CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number(s)	103795, S-5552
Priority or Standard	Standard
Submit Date(s)	January 5, 2016
Received Date(s)	January 5, 2016
PDUFA Goal Date	November 5, 2016
Division / Office	Division of Dermatology and Dental Drug Products/Office of New Drugs III
Reviewer Name(s)	Roselyn E. Epps, M.D.
Review Completion Date	September 23, 2016
Established Name	Etanercept
(Proposed) Trade Name	Enbrel®
Therapeutic Class	Tumor Necrosis Factor (TNF) Receptor Blocker
Applicant	Immunex Corporation
Formulation(s)	Solution for subcutaneous injection
Dosing Regimen	0.8mg/kg (maximum 50mg) subcutaneously once weekly
Indication(s)	Chronic severe plaque psoriasis, who are candidates for systemic therapy or phototherapy
Intended Population(s)	Pediatric patients 4 years to 17 years

Table of Contents

APPEARS THIS WAY ON ORIGINAL

Table of Tables

APPEARS THIS WAY ON ORIGINAL

Table of Figures

Glossary

AC	advisory committee
ACD	allergic contact dermatitis
AE	adverse event
AS	ankylosing spondylitis
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CSA	cyclosporine A
CTC	Common Toxicity Criteria
DB	double-blind
DMC	data monitoring committee
DRISK	Division of Risk Management
DODAC	Dermatologic and Ophthalmic Drug Advisory Committee
ECG	electrocardiogram
eCTD	electronic common technical document
EOT	end of treatment
ePV	enhanced pharmacovigilance
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASI	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HCl	Hydrochloride
HPV	Human papilloma virus

IBD	inflammatory bowel disease
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IVRS	interactive voice response system
IXE	ixekizumab
JIA	juvenile idiopathic arthritis
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MS	multiple sclerosis
MTX	methotrexate
NB-UVB	Narrow band UVB
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
ng	nanogram
NME	new molecular entity
OCS	Office of Computational Science
OLE	Open Label Extension
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PASI	psoriasis area severity index
PBRER	Periodic Benefit-Risk Evaluation Report
PC	placebo-controlled
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PLR	Physician Labeling Rule
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PsA	psoriatic arthritis

PsO	psoriasis
PSUR	Periodic Safety Update report
RA	rheumatoid arthritis
RCT	randomized controlled trial
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
sPGA	static physician's global assessment
TB	tuberculosis
TEAE	treatment emergent adverse event
TNFR:Fc	tumor necrosis factor Fc receptor
Tx	Treatment
UC	ulcerative colitis

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends a complete response to supplemental BLA 103795/5552 Enbrel® (etanercept) for the treatment of severe plaque psoriasis in children 4 to 17 years of age, as proposed by the applicant.

The applicant has completed Study 20030211 as specified in the approval letter dated April 30, 2004 as a post marketing commitment for the indication of moderate to severe plaque psoriasis in adults. Pursuant to 21 CFR 601.3(a)(2), there are insufficient efficacy and safety data in the population with severe psoriasis (6 subjects) to justify the indication of severe plaque psoriasis in patients 4 to 17 years, despite the demonstration of efficacy in the studied population overall.

The submission for approval of etanercept for chronic moderate to severe pediatric psoriasis consisted of data from Study 20030211. The Agency gave the application a complete response in July 2008 (b) (4) [redacted]. Effects of the use of etanercept on the immune system throughout childhood and the response to recommended vaccines are not known and have not been investigated satisfactorily in this application.

In this supplemental application, the immunogenicity assays performed for etanercept antibodies and neutralization antibodies were not validated and therefore inadequate; claims regarding the absence of neutralizing antibodies cannot be made and may result in mislabeling.

Safety concerns remain regarding the potential for malignancies and serious infectious morbidities, which appear to outweigh the potential, temporary benefit of this systemic agent in pediatric severe psoriasis patients. Brief exposures to drugs[1] and environmental substances[2] in childhood have been shown to have long-term or lifelong sequellae.

The risk-benefit analysis for pediatric plaque psoriasis, especially severe plaque psoriasis, is different from the indication for juvenile idiopathic arthritis, which was approved by the Agency on May 17, 1999. While psoriasis in children can substantially impact the quality of life, it is not a life-threatening disorder.

1.2 Risk Benefit Assessment

Psoriasis is a common, chronic, autoimmune disease which has significant medical burden nationally and globally. Reported in all countries, the World Health Organization has noted that the prevalence of psoriasis varies from 0.09% to 11.4%, with at least 100 million persons affected internationally.[3] In the United States, according to National Health and Nutrition Examination Surveys (NHANES), the estimated prevalence of psoriasis is 3.1%; when extrapolated, 6.7 million adults ≥ 20 years are affected by the disease.[4] While the onset is usually in adulthood, up to one-third of adults with psoriasis report onset during childhood.[5] The incidence of psoriasis in children has more than doubled between 1970 and 2000.[6] There are five recognized types of psoriasis (plaque, guttate, pustular, inverse, erythrodermic); the diagnosis is usually made clinically but may require a skin biopsy. Psoriasis also affects the joints (psoriatic arthritis) and nails. The most frequent type is plaque psoriasis, which features well-defined, red to purple-brown plaques with silvery scales. The course of plaque psoriasis in children is comparable to that in adults. While most pediatric and adult psoriasis patients have local disease, a smaller group is affected by severe disease. The number and proportion of patients affected by severe disease has been difficult to quantify by survey or extrapolation.

Although psoriasis is not life-threatening, it can be serious and associated with significant morbidity. Co-morbidities associated with psoriasis in children and adults include psoriatic arthritis, obesity, hypertension, hyperlipidemia, diabetes mellitus, rheumatoid arthritis, Crohn's disease, and depression.[4,7]

1 Paediatr Respir Rev. 2014 Jun;15(2):120-3.
2 www.cdc.gov/nceh/lead/
3 World Health Organization, Global report on Psoriasis, 2016.
4 Am J Prev Med. 2014 Jul;47(1):37-45
5 Pediatric Dermatology Vol. 17 No. 3 174–178, 2000
6 Paediatr Drugs. 2015; 17: 373–384
7 JAMA Dermatol. 2016;152(1):73-79

Chronic plaque psoriasis is difficult to treat; therefore, systemic therapy or phototherapy may be required to control the disease when there is significant body surface area (BSA) involved or a lack of response to conventional treatment. Currently, no systemic agent is approved to treat psoriasis in children. The approved options in pediatric psoriasis are a limited number of topical corticosteroids, a vitamin D analogue, and a retinoid, as well as phototherapy; however, multiple approved therapies for adult psoriasis are available and are used in the pediatric psoriasis population, including etanercept. (Table 1)

In April 2004, etanercept was approved in adults with moderate to severe psoriasis in the U.S. As a part of the postmarketing commitment for licensure of etanercept to treat psoriasis in adults, one randomized, placebo-controlled trial (RCT) was completed in pediatric patients 4 to 17 years with moderate to severe psoriasis. In 2007, the sponsor submitted a supplemental BLA application supported by this RCT Study 20030211 for the treatment of moderate to severe plaque psoriasis in children. The single RCT was conducted in 211 children with both moderate and severe psoriasis, and showed efficacy at 12 weeks. Four serious adverse events were reported but there was no specific pattern suggesting a safety signal in the application. During the review cycle, an Advisory Committee panel was convened. The panel wanted additional safety data in children and advised that the risk/benefit favored severe psoriasis, not moderate disease, even though the majority supported approval. The Agency gave this application a complete response.

From August 2005 until December 2011, an open label extension (OLE) study for safety treated 181 pediatric psoriasis subjects from the original RCT trial, which collected data for 6 years. The applicant submitted this supplemental BLA including safety data in January 2016, which is evaluated in this review. Twenty-one serious adverse events were reported, but no specific safety signal was detected due to an insufficient number of subjects.

The six subjects with severe psoriasis enrolled in the RCT trial (three subjects in the treatment arm, one subject showing efficacy) are not adequate to assess efficacy in severe psoriasis in children. Additionally, only four subjects with severe psoriasis entered the OLE study, which is inadequate to assess safety in severe psoriasis in children. No conclusions can be drawn from the small severe psoriasis cohort studied, the indication for which the sponsor applied.

The safety concerns for etanercept are the same as those associated with the TNF inhibitor class. Subsequent to approval for Psoriasis in adults, enhanced pharmacovigilance and postmarketing data reported deaths, malignancies, opportunistic infections, and hospitalizations in pediatric psoriasis patients treated with etanercept worldwide. The most frequent causes of death were opportunistic infections and other serious infections. Of 101 cases of cancer reported for the TNF inhibitors, 11 malignancies were HPV related. The cases of human papilloma virus (HPV)-related malignancy were higher than expected, specifically for cervical cancer. Lymphoma, leukemia, and opportunistic infections cannot be mitigated. For cervical cancer and HPV-related malignancies, the HPV vaccine series may be given prior to beginning etanercept use.

Finally, the effects of etanercept on vaccines and the immune system in children were not adequately evaluated in this application. According to guidance documents of the FDA, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and United States Pharmacopeia (USP), the anti-etanercept assay and neutralization antibody assays were not appropriately validated to accurately determine the incidence of anti-drug antibodies; therefore, expanding the indication to include children cannot be supported by this reviewer.

In conclusion, the benefits were not shown to outweigh the risks for etanercept treatment of children with severe plaque psoriasis due to a lack of data. Children with severe plaque psoriasis are the patients most likely to receive systemic treatments for longer periods of time, and as such, are potentially the main candidates for etanercept therapy, if it is proven effective. No conclusions can be drawn regarding etanercept treatment of severe psoriasis in children, the indication for which the sponsor applied. Additionally, data are lacking regarding the development of anti-etanercept antibodies and the short-term and long-term effects of etanercept on the developing immune system in children. Opportunistic infections and malignancies (especially lymphoma and leukemia), have been reported and cannot be mitigated. This reviewer recommends that the applicant:

- Conduct an additional study in pediatric patients with severe plaque psoriasis with an adequate number of subjects to achieve statistical power for analysis;

- Modify the anti-etanercept antibody assay and the neutralization assay to achieve validity and reliability, and assess the development of antibodies to etanercept,. The anti-etanercept antibody and neutralization assays need to be specific, sensitive, accurate, tolerant to on-board drug levels, and performed in the indicated population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No additional recommendation is made for postmarket risk evaluation.

Any risk for malignancy needs to be mitigated, if possible. To minimize the risk for human papilloma virus (HPV)-related malignancy, this reviewer recommends that all patients become fully immunized with the HPV vaccine prior to beginning etanercept therapy. Methods to minimize the risk of other malignancies are not known.

1.4 Recommendations for Postmarket Requirements and Commitments

This reviewer does not recommend postmarket requirements, as it is the opinion of this reviewer that premarketing requirements for approval for the indication of severe psoriasis in children have not been met.

2 Introduction and Regulatory Background

2.1 Product Information

Etanercept is a dimeric soluble form of the p75 tumor necrosis factor (TNF) receptor that can bind TNF molecules. Etanercept inhibits binding of TNF-α and TNF-β to call surface TNF receptors, rendering TNF biologically inactive.

Etanercept (Enbrel) is an approved biologic product indicated for the treatment of:

- Rheumatoid arthritis (RA),
- Psoriatic arthritis (PsA),
- Ankylosing spondylitis (AS), and
- Plaque psoriasis in adults, and
- Polyarticular juvenile idiopathic arthritis (JIA).

2.2 Table of Currently Available Treatments for Proposed Indications

In this BLA supplement (BLAs) the applicant is seeking approval of etanercept for the indication of severe plaque psoriasis in pediatric patients age 4 to 17 years who are candidates for systemic or phototherapy.

Products approved for the treatment of moderate to severe psoriasis in adult patients are listed in the table below. Ultraviolet light therapy as a device is approved for all ages. For children 12 years and older, betamethasone dipropionate/calcipotriene ointment and tazarotene gel are approved. Mometasone furoate is approved for corticosteroid-responsive dermatoses in patients ≥ 2 years. There are no approved systemic therapies for the treatment of pediatric psoriasis patients.

Table 1: Summary of Systemic Treatments for Moderate to Severe Psoriasis

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Antimetabolite/Immunosuppressant						
Methotrexate	Severe, recalcitrant, disabling, psoriasis not adequately responsive to other forms	1972	Psoriasis: Starting Dose Schedules 1. Weekly single oral, IM or IV dose schedule: 10 to	No efficacy information for psoriasis in the label. AAD guidelines[6]- 3 trials quoted Heydendael et al[8]:	Boxed Warning (BW)- potentially fatal toxic reactions including hepatotoxicity,	Major AE derm dosing: ↑LFT's stomatitis, diarrhea, nausea and vomiting,

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
	of therapy		25 mg per week until adequate response is achieved. 2. Divided oral dose schedule: 2.5 mg at 12-hour intervals for three doses. 30 mg/week should not be exceeded ordinarily.	MTX vs CSA (no placebo arm), PASI 75 at 16 weeks 60% -MTX vs 71% CSA (no statistically significant difference) Flytström et al[9] MTX vs CSA (no placebo arm), mean PASI change from baseline 58%-MTX vs 72%-CSA Saurat et al[10] DB,PC MTX vs adalimumab vs placebo PASI 75 at 16 weeks MTX-36% vs adalimumab-80% vs placebo-19%	bone marrow suppression, aplastic anemia, gastrointestinal toxicity, pulmonary toxicity and opportunistic infections, malignant lymphoma, tumor lysis syndrome, severe skin toxicity, fetal death and anomalies "should not be used in pregnant women with psoriasis"	lymphoproliferative disorders Pregnancy: X
Tumor Necrosis Factor Inhibitors						
Infliximab (Remicade)	Chronic Severe (extensive or disabling) plaque psoriasis, candidates for phototherapy or systemic therapy	2006	5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks	From the label: 3 R,DB,PC trials PASI 75 at week 10 1-Infliximab (Inflix) (5mg/kg)- 80% vs 3% placebo 2- Inflix (5mg/kg)-75% vs 2% placebo 3- Inflix (5mg/kg)-88% vs Inflix (3mg/kg) 72% vs 6% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), Hepatosplenic T-cell lymphomas (adolescents and young adults) Warnings: Hep B reactivation, heart failure, hepatotoxicity, cytopenias, hypersensitivity events,	Pregnancy: B

8 N Engl J Med. 2003 Aug 14;349(7):658-65.
9 Br J Dermatol. 2008 Jan;158(1):116-21.
10 Br J Dermatol. 2011 Aug;165(2):399-406

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
					malignancy	
Adalimumab (Humira)	Moderate to severe chronic plaque psoriasis, candidates for phototherapy or systemic therapy	2008	80 mg initial dose, followed by 40 mg every other week starting one week after initial dose	From the label: 2 Randomized, DB, PC trials PASI75 at week 16 1- Adalimumab 71% vs 7% placebo 2- Adalimumab 78% vs 19% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), Warnings: hypersensitivity reactions, Hepatitis B reactivation, demyelinating disease, cytopenia, heart failure, Lupus-like syndrome	Pregnancy: B
Etanercept (Enbrel)	Chronic moderate to severe psoriasis, candidates for phototherapy or systemic therapy	2004	50 mg twice weekly for 3 months, followed by 50 mg once weekly	From the label: 2 Randomized, DB, PC5 trials PASI75 at 3 months 1- Etanercept -47% vs 4% placebo 2-Etan-46% vs 3% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), lymphomas, other malignancies Warnings: demyelinating disease, pancytopenia, malignancy, Hepatitis B reactivation	Pregnancy: B
IL-12 and 23 Antagonist						
Ustekinumab (Stelara)	Moderate to Severe psoriasis, candidates for phototherapy or systemic therapy	2009	For patients weighing <100 kg :45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks For patients	From the label: 2 Randomized, DB, PC trials PASI 75 at week 12 1)-ustekinumab (90mg)-66% vs ustekinumab (45mg)-67% vs 3% placebo	Warnings and Precautions (W&Ps): Infections (serious bacterial, fungal and viral), theoretical risk for serious	Pregnancy: B

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
			weighing >100 kg: 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks	2)-ustekinumab (90mg)-76% vs ustekinumab (45mg)-67% vs 4% placebo	infections, malignancy, reversible posterior leukoencephalopathy syndrome, pretreatment eval for TB.	
IL- 17A Antagonist						
Secukinumab (Cosentyx)	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	2015	300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4 followed by 300 mg every 4 weeks. For some patients, a dose of 150 mg may be acceptable	From the label: 4 Randomized, DB, PC trials PASI75 at week 12 1-secukinumab (sec) (300mg)-82% vs sec (150mg) 71% vs 4% placebo 2-sec (300mg)-76% vs sec (150mg)-67% vs 5% placebo 3-sec (300mg)-75% vs sec (150mg)-69% vs 0% placebo 4-sec (300mg)-87% vs sec (150mg)-70% vs 3% placebo	W&Ps: Infections (serious bacterial, fungal and viral), theoretical risk for serious infections, Crohn's disease, hypersensitivity reactions, pretreatment evaluation for TB.	Pregnancy: B
T-Cell Inhibitor / Immunosuppressant						
Cyclosporine	Severe recalcitrant disabling psoriasis who have failed at least one systemic therapy	1997	Starting dose: 2.5 mg/kg/day, taken twice daily, dosage ↑ by 0.5 mg/kg/day at 2-week intervals, to a maximum of 4.0 mg/kg/day.	From the label: PASI 75 - 51% at 8 weeks, 79% at 16 weeks	BW-Should only be used by MDs experienced in management of systemic immunosuppressive Rx, ↑ susceptibility to infections and development of neoplasia including lymphoma, also hypertension, nephrotoxicity which ↑ with ↑	Pregnancy: C

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
					doses. In psoriasis patients with history of PUVA, UVB, coal tar or radiation Rx- ↑ risk of skin malignancies	
Retinoid						
Acitretin (Soriatane)	Severe psoriasis unresponsive to other therapies or whose clinical condition contraindi-cates the use of other treatments	1996	Starting dose: 25 to 50 mg per day, Maintenance doses of 25 to 50 mg per day may be given dependent upon an individual patient's response to initial Rx	BW-pregnancy must be prevented during Tx and for 3 years following due to teratogenicity, no ethanol ingestion by females of childbearing potential (FOCBP) due to metabolism to etretinate and ↑ ½ life, REMS (Do Your P.A.R.T.) participation required for FOCBP-see Drugs@FDA for details. Patients cannot donate blood for 3 years post Tx. See label for data on pregnancies in partners of male patients on acitretin	W&P: hepatotoxicity, skeletal abnormalities, lipids↑, Cardiovascular risk ↑, Ophthalmologic effects, Pancreatitis, capillary leak syndrome, pseudotumor cerebri, exfoliative dermatitis, depression	Pregnancy: X
Phosphodiesterase 4 (PDE4) Inhibitor						
Apremilast (Otezla)	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	2014	To reduce risk of gastro-intestinal symptoms, titrate to recommended dose of 30 mg twice daily	From the label: 2R, DB, PC trials PASI 75 at 16 weeks 1- apremilast 33% vs placebo 5% 2-apremilast 28.8% vs placebo 5.8%	W&P: depression, weight decrease, drug interactions with strong P450 enzyme inducers (rifampin, phenobarbital, carbamazepine,	Diarrhea, nausea, URI, headache Pregnancy: C

