoma	2 (1.2)
Injection site swelling	2 (1.2)
Injection site discolouration	1 (0.6)
Injection site irritation	1 (0.6)
Injection site pain	1 (0.6)

N = Number of subjects who received at least one dose of investigational product.
Coded using MedDRA version 14.1.

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-ae-inc-pref-p.sas
Output: t14-06-001-030-ae-inc-pref-isr-dint0-p.rtf (Date Generated: 09MAR12:15:18:31) Source Data: crt.ptinfo, crt.ae

Table 11-2. Subject Incidence of Adverse Events ≥ 5% by Preferred Term in Descending Frequency

Preferred Term	Etanercept 0.8 mg/kg QW (N = 181) n (%)
Number of subjects reporting adverse events	161 (89.0)
Upper respiratory tract infection	68 (37.6)
Nasopharyngitis	47 (26.0)
Headache	39 (21.5)
Acne	33 (18.2)
Pharyngitis streptococcal	27 (14.9)
Sinusitis	24 (13.3)
Skin papilloma	24 (13.3)
Cough	22 (12.2)
Influenza	21 (11.6)
Oropharyngeal pain	20 (11.0)
Bronchitis	18 (9.9)
Nasal congestion	17 (9.4)
Pyrexia	17 (9.4)
Pharyngitis	15 (8.3)
Arthralgia	14 (7.7)
Gastroenteritis	14 (7.7)
Gastroenteritis viral	14 (7.7)
Psoriasis	14 (7.7)
Nausea	13 (7.2)
Ear infection	12 (6.6)
Procedural pain	12 (6.6)
Urinary tract infection	12 (6.6)
Abdominal pain upper	11 (6.1)
Dermatitis contact	11 (6.1)
Diarrhoea	11 (6.1)
Ligament sprain	11 (6.1)
Viral upper respiratory tract infection	11 (6.1)
Excoriation	9 (5.0)
Pruritus	9 (5.0)

N = Number of subjects who received at least one dose of investigational product.
n = Number of subjects with adverse event.
Coded using MedDRA version 14.1.
MedDRA = Medical Dictionary for Regulatory Activities; QW = each week.
Source: Table 14-6.1.35 (09MAR2012)

The most frequently reported non-infectious adverse events by preferred term were headache (39 subjects, 21.5%), acne (31 subjects, 17.1%), skin papilloma (21, 11.6%), and cough (19, 10.5%) (Table 14-6.1.2).

Fourteen subjects (7.7%) reported at least 1 CTC Grade 3 non-infectious adverse event (Table 14-6.2.4), and 5 subjects (2.8%) reported at least 1 Grade 3 infection (Table 14-6.2.5). No CTC Grade 4 or Grade 5 adverse events were reported. All severe adverse events occurred in only 1 subject each.
Complete details on all adverse events, including relatedness to investigational product, are provided in Listing 14-6.6 (Appendix 19).

<u>All Adverse Events – Exposure-adjusted Rates</u>
Person-time-of-exposure safety analyses were based on exposure-adjusted event rates for all 181 subjects who received ≥ 1 dose of investigational product during the first 264 weeks of the study and included all adverse events experienced by subjects while they were receiving etanercept and up to 30 days after their last dose of investigational product. Total exposure to etanercept in the study through week 264 was 621.0 subject-years. In Table 11-3, all events occurring at exposure-adjusted rates greater than 10 events per 100 subject-years are listed by preferred term. The event profile in Table 11-3 is similar to the profile seen when adverse events were assessed by crude rate in Table 11-2 of Section 11.7.

Table 11-3. All Events Through Week 264, Exposure-adjusted Rates by Preferred Term in Descending Frequency Based on Person-time of Exposure, Incidence > 10 Events

Preferred Term	Etanercept 0.8 mg/kg QW (Total N = 181) (Total Subj-yr = 621.0) n	(r)
Total Number of Adverse Events Reported	1340	(215.8)
Upper respiratory tract infection	144	(23.2)
Nasopharyngitis	93	(15.0)
Headache	55	(8.9)
Pharyngitis streptococcal	36	(5.8)
Oropharyngeal pain	32	(5.2)
Sinusitis	31	(5.0)
Influenza	28	(4.5)
Pyrexia	27	(4.3)
Cough	26	(4.2)
Nasal congestion	26	(4.2)
Abdominal pain upper	21	(3.4)
Acne	21	(3.4)
Pharyngitis	20	(3.2)
Bronchitis	19	(3.1)
Psoriasis	18	(2.9)
Viral upper respiratory tract infection	18	(2.9)
Ear infection	17	(2.7)
Skin papilloma	17	(2.7)
Procedural pain	16	(2.6)
Urinary tract infection	16	(2.6)
Gastroenteritis viral	15	(2.4)
Nausea	15	(2.4)
Gastroenteritis	14	(2.3)
Ligament sprain	13	(2.1)
Diarrhoea	12	(1.9)
Excoriation	12	(1.9)
Arthralgia	11	(1.8)
Dermatitis contact	11	(1.8)