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
					phenytoin)	
Immunoglobulin G subclass 4 (IgG4) Monoclonal Antibody						
Ixekizumab (Taltz)	Moderate-to-severe psoriasis, candidates for phototherapy or systemic therapy	2016	Week 0: two 80 mg injections; 80 mg weeks 2, 4, 6, 8, 10, 12; then 80 mg every 4 weeks	From the label: 3 PC and AC trials PASI75 at 12 weeks	W&P: infections, tuberculosis, hypersensitivity, inflammatory bowel disease	Nausea, URO, tinea infections Pregnancy: No available data
Phototherapy						
PUVA-8-MOP (methoxsalen + UVA) therapy	Severe, recalcitrant, disabling psoriasis not responsive to other forms of therapy	? year approved	20 -70 mg (based on weight) taken 2-4 hours before exposure to UVA light	No efficacy information for psoriasis in the label. AAD Guidelines: 2 systematic reviews: 70-100% of patients achieved skin clearing	BW: Should only be used by MDs who have special competence in psoriasis management, serious skin burning, ocular damage, aging of the skin, skin cancer (including melanoma)	Nausea, erythema, pruritus, must avoid all exposure to sunlight (even through windows) to eyes and skin for 24 hours after ingestion Pregnancy: C
Combination Vitamin D analogue and corticosteroid						
Betamethasone dipropionate and Calcipotriene (Enstilar)	Plaque psoriasis	2015	Apply once daily for up to 4 weeks	Randomized, DB, PC trial For ages 12 and older	W&P: hypercalcemia, hypercalciuria, HPA axis suppression	Pregnancy: C
Topical Corticosteroid						
Clobetasol propionate cream (Temovate E)	Moderate to severe plaque psoriasis	1994	Apply thin layer twice daily, up to 2 consecutive weeks, up to 50g/wk	Controlled trial For ages 16 years and older	W&P: HPA axis suppression (as low as 2 g/day), Cushing's syndrome, hyperglycemia, glycosuria. Local-folliculitis, acneiform eruptions, striae, hypertrichosis, hypopigmentation,	Pregnancy: C

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
					ACD, miliaria, secondary infection	
Mometasone furoate cream (Elocon®)	Corticosteroid –responsive dermatoses	1987	Apply a thin film up to twice daily, up to 3 weeks	Two DB, PC trials age 12 -81 years; in atopic and psoriasis. Open label pediatric trial ages 2 to 12 years	W & P: HPA axis suppression, skin atrophy	Pregnancy: C
Other Treatments –						
Ultraviolet Light	Approved as devices	Multiple years	Per clinician's judgment	Approved for all ages	Risk of burns, pigmentation; skin cancer with increased dosing	Presumed safe in pregnancy
Laser Therapy						
Excimer UVB laser (308nm UVB)	Mild, moderate, severe psoriasis, less than 10% BSA	2003	Initial dose by skin type and plaque thickness, then increase/ decrease with clinical response. Treat 2 to 3 times a week until clear.	Approved in adults	W & P: Erythema, hyperpigmentation, blistering possible at higher doses.	Not studied in pregnant women. Presumed to be safe
Pulse dye laser system 595 nm	Chronic localized psoriasis	2004	Treat every 3 weeks	Approved in adults	W & P: Bruising, scarring	Not studied in pregnant women. Presumed to be safe

Source: Reviewer's Table

2.3 Availability of Proposed Active Ingredient in the United States

Etanercept is widely available in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Safety warnings have been issued for etanercept use as well as other TNF inhibitors. Labeling for etanercept carries a boxed warning that includes the risk of serious infections leading to hospitalization or death form tuberculosis, bacterial sepsis, viral infections, invasive fungal infections and infections due to opportunistic pathogens. In addition, lymphoma and other malignancies (some fatal), in children and adolescent patients, as well as hepatosplenic T-cell

lymphomas, a rare type of T-cell lymphoma, in adolescent and young adults with inflammatory bowel disease, have been reported. Similar boxed warnings have been included in labeling of other approved TNF inhibitor biologic products, including: infliximab (REMICADE); adalimumab (Humira); golimumab (SIPMPONI); certolizumab (CIMZIA).
The Agency issued safety communications after licensing of etanercept. The warnings and communications were for the TNF blocker class, and described changes to labeling.

• Early Communication About an Ongoing Safety Review of Tumor Necrosis Factor (TNF) Blockers (marketed as Remicade, Enbrel, Humira, and Cimzia) 6/4/2008

• Information for Healthcare Professionals: Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), and Remicade (infliximab)
FDA ALERT 9/4/2008

• FDA: Cancer Warnings Required for TNF Blockers 8/4/2009

• Follow-up to the June 4, 2008 Early Communication about the Ongoing Safety Review of Tumor Necrosis Factor (TNF) Blockers (marketed as Remicade, Enbrel, Humira, Cimzia, and Simponi) 8/4/2009

• Information for Healthcare Professionals: Tumor Necrosis Factor (TNF) Blockers (marketed as Remicade, Enbrel, Humira, Cimzia, and Simponi) 8/4/2009

• FDA Drug Safety Communication: Safety Review update on reports of Hepatosplenic T-Cell Lymphoma in adolescents and young adults receiving tumor necrosis factor (TNF) blockers, azathioprine and/or mercaptopurine 4/14/2011

• FDA Drug Safety Podcast for Healthcare Professionals: Safety Review update on reports of Hepatosplenic T-Cell Lymphoma in adolescents and young adults receiving tumor necrosis factor (TNF) blockers, azathioprine and/or mercaptopurine 4/18/2011

• FDA Drug Safety Communication: Drug labels for the Tumor Necrosis Factor-alpha (TNFα) blockers now include warnings about infection with Legionella and Listeria bacteria 9/7/2011

• FDA Drug Safety Communication: UPDATE on Tumor Necrosis Factor (TNF) blockers and risk for pediatric malignancy 11/3/2011

Reviewer's comment:
The specific warnings regarding malignancy and pediatric and adolescent cancer regarding TNF blockers are of concern. Cancer is uncommon in pediatric psoriasis; studies regarding the incidence of cancer in psoriasis were conducted in adults.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Enbrel was licensed for the treatment of chronic moderate to severe plaque psoriasis in adults, who are candidates for systemic therapy or phototherapy on April 30, 2004. The approval letter dated April 30, 2004 for adult psoriasis defined the post-marketing commitment (PMC) as follows:

> *"To conduct study protocol 20030211, a 48 week 200 pediatric patient, multicenter placebo-controlled clinical trial, to determine the safety and efficacy of etanercept in pediatric patients, 4 to 17 years of age, with chronic plaque psoriasis. The final study protocol will be submitted August 31, 2004, the study will be initiated by December 31, 2004, patient accrual will be completed by December 31, 2005, the study will be completed by December 31, 2006, and the final study report with revised labeling, if applicable, will be submitted by September 30, 2007".*

On September 26, 2007, the applicant submitted an efficacy supplement BLA 103795/S5350 for the indication of treatment of moderate to severe plaque psoriasis in pediatric patients age 4 to 17 years. During the review of the supplement, a Dermatologic and Ophthalmic Advisory Committee (DODAC) meeting was convened June 18, 2008, to consider the risk/benefit assessment of Enbrel in the treatment of pediatric patients. The advisory committee (AC) recommended approval for the treatment of plaque psoriasis in pediatric patients. Also, the AC voted that data were insufficient to make conclusions regarding safety in pediatric plaque psoriasis. The AC also suggested that the moderate psoriasis patient population not be considered for approval. Concern was expressed by AC members that participation for children age 4 to 8 years was low, and the data were limited.

On June 23, 2008, the Enbrel REMS was established when Enbrel Patient Information was converted to a Medication Guide.

On July 24, 2008, the Division issued a complete response letter (b) (4)

Additionally, the deficiencies were listed as follows:

(b) (4)

(b) (4)

- November 18, 2009 – New safety information was added to labeling pertaining to the risk of malignancies in pediatric patients, leukemia in adults, and psoriasis-like lesions associated with use of products within the class of TNF-blockers.

- April 8, 2010 - REMS was approved (Medication Guide, Communication Plan, Timetable for Assessments) for new safety information regarding recognizing and appropriately treating histoplasmosis and other invasive fungal infections in individuals taking TNF blockers. These infections may go unrecognized and untreated, leading to death.

- July 29, 2010 – New safety information was added to labeling pertaining to the risk of peripheral demyelinating disorders, including Guillain-Barre syndrome, demyelinating polyneuropathy, and multifocal motor neuropathy, associated with the use of the class of TNF blockers.

- March 14, 2011- labeling updated to provide for addition of hepatosplenic T-cell lymphoma (HSTCL) to the Boxed Warnings and Warnings and Precautions sections; and serious infection with the concomitant use with abatacept or anakinra to the Warnings and Precautions section.

- On June 26, 2015, the applicant requested a Type B pre-BLA meeting regarding pediatric psoriasis. A pre-BLA meeting was scheduled for September 30, 2015. After the Agency responded to the meeting questions, the applicant cancelled the meeting.

- On January 5, 2016, the applicant submitted a supplemental BLA application for chronic severe psoriasis in children. The RCT Study 20030211 enrolled 211 pediatric subjects age 4 to 17 years with moderate to severe psoriasis; 182 subjects from the RCT study were then enrolled in the OLE Study 20050111.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

To evaluate submission quality and integrity, the Office of Scientific Investigations (OSI) performed inspection of two investigational sites for Phase 3, RCT Study 20030211.

The subject population in the OLE study 20050111 was derived from RCT Study 20030211, and the investigational sites were the same as in the RCT Study 20030211; therefore, no additional inspections were necessary.

3.2 Compliance with Good Clinical Practices

The applicant stated that studies were designed, monitored, and conducted in accordance with Good Clinical Practice (GCP) requirements and ethical principles. The responsible Institutional Review Board (IRB) reviewed trial protocols, subject information and informed consent forms, and subject recruitment procedures prior to study initiation.

3.3 Financial Disclosures

The applicant completed Form 3454 to document financial conflicts of interest and arrangements with clinical investigators. The applicant certified that no financial arrangement was entered into with the listed clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

For study 20050111, financial disclosure status was not documented for three sub-investigators at two sites. The three individuals did not respond to at least two requests by the applicant to provide information. One principal investigator (PI) received payments as honoraria for speaking fees, and one PI received two grants to fund clinical trials.

Reviewer's comment:
The applicant needed to submit financial disclosure status documentation for sub-investigators. Two requests were sent to the three sub-investigators, and there was no response. The lack of response is not compliant with Good Clinical Practice (GCP) guidelines.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Chemistry manufacturing and control testing was not addressed in the efficacy supplement review.

4.2 Clinical Microbiology

Clinical microbiology was not evaluated during the efficacy supplement review.

4.3 Preclinical Pharmacology/Toxicology

The applicant did not submit any new preclinical pharmacology/toxicology information in support of this efficacy supplement review.

4.4 Clinical Pharmacology

The sponsor evaluated the pharmacokinetics and immunogenicity of etanercept in pediatric subjects with psoriasis. This section discusses pharmacokinetics of etanercept in pediatric subjects with psoriasis. Immunogenicity will be presented in Section 7.4.6 of this review.

4.4.1 Mechanism of Action

Etanercept is a dimeric soluble form of the p75 TNF receptor that binds TNF molecules. Etanercept inhibits binding of TNF-α and TNF-β to cell surface TNF receptors, rendering TNF biologically inactive (blocking TNF binding to the receptor).

4.4.2 Pharmacodynamics

Etanercept modulates biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (e.g., E-selectin, and to a lesser extent, intercellular adhesion molecule-1 [ICAM-1]), serum levels of cytokines (e.g., IL-6), and serum levels of matrix metalloproteinase-3 (MMP-3 or stromelysin).

4.4.3 Pharmacokinetics

The applicant evaluated the pharmacokinetics (PK) of etanercept in pediatric subjects during RCT Study 20030211. The etanercept dose for all subjects was 0.8 mg/kg once a week subcutaneously (maximum dose 50 mg). Serum etanercept concentrations were determined from all etanercept-treated subjects with samples at baseline and 12, 24, and 48 weeks. The results of the PK studies are in Table 2 below.

Table 2: Serum Etanercept Concentrations in Pediatric Psoriasis Subjects, Age 4 to 17 Years

	Etanercept Serum Concentrations (ng/mL)					
Time Point	N	Mean	SD	Median	Min	Max
Day 1	124	1.50	3.13	BQL	BQL	16.7
Week 12	99	1614	828	1574	17.3	4224
Week 24	191	2104	1255	1886	2.32	6546
Week 48	106	1650	1126	1621	BQL	4831

N=number of subjects
BQL=below quantitation limit
SD=standard deviation
Source: Applicant Submission, Summary of Clinical Pharmacology Studies, Table 1.

The results showed that the steady state trough serum etanercept concentrations were highly variable. At 24 weeks, the serum etanercept levels ranged from 2.32 to 6546 ng/mL. Additionally, the mean etanercept serum trough concentrations obtained were higher at week 24 compared to week 12 and 48.

The steady-state trough serum etanercept concentrations in patients with pediatric psoriasis were comparable to those seen in adult psoriasis patients treated with etanercept 25 mg twice a week. Additionally, the steady-state trough serum etanercept concentrations in patients with pediatric psoriasis were comparable to those seen in patients with juvenile idiopathic arthritis (JIA), 4 to 11 years old, who were treated with 0.4 mg/kg of etanercept twice a week for up to 18 weeks.

Pharmacokinetic analyses indicated no apparent differences regarding exposure between pediatric and adult subjects. Exposure was also comparable between pediatric psoriasis and subjects in trials for juvenile idiopathic arthritis.

Reviewer's comment:
The serum etanercept concentrations in pediatric subjects were highly variable, and the clinical significance of the increased systemic exposure at week 24 is unknown. Also, the applicant did not provide an explanation for the variability in serum concentrations.

5 Sources of Clinical Data

5.1 Table of Studies/Clinical Trials

The clinical trial and study supporting this application are presented in Table 3 below.

Table 3: Trials Supporting the Application

Trial Number	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
20030211	Phase 3, 12-weekrandomized, placebo-controlled, double-blind treatment (Tx) period, open-label Tx period, then double-blind withdrawal retreatment period	Etanercept 0.8 mg/kg up to 50 mg given weekly; subcutaneous	Efficacy: PASI[1] 75 after 12 weeks, sPGA[2] Safety: adverse events	12-week Tx period, then 132-week open label Tx period	211	Pediatric subjects with moderate to severe plaque psoriasis 4-17 years	42 centers United States and Canada
20050111	Multicenter, open-label extension study	0.8 mg/kg Maximum 50 mg given weekly; subcutaneous	Safety: adverse events, serious and infectious	Up to 264 weeks; some continue until 18 yrs	182	Pediatric subjects with moderate to severe plaque psoriasis 4-17 years	38 centers United States and Canada

1 PASI= Psoriasis Area and Severity Index
2 sPGA = Static Physicians Global Assessment

5.2 Review Strategy

This efficacy supplement review uses the following strategy:

For efficacy, Phase 3 RCT Study 20030211 is reviewed.

For safety, RCT Study 20030211 and Study 20050111 are reviewed. Because the same population from RCT Study 20030211 enrolled into study 20050111, no pooling of data is performed.

In addition to the applicant's submission, case report forms were reviewed. Information requests were made.

5.3 Discussion of Individual Studies/Clinical Trials

The applicant conducted two Phase 3 studies in support of this BLA efficacy supplement, RCT Study 20030211 and OLE Study 20050111.

Phase 3 Trial: RCT Study 20030211

Study Title: Placebo-controlled Multicenter Study With Etanercept to Determine Safety and Efficacy in Pediatric Subjects With Plaque Psoriasis (PEDS)

Study Period: September 8, 2004 to November 6, 2006
Number of Centers: 42 centers in the United States and Canada

Study Objective: To evaluate safety and efficacy of etanercept compared to placebo in pediatric subjects with moderate to severe psoriasis

Study Design: Multicenter, randomized, placebo-controlled trial

Number of Subjects: 211

Study Population: Moderate to severe plaque psoriasis

Key Inclusion Criteria

1. Between 4 and 17 years old, inclusive
2. History of psoriasis for ≥ 6 months at the time of randomization
3. Must meet either of the following criteria:
    - Current or past treatment with phototherapy or systemic psoriasis therapy
    - Poorly controlled, persistent psoriasis despite topical psoriasis therapy
4. During the screening period, must have had stable moderate to severe plaque psoriasis, as defined by
    - stable moderate to severe plaque psoriasis and Static Physician's Global Assessment of Psoriasis (sPGA) score of ≥ 3 (moderate)
    - involvement of ≥ 10% of the BSA
    - PASI score of ≥ 12
5. Must have had an updated immunization schedule according to the American Academy of Pediatrics guideline in the US or the Canadian Immunization Guide in Canada

Key Exclusion Criteria

1. Presence of guttate, erythrodermic, or pustular psoriasis during the screening period
2. Any grade 3 or 4 adverse event, infection, or laboratory toxicity based on the Common Toxicity Criteria (CTC) version 2.0 at the time of the screening visit or between the screening visit and initiation of investigational product administration Any grade 3 or 4 infection within 30 days before the first screening visit or during the screening period
3. Any chronic or recurrent active infection within 6 months of screening (Any acute infection must have been treated and clinically resolved before enrollment.)

4. Psoralen with ultraviolet A phototherapy (PUVA), ultraviolet B (UVB) phototherapies, and ultraviolet A phototherapy (UVA) within 14 days before the first dose of investigational product
5. Previous receipt of etanercept or any other anti-TNF agent, or receipt of systemic biologic agents within 30 days before the first dose
6. Receipt of any other systemic psoriasis therapy or oral parenteral corticosteroids within 14 days before the first dose of investigational product
7. Topical steroids greater than moderate strength, topical vitamin A or D analog preparations, anthralin, or calcineurin inhibitors within 14 days before the first dose of investigational product
8. Receipt of live attenuated vaccine or intranasal influenza vaccine within 12 weeks before the first dose of investigational product
9. Current use of medication known to aggravate psoriasis
10. Significant concurrent medical conditions, including
    - diagnosis of multiple sclerosis or any other demyelinating disease
    - insulin-dependent diabetes mellitus
    - history of cancer
    - known human immunodeficiency virus, hepatitis B virus or hepatitis C virus infection
11. Any evidence of cutaneous basal or squamous cell carcinoma or melanoma during screening

The static Psoriasis Global Assessment (sPGA) and Psoriasis Area and Severity Index (PASI) were used to evaluate psoriasis for the subjects in both trials. (Tables 4 and 5)

Table 4: Static Psoriasis Global Assessment Scale (sPGA)

5	*Severe*	Very marked plaque elevation, scaling, and/or erythema
4	*Marked*	Moderate plaque elevation, scaling, and/or erythema
3	*Moderate*	Intermediate between moderate and mild
2	*Mild*	Slight plaque elevation, scaling, and/or erythema
1	*Almost clear*	Intermediate between mild and clear
0	*Clear*	No signs of psoriasis (postinflammatory hyperpigmentation may be present)

Source: Adapted from Langley, RG, Ellis CN Evaluating psoriasis with Psoriasis Area and Severity Index, Psoriasis Global Assessment, and Lattice System Physician's Global Assessment, J Am Acad Derm, (51):4, October 2004, Pages 563–569.

Table 5: Psoriasis Area and Severity Index (PASI)

0	clear, except for residual discoloration
1	majority of lesions have individual scores for induration[a], erythema[b] and scaling[c] (IES) that **averages 1**
2	majority of lesions have individual scores for induration[a], erythema[b] and scaling[c] (IES) that **averages 2**
3	majority of lesions have individual scores for induration[a], erythema[b] and scaling[c] (IES) that **averages 3**
4	majority of lesions have individual scores for induration[a], erythema[b] and scaling[c] (IES) that **averages 4**
5	majority of lesions have individual scores for induration[a], erythema[b] and scaling[c] (IES) that **averages 5**

[a] **induration**
- *0 no evidence of plaque elevation*
- *1 minimal plaque elevation, ≈ 0.5 mm*
- *2 mild plaque elevation, ≈ 1 mm*
- *3 moderate plaque elevation, ≈ 1.5 mm*
- *4 marked plaque elevation, ≈ 2 mm*
- *5 severe plaque elevation, ≈ 2.5 mm or more*

[b] **erythema**
- *0 no evidence of erythema, hyperpigmentation may be present*
- *1 faint erythema*
- *2 light red coloration*
- *3 moderate red coloration*
- *4 bright red coloration*
- *5 dusky to deep red coloration*

[c] **scaling**
- *0 no evidence of scaling*
- *1 minimal; occasional fine scale over less than 5% of the lesion*
- *2 mild; fine scale predominates*
- *3 moderate; coarse scale predominates*
- *4 marked; thick, non-tenacious scale predominates*
- *5 severe; very thick tenacious scale predominates*

Source: Applicant's submission, OLE Study 20050111, Appendix 3.

Visits and Procedures

The study consisted of three treatment periods; a 12-week double-blind treatment period; a 24-week, open label treatment period; 12-week a randomized double-blind withdrawal- retreatment period. Etanercept was dosed with 0.8mg/kg (up to 50 mg) per dose, once a week, subcutaneously.

The first study period was a 12-week, randomized, double-blind placebo-controlled treatment period, during which subjects were randomized in a 1:1 ratio to receive etanercept or placebo. At or after week 4 of this period, subjects with > 50% worsening (i.e., increase) in Psoriasis Area and Severity Index (PASI) score compared with baseline, and an absolute increase of at least 4 points, were allowed to immediately enter an escape arm to receive open-label etanercept QW through week 12. For subjects who had a ≥ 25% but ≤ 50% worsening in PASI score from baseline, the disease severity was to be reassessed by a repeat PASI measurement at the next scheduled visit or sooner if deemed needed (in 7 days). If the PASI at this reassessment visit remained at ≥ 25% worsening in PASI score from baseline and an absolute increase of at least 4 points, the subject was permitted to enter the escape arm and begin open-label etanercept QW at that time.

The second treatment study period was a 24-week open-label treatment period. Those subjects who achieved a PASI 50 response at week 24 and a PASI 75 response at week 36 were

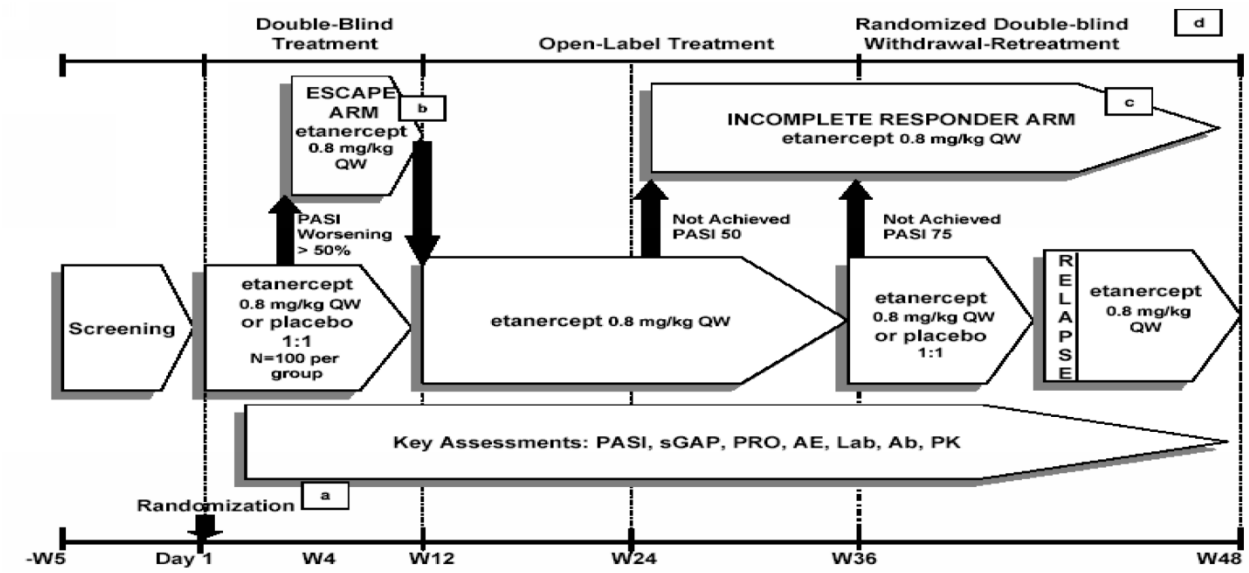
considered responders, and eligible to enter the investigational withdrawal period. Those subjects who did not achieve a PASI 50 response at week 36 entered the incomplete responder arm through week 48 and were not eligible for the withdrawal-retreatment period (period 3).

The third treatment study period was the 12-week withdrawal-retreatment period, for the responders. Subjects who achieved a PASI 75 were considered to be responders to therapy and were to be re-randomized to placebo or etanercept QW in a double-blind manner for the 12-week of treatment. All subjects were to be followed every 4 weeks and assessed for disease relapse during the blinded treatment. Relapse was defined as a loss of PASI 75 response or < 75% decrease (i.e., improvement) in PASI score compared with baseline. Upon relapse, subjects were to resume open-label treatment with etanercept QW through week 48.

The schedule of study procedures is presented in Figure 1 below.

Subjects who did not achieve a PASI 75 response at week 36 were given the option to discontinue the study or to enter the incomplete-responder arm. Incomplete responders were to continue to receive etanercept QW until the end of the study, and had the additional option of receiving topical standard of care at the discretion of the investigator.

Figure 1: Study Design Schematic, RCT Study 20030211



a Subjects were considered to be enrolled after the subject was determined to be eligible for the study and a randomization call was made into the interactive voice response system. Randomization was stratified based on age group (4 to 11 vs 12 to 17 years of age). Baseline assessments and the first dose administration were to be done on the same day. If unavoidable, randomization could have been done 1 business day earlier.
b Subjects who had a disease worsening on or after week 4 through 12 were eligible to receive open-label etanercept treatment.
c Subjects who did not achieve a PASI 50 response at week 24 or did not achieve a PASI 75 response at Week 36 were eligible to enter the incomplete-responder arm.
d Subjects who achieved a PASI 75 response at week 36, not including those already in the incomplete responder arm, were to be randomized to the active or placebo arm, and resumed open-label treatment
upon disease relapse.
e Etanercept 0.8 mg/kg (up to an intended dose of 50 mg) was to be administered QW using 1 or 2 vials.
Ab = anti-etanercept antibodies; AE = adverse events; Lab = laboratory; PK = pharmacokinetics;
PRO = patient reported outcomes; QW = once weekly; sPGA = static physician global assessment

Source: Applicant's Submission, 20030211, page 1326.

Table 6: Schedule of Procedures, RCT Study 20030211

			DB Treatment Period				**OL Treatment** Period				**Randomized DB-Withdrawal-Retreatment Period**	Week 48 or **Early Termination**	FU Visit
Visit	Screen/ Washout	Baseline	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16,20	Wk 24	Wk 28,32	Wk 36	Wk 40,44	EOT	
Day*	–35 to 0	Day 1	15	29	57	85	113, 141	169	197, 225	253	281, 309	337	
Assessment													
Informed Consent[1]	X												
Medical & Medication history[2]	X												
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X
Static Physician global assessment	X	X	X	X	X	X	X	X	X	X	X	X	
Body Surface Area Involvement	X	X	X	X	X	X	X	X	X	X	X	X	
CDLQI		X	X	X		X		X		X		X	
Peds QL		X				X		X		X		X	
Stein Impact on Family[3]		X				X		X		X		X	
Harter's Self Perception Profile for Children		X				X		X				X	
Joint pain[4]		X		X		X		X		X		X	
Photos[4]		X		X		X		X		X		X	
Nail Photos & NAPSI[4,5]		X		X		X		X		X		X	
Hematology profile	X			X		X		X		X		X	
Chemistry profile	X			X		X		X		X		X	
Urinalysis	X			X		X		X		X		X	
Serum Pregnancy test[6, 7]	X												
Urine Pregnancy test[6]		X											
Serum sample for vaccination[8]		X[8]											
Anti-nuclear Antibodies		X										X	
Varicella zoster antibody titers[8]		X											
Pharmacokinetic serum sample[9]		X				X		X				X	X[11]
Anti-Etanercept antibodies		X				X						X	X[11]
Adverse events[10]		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X
Drug Dispensed		X		X	X	X	X	X	X	X	X		

* As baseline is day one, all visits will be at the end of the corresponding week + 1 day
1 Informed consent may be obtained more than 35 days before day 1
2 If considered to be at high risk for TB, screen and treat according to the CDC guideline
3 Caregiver must attend visit with child
4 If applicable
5 NAPSI will be scored centrally
6 If female subject of childbearing potential
7 Serum pregnancy test must be repeated during the study if suspicious of pregnancy
8 Baseline sample will be collected from all subjects; follow-up sample will be collected at ≥4 weeks (next visit) following any inactivated vaccine immunization and/or VZV infection that occur during the study
9 Draw sample prior to dose
10 Adverse events will be assessed after the 1st dose
11 Draw sample if anti-etanercept antibody or pharmacokinetic sample not drawn at End of Treatment (week 48)

Source: Applicant's table, RCT Study 20030211, Appendix A, page 1385.

Prohibited Medications and Procedures

Use of systemic psoriasis agents, parenteral steroids, topical steroids of greater than moderate strength, and ultraviolet light treatments were prohibited.

Safety Evaluations

The following safety procedures were conducted:
Physical examination: At screening; Baseline; Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48; follow up visit.
Vital signs: At screening; Baseline; Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48.
Height: At screening; Baseline; Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48.
Weight: At screening; Baseline; Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48.

Pregnancy test: At screening; Baseline; as appropriate.
Laboratory Evaluations (Hematology profile, Chemistry profile, Urinalysis): At screening; Weeks 4, 12, 24, 36, 48.
Anti-nuclear antibodies: Baseline; Week 48.
Varicella zoster antibody titers: Baseline.
Pharmacokinetic serum samples: Baseline; Weeks 12, 24, 48.
Anti-etanercept antibodies: Baseline; weeks 12, 48.

Efficacy Evaluation
The primary efficacy endpoint was the PASI 75 response at week 12. PASI 75 response was defined as 75% or greater improvement from baseline in PASI score.

Secondary endpoints were:
1. PASI 50 response at week 12
2. PASI 90 response at week 12
3. Clear or almost clear status of Static Physician Global Assessment of psoriasis (sPGA) at week 12
4. Percent improvement from baseline in Children's Dermatology Life Quality Index (CDLQI) at week 12

Phase 3 Trial: OLE Study 20050111

Study Title: An Open-label Extension Study to Evaluate the Safety of Etanercept in Pediatric Subjects with Plaque Psoriasis

Study Period: August 11, 2005 to February 22, 2012.

Number of Centers: 38 centers in the United States and Canada.

Study Objective: To evaluate the long-term safety and efficacy of etanercept in pediatric subjects with moderate to severe psoriasis who participated in RCT Study 20030211.

Study Design: This was a multicenter, open label extension trial.

Number of Subjects: 182

Study Population: Chronic moderate to severe pediatric psoriasis subjects from RTC Study 20030211

Key Inclusion Criteria

1. Subjects must have met one of the following conditions:
   a. Complete the week 48 visit on the RCT Study 20030211, or

   b. Complete at least the week 12 visit on the RCT Study 20030211 and have received benefit from the investigational product therapy as demonstrated by achieving ≥ PASI 50 on or after week 12.
2. Subjects entering the study following an interruption of investigation product administration > 4 weeks between the last dose on the RCT Study 20030211 and the first dose on this extension study 20050111, must meet the following additional criteria:
   a. No active guttate, erythrodermic, or pustular psoriasis during the screening period.
   b. No presence of a grade 3 or 4 infection ≤ 30 days before the first screening visit or during the screening period.
   c. ALT or AST ≤ 2.0 times the upper limit of normal for the age range
   d. Creatinine ≤ 1.5 times the upper limit of normal for the age range.
   e. White blood cell count ≥ 2.0 x 109/L.
   f. Hemoglobin ≥ 8.5 g/dL.
   g. Platelet count ≥ 150 x 109/L.
   h. Female subjects of childbearing potential must have negative serum pregnancy test at screening and a urine pregnancy test at day 1.

Key Exclusion Criteria

1. Any serious adverse event reported during the RCT Study 20030211 and considered to be related to investigational product.
2. Any grade 3 or 4 adverse event reported during the RCT Study 20030211 and considered related to study drug must be discussed between Amgen and the investigator.
3. Receipt of PUVA, UVB, UVA, systemic psoriasis therapy other than etanercept, parenteral corticosteroids, oral corticosteroids, or potent topical steroids ≤ 14 days before the first dose on OLE study 20050111 (potent topical steroids are defined as greater than moderate strength)
4. Receipt of systemic biologics or investigational product(s) other than etanercept ≤ 30 days before the first dose on Study 20050111.
5. Receipt of live attenuated vaccines ≤ 12 weeks prior to the first dose on this extension study 20050111.

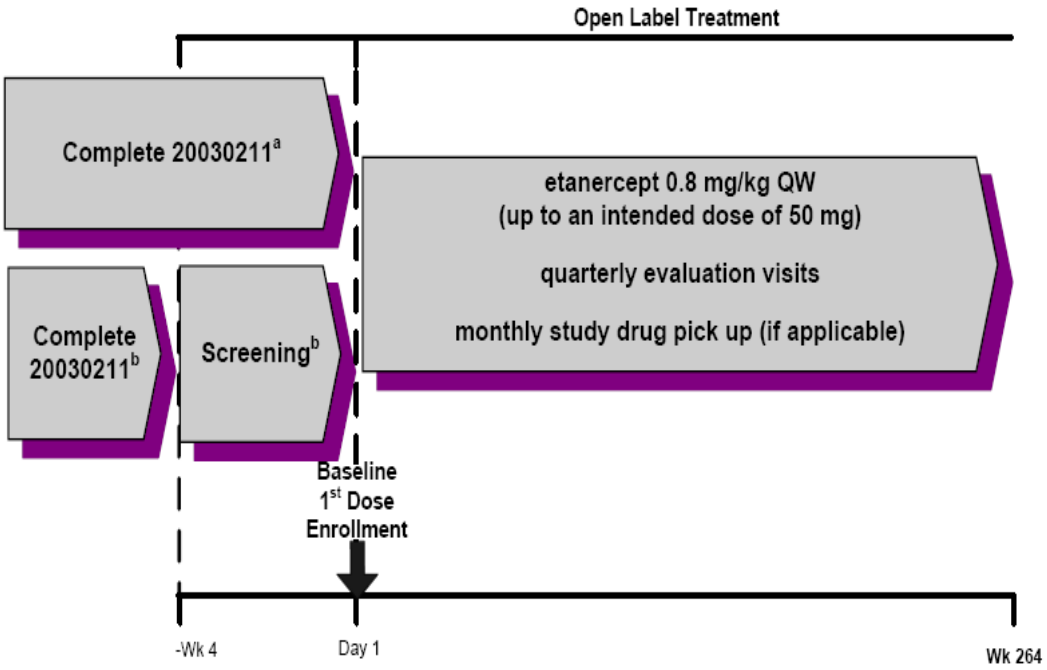
OLE Study 20050111 Visits and Procedures

This study consisted of an open-label treatment period for subjects who had participated in RCT Study 20030211 and met the inclusion criteria. Etanercept 0.8 mg/kg (up to 50 mg) subcutaneously was given once a week up to 264 weeks, or until the visit after the subject turned 18 years (if later than week 264). Study visits were scheduled quarterly.

Subjects with a Static Physician Global Assessment (sPGA) score of clear (0) or almost clear (1) were allowed to stop treatment with investigational product at Week 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, or 252. Subjects were allowed to restart treatment at any time. A subject was allowed to stop and restart treatment with investigational product more than once if appropriate. Subjects with an sPGA of clear/almost clear and stopped treatment with investigational product at or after Week 96 continued safety evaluations every 12 weeks.

The schedule of study visits and procedures is below. (Figure 2)

Figure 2: Open Label Study Design Schematic, OLE Study 20050111



Subjects may continue to Week 264 or until the quarterly visit after the subject's 18th birthday, whichever is later.
Source: Applicant's Submission, protocol 20050111.

APPEARS THIS WAY ON ORIGINAL

Table 7: Schedule of Procedures, OLE Study 20050111

	>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[5]
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[4]		X[5]
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]																		

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

Source: Applicant's submission, Study 20050111, page 1181.

Prohibited Medications and Procedures
Parenteral steroids and topical steroids stronger that moderate strength, systemic psoriasis medications, and ultraviolet light treatments were prohibited.

Safety Evaluations
Evaluations for safety were conducted during the OLE study quarterly visits and at the end of treatment visit (EOT) according to the schedule. If the subject had not received a dose of etanercept in over four weeks prior to entering the OLE Study, screening and baseline evaluations were to be performed. Subjects who had not reached age 18 years by week 264 were allowed to continue in the study with quarterly visits, until the quarterly visit after turning 18 years.

The following safety procedures were conducted at each quarterly visit/EOT:

- Physical examination
- Vital signs
- Height
- Weight
- Laboratory Evaluations (Hematology profile, Chemistry profile)
- Adverse event and concomitant medication review

The following safety evaluations were performed according to the following schedule:

- Pregnancy test: as appropriate.
- Urinalysis: Weeks 24, 48, 96, 120, 144, 168, 192, 216, 240, 264/EOT.
- Anti-nuclear antibodies: Weeks 48, 96, 144, 168, 264/EOT.
- Anti-etanercept antibodies: Baseline; 48, 96, 144, 168, 264/EOT.

6 Review of Efficacy

Efficacy Summary

The primary evidence of efficacy was based on RCT Study 20030211, a Phase 3, placebo-controlled, double-blind, 48 week trial evaluating the safety and efficacy of etanercept 0.8 mg/kg subcutaneously once a week for the treatment of moderate to severe psoriasis in children 4 to 17 years, who are candidates for phototherapy or systemic therapy.

RCT Study 20030211 enrolled 211 subjects, age 4 to 17 years, with plaque psoriasis. Etanercept 0.8 mg/kg subcutaneously once a week or placebo was administered weekly for 12 weeks.

The primary efficacy endpoint for RCT Study 20030211 was the number of subjects achieving Psoriasis Area and Severity Index (PASI) 75 response at week 12. After 12 weeks of etanercept treatment, 60 (56.6%) of etanercept-treated subjects achieved PASI 75 compared with 12 (11.4%) of subjects receiving placebo.

The co-primary endpoint was sPGA status clear or almost clear (0 or 1 on a five point scale), or 2 point improvement in sPGA score at week 12.

6.1 Indication

The applicant's proposed indication is for the treatment of pediatric patients ages 4 to 17 years with chronic severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

6.1.1 Methods

The applicant is relying on RCT Study 20030211 to provide evidence of efficacy to support approval. The data from this trial was reviewed previously during the review cycle of efficacy supplement #5350 of this BLA. Efficacy data will not be re-analyzed by this reviewer.

The intent-to-treat (ITT) analysis set includes all randomized subjects regardless of the receipt of etanercept. The subjects were analyzed according to their original randomized treatment group, placebo or etanercept.

6.1.2 Demographics

Overall, baseline demographic characteristics of the study population were similar across the study arms. The majority of subjects were white, belonged to 12-17 year age group and overweight. These demographic characteristics are consistent with that of pediatric population with moderate to severe psoriasis. Baseline characteristics of the study population are presented in Table 8 below.

Table 8: Baseline Demographic Characteristics, Initial 12 Week Double-Blind Period (RCT Study 20030211)

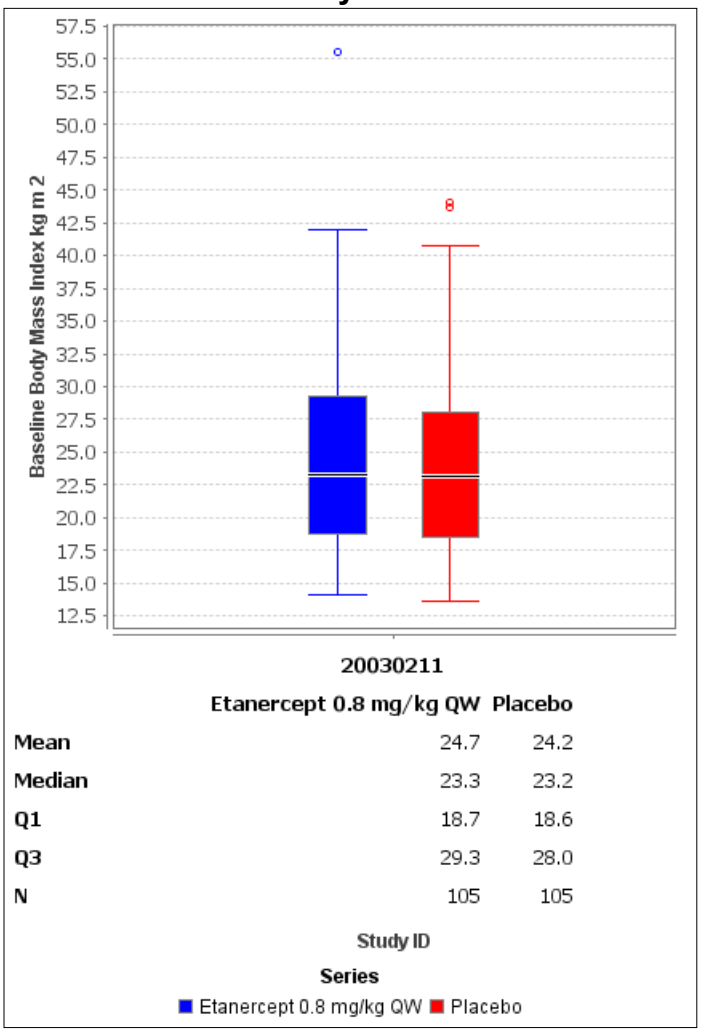
Demographic Parameters	Etanercept 0.8 mg/kg QW (N=106) n (%)	Placebo (N=105) n (%)	Total (N=211) n (%)
Sex			
Male	55 (51.9)	53 (50.5)	108 (51.2)
Female	51 (48.1)	52 (49.5)	103 (48.8)
Age			
Mean years (SD)	12.8 (3.7)	12.6 (3.5)	12.7 (3.6)
Median (years)	14	13	13
Min, Max (years)	4, 17	4, 17	4, 17
Age Group			
>= 4 <= 11	38 (35.8)	38 (36.2)	76 (36.0)
>= 12 <= 17	68 (64.2)	67 (63.8)	135 (64.0)
Race			
White	83 (78.3)	75 (71.4)	158 (74.9)
Black or African American	3 (2.8)	8 (7.6)	11 (5.2)
Asian	9 (8.5)	6 (5.7)	15 (7.1)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	1 (0.9)	0 (0.0)	1 (0.5)
Other	10 (9.4)	16 (15.2)	26 (12.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity			
Hispanic or Latino	8 (7.5)	14 (13.3)	22 (10.4)
Not Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)
Missing	98 (92.5)	91 (86.7)	189 (89.6)
Region			
United States	72 (67.9)	79 (75.2)	151 (71.6)
Canada	34 (32.1)	26 (24.8)	60 (28.4)
Africa	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)

n=number of subjects
SD=standard deviation
Data Source: ptinfo; Applicant's submission, Table 8.2.

Reviewer's comment:
Psoriasis subjects age 4 to 11 years were underrepresented; only 36% of subjects in this age group were enrolled. Also, African Americans were underrepresented, and Asians were overrepresented in this trial when compared to the general population affected by psoriasis.

The mean body mass index (BMI) for RCT Study 20030211 was comparable for the etanercept and placebo groups. The BMI was increased for both etanercept and placebo groups compared with the general population with significantly high outliers for both the treatment and placebo groups.

Figure 3: Body Mass Index, Etanercept and Placebo Groups, RCT Study 20030211



Source: Reviewer's Figure.

Reviewer's comment:
Pediatric psoriasis has been associated with obesity and high BMI. One retrospective pilot study of 37 children with psoriasis reported the mean BMI was the 96th percentile, with 30% overweight and 70% obese.[11]

11 Becker L, et al. *JAMA Dermatol.* 2014;150(5):573-574

Baseline Disease Characteristics

The baseline disease characteristics were similar across treatment arms. (see Table 9) The psoriasis body surface area (BSA) mean was 25.88%, with a range from 10 to 95% involvement.

The mean duration of psoriasis was 6.1 years, with a range of 0 to 18 years.

The median PASI score was 16.40, with a SD of 6.9 and median of 16.6, and range from 12.00 to 56.70.

For the sPGA, 64.9% subjects were classified with moderate psoriasis (score 3), and 31% with marked psoriasis. Only 6 subjects (3.0%) entering RCT Study 20030211 were classified as affected by severe psoriasis (5). Psoriatic arthritis was noted in 19 (9.3%) of subjects. The majority of study subjects had used systemic or phototherapies, at 58.8%. Baseline disease characteristics are presented in Table 9.

Table 9: Baseline Disease Characteristics, RCT Study 20030211

	Study 20030211 Placebo (N=105)	Study 20030211 Etanercept 0.8 mg/kg QW (N=106)	Total (N=211)
Psoriasis BSA (%)			
mean	24.78	26.06	25.42
SD	14.97	15.93	15.43
Min, Max	10.00, 95.00	10.00, 90.00	10.00, 95.00
Psoriasis area and Severity Index (PASI)			
n	91	89	180
Mean	5.270	4.391	4.836
SD	5.656	3.822	4.843
Min, Max	0.00, 26.90	0.00, 18.60	0.00, 26.90
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	1 (0.9)	1 (0.9)	2 (0.9)
3	68 (64.7)	69 (65.0)	137 (64.9)
4	33 (31.4)	33 (31.1)	66 (31.2)
5	3 (2.8)	3 (2.8)	6 (2.8)
Previous Use of Systemic therapy or Phototherapy = n (%)			
No	43 (40.9)	48 (45.2)	91 (43.1)
Yes	62 (59.0)	58 (54.7)	120 (56.8)
Psoriatic Arthritis			
No	91 (86.6)	101 (95.2)	192 (90.9)
Yes	14 (13.3)	5 (4.7)	19 (9.0)

N=number of subjects
SD=standard deviation
Source: Adapted from Applicant's submission, RCT Study 20030211, Table 8-3.

Reviewer's comment:
Only six subjects with severe psoriasis (sPGA score of 5) were enrolled. With three subjects in each the etanercept and placebo arms, only three subjects with severe psoriasis were exposed to study drug. Three subjects exposed to etanercept are inadequate to assess severe psoriasis in pediatric subjects.

The baseline assessment of psoriasis severity for RCT Study 20030211, by age group, is presented in Table 10. Approximately twice as many subjects were in the moderate severity group, as compared to the marked and severe groups. The number of subjects in the severe psoriasis group is six subjects, with 2 subjects in the 4 to 11 year age group.

Table 10: Dermatologist Assessment of Psoriasis Severity by Age Group, at Baseline, for RCT Study 20030211

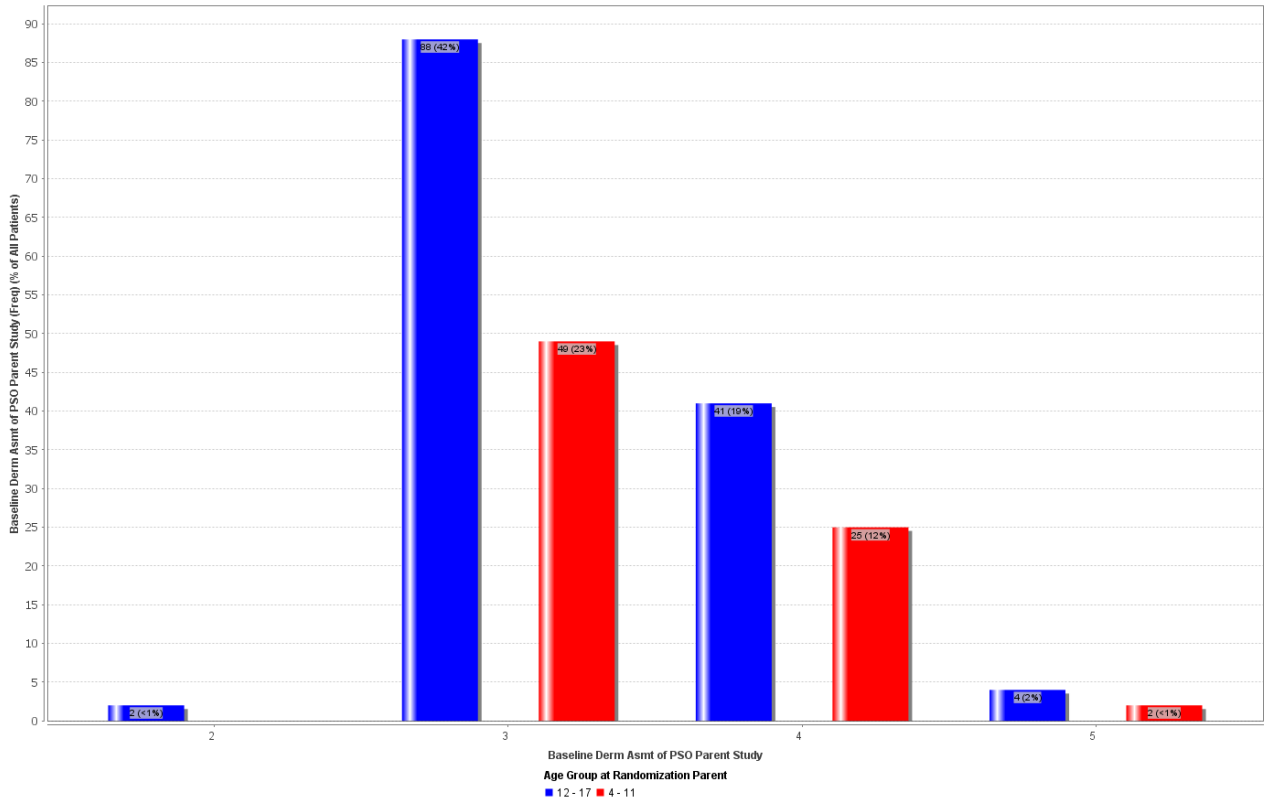
Age Group n (%)	Clear	Mild	Moderate	Marked	Severe	Total Subjects
Age 4 to 11 years	0	0	49	25	2	76
Age 12 to 17 years	0	2	88	41	4	135
Total Subject Severity	0	2	137	66	6	211

Source: Reviewer's Table

Reviewer's comment:
Two subjects in the 4 to 11 year age group are too few to draw conclusions regarding severe pediatric psoriasis.

The sPGA at baseline by age groups (4 to 11 years and 12 to 17 years) for RCT Study 20030211 is shown in Figure 4. For each age group, most subjects were in the moderate psoriasis severity group, followed by the marked psoriasis severity group.

Figure 4: Baseline sPGA Score by Age Group, 4 to 11 Years and 12 to 17 years



Source: Reviewer's figure.

APPEARS THIS WAY ON ORIGINAL

6.1.3 Subject Disposition

For RCT Study 20030211, 91.9% of the subjects completed the study. For subject disposition of subjects in Study 20030211, see Table 11 below.

Table 11: Subject Disposition for RCT Study 20030211

	Placebo	Etanercept 0.8 mg/kg QW	Total
Subjects who received at least one dose of IP in Study 20030211	105	106	211
Subjects who completed Study 20030211 - n (%)	96 (91.4)	98 (92.5)	194 (91.9)
Subjects who discontinued Study 20030211 - n (%)	9 (8.6)	8 (7.5)	17 (8.1)
Adverse event	3 (2.9)	3 (2.8)	6 (2.8)
Lost to follow-up	2 (1.9)	3 (2.8)	5 (2.4)
Consent withdrawn	2 (1.9)	2 (1.9)	4 (1.9)
Administrative decision	1 (1.0)	0 (0.0)	1 (0.5)
Noncompliance	1 (1.0)	0 (0.0)	1 (0.5)

N = number of subjects who were randomized in RCT Study 20030211.
Treatment groups represent original randomized treatment from RCT Study 20030211.
Source: Applicant's Submission, Integrated Summary of Safety, Table 14-1.1.1, page 12.

Reviewer's comment:
During the double-blind period, one subject with severe psoriasis treated with etanercept withdrew due to an adverse event.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for RCT Study 20030211 was PASI 75 at week 12.

Table 12: Primary Efficacy Results for RCT Study 20030211

	Placebo N=105 (%)	Etanercept N=106 (%)	P-value[1]
PASI 75 Number of Successes	12 (11.4%)	60 (56.6%)	<0.0001

[1]p-value was calculated using CMH test, stratified by age group.
All missing values were imputed as failures.
Source: Applicant's submission, Summary of Clinical Efficacy, Table 7.

Reviewer's comment:
The difference between etanercept group and placebo for PASI 75 successes at 12 weeks was statistically significant. Statistical analysis was not conducted for severe psoriasis, as there were too few severe subjects to perform any analyses.

6.1.5 Analysis of Secondary Endpoints

The applicant's secondary efficacy endpoints for the placebo-controlled study showed that a statistically significant proportion of subjects in the etanercept group achieved PASI 50 and PASI 90 responses compared with placebo at week 12. (Table 13)

Table 13: Number of Subjects Achieving PASI 50 and PASI 90 in RCT Study 20030211 at 12 Weeks

	Placebo N=105 n (%)	Etanercept N=106 n (%)
PASI 50	24 (22.9)	79 (74.5)
PASI 90	7 (6.7)	29 (27.4)

Missing values were imputed as failures.
Source: Reviewer's table.

Reviewer's comment:
The PASI 90 successes are significant at 12 weeks. PASI 50 successes are not considered a clinically significant endpoint by the Agency, and this endpoint and results will not be included for labeling.

The sPGA score at Week 12 was considered a co-primary endpoint by the Agency and a secondary endpoint by the applicant. Statistically significant improvements for sPGA for the etanercept subjects relative to placebo subjects for clear/almost clear status were noted at Week 12. (Table 14) The sPGA score at Week 12 showed few subjects who were clear, and there was little difference between placebo and etanercept groups. For the subjects who were clear/almost clear, there was a statistically significant difference between placebo and etanercept groups due to those who were almost clear.

Table 14: Static Physician's Global Assessment (sPGA) at 12 weeks, RCT Study 20030211

	Placebo N=105 n (%)	Etanercept 0.8 mg/kg QW N=106 n (%)	P value[1]
Clear (0)	3 (2.8)	7 (6.6)	0.2005
Clear (0)/Almost Clear (1)	14 (13.3)	56 (52.8)	< 0.0001

N= number of subjects in arm
n=number of subjects responding
[1] Two-sided Cochran-Mantel-Haenszel test stratified by age group
Source: Adapted from Applicant's Submission, RCT Study 20030211, and Table 9-2.

Reviewer's Comments:
A statistical difference in psoriasis improvement between etanercept and placebo groups was achieved for the primary endpoint of PASI 75 and for the secondary endpoint (Agency co-primary endpoint) of clear or almost clear on sPGA at Week 12. Only seven subjects treated with etanercept were clear, therefore, the statistical difference in the trial was due to those subjects assessed as almost clear.

The secondary endpoint of PASI 50 is not considered as clinically meaningful change and, therefore, will not be included in labeling.

The Children's Dermatology Life Quality Index (CDLQI) is a patient reported outcome endpoint (PRO). This endpoint was not validated by the applicant, therefore this endpoint measure is not eligible for labeling and will not be discussed.

6.1.6 Other Endpoints

No other endpoints were assessed.

6.1.7 Subpopulations

In all subgroups, the numbers of subjects achieving PASI 75 and sPGA success were greater in the etanercept arm than the placebo arm. The percentage of female subjects achieving PASI 75 score was greater than the percentage of male subjects. While a slightly greater percentage of subjects in the 4 to 11 year group achieved PASI 75 compared to the 12 to 17 year group, the number of subjects was small and to make a conclusion based on limited data is difficult. The percentage of subjects achieving PASI 75 was nearly equal across the white and non-white age groups; the number of non-white subjects receiving etanercept was small and therefore

combined. Table 15 below represents analysis of PASI 75 and sPGA successes by age, sex, and race.

Table 15: Number and Percent of PASI 75 and sPGA Successes at 12 weeks by Sex, Age, and Race, RCT Study 20030211

	Placebo N= 105 n (%)	Etanercept 0.8 mg/kg QW N=106 n (%)
Sex		
Male		
Total	53	55
PASI 75	6 (11.3)	30 (54.5)
sPGA	8 (15.1)	25 (45.5)
Female		
Total	52	51
PASI 75	6 (11.5)	30 (58.8)
sPGA	6 (11.5)	30 (58.8)
Age Group		
4-11 years		
Total	38	38
PASI 75	4 (10.5)	22 (57.9)
sPGA	4 (10.5)	19 (50.0)
12-17 years		
Total	67	68
PASI 75	8 (11.9)	38 (55.9)
sPGA	10 (14.9)	36 (52.9)
Race		
White		
Total	75	83
PASI 75	17 (22.6)	47 (56.6)
sPGA	10 (14.9)	46 (55.4)
Non-White		
Total	30	23
PASI 75	4 (13.3)	13 (56.5)
sPGA	4 (13.3)	9 (39.1)

Source: Reviewer's Table
All missing values were imputed as failures.

The number of subjects categorized by baseline sPGA achieving PASI 75 success is shown below. The number and percentage of etanercept-treated subjects with a positive response is greater than placebo in moderate to severe categories. (Table 16)

Table 16: Number and Percentage of PASI 75 Successes based on Baseline sPGA Disease Severity, RCT Study 20030211

	PASI 75	
Baseline sPGA	Placebo N=105 n (%)	Etanercept 0.8 mg/kg QW N=106 n (%)
2 (Mild)		
Total	1	1
Successes	0 (0)	1 (100)
3 (Moderate)		
Total	68	69
Successes	9 (13.2)	36 (52.2)
4 (Marked)		
Total	33	33
Successes	3 (9.1)	20 (60.6)
5 (severe)		
Total	3	3
Successes	0 (0)	3 (100)

All missing values were imputed as failures
Source: Reviewer's Table.

The number of subjects categorized by baseline severity (mild to severe) achieving sPGA success of 0 to 1 is shown below. (Table 17) The number and percentage of etanercept-treated subjects achieving sPGA success is greater than placebo in moderate to severe categories.

Table 17: Number and Percentage of sPGA Successes Based on Baseline sPGA Disease Severity, RCT Study 20030211

	sPGA Success	
Baseline sPGA	Placebo N=105 n (%)	Etanercept 0.8 mg/kg QW N=106 n (%)
2 (Mild)		
Total	1	1
Successes	0 (0)	0 (0)
3 (Moderate)		
Total	68	69
Successes	12 (17.6)	38 (55.1)
4 (Marked)		
Total	33	33
Successes	2 (6.1)	16 (48.5)
5 (severe)		
Total	3	3
Successes	0 (0)	1 (33.3)

All missing values were imputed as failures.
Source: Reviewer's Table

Reviewer's comments:
There was a 3 to 8-fold difference in the sPGA successes favoring the etanercept-treated groups (moderate and marked) over the placebo-treated group.

Of the three severe subjects dosed with etanercept, only one subject in the severe psoriasis group achieved sPGA success, defined as clear or almost clear. The total number of subjects with severe disease was small (6 total), therefore, no conclusion regarding the efficacy in this group of subjects can be drawn. One subject with mild disease was included in the analysis. This subject achieved PASI 75 success but did not achieve sPGA success.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The etanercept dose and regimen was determined in Etanercept JRA trials. Study 20021616 established dose and regimen etanercept 0.4 mg/kg per dose (up to 25 mg) subcutaneously twice a week. Study 20021631 compared 0.4 mg/kg twice a week to 0.8 mg/kg per dose (up to 50 mg) once a week. FDA approved this dose and regimen.

Reviewer's comment:
Etanercept 0.8 mg/kg per week, up to a maximum of 50 mg once per week was the only dose and regimen evaluated in RCT Study 20030211 and OLE Study 20050111. No dose-ranging studies or analyses were conducted during the development of etanercept in the pediatric psoriasis population.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In this section, persistence of efficacy of etanercept 0.8 mg/kg subcutaneously once a week will be discussed as an exploratory endpoint.

In the RCT Study 20030211, the randomized double-blind withdrawal-retreatment period assessed efficacy over time. During this period, subjects who achieved a PASI 50 at 24 weeks or PASI 75 response at 36 weeks were re-randomized to placebo or etanercept 0.8 mg/kg once a week arms. Maintenance of efficacy was evaluated by sPGA and PASI 75 at 40, 44, and 48 weeks. The maintenance of effect was decreased for sPGA success and PASI 75 at weeks 44 and 48. (Table 18)

Table 18: Number of Subjects (%) Maintaining Successes in sPGA and PASI 75 over time, Withdrawal Retreatment Phase, RCT Study 20030211

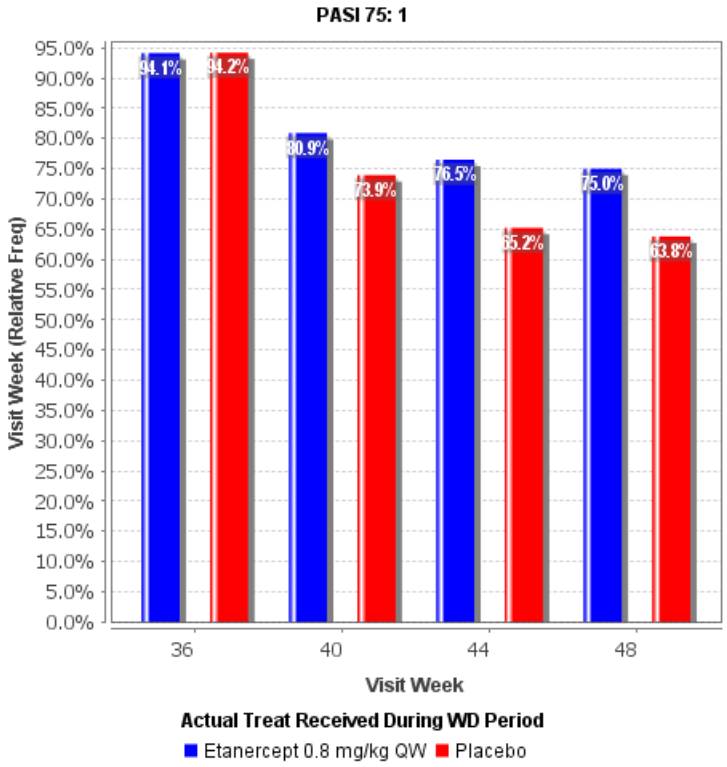
Endpoint	Week	Etanercept N=68 n (%)	Placebo N=69 n (%)
sPGA	36	51 (75.0)	52 (75.4)
	40	41 (62.1)	42 (60.9)
	44	38 (55.1)	30 (43.5)
	48	33 (47.8)	27 (39.1)
PASI 75	36	64 (94.1)	65 (94.2)
	40	54 (79.4)	52 (75.4)
	44	49 (72.1)	40 (58.0)
	48	44 (64.7)	34 (49.3)

N= subjects randomized at week 36, received at least 1 dose etanercept
WD=Withdrawal
RT=Retreatment
Source: Reviewer's Table.

Reviewer's comment:
The sPGA success, clear or almost clear, was not maintained by 18 of the 51 (35.1%) subjects randomized to the etanercept group through week 48. For those randomized to the placebo group, 25 of 52 (48.0%) subjects did not maintain sPGA success through week 48.

For the PASI 75 successes during the withdrawal retreatment period, both the etanercept and placebo arms showed loss of effect. By week 48, the PASI 75 successes for the etanercept group decreased by 31.2%, while the PASI 75 successes for the placebo group decreased by 47.6%, a difference of 16.4% between study drug and placebo. For the etanercept group, loss of PASI 75 was reported for almost one third of the subjects by week 48. The decrease in PASI 75 over time was less in the etanercept group, and more rapid in the placebo group. (Figure 5)

Figure 5: PASI 75 Successes, Withdrawal Retreatment Period, RCT Study 20030211



Source: Reviewer's Figure.

Reviewer's comment:
The decrease in PASI 75 over 12 weeks in the withdrawal-retreatment period for the etanercept-treated group was over 31%. This proportion of subjects treated with etanercept did not maintain efficacy for 3 months. The sPGA success of clear or almost clear was not maintained by over 35% of subjects who achieved success, or by 31.1% of those who entered the treatment arm of RCT Study 20030211.

6.1.10 Additional Efficacy Issues/Analyses

No additional etanercept efficacy analyses were performed.

7 Review of Safety

Safety Summary

The review of the etanercept clinical safety database identified several areas of safety concern associated with etanercept administration in pediatric psoriasis. All of the concerns are known risks in the TNF inhibitor class. Serious adverse events were reported, including severe infections and hospitalizations. These events occurred in the etanercept arm, and not in the placebo arm.

No deaths or malignancies occurred during the pediatric psoriasis etanercept development program; however, this study population was inadequate and the duration of observation too brief to detect any malignancy signals for childhood exposure.

One subject in the open label RCT Study 20030211 treatment arm reported an ovarian mass, and subjects in the OLE Study 20050111 reported a brain mass and a thyroid mass. Reports indicated that each event was associated with significant morbidity.

Postmarketing and pharmacovigilance of etanercept reported cases of malignancy, including lymphoma, leukemia, solid tumors, and melanoma or nonmelanoma skin cancer (NMSC). Two cases of hepatosplenic T-cell lymphoma were reported; one in a psoriasis patient and one in a JIA patient. While the patients may have reported use of medications including methotrexate or another biologic, exposure to etanercept occurred in all cases.

Cervical carcinoma and HPV-related malignancies are a potential new signal, observed at an increased rate and at younger ages than expected. The risk for HPV-related malignancy may be mitigated by administering the HPV vaccine series before etanercept treatment; however, use of the HPV vaccine and the effect on related cancers was not investigated during the development program.

Increased numbers of serious infections and other infectious events attributed to etanercept treatment were reported during the RCT Study when compared to placebo as well as during the OLE Study. Serious infections are not a feature of psoriasis in children, and constitute a risk which cannot be mitigated.

Neuropsychiatric events were not specifically evaluated or monitored for during RCT Study 20030211 or OLE Study 20050111. Nine serious events, including hospitalizations, were detected upon review of the case report forms and this application. Though depression has been associated with psoriasis, the severity of psoriasis was not related to the risk of major depression.[5]

Cardiovascular events and neurologic adverse events occurred during the trial; however, there is insufficient information to determine risk with the use of etanercept in pediatric psoriasis.

Finally, 95% of the pharmacovigilance reports were spontaneous reports, which are known to be associated with underreporting of significant adverse events, malignancies, and possibly deaths.

7.1 Methods

For the RCT Study 20030211, adverse events, infections, injection site reactions, laboratory toxicity (based on Common Toxicity Criteria version 2.0), vital signs, etanercept antibodies, and disease rebound during the randomized double-blind withdrawal period were reported. Disease rebound was defined as a post-baseline PASI score that was > 125% of baseline PASI within 3 months of treatment discontinuation. Safety evaluations reported at baseline, and 2, 4, 8, and 12 weeks were analyzed.

During the open label period and end of treatment, safety assessments were limited to chemistry profile, hematology profile, and urinalysis.

During the OLE Study 20050111, all subjects received etanercept 0.08 mg/kg (up to 50 mg) subcutaneously once a week. Safety evaluations were conducted quarterly until week 264 or until the 18th birthday, whichever occurred later.

Changes in laboratory, physical exam, and vital sign values and the presence or absence of an antibody response will also be analyzed for safety.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database consists of data from one RCT Study 20030211 and one OLE Study 20050111.

7.1.2 Categorization of Adverse Events

For RCT Study 20030211, the adverse events were categorized by Medical Dictionary for Regulatory Activities (MedDRA); the MedDRA version was not specified.

For the OLE study 20050111, all adverse events were coded using MedDRA version 14.1. The narrative reports were coded using MedDRA version 15.0. According to the statistical analysis plan, the safety analyses used MedDRA version 18.0 to code all adverse events, and the integrated data will be migrated to the later version.

The applicant established a Data Monitoring Committee (DMC) to review safety data, including adverse events, eligibility, protocol deviations. The DMC met regularly (at least biannually) to discuss the OLE study. The voting members of the committee were independent of the drug manufacturing company. The committee was discontinued after five years.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The data from the placebo-controlled study and OLE Study 20050111 are derived from the same subject population. For this reason the safety data from these two studies will be reviewed separately.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

During the RCT Study 20030211, the number of subjects with etanercept exposure was 179 (85.2%) at one year; RCT Study 20030211 ended at 48 weeks. Afterwards, the number of subjects receiving etanercept decreased due to entry criteria for OLE Study 20050111, and subject discontinuation which occurred due to adverse events, withdrawal of consent, lost to follow up, and administrative concerns. (See Section 7.3.3)

Table 19: Number of Subjects Receiving Etanercept, and Cumulative Exposure Duration

Duration of cumulative exposure – n (%)	
≥ 1 dose	210 (100.0)
≥ 3 months	206 (98.1)
≥ 6 months	199 (94.8)
≥ 12 months	179 (85.2)
≥ 24 months	153 (72.9)
≥ 36 months	125 (59.5)
≥ 48 months	103 (49.0)
≥ 60 months	79 (37.6)
≥ 72 months	18 (8.6)

N = number of subjects who received at least one dose of etanercept.
Etanercept exposure does not include the time periods when subjects were not receiving etanercept per study design.
Source: Adapted from Applicant's submission, Integrated Summary of Safety, Table 14-5.1.1, page 13.

For RCT Study 20030211, 194 (91.9%) subjects completed the trial. From this study, 182 subjects enrolled in the OLE Study 20050111. During the OLE Study, the number of participating subjects decreases to 15% participation at week 264.

Table 20: Disposition of Subjects, RCT Study 20030211 and OLE Study 20050111

	Etanercept n	Placebo n
Subjects randomized in RCT Study 20030211	106	105
Subjects completing RCT Study 20030211	98	96
Subjects enrolled in OLE Study 20050111	90	92

Study 20050111	Etanercept (N=182) n (%)
Completed Week 48	168 (92)
Completed Week 96	140 (77)
Completed Week 264	63 (35)
Remaining on Study past Week 264	28 (15)

n= number of subjects
N=total number of subjects enrolled
Source: Table prepared by Dr. Kathleen Fritsch, Statistical Reviewer.

Reviewer's comment:
The low number of subjects enrolled at the conclusion of OLE Study 20050111 is not unusual for a prolonged clinical observational study. At week 264, only one subject assessed with severe psoriasis at baseline remained in the study.

Demographics of the target population

Baseline demographics of the study population were similar across the treatment arms for the placebo-controlled arms. The majority of the subjects were white, age 12 to 17 years, and from U.S. centers. Male and female subjects were approximately equal in number overall.

The baseline disease characteristics for subjects entering RCT Study 20030211 were discussed in section 6.1.2.

The baseline disease characteristics for subjects entering OLE Study 20050111 are described in Table 21, below.

Table 21: Baseline Disease Characteristics for OLE Study 20050111, Based on RCT Study 20030211

	RCT Study 20030211		
	Placebo (N=92)	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
Median	22.000	21.550	21.800
Min, Max	10.00, 95.00	10.00, 95.00	10.00, 95.00
Psoriasis area and Severity Index (PASI)			
n	92	90	182
Mean	18.715	18.750	18.732
SD	6.821	7.028	6.905
Median	16.450	16.950	16.600
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)

n=number of subjects
SD=standard deviation
SE=standard error
Source: Adapted from Applicant's submission, Study 20050111, Table 8-3.

Reviewer's comment:
The moderate psoriasis group accounted for 66.5% of OLE Study participants. The number of subjects affected by severe psoriasis who enrolled in OLE Study 20050111, the proposed indication, was low at 4 subjects. Only one subject assessed with severe psoriasis in the 4 to 11 year age group was enrolled in OLE Study 20050111, an inadequate number of severe subjects in the younger age group. No conclusions regarding safety in severe pediatric psoriasis could be performed due to the inadequate number of severe psoriasis subjects.

Study Discontinuations

Seventeen subjects discontinued from RCT Study 20030211; the reasons for discontinuation were discussed in Section 6.1.3. For OLE Study 20050111, 62.4% of subjects discontinued before Week 264. See Table 22 below.

Table 22: Reasons for Discontinuation from OLE Study 20050111, Through Week 264

Reason for Discontinuation	Etanercept N=181 n (r)
Total number discontinued	113 (62.4%)
Consent withdrawn	42 (23.2%)
Lost to Follow up[1]	19 (10.4%)
Noncompliance[2]	17 (9.3%)
Lack of Efficacy/Disease progression	11 (6.0%)
Adverse event	6 (3.3%)
Protocol deviation	7 (3.8%)
Pregnancy	4 (2.2%)
Other	4 (2.2%)
Ineligibility determined	2 (1.1%)
Administrative decision	2 (1.1%)

[1]Subjects missed 6 consecutive doses of etanercept

[2]Subjects used topical steroids greater than moderate strength

Source: Reviewer's Table, adapted from Table 14-1.1.1, Case report forms.

Reviewer's comment:

In reviewer's Table 22, the numbers for reasons leading to discontinuation differ from the applicant's tables. According to the applicant's submission, four subjects who discontinued for "other" reasons listed the reason for discontinuation as due to disease progression and "lack of efficacy". Those subjects are listed in the lack of efficacy column accordingly.

The seventeen noncompliant subjects used topical steroids of stronger than moderate potency for their psoriasis. (Applicant submission, Listing 14-3.1) Use of potent topical steroids was reported in 9.3% of subjects on etanercept in the OLE Study 20050111. Use of greater than mild to moderate steroids for these subjects may indicate lack of etanercept efficacy.

Protocol Deviations

Protocol deviations were recorded in 47% of the subjects in OLE Study 20050111. Seven subjects were enrolled though they did not meet criteria. Of the 41 subjects who received an excluded concomitant treatment, 32 subjects used stronger than moderate topical steroids. Two subjects who became pregnant while on study drug continued in the study though they should have been discontinued at the time of pregnancy diagnosis. The 17 subjects who missed at least 6 consecutive doses were categorized as lost to follow up.

Table 23: Important Protocol deviations for OLE Study 20050111

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)

PD=protocol deviation
N = Number of subjects who received at least one dose of investigational product.
n = Number of subjects with protocol deviation.
Source: Applicant's Submission, OLE Study 20050111, Table 14-3.1.

Reviewer's Comment:
The numerous protocol deviations indicate a failure to adhere to the protocol, and inadequate oversight by the Applicant. Nearly half of the subjects (47%) reported at least one important protocol deviation. Seven subjects entered the study despite not meeting criteria. Twenty-five subjects (13.8%) did not have a properly executed informed consent and/or PPD application required for entry into OLE Study 20050111. Specifically, 16 protocol deviations related to PPD testing upon entry into the OLE Study 20050111. Multiple investigators at different sites failed to adhere to protocol, which affected accurate tuberculosis screening and evaluation for subjects entering OLE Study 20050111.

Forty-one (22.7%) subjects used prohibited concomitant treatments, which suggests that etanercept was insufficient treatment for psoriasis or lost its effectiveness.

7.2.2 Explorations for Dose Response

Etanercept 0.8 mg/kg once a week subcutaneously (maximum of 50 mg) was given to each subject. No dose response studies were conducted.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro studies were conducted.

7.2.4 Routine Clinical Testing

In the OLE Study 20050111, routine safety monitoring included clinical evaluation and laboratory testing at specified time points:

- Physical examination
- Height and weight
- Vital signs, including temperature, pulse, and blood pressure
- Laboratory evaluations: clinical chemistry; complete blood count; urinalysis; pregnancy test for female subjects of childbearing potential, ANA,

7.2.5 Metabolic, Clearance, and Interaction Workup

No new studies were conducted to evaluate metabolism, clearance, and interactions. No formal studies were conducted in subjects with renal or hepatic impairment.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Etanercept belongs to the class TNF-α inhibitor biologic products. The labeling for etanercept includes a boxed warning for the risk of serious infections, opportunistic infections, lymphomas, and other malignancies. Similar boxed warnings have been included in labeling of other approved TNF inhibitor biologic products, including adalimumab (Humira), infliximab (REMICADE), golimumab (SIMPONI), and certolizumab (CIMZIA).

The applicant defined a set of adverse events of special interest, and evaluated the following:

Infections
- All infections
- Serious infections
- Opportunistic infections
- Tuberculosis

Malignancies
Immune Reactions
Cardiovascular
Respiratory
Gastrointestinal Events
Skin and Subcutaneous Tissue Disorders
Nervous System Disorders
Psychiatric Disorders
Hematologic Disorders
Hepatic Events
Other: Injection Site Reactions

The rate of adverse events of special interest (AESI) per 100 patient years of exposure was calculated.

7.3 Major Safety Results

7.3.1 Deaths

No subject death was reported by the applicant during the RCT Study 20030211 and the OLE Study 20050111 through 264 weeks.

7.3.2 Nonfatal Serious Adverse Events

During the RCT Study 20030211, there were 4 serious adverse events during the open-label period, as reported in the previous review. The reports are listed in Table 24 below.

Table 24: Serious Adverse Events, RCT Study 20030211

	Double-Blind Period 0-12 Weeks		Open Label Tx/DB[1], WR[2] Period 12-48 weeks
Serious Adverse Event	**Placebo N=105 n=4**	**Etanercept N=106 n=0**	**Etanercept N= n=4**
Major depression	1	-	-
Migraine	1	-	-
Syncope vasovagal	1	-	-
Pruritus	1	-	-
Pneumonia	-	-	1
Gastroenteritis	-	-	1
Dysmenorrhea	-	-	1
Ovarian mass	-	-	1

Source: Reviewer's Table; FDA Clinical Review, July, 28, 2008, Section 7.1.2, p. 36.
DB[1]= double-blind
WR[2]= withdrawal retreatment

For the serious adverse events in OLE Study 20050111 described below, case report forms, applicant narrative summaries, and integrated summary of safety (ISS) were utilized.

During the open-label OLE Study 20050111, twenty-one serious adverse events were reported in twelve subjects. Two events each were reported for anxiety, depression, self-injurious behavior, and osteonecrosis of the hip. Deafness, transitory in nature, was reported for one subject.

Table 25: Serious Adverse Events Reported in One or More Etanercept-Treated Subjects, OLE Study 20050111

MedDRA Preferred Term	Applicant reported, Etanercept	Etanercept (N=181) n (%)
TOTAL	17	21
Anxiety	1	2 (1.1)
Depression	1	2 (1.1)
Self-Injurious Behavior	1	2 (1.1)
Abnormal Behavior	1	1 (0.5)
Deafness		1 (0.5)
Hematuria	1	1 (0.5)
Cellulitis (Elbow)	1	1 (0.5)
Joint Dislocation (Elbow)	1	1 (0.5)
Osteonecrosis, Hip	2	2 (1.1)
Bowel Obstruction	1	1 (0.5)
Bladder Rupture	1	1 (0.5)
Thyroid Cyst	1	1 (0.5)
Brain Mass	1	1 (0.5)
Ovarian Mass	1	1 (0.5)
Elective Abortion	1	1 (0.5)
Partial Placental Abruption	1	1 (0.5)
Infectious Mononucleosis	1	1 (0.5)

Source: Reviewer's Table

1. Subject 501002 was a 16 year-old white male with a past medical history of anxiety, depression and substance abuse. The subject was on etanercept therapy for thirteen months at the time of the SAE report; the last dose was three days before the subject was hospitalized for anxiety/anxiety exacerbation. Treatment consisted of counseling and anti-anxiety and anti-depressant medications. The subject was discharged after 11 days, and readmitted 6 days later for anxiety. Treatment was observation only. Etanercept was restarted after discharge, and continued for an additional 18 months. It was the opinion of the investigator that the events were not related to etanercept.

***Reviewer's Comment**:*
This reviewer does not agree with the investigator's assessment that this SAE was not related to etanercept treatment. The exacerbation in the subject's anxiety symptoms occurred while taking the study drug. It is not possible to rule out a contribution to the above event by etanercept.

2. Subject 505015 was a 4 year-old white female with a past medical history of depression and anxiety. The subject was on etanercept therapy for four years and 10 months at the time of SAE report; however, the date the last dose of Etanercept was given was not reported. The subject developed fearlessness and self-injurious behavior (hitting her head) for which she was hospitalized. The subject was diagnosed with mood disorder, adjustment disorder, with mixed anxiety, and depressed mood. Treatment included trazodone, fluoxetine hydrochloride, guanfacine, diphenhydramine hydrochloride. The subject underwent magnetic resonance imaging (MRI) that revealed a frontal lobe mass. No additional information regarding actions taken, subject disposition, or the outcome of the event, was provided. It was the opinion of the investigator that the events were not related to etanercept.

Reviewer's Comment:
This reviewer does not agree with the assessment of the investigator that this SAE was not related to etanercept treatment. The subject was treated with etanercept for almost 5 years prior to the onset of this SAE. Although the information on exact timing of etanercept dosing and the onset of the SAE is unknown, it is reasonable to conclude that the brain mass may have been present prior to the onset of behavioral changes and while on treatment with etanercept. Therefore, causal relationship between study drug treatment and the SAE of brain mass cannot be completely excluded.

3. Subject 510005 was a 16 year-old white male with a past medical history of bilateral acetabular dysplasia, retinitis pigmentosa, hypertension, and depression. The subject was on etanercept for two years and 11 months when the subject developed avascular necrosis (AVN) of the right hip. He underwent hip osteotomy surgery, and was discharged after 8 days. Etanercept was restarted. One year later, the subject developed AVN of the left hip, was hospitalized and underwent osteotomy the day of admission. Etanercept was restarted after discharge. One year, 6 months after the second hip surgery, the subject was diagnosed with glomerulonephritis, hospitalized, and discontinued from the study. No other details were given. It was the opinion of the investigator that the AVN of the hips was unrelated to etanercept, and the adverse event glomerulonephritis was related to etanercept.

***Reviewer's comment**:*
This reviewer does not agree with the investigator's assessment that the SAE's were not related to etanercept treatment. The avascular necrosis of the hips occurred while the subject was on etanercept. It is not possible to rule out etanercept as a contributing factor. Additionally, the glomerulonephritis was likely related to etanercept (See adverse events).

4. Subject 510008 was a 16 year-old white female who was hospitalized for a thyroid cyst. The subject was on etanercept for 3 years, 10 months prior to diagnosis; the last dose was 7 prior to this event. Treatment included surgical removal. The hospital length of stay was 38 days; reason for the prolonged hospitalization was not specified. The investigator reported the event as resolved. Etanercept was restarted. No other information was provided by the sponsor. It was the opinion of the investigator that the event was not related to etanercept.

Reviewer's Comment:
This reviewer does not agree with the applicant's assessment that this SAE was not related to etanercept treatment. It is not possible to rule out etanercept as a contributing factor to thyroid cyst development. This subject had received etanercept for several years prior to cyst diagnosis.

5. Subject 513008 was an 11 year-old white male with a past medical history of congenital bladder exstrophy. He received etanercept for 8 months, was randomized to placebo for 2 months, and then enrolled in the OLE study. Two years, 4 months after the first etanercept dose, he underwent surgery to correct bladder exstrophy without complication. One month after surgery and five days after an etanercept dose, the subject was hospitalized for bowel obstruction for three days. Subsequently, the subject reported urinary incontinence, recurrent urinary tract infections, and cystostomy. Nine years, 1 month after the first dose, the subject was diagnosed with a ruptured urinary bladder, which was surgically repaired on an unknown date. Additional treatment included IV antibiotics and hydration. The last reported dose of etanercept was 15 days after bladder rupture; the last confirmed study drug dose was 15 months prior to bladder rupture. It was the opinion of the investigator that the events were not related to etanercept.

Reviewer's Comment:
This reviewer agrees with the investigator that the above events were unrelated to etanercept. Bowel obstruction and bladder rupture have been reported as postoperative complications of bladder exstrophy corrective surgery.[12,13]

6. Subject 518008 was a 14 year-old white female with a past medical history of asthma, duodenal ulcer, obesity, cholecystectomy, dust allergy, and mild mental retardation. She received etanercept for one month in the RCT Study 20030211, and rolled over into the OLE study 20050111 one year later. Three months after the first etanercept dose, the subject was hospitalized for a right ovarian mass associated with abdominal pain. An abdominal scan showed a right ovarian cyst, mesenteric adenitis, and a large amount of stool. Treatment was analgesics and stool softeners. She was discharged after approximately five days. One month later she was readmitted for the right ovarian mass, and underwent removal of the right ovary and right fallopian tube. Surgical pathology was benign. She was discharged after four days. The event was reported as resolved, and the subject resumed etanercept therapy for an unknown period of time. It was the opinion of the investigator that the events were not related to etanercept.

12 J Pediatr Urol. 2014 Dec;10(6):1043-50.
13 Urology. 2003 Oct;62(4):737-41. Review.

Reviewer's comment:
This reviewer does not agree with the investigator's assessment that the SAE's were not related to etanercept treatment. It is not possible to rule out etanercept as an exacerbating or contributing factor to ovarian mass development and the hospital admissions.

7. Subject 520007 was a 14 year-old white female who was hospitalized for cellulitis of the elbow. The subject had been treated with etanercept for 4 years and 2 months when the infection occurred; the previous dose was 5 days prior to admission. She was treated with IV clindamycin for 2 days, followed by oral therapy to complete 14 days. Etanercept was resumed after discharge, for an additional 6 months. It was the opinion of the investigator that there was a reasonable possibility that the event was related to etanercept.

Reviewer's Comment:
This reviewer agrees with the investigator that it is reasonable that the above events were related to etanercept. The cellulitis developed after receiving etanercept for over four years. No other contributing factor was noted.

8. Subject 540002 was a 7 year-old Hispanic male with a past medical history of hematuria, and a family history of diabetes mellitus and depression. Six years, 8 months after the first etanercept dose, the subject developed gross hematuria with consistent microscopic hematuria. One month later the subject underwent biopsy of a penile lesion diagnosed as calcinosis cutis, and cystoscopy confirmed "idiopathic calcinosis cutis". Further evaluation was not conclusive. Six years, 9 months after the first etanercept dose, the subject developed depression and anger symptoms. Two emergency room (ER) visits as well as police intervention occurred 6 months later. He was prescribed lorazepam and counseling. Two months after the ER visits, a mental health evaluation revealed the subject reported thoughts of hurting himself, and had cut himself with a knife on three occasions, resulting in bleeding for 10 to 15 minutes. He was diagnosed with major depressive disorder; hospitalization was recommended but did not occur. One month later the subject possessed knives and alcohol; he was admitted for treatment of major depression and treated with fluoxetine hydrochloride. Two weeks later, trazadone was added. The hospitalization duration was not specified. The last dose of etanercept was 7 weeks after admission. One month off etanercept, the investigator reported that the subject's symptoms had improved. There were no additional reports of self-injurious behavior or emergency room visits. The event was unresolved. No other details were provided. It was the opinion of the investigator that there was no reasonable possibility that the event was related to the IP.

Reviewer's Comment:
This reviewer does not agree with the investigator that the hematuria was unrelated to etanercept. It is not possible to rule out etanercept as an exacerbating or contributing factor to the hematuria. Prior to enrollment in the study, the patient had a past medical history of hematuria. Onset of hematuria was six years and nine months after the first etanercept dose. Calcinosis cutis of the penis was found; cystoscopy was performed and only idiopathic calcinosis cutis was confirmed. The hematuria was considered unresolved and further investigations were considered.

This reviewer does not agree with the applicant that the psychiatric events were unrelated to etanercept. There is a reasonable possibility that the events were related. The onset occurred while the subject was on study drug; he has no past medical history of psychiatric symptoms, and the subject improved one month after discontinuing etanercept.

In one instance, hospitalization was recommended for this patient's major depressive disorder but the patient declined admission and it did not occur. While the patient was not admitted, depression, for which hospitalization was recommended, is a serious adverse event. The self-injurious behavior noted in this subject's case report form (cutting himself) was not included in the applicant's adverse report statistical analysis.

9. Subject 556002 was a 13 year-old white female treated with etanercept for 2 years and 7 months, and the last dose was 2 weeks before onset. The subject was hospitalized with abdominal pain and dehydration. An ultrasound confirmed an intrauterine pregnancy, 6.6 weeks' gestation. Etanercept was discontinued. The patient was treated with IV hydration and discharged approximately 1 day later. Two weeks after admission the patient underwent an abortion (8 weeks gestation). Etanercept was resumed 1 week later. It was the opinion of the investigator that there was no reasonable possibility that the event was related to etanercept.

Reviewer's Comment:
This reviewer agrees with the Applicant that the above events were unrelated to etanercept. The subject was pregnant and dehydrated, and the abdominal pain may have been related to the pregnancy and dehydration. The symptoms resolved in one day after hydration.

10. Subject 556006 was a 16 year-old white female whose past medical history was significant for goiter, depression, tobacco smoking. The subject was on etanercept four years, one month after the first etanercept dose, when she was diagnosed as pregnant. Etanercept was discontinued. Eight months after the last etanercept dose, the subject was hospitalized for partial placental abruption; a cesarean section was performed. A live male was delivered: weight 2768 g; the Apgar scores were 5 and 8 at 1 and 5 minutes, respectively. The newborn was intubated for 24 hours for low oxygen saturation. There was no congenital anomaly or other complications reported. The subject and newborn were discharged 3 days after birth. It was the opinion of the investigator that there was no reasonable possibility that the event was related to etanercept.

Reviewer's Comment:
This reviewer agrees with the applicant that the above events were unlikely related to etanercept. Placental abruption occurred 8 months after the last etanercept dose. The elimination half-life of etanercept is 115 days, such that the blood level of drug at delivery was nonexistent.

11. Subject 556010 was a 10 year-old white male who was otherwise healthy. The subject was on etanercept for six years, 2 months. The last dose of etanercept was given 1 week prior to the AE. The subject developed a complete dislocation of the elbow, while playing rugby. Attempts to reduce the dislocation in the ER were unsuccessful. He was hospitalized, and 2 days later the

dislocation was reduced and the subject was discharged. Etanercept was restarted, date unknown. It was the opinion of the investigator that there was no reasonable possibility that the event was related to etanercept.

Reviewer's Comment:
This reviewer agrees with the applicant that the above event is likely due to trauma, and unrelated to etanercept.

12. Subject 555003 was a 15 year-old white male who developed a sore throat, fever, chills and left abdominal pain. The subject received etanercept for four years, six months prior to onset. The last dose of etanercept prior to onset was not reported. Four days after symptom onset he was hospitalized and diagnosed with infectious mononucleosis. On physical examination he had posterior cervical and inguinal lymphadenopathy. Blood tests showed leukocytosis and lymphocytosis. An abdominal X-ray revealed splenomegaly; a computerized tomography (CT) scan noted diffuse splenic infarcts. After observation, the subject was discharged after 8 days. Five weeks after discharge the repeat CT scan was negative, and etanercept was resumed for 11 additional months, for a total of 6 years. It was the opinion of the investigator that there was no reasonable possibility that the event was related to etanercept.

Reviewer's Comment:
This reviewer does not agree with the applicant's assessment that the SAE's were not related to etanercept treatment. The infection onset and complications, including splenic infarcts, occurred while the subject was on study drug. An increased risk of bacterial and viral infections has been noted during exposure to etanercept.

13. Subject 562001 was a 13 year-old Asian male who reported hearing loss (MeDRA Preferred Term, Deafness) after returning from camp, 3 years 4 months after beginning etanercept. The hearing loss lasted at least one month. No treatment was documented. Etanercept was resumed, then consent was withdrawn at 222 weeks. An information request was sent to the applicant requesting additional information regarding hearing loss; the response was that since the event was not considered serious, no additional information would be provided. The subject developed hypertension 30 days after hearing loss onset was reported. A renal ultrasound showed a kidney size in lower range. Hypertension was treated with enalapril, and was ongoing when the subject withdrew consent. Other adverse events reported while on study drug were weight gain, impetigo, influenza, headache, cough, and stuffy nose. His concomitant medications were betamethasone valerate, coal tar, corticosteroids, salicylic acid, hydrocortisone valerate, calcipotriol, mupirocin, vitamin D, ibuprofen, paracetamol, and cough and cold preparations.

Reviewer's Comment:
This reviewer does not agree with the applicant's assessment that the hearing loss was not related to etanercept treatment. Hearing loss, even when temporary, is a serious adverse event that may be considered drug-related even when occurring rarely (one to three events).

The cumulative serious adverse events for RCT Study 20030211 and OLE Study 20050111 are reported by system organ class and preferred term in Table 26. Psychiatric disorders, infections, and musculoskeletal disorders were reported > 1%.

Table 26: Serious Adverse Events by System Organ Class and Preferred Term, RCT Study 20030211 and OLE Study 20050111 Through Week 264

System Organ Class Preferred Term	Etanercept N=210 n
Infections	**3**
Lobar Pneumonia	1
Cellulitis	1
Gastroenteritis	0
Infectious mononucleosis	1
Gastrointestinal	**2**
Intestinal obstruction	1
Abdominal pain	1
Psychiatric Disorders	**9**
Anxiety	3
Depression	2
Abnormal behavior	2
Intentional self-injury	2
Nervous system disorders	**1**
Brain mass	1
Syncope vasovagal	0
Migraine	0
Reproductive system/breast disorders	**2**
Ovarian mass	1
Dysmenorrhea	1
Musculoskeletal and connective tissue disorders	**3**
Osteonecrosis	2
Joint dislocation	1
Endocrine disorders	**1**
Thyroid cyst	1
Metabolism and nutrition	**1**
Dehydration	1
Renal and urinary disorders	**1**
Hematuria	1
Surgical and medical procedures	**2**
Abortion induced	1
Bladder rupture	1

n=events
Source: modified from applicant's submission; ISS, Listings 16-2.7.1, and 14-6.2.5, and case report forms.
MedDRA version 18.0

Reviewer's comment:
The serious adverse events reported were highest for psychiatric events. Placebo events were not included in Table 26; over time, all subjects were exposed to etanercept during RCT Study 20030211 after 12 weeks and OLE Study 20050111.

7.3.3 Dropouts and/or Discontinuations

Seven subjects were discontinued due to AEs in RCT Study 20030211, and eight subjects discontinued due to AEs in study 20050111. Discontinuations due to AEs are presented in Table 27 and Table 28, below. The AEs leading to discontinuation in RCT Study 20030211 were discussed in the previous review.

Table 27: Adverse Events Leading to Study Discontinuation, RCT Study 20030211

Adverse Event Preferred Term	Double Blind Period 0-12 weeks		Open Label Period 12-48 weeks
	Placebo N=105	Etanercept N=106	Etanercept N=210
Bronchospasm		1	
Skin infection			1
Psoriasis progression	1		
Atopic dermatitis			1
Muscle cramps			1
Lobar pneumonia		1	
Upper respiratory infection			1

Source: Adapted from Applicant's table 14-6.2.1 p. 755, Study 20030211, and Listing 19-3.0, ISS 16-2.7.2, case report forms.

Reviewer's comment:
An additional subject was identified from the ISS table, who discontinued RCT Study 20030211 during the open label period due to upper respiratory tract infection.

There were eight adverse events leading to subject discontinuation during OLE Study 20050111. The leading reason for discontinuation was infection, for seven subjects. Two subjects discontinued due to worsening psoriasis, one of whom was on placebo. Overall, the number of adverse events leading to study discontinuation was low.

Table 28: Adverse Events Leading to Etanercept Discontinuation, To 264 weeks, OLE Study 20050111

Adverse Event Preferred Term	Etanercept 0.8 mg/kg weekly N=181 N (%)
Total number	8
Crohn's Disease	2
Bronchitis	1
Cystitis	1
Glomerulonephritis	1
Psoriasis	1
Sinusitis	1
Cranial Nerve VII Paralysis	1

Source: Applicant Submission, Table 14-6.1.34, Case report forms.

Reviewer's comments:
The applicant reported 5 adverse events leading to study discontinuation. The additional AEs leading to discontinuation identified by this reviewer were noted in the narrative case report forms, submitted separately.

Table 29 reports the reasons for discontinuation from both studies. Overall, the leading reason for subject discontinuation was withdrawal of consent. Noncompliance, lost to follow-up, lack of efficacy and disease progression were the other leading causes of discontinuation.

Upon further review of lost to follow-up and consent withdrawn groups, twelve subjects were identified that had used stronger than moderate topical steroids; ten additional subjects were identified in the consent withdrawn group, and two subjects were noted in the lost to follow-up group. Additionally, two subjects in the consent withdrawn group used a topical vitamin D analogue, also a protocol deviation.

Table 29: Reasons for Discontinuation from RCT Study 20030211 and OLE Study 20050111, through week 264

Reason for Discontinuation	20030211 Placebo	20030211 Etanercept 0.8 mg/kg	Etanercept OLE Study 20050111 0.8 mg/kg	Total for 20030211 and 20050111
	N=105	N= 106	N=181	N=211
Consent withdrawn	2	1	42 (23.2%)	45
Lost to Follow up[1]	2	3	19 (10.4%)	24
Noncompliance	1	0	17[2] (9.3%)	18
Lack of Efficacy/ Disease progression	1	1[3]	11 (6.0%)	13
Adverse event	2	5	8 (%)	15
Protocol deviation	0	0	7 (3.8%)	7
Pregnancy	0	0	4 (2.2%)	4
Other	0	0	4 (2.2%)	4
Ineligibility determined	0	0	2 (1.1%)	2
Administrative decision	1	0	2 (1.1%)	3
Total Discontinued	9	8	113 (62.4%)	130

[1]Subjects missed 6 consecutive doses of study drug
[2]Subjects used topical steroids greater than moderate strength
[3]Subject experienced worsening of psoriasis, then withdrew consent
Source: Reviewer's Table, from Table 14-1.1.1, Case report forms, Listings 19-3.0 and 19-17.0.

Protocol Deviations

Protocol deviations were recorded in 47% of the subjects in OLE Study 20050111. Seven subjects (3.9%) were enrolled in the OLE Study 20050111 though they did not meet study criteria. Of the 41 subjects who received an excluded concomitant treatment, 32 subjects used stronger than moderate topical steroids; two subjects used systemic psoriasis therapies, including adalimumab for psoriasis and oral prednisone for guttate psoriasis, and 2 subjects had ultraviolet light treatments. Two subjects who became pregnant while on study drug continued in the study though they should have been discontinued at the time of pregnancy diagnosis. The 17 subjects who missed at least 6 consecutive doses were categorized as lost to follow up.

Important protocol deviations reported for OLE Study 20050111 are listed in Table 30 below.

Table 30: Summary of Protocol Deviations, OLE Study 20050111

Category Subcategory	Etanercept 0.8 mg/kg weekly N=181
At least one protocol deviation	85 (47.0)
Received Excluded Concomitant Medication	41 (22.7)
Moderate topical steroid or stronger	32 (17.7)
Systemic Therapy	2 (1.1)
Ultraviolet B Light	2 (1.1)
Received wrong treatment or incorrect dose	26 (14.4)
Did not meet revised consent or PPD criteria	25 (13.8)
Entered study though criteria not satisfied	7 (3.9)
Missing Data	2 (1.1)
Developed withdrawal criteria, not withdrawn (Pregnancy)	2 (1.1)

Source: Applicant submission, Table and Listing 14-3.1,

Reviewer's comment:
Nearly half of the subjects had a protocol deviation. Of the 85 deviations, 48.2% of the subjects received excluded concomitant psoriasis treatment. The supplementary stronger topical and systemic psoriasis treatments in addition to etanercept treatment suggest that etanercept was insufficient to control or maintain the treatment effect.

7.3.4 Significant Adverse Events

There were unexpected adverse events reported during the OLE Study 20050111.

Cranial Nerve Paralysis
Two subjects developed cranial nerve VII paralysis.

Subject 531001 was a Hispanic or Latino girl enrolled at age 12 years, who developed left cranial nerve VII palsy after 5 years on etanercept. An uncomplicated ear infection was diagnosed the day prior to cranial nerve palsy onset. She was treated with systemic steroids for the cranial nerve palsy, and tetracycline, naproxen, and Neosporin Eye and Ear. Twenty-eight days after cranial nerve VII palsy onset, the subject was removed from the study due to this adverse event. This subject reported positive anti-etanercept antibodies by immunoassay at weeks 96, 144, 168, and at early termination. Other adverse events reported while on etanercept treatment included psoriasis of the face, insulin resistance, weight gain, occasional headaches. Her concomitant medications were paracetamol for headaches, pioglitazone for insulin resistance, and hydrocortisone probutate topically for psoriasis. An information request was sent to the applicant; the adverse event was not considered to be serious and no additional information was provided.

Subject 504003 was a 16 year-old white male with a medical history of acne and asthma who reported cranial nerve VII palsy. Three days prior to palsy onset, he reported a headache. He was treated with oral prednisone for 5 days, and doxycycline, and the palsy was reported as resolved after 34 days. His other reported adverse events on study drug were GERD, hypertension, nasal congestion, URI (6 visits), streptococcal throat infection, Lyme disease, left foot fracture, bronchitis, and productive cough, His concomitant medications were montelukast sodium, seretide, Thomapyrin n, betamethasone valerate topical, adapalene, topical clindamycin, medinite, Robitussin, amoxicillin, paracetamol, doxycycline, oral prednisone, pseudoephedrine hydrochloride (HCl), Novahistine dmx, ranitidine, HCl, oxycodone, and Vicodin. He continued in the OLE study until he withdrew from the study 3 years later. An information request was sent to the applicant; they did not consider the adverse event serious and no additional information was provided.

Reviewer's comment:
This reviewer does not agree with the applicant's assessment that the cases of cranial nerve VII palsy were not related to etanercept. When a cause can be identified, cranial nerve VII palsy in children has been shown to be associated with certain viral infections(e.g. varicella zoster virus), bacterial ear infections including Borrelia infection or those complicated by mastoiditis or labrynthitis, and trauma[14]. An ear infection which was otherwise uncomplicated would not be expected to predispose the subject to cranial nerve VII palsy. The applicant provided no explanation regarding the etiology of hearing loss, and etanercept treatment may have been a contributing factor.

Though the applicant attributed the cranial nerve VII palsy to Lyme disease, there was no documentation of disease manifestations and no Lyme disease titers were drawn. Additionally, an information request was made and no evidence of Lyme disease was provided by the applicant.

Deafness/Hearing Loss

Two cases of hearing loss were reported.

Subject 562001 was a 13 year-old Asian male who reported hearing loss (MeDRA Preferred Term 19.0, Deafness) after returning from camp, 3 years 4 months after beginning etanercept. See section 7.3.2.

Subject 510016 was a 9 year old Hispanic or Latino male who reported difficulty hearing (MedRA Preferred Term 19.0, Hypoacusis) after 4.5 months of etanercept, during the open label period of RCT Study 20030211. The episode of hypoacusis lasted 9 weeks. No treatment was given. Other adverse events reported while on study drug were chest pain, palpitations, runny nose and otitis media during the double-blind period, and leg, knee and thigh pain during the open label period. The ANA was positive at baseline, and anti-etanercept antibodies were positive, titer 1:50, at 48 weeks.

14 Otol Neurotol. 2013 Sep;34(7):e82-7

Reviewer's comment:
Partial hearing loss, even when temporary, is of concern and possibly due to medications, and therefore related to etanercept exposure. Causes of acquired hearing loss in children include ear infections, autoimmune disorders, trauma, and cranial tumors. This subject had a positive ANA at baseline and an ear infection prior to onset, and anti-etanercept antibodies after hearing loss resolution. No investigations were reported by investigators to evaluate hearing loss, and the applicant provided no explanation regarding the etiology of the partial hearing loss.

7.3.5 Submission Specific Primary Safety Concerns

The applicant evaluated AESI, as discussed in Section 7.2.6 of this review. During the development of etanercept for psoriasis in pediatric patients age 4 to 17 years, no subject treated with etanercept reported the following AESI:

Malignancies
Infections
Immune Reactions
Cardiovascular Events
Respiratory Events
Gastrointestinal Events
Skin and Subcutaneous Tissue Events
Neuropsychiatric Events
Hematologic Events
Hepatic Events
Injection Site Reactions

Malignancies

No malignancy was reported in RCT Study 20030211 or OLE Study 20050111.

Infections

Subjects were monitored for serious infections, opportunistic infections, and tuberculosis in the OLE Study 20050111.

Serious Infections
The applicant reported five serious infections in OLE Study 20050111 as serious cases. They were bronchitis, cellulitis, infectious mononucleosis, tonsillitis, and urinary tract infection. All were categorized as CTC 3.

Opportunistic infections

There were three reports of infections related to varicella zoster virus (VZV).

Subject 556010 was a 13 year-old white male who developed varicella after 103 weeks on etanercept. The case was of moderate severity; he was treated with ibuprofen, paracetamol, and diphenhydramine orally. No other information was provided. It was the opinion of the investigator that the event was unrelated to etanercept.

Reviewer's comment:
This reviewer does not agree that the case of varicella is unrelated to study drug. The VZV vaccine was given to all subjects prior to entry into RCT Study 20030211. After 103 weeks on etanercept, it is possible that the study drug diminished the immune response to VZV exposure, allowing VZV infection and disease to occur.

Two cases of herpes zoster were reported.
Subject 513006 was a 18 year-old Asian female who developed herpes zoster after 172 weeks on etanercept. The case was of moderate severity. She was treated with valacyclovir, paracetamol, and codeine orally and topical acyclovir. No other information was provided. It was the opinion of the investigator that this case of herpes zoster was related to study drug.

Subject 526002 was a 16 year-old white female who developed herpes zoster after 23 days on etanercept. The case was of moderate severity. She was treated with oral acyclovir. No other information was provided. It was the opinion of the investigator that the case was unrelated to etanercept.

Reviewer's comment:
It is possible that both cases of herpes zoster were related to etanercept use. The effects of etanercept on the immune system are not fully known and were not investigated in this application. All subjects were fully immunized to VZV prior to entry into RCT Study 20030211.

No opportunistic fungal infections were reported during the placebo-controlled or OLE studies.

Tuberculosis

Subjects were monitored for tuberculosis by PPD testing per protocol.
Subject 502005, a 17 year-old Hispanic or Latino male, had a protocol deviation upon entry into the OLE study and a PPD was not done. After reconsent and PPD testing, a positive PPD was reported. He was treated with isoniazid (INH) and pyridoxine hydrochloride for 9 months. Consent was withdrawn after 155 weeks. No other information was provided.

No case of tuberculosis was reported.

Immune Reactions

Anti-etanercept antibodies and neutralization studies were conducted during RCT Study 20030211and OLE Study 20050111. RCT Study 20030211results were reviewed during the previous clinical review.

During the OLE Study 20050111, 169 subjects were tested for anti-etanercept antibodies at baseline and post-treatment. Eighteen subjects (10.7%) developed anti-etanercept antibodies. All neutralizing antibody tests were negative.

Anti-nuclear antibody (ANA) titers were studied. Of 158 subjects tested at baseline, eleven (6.1%) reported a positive ANA. Ten additional subjects reported a positive ANA during the OLE Study. At Week 264, two subjects of 47 tested (4.3%) reported a positive ANA.

Reviewer's comment:
According to the Division of Biotechnology Review, the anti-etanercept antibody assay and neutralization assay were inadequate and there were multiple deficiencies. The assay detection antibody targeted only immunoglobulin G (IgG), and did not detect anti-etanercept antibodies of the IgM sub-type. Also, the sampling did not include time points to capture IgM responses one to two weeks after the first etanercept dose, or optimal IgG responses 4 to 6 weeks after the first etanercept dose.

The assay cut-point was not determined according to FDA, ICH, and USP guidance. Although these guidance documents were not available at the time the applicant validated the assays, the guidances were available when the OLE Study 20050111 samples were tested.

Cardiovascular Events

Cardiovascular events occurred during the OLE Study 20050111.
Syncope was reported in four subjects; one subject reported neurocardiogenic syncope and one had hypoglycemia.

Subject 505003 was a 17 year-old white female subject diagnosed with neurocardiogenic syncope (Week 139), for which she was treated with atenolol, midodrine, and fludrocortisone acetate. She underwent a tilt test. She was found to have cardiomegaly (Week 155). A positive ANA titer was reported Week 186. An information request was sent to the Applicant; the written response from the applicant stated that cardiomegaly was not considered a serious adverse event, and no further information would be provided.

Reviewer's comment:
This reviewer does not agree that cardiomegaly and neurocardiogenic syncope were unrelated to study drug use. The adverse events occurred while the subject had been treated with etanercept for over 2 years. The applicant provided no explanation regarding the etiology of the cardiomegaly.

Respiratory Events

Respiratory adverse events occurred during RCT Study 20030211and OLE Study 20050111. None was serious during OLE Study 20050111, but one event led to drug discontinuation.

Subject 510013 was a 17 year-old Hispanic or Latino male who was enrolled in RCT Study 20030211and OLE Study 20050111. Two weeks after his first etanercept dose during the RCT Study 20030211 open label period, the subject reported an upper respiratory tract infection. He continued etanercept into the OLE Study 20050111, when after 46 months of etanercept he developed severe bronchitis. An oral antibiotic was given. Etanercept was discontinued, but the subject remained on the study. The bronchitis resolved one month after the last etanercept dose. It was the opinion of the investigator that the development of bronchitis was related to etanercept.

Reviewer's comment:
This reviewer agrees with the applicant that this subject's bronchitis was likely related to etanercept use. The bronchitis occurred while the subject was on study drug. No other past medical history was provided as a contributing factor.

Gastrointestinal Events

There were gastrointestinal adverse events during the RCT Study 20030211and OLE Study 20050111. During the double-blind period of RCT Study 20030211, vomiting (4), upper abdominal pain (3), and nausea (3) were reported most frequently. During the open-label period, one subject was hospitalized for gastroenteritis and dehydration.

During the OLE Study 20050111, fifty-two subjects (28.7%) reported AEs, including abdominal pain 19 (10.5%), nausea 13 (7.2%), and abdominal pain 11 (6.1%). Two subjects were diagnosed with Crohn's Disease; the case reports are below.

Subject 554002 was an 8 year-old white female who was enrolled in the RCT Study 20030211 and OLE Study 20050111. While on placebo during the placebo-controlled period of RCT Study 20030211, the subject reported stomach cramps and abdominal pain at one visit. She reported no additional symptoms until after participating in the OLE study 20050111 for nine months, when she reported diarrhea at 2 visits. She was diagnosed with Crohn's disease after 66 weeks on etanercept. The investigator concluded that the development of Crohn's disease was unrelated to etanercept.

Reviewer's comment:
This reviewer does not agree that the development of Crohn's disease is unrelated to etanercept. The abdominal pain was reported on only one occasion during placebo use and did not recur; however, diarrhea began after nine months of etanercept use, and recurred. Etanercept cannot be ruled out as a contributing and/or exacerbating factor for Crohn's disease development in this subject.

Subject 554003 was a 12 year-old white female received placebo, received etanercept treatment through the escape arm from two weeks for 10 months, and then entered the OLE Study 20050111 after 11 months. The abdominal pain began after nine months of etanercept treatment, and the subject reported abdominal pain at nine subsequent visits. She was diagnosed with Crohn's disease two years, five months after symptom onset. The investigator concluded that the development of Crohn's disease was related to etanercept use.

Reviewer's comment:
This reviewer agrees that the onset of Crohn's disease may be related to etanercept use. The subject developed symptoms nine months after the first etanercept dose.

Skin and Subcutaneous Tissue Events

During the OLE Study 20050111, 13 (7.2%) subjects reported psoriasis exacerbation while on etanercept. Five of these subjects experienced a flare of guttate psoriasis, a different type than plaque psoriasis. Only one subject reported streptococcal pharyngitis associated with the flare of guttate psoriasis. None of the subjects with psoriasis flares reported anti-etanercept antibodies during the study period. Nine subjects discontinued the study with ongoing psoriasis symptoms related to the flares.

Reviewer's comment:
Though there was initial improvement for these subjects, exacerbation of psoriasis occurred while on study drug. Except for one subject (streptococcal infection), the applicant did not identify causes for psoriasis exacerbation. Antibodies to etanercept were not reported for these subjects. Psoriasis exacerbation while on etanercept suggests a loss of effectiveness.

Neuropsychiatric Events

Neurologic events were reported in section 7.3.4.

Psychiatric serious adverse events or adverse events were reported in twelve subjects. Hospitalizations occurred in three subjects related to anxiety, depression, and/or self-injurious behavior. The hospitalizations are discussed in serious adverse event section 7.3.2.

Hematologic Events

Four subjects reported abnormal blood test results during OLE Study 2050111. All laboratory evaluations reported below were Common Toxicity Criteria (CTC) version 2.0, Grade 3 (severe); none was life-threatening, disabling (Grade 4) or fatal (Grade 5). Treatment was administered to one subject.

- Subject 506003 was an African American female who reported low hemoglobin at 5 visits: Weeks 36, 108, 120, 168, and 180. She was treated with oral ferrous sulfate throughout OLE Study 20050111for worsening anemia.
- Subject 532002 reported increased hemoglobin on Weeks 96 and 108.
- Subject 560003 reported increased white blood cell count on week 36.
- Subject 522002 reported decreased platelets on Week 48.

Reviewer's comment:
Only four adverse hematologic events occurred, none was life-threatening. Other than the case of anemia, the abnormal findings were transient. No hematologic signal could be detected due to the small number of subjects in the study.

Hepatic Events

The hepatic events were listed in the adverse event section; no case report forms were completed.

- Hepatic steatosis or preferred term fatty liver *(MeDRA version 14.1),* was reported in two subjects in OLE Study 20050111. No hepatic adverse event was reported in RCT Study 20030211.

- Subject 505005 was a 9 year-old white male who developed hepatic steatosis after 256 weeks on etanercept. Weight gain was also reported on Week 240.

- Subject 504002 was a 13 year-old white female who developed hepatic steatosis after 114 weeks on etanercept. Weight loss was reported. She withdrew from the study 3 weeks later due to Crohn's disease.

Reviewer's comment:
No signal could be determined due to the small number of subjects in the study.

Injection Site Reactions

There were 78 injection site reactions reported as adverse events, for an exposure-adjusted (A-E) event rate per 100 subject-years of 10.2%. For subjects 4 to 11 years of age, there were 20 reactions (AE event rate 6.7) and for subjects 12 to 17 years, there were 58 injection site reactions (AE event rate 12.3). (Table 31)

Table 31: Injection Site Reactions, Exposure-Adjusted, RCT Study 20030211 and OLE Study 20050111, through Week 264

System Organ Class Preferred Term	Etanercept 0.8 mg/kg QW[a] (E=764.7) (N = 210) n (r)
Total number of injection site reactions adverse events reported	78 (10.2)
General disorders and administration site conditions	78 (10.2)
Injection site bruising	15 (2.0)
Injection site pruritus	14 (1.8)
Injection site erythema	13 (1.7)
Injection site pain	13 (1.7)
Injection site reaction	12 (1.6)
Injection site nodule	3 (0.4)
Injection site haemorrhage	2 (0.3)
Injection site swelling	2 (0.3)
Injection site discolouration	1 (0.1)
Injection site hypoaesthesia	1 (0.1)
Injection site irritation	1 (0.1)
Injection site warmth	1 (0.1)

N = number of subjects who received at least 1 dose of etanercept.
E = total number of etanercept exposure years.
n = number of adverse events that occurred during etanercept exposure.
r = exposure-adjusted event rate per 100 subject-years (= n / E * 100).
Coded using MedDRA version 18.0.
Source: Applicant's submission, ISS, Table 14-6.2.14

Reviewer's comment:
Injection site reactions were common during the studies and were expected. Nearly twice the adjusted rate of injection site reactions was reported in the 12 to 17 year age group.

Supportive Safety Results

7.4.1 Common Adverse Events

Treatment emergent adverse events (TEAE) were not considered separately. Adverse events occurring during the placebo-controlled RCT Study 20030211and OLE study 20050111 were reported.