N = Number of subjects who received at least one dose of investigational product.
Subj-yr = Total subject years of exposure to investigational product.
n = Number of events.
r = Exposure-adjusted event rate per 100 subject years (n/Subj-yr*100).
Multiple occurrences of the same event for a subject are counted as multiple events.
Based on patient experience of adverse events up to 30 days after their last dose of investigational product.
MedDRA = Medical Dictionary for Regulatory Activities; QW = each week.

In addition to calculating event rates up to 30 days after the last dose of investigational product, the exposure-adjusted event rate was also calculated for all adverse events experienced by subjects up to 30 days after the end of the study, including the follow-up period; this is known as person-time-of-observation. The rate using the observation calculation (Table 14-6.5.2) was similar to that of the experience calculation shown in Table 11-3.

Clinical Laboratory Evaluation

Most changes in laboratory parameters were mild to moderate (CTC grade 1 or 2), and no CTC grade 4 laboratory changes were reported through 264 weeks of the study (Table 14-7.4.1). During the first 264 weeks of the study there were 5 laboratory changes considered CTC grade 3 (Table 14-7.4.2): creatinine (increase), hemoglobin (1 increase, 1 decrease), alanine amino transferase (increase), and white blood cell count (increase). All laboratory abnormalities occurred in only 1 subject each and in all cases laboratory values returned to normal levels. None of the laboratory changes were associated with any clinical reports of serious adverse events (Appendix 19, Listings 14-6.7 and 14-6.8). Laboratory results for all subjects are summarized in Tables 14-7.2.1 to 14-7.2.10. Grade 3 laboratory changes are listed by subject number in Listing 14-7.1 (Appendix 19).

Table 14-7.4.1. Summary of Laboratory Toxicities by CTC Grade

Laboratory Parameter Grade	Etanercept 0.8 mg/kg QW (N = 181) n (%)
Bun High	179 (98.9)
Grade 0	178 (98.3)
Grade 1	1 (0.6)
Creatinine High	179 (98.9)
Grade 0	177 (97.8)
Grade 2	1 (0.6)
Grade 3	1 (0.6)
HGB High	179 (98.9)
Grade 0	130 (71.8)
Grade 1	32 (17.7)
Grade 2	16 (8.8)
Grade 3	1 (0.6)
HGB Low	179 (98.9)
Grade 0	153 (84.5)
Grade 1	23 (12.7)
Grade 2	2 (1.1)
Grade 3	1 (0.6)
Platelets High	179 (98.9)
Grade 0	165 (91.2)
Grade 1	14 (7.7)
Platelets Low	179 (98.9)
Grade 0	173 (95.6)
Grade 1	6 (3.3)
SGOT High	179 (98.9)
Grade 0	138 (76.2)
Grade 1	36 (19.9)

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

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-lb-sum-tox-p.sas
Output: t14-07-004-001-lb-sum-tox-p.rtf (Date Generated: 09MAR12:17:45:03) Source Data: crt.ptinfo, crt.lab

Laboratory Parameter Grade	Etanercept 0.8 mg/kg QW (N = 181) n (%)
SGOT High (Cont'd)	
Grade 2	5 (2.8)
SGPT High	179 (98.9)
Grade 0	138 (76.2)
Grade 1	37 (20.4)
Grade 2	3 (1.7)
Grade 3	1 (0.6)
WBC High	179 (98.9)
Grade 0	144 (79.6)
Grade 1	33 (18.2)
Grade 2	1 (0.6)
Grade 3	1 (0.6)
WBC Low	179 (98.9)
Grade 0	152 (84.0)
Grade 1	22 (12.2)
Grade 2	5 (2.8)

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

Program: /stat/amg916/derm/20050111/analysis/interim/tables/t-lb-sum-tox-p.sas
Output: t14-07-004-001-lb-sum-tox-p.rtf (Date Generated: 09MAR12:17:45:03) Source Data: crt.ptinfo, crt.lab

Vital Signs

No clinically significant changes in vital signs were observed during the study. Summaries of vital signs are provided in Tables 14-7.1.1 to 14-7.1.5.