The most frequent adverse reactions for subjects on etanercept were infections and injection site reactions. The applicant attributed the following adverse reactions to Etanercept during OLE Study 20050111. (Table 32)

Table 32: Subject Incidence of Adverse Events ≥ 5% by Preferred Term for OLE Study 20050111, Applicant Reported

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)

Source: Applicant's Table 14-6.1.35, OLE Study 20050111.

For RCT Study 20030211 and OLE Study 20050111, 198 subjects (94.2%) reported at least one adverse event. Infections and injection site reactions were reported most frequently, at 26% and 30%, respectively. Only ecchymosis was reported in the placebo group more frequently, at 4.0% of placebo subjects versus 0.9% of etanercept subjects. The adverse events reported most commonly at a rate of ≥ 2 % are in Table 33 below.

Table 33: Adverse Reactions ≥ 2 % For RCT Study 20030211 and Through Week 48 of OLE Study 20050111, As Reported by the Applicant

Adverse Reaction	**Placebo N=149 Subjects (%)**	**Etanercept N=210 Subjects (%)**
Total Events	**26**	**198**
Total Infections	**3 (2.0)**	**56 (26.6)**
Upper Respiratory Tract infection	0	10 (4.7)
Streptococcal Pharyngitis	0	8 (3.8)
Sinusitis	0	7 (3.3)
Bronchitis	0	6 (2.8)
Skin Infection	0	5 (2.3)
Nervous System Disorders	**7 (4.6)**	**16 (7.6)**
Headache	7 (4.6)	9 (4.2)
Gastrointestinal Disorders	**0**	**14 (6.6)**
Abdominal Pain	0	6 (2.8)
Respiratory Disorders	**4** (2.6)	**14** (6.6)
Skin and Subcutaneous Disorders	**6 (4.0)**	**14 (6.6)**
Ecchymosis	6 (4.0)	2 (0.9)
Neoplasms, Benign and Malignant	**2** (1.3)	**6** (2.8)
Skin papilloma (verruca)	2 (1.3)	6 (2.8)
Reproductive System/Breast	**0**	**5** (2.3)
General disorder / Injection Site Reactions	**3 (2.0)**	**63 (30.0)**
Injection site bruising	1 (0.6)	13 (6.1)
Injection site pain	0	12 (5.7)
Injection site pruritus	0	12 (5.7)
Injection site erythema	0	10 (4.7)
Injection site reaction	1 (0.6)	8 (3.8)

Source: Adapted from Applicant's Table.

7.4.2 Laboratory Findings

Criteria for clinically notable abnormalities were based on Common Toxicity Criteria (CTC) version 3 [Common Terminology Criteria for Adverse Events (CTCAE) version 3.0]. All laboratory toxicities were CTC Grade 3; no laboratory Grade 4 toxicity was reported. (Table 34)

Hematology

In OLE Study 20050111, decreased hemoglobin for one subject was documented at 5 visits, weeks 36, 108, 120, 168, and 180. An increased hemoglobin level was reported for one subject at two visits. The platelet count was decreased for one subject, and the white blood cell count was increased for one subject, at one visit.

Chemistry

Two elevations were noted for chemistry laboratory evaluations. One subject reported an elevated creatinine, and one subject reported an increased alanine amino transferase.

Table 34: Listing of Grade 3 Laboratory Toxicities for OLE Study 20050111

	Etanercept 0.8mg/kg weekly N=181
Laboratory Test	**n (%)**
Hemoglobin elevated	1 (0.5%)
Hemoglobin decreased	1 (0.5%)
White Blood Cell Count elevated	1 (0.5%)
Platelet Count decreased	1 (0.5%)
ALT elevated	1 (0.5%)
Creatinine elevated	1 (0.5%)

N=number of subjects receiving at least one dose of etanercept.
n=number experiencing AE
Source: Adapted from Applicant submission, OLE Study 2050111, Listing 14-7.1.

Reviewer's comment:
This reviewer could not associate abnormal lab values with other adverse events. While the anemia was persistent, the alterations in the hematology and chemistry evaluations were transient and unlikely related to etanercept.

7.4.3 Vital Signs

Seven hypertension adverse events were reported in OLE Study 20050111 in four subjects. All cases were mild in severity. All subjects were male.

Subject 562001 was in the 4 to 11 year age group. This subject experienced 2 episodes of hypertension. A renal ultrasound showed kidney size in lower range. He also had weight gain. Hypertension was unresolved at the End of Study visit.

Reviewer's comment:
This reviewer could not attribute hypertensive events to etanercept treatment. The hypertension for Subject 562001 could be attributed to other concomitant conditions.

7.4.4 Electrocardiograms (ECGs)

Electrocardiogram testing was not performed during the OLE study.

7.4.5 Special Safety Studies/Clinical Trials

QT studies were not performed in the OLE Study 20050111.
No specific safety study was conducted during OLE Study 20050111.

7.4.6 Immunogenicity

An ELISA assay for detection of serum antibodies to etanercept tumor necrosis factor Fc receptor (TNFR:Fc) was performed. The level of titration was also determined.

For RCT Study 20030211, 210 subjects received at least one dose of etanercept. Pre-dose and post-dose anti-etanercept serum samples were obtained from 208 subjects. Twenty subjects developed anti-etanercept antibodies by week 48 or the last study visit. One subject had a positive etanercept antibody titer of 1:100 for the 12 and 48 week visits. No TNFR:Fc neutralizing antibodies were detected for any subjects.

Table 35: Subjects with Anti-Etanercept Antibodies, RCT Study 20030211

	Total subjects with blood samples	positive anti-etanercept antibodies Etanercept 0.8 mg/kg QW n (%)
Total	207	20 (9.6)
12 Weeks	187	9 (4.8)
24 Weeks, or last visit	179	10 (5.5)

n=number of subjects
Source: Adapted from Applicant's submission, RCT Study 20030211, Table 1.

Table 36: Anti-Etanercept Antibody Titers, RCT Study 20030211

	Anti-Etanercept Antibody Endpoint Titer n = number of positive samples				
Time point	< 1:50	= 1:50	1:100	1:200	Total
12 weeks	4	5	2	0	11
48 weeks	1	6	2	1	10

Source: Adapted from
Applicant's Submission, RCT Study 20030211, Table 2 Data.

Of 181 subjects treated in OLE Study 20050111, 169 subjects were tested for anti-etanercept antibodies while on study drug. Anti-etanercept antibodies were detected by immunoassay, and positive immunoassay results were analyzed further for neutralizing antibodies utilizing bioassay testing.

Reviewer's comment:
According to the Office of Biotechnology Products, Division of Biotechnology review, the anti-etanercept antibody and neutralization antibody assays were not appropriately validated. The assay included a detection antibody that only targeted IgG, which did not detect anti-etanercept antibodies of IgM sub-type.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

One dose regimen, etanercept 0.8 mg/kg weekly, was compared to placebo during RCT Study 20030211. For the OLE Study 20050111, all subjects received etanercept 0.8 mg/kg (up to a maximum 50 mg) weekly.

7.5.2 Time Dependency for Adverse Events

No analysis regarding the occurrence of adverse events over time was performed.

7.5.3 Drug-Demographic Interactions

A total of 2317 adverse events occurred during RCT Study 20030211and OLE Study 20050111 for 210 subjects.

Male and female subject numbers were nearly equal in exposure years. The exposure- adjusted rate of adverse events was higher in females compared with the rate for males.

Of the 210 exposed subjects, 36% were in the 4 to 11 year age group, and the etanercept exposure was less. Exposure-adjusted adverse events occurred at a higher rate in the 4 to 11 year age group than in the 12 to 17 year age group.

The exposure years for white subjects are significantly higher than for subjects in other racial and ethnic groups. The exposure-adjusted rate of adverse events is higher for the white subject group than Asian, black, Hispanic, and other groups. The rate for Native Hawaiian or Pacific Islander group is lowest at 68.9 per 100 subject years; this group had one subject.

Canadian subjects accounted for 28% of the participants, had a lower etanercept exposure years, but a higher exposure-adjusted adverse event rate than U.S. subjects.

Table 37: Adverse Events reported for Any Subject Receiving Etanercept, by Demographics, Exposure-Adjusted

Demographic Parameters	Etanercept 0.8 mg/kg QW	
	Demographic Characteristics N (E)	Safety Endpoint n (r)
Overall	210 (764.7)	2317 (303)
Sex		
Male	108 (371.5)	979 (263.5)
Female	102 (393.2)	1338 (340.3)
Age Group		
>= 4 <= 11	76 (294.7)	947 (321.4)
>= 12 <= 17	134 (470)	1370 (291.5)
Race		
White	157 (574.8)	1840 (320.1)
Black or African American	11 (41.1)	85 (206.8)
Asian	15 (61.3)	186 (303.4)
American Indian or Alaska Native	0 (0)	0 (0)
Native Hawaiian or Other Pacific Islander	1 (5.8)	4 (68.9)
Other	26 (81.7)	202 (247.2)
Missing	0 (0)	0 (0)
Ethnicity		
Hispanic or Latino	21 (70.2)	171 (243.5)
Not Hispanic or Latino	0 (0)	0 (0)
Missing	189 (694.5)	2146 (309)
Region		
United States	151 (528)	1506 (285.2)
Canada	59 (236.7)	811 (342.6)

N = number of subjects who received at least 1 dose of etanercept
E = total number of etanercept exposure years
n = number of adverse events that occurred during etanercept exposure
r = exposure-adjusted event rate per 100 subject-years (= n / E * 100)
Data Source: ptinfo, ae. Reviewer's Table.

Reviewer's comment:

The differences in exposure-adjusted adverse event rates for non-white racial groups are difficult to assess due to low enrollment numbers when compared to the white subject group rate.

7.5.4 Drug-Disease Interactions

In OLE Study 20050111, etanercept use resulted in a change in disease. Fifteen subjects (8.2%) experienced an exacerbation of psoriasis. Six subjects (3.3%) reported guttate psoriasis during the open label extension study.

Reviewer's comment:
Psoriasis change in morphology and change in severity has been previously reported as an adverse event of interest in patients treated with etanercept. In this trial, all subjects were enrolled with plaque type psoriasis but there were exacerbations of the disease as well as changes in morphology to guttate type.

7.5.5 Drug-Drug Interactions

The applicant listed concomitant medications reported did not analyze interactions between etanercept and concomitant medications. In OLE Study 20050111, 172 (95%) of the subjects reported use of at least one medication. The most frequent medication taken by subjects was systemic antibiotics, followed closely by analgesics and topical steroids. The number of medications surpasses the number of subjects; it is not surprising that subjects took more than one medication during the 264 week study. For a summary of concomitant medications of interest, see Table 38.

Table 38: Summary of Use of Concomitant Medications of Interest, in Descending Frequency, OLE Study 20050111

Medication	Etanercept 0.8 mg/kg QW N=181 n
Antibiotics, systemic	261
Analgesics	259
Topical steroids	216
Cough and Cold	151
Allergy	98
Vaccinations	91
Anti-acne, topical	68
Vitamins and supplements	55
Contraceptives	52
Vitamin D Analogue	24
Antibiotics, topical	22
Antifungal, topical	22
ADHD medications	20
Coal Tar products	17
Salicylic Acid	16
Calcineurin Inhibitors, Topical	14
Benzodiazepines	11

N=number of subjects
n=number of reports of medication use
Source: Adapted from Applicant's submission, OLE Study 20050111, Table 14-8.1.1.

Reviewer's comment:
The total number of concomitant medications listed by the applicant differs from this reviewer's table. The list of concomitant medications included 469 preferred term entries. Many of the listings were redundant or synonymous; the generic, trade, and chemical names of medications were listed separately.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The risk of malignancy is a safety concern in patients treated with immunosuppressive products, including etanercept.

In September 2011, the FDA requested all sponsors of tumor necrosis factor alpha (TNF-α) blockers to perform enhanced pharmacovigilance (ePV) for malignancies in patients age 30 and younger.

Nine etanercept clinical trials and studies conducted previously were submitted by the applicant and reviewed for malignancies. Eight trials were conducted in children with juvenile rheumatoid arthritis (later juvenile idiopathic arthritis, JIA); one trial was conducted in subjects with JIA, enthesitis arthritis, and psoriatic arthritis.

Reviewer's comment:
Malignancies would not be expected to occur during the time frame of these clinical trials, with durations varying from 12 weeks to 13 months. Additionally, the background malignancy rate in JIA is higher than the background malignancy rate in pediatric psoriasis.

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies were reported during RCT Study 20030211. There were 7 pregnancies during the OLE Study 20050111.

Subject 556002 was 13 year-old white female at baseline, who was admitted for abdominal pain and dehydration two years, seven months after the first etanercept dose; she was diagnosed as pregnant. The subject received etanercept the day of admission. The pregnancy was electively terminated two weeks later. The subject was continued on etanercept in the OLE study. This case was also reported as a serious adverse event.

Reviewer's comment:
Pregnancy during the study was an exclusion criteria and the subject should have been discontinued. The sponsor acknowledged that continuing this subject in the study after confirming pregnancy was a protocol violation. This subject was discontinued after 166 weeks for noncompliance.

Subject 556006 was a 16 year-old white female who was diagnosed as pregnant 4 years, one month after the first etanercept dose. Etanercept was discontinued. Eight months after the last dose, she experienced placental abruption, and a cesarean section was performed. The infant delivered was intubated for 24 hours for low oxygen saturation. No other complication or congenital anomalies were noted. On day three of life the infant and mother were discharged.

Reviewer's comment:
The placental abruption occurred eight months after the last etanercept dose. There is no evidence that etanercept is related to the placental abruption in this case.

Four subjects (508005, 510004, 515006, and 537002) were discontinued from the OLE study due to pregnancy. No details were reported regarding the pregnancies, pregnancy outcomes, or the time of exposure.

Subject 504010 was discontinued due to noncompliance after missing six consecutive doses and scheduled two visits after Week 248. During OLE Study 20050111 she was treated for trunk, extremity and face psoriasis with calcipotriol, hydrocortisone valerate, and pimecrolimus. Other findings during OLE Study 20050111 were high urine specific gravity results at Baseline and Weeks 24, 144, and 216, and a positive ANA at Week 144. Five months after the subject was discontinued from the study she presented pregnant, seven weeks prior to the estimated date of delivery. No information was available regarding the exposure to the study drug during pregnancy or on the outcome of the pregnancy.

Reviewer's comment:
No additional information was provided regarding pregnancy and pregnancy outcome in five adolescent psoriasis subjects.

There were no reports regarding lactation.

7.6.3 Pediatrics and Assessment of Effects on Growth

Height and weight growth analyses were conducted at Week 48 of the RCT Study 20030211. For proper analysis, growth must be compared between children who are the same sex and year of age. The sample size is inadequate to assess mean growth rate for this trial.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The effect of etanercept overdose is unknown. In RCT Study 20030211, Subject 512003 received two doses of etanercept twice a week for 2 weeks. No AEs were reported in this subject.

During the OLE Study 20050111, one subject received two doses. No adverse event was reported secondary to the overdose

Based on the mode of action, there is no reason to assume that there is a potential for abuse or dependency for etanercept.

7.7 Additional Submissions / Safety Issues

The 120 day safety update provided new safety data from etanercept studies obtained after the data cutoff date for this supplemental BLA submission (19 October 2015). The safety update data interval was 19 October 2015 to 08 January 2016. Subjects in OLE Study 20050111 were allowed to continue to Week 264 or the 18th birthday, whichever occurred later. Five subjects were still enrolled at the time of the safety update. The update also included cumulative tabulations of serious adverse events and deaths through 02 February 2016.

Four cases of serious infections were reported during the safety update: Escherichia infection; nasopharyngitis; joint abscess; streptococcal pharyngitis.

The Periodic Benefit-Risk Evaluation Report (PBRER) was submitted on 12 April 2016. The reporting period was from 03 February 2015 to 02 February 2016. Discussion of the results are included in Section 8 of this review.

8 Postmarket Experience

The postmarketing safety data for pediatric psoriasis from initial licensure date November 2, 1998 through February 2, 2016 was reviewed. The applicant reported 2145 serious adverse events related to etanercept across all indications, including psoriasis, for patients less than 18 years. The Amgen Global Safety Database receives reports from clinical trials, approved indications, and off-label use worldwide.

For pediatric psoriasis patients ≤ 17 years of age, 236 serious adverse events were reported for the postmarketing data interval period 03 February 2015 to 02 February 2016. This data includes data from eight interventional studies.

Deaths

As of February 02, 2016, for all etanercept indications, infections were the most common cause of death. In the safety summary, the applicant provided a table listing 47 deaths world-wide for pediatric psoriasis patients on etanercept through February 2015 (Table 39).

During postmarketing period for the year 2014 for psoriasis, four deaths were reported. Three deaths were associated with transplacental exposure, where the etanercept recipient was the adult patient. The causes of fetal death were immature respiratory system, fetal death, and unknown.

The fourth death was due to suicide, reported spontaneously by a consumer:
Case **USASP201101690** reported a 17-year-old male who completed suicide. Enbrel therapy was begun January 1, 2003. No date was given for the suicide. The concomitant medications were not specified. An information request was sent; the applicant provided no additional details.

Table 39: Cumulative Deaths with Etanercept Exposure, Through February 2, 2015

System Organ Class	Preferred Terms	Total Number of Cases
Infections and infestations	Sepsis (4 cases), Bronchopneumonia, Cytomeglovirus infection (2 cases each), Adenovirus infection, Arthritis bacterial, Bacterial sepsis, Broncopulmonary aspergillosis, Disseminated tuberculosis, Infection, Meningitis pneumoccal, Pneumocystis jirovecii infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pseudomonal sepsis, Septic shock, Superinfection (1 case each)	21
Cardiac disorders	Cardiopulmonary failure, Cardio-respiratory arrest, Left ventricular failure (1 case each)	3
Hepatobiliary disorders	Hepatic failure, Liver disorder, Venoocclusive liver disease (1 case each)	3
Immune system disorders	Anaphylactic reaction, Hypersensitivity, Immunodeficiency (1 case each)	3
Respiratory, thoracic and mediastinal disorders	Pneumonia lipoid, Pulmonary hypertension, Respiratory failure (1 case each)	3
Neoplasms benign, malignant and unspecified	Acute myeloid leukaemia recurrent, Renal cell carcinoma (1 case each)	2
Nervous system disorders	Cerebral haemorrhage, Haemorrhage intracranial (1 case each)	2
Vascular disorders	Angiopathy, Diffuse vasculitis (1 case each)	2
All others	Death[a] (5 cases), Histiocytosis haematophagic (2 cases), Completed suicide (1 case)	8

[a] The cause of death was not provided at the time of reporting. Attempts to obtain additional information are made in compliance with Standard Operating Procedures. In the category All others, three were fetal deaths.
Source: Applicant's table, Section 5.3.6, Table 1-7, p. 35.

Serious Infectious Events

Overall, 160 infections were reported in pediatric psoriasis patients treated with etanercept through February 2, 2015. Of these, 38 serious infectious events were reported in 31 pediatric psoriasis patients during the postmarketing phase. (Table 40) Also, two additional cases of Herpes zoster were identified.

Table 40: Serious Infectious Events in Pediatric Psoriasis Patients Treated with Etanercept, Cumulative, through February 2, 2015

HLGT	HLT	Preferred Terms (number of Events)	Total Number of Events
Infections - pathogen unspecified	Urinary tract infections	Urinary tract infection (3), Cystitis (2), Pyelonephritis	6
	Lower respiratory tract and lung infections