Concomitant Medications

Ninety-five percent of all subjects used a concomitant medication at least once during the study (Table 14-8.1.1). The most frequently used concomitant medications (by >20% of subjects) included ibuprofen, paracetamol, amoxicillin, and azithromycin. Concomitant medication use is listed by subject number in Listing 14-8.1.1 (Appendix 19).

Antibody Data and Their Relationship to Safety Data
No formal analyses of the relationship between antibody and safety results were performed.

Comment: No safety signal was evident from the line listings of ADA positive patients.

MAH Discussion on clinical aspects

The primary objective of this study was to evaluate the long-term safety of etanercept in the pediatric moderate to severe psoriasis setting. No deaths, malignancies, or opportunistic infections occurred in the study. Of the 7 serious adverse events, only a cellulitis infection was considered by the investigator to be related to etanercept treatment.

The types of adverse events and infections reported in this study were similar to those seen in previous studies in adults with moderate to severe plaque psoriasis. The most common adverse events during the study were upper respiratory tract infection, nasopharyngitis, headache, acne, pharyngitis streptococcal, sinusitis, skin papilloma (warts on hand, feet, and face), cough, influenza, and oropharyngeal pain. The adverse event profile based on exposure-adjusted rates, which included all adverse events up to 30 days after last dose of investigational product, was similar to the crude rate. No new safety concerns for etanercept were observed in this study.
The level of efficacy observed in Study 20030211 was generally maintained through 264 weeks for subjects who remained on study. PASI 50, 75, and 90 responses and sPGA responses were generally maintained from baseline through week 264 and a clear/almost clear status of the sPGA had been achieved by approximately 38% of subjects. Percent improvements from study 20030211 baseline in the CDLQI also remained steady through week 264.
In conclusion, etanercept treatment at a dose of 0.8 mg/kg QW (up to a maximum dose of 50 mg) administered to pediatric subjects with moderate to severe psoriasis for up to 264 weeks maintained efficacy and did not elicit any new safety signals.

MAH Overall Benefits and Risks Conclusions

Etanercept has been shown to have a favorable safety profile in clinical trials of pediatric subjects with JIA1 and pediatric subjects with psoriasis.2 Etanercept was approved in the EU for use in pediatric patients with chronic severe plaque psoriasis aged 8 to 17 years in December 2008, and subsequently in pediatric patients with chronic severe plaque psoriasis from 6 years of age in August 2011.
Since the original variation for pediatric psoriasis (EMEA/H/C/262/II/94), additional longterm safety and efficacy data have been collected in pediatric subjects with psoriasis in the long-term extension study 20050111 that subjects entered after study 20030211. The results from the 264-week analysis of study 20050111 do not raise new safety concerns nor do they show increased rates of adverse events, infections, or malignancies associated with long-term etanercept treatment through 264 weeks in pediatric subjects with psoriasis aged 4 to 17 years.
The results from study 20050111 through 264 weeks of treatment are consistent with those already presented for the pediatric psoriasis indication in the Summary of Product Characteristics (SPC). Therefore, the MAH does not intend to submit a variation to amend the SPC.

Conclusions: In conclusion, etanercept treatment at a dose of 0.8 mg/kg QW (up to a maximum dose of 50 mg) administered to paediatric subjects with moderate to severe psoriasis for up to 264 weeks maintained efficacy and did not elicit any new safety signals.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Recommendation**

The MAH has provided the requested CSR in fulfilment of P46 FUM 134.
No change to the positive benefit:risk balance for Enbrel in paediatric plaque psoriasis nor any changes to the SmPC result from the submitted data.
The MAH is requested to provide responses to the points below. (see section IV "Additional clarifications requested")

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Based on the data submitted, the MAH should provide response to the following points

1. It is not clear why one case of Crohn's disease AE was considered relate to Enbrel but the other case of Crohn's disease was not considered related and the MAH is asked to comment.
2. For the 28 subjects who are continuing treatment until they reach age 18, the MAH is requested to provide the expected date for this data and commit to providing this additional information

The timetable as proposed by the Rapporteur is as follows:

a 30 day response timetable without clock stop will apply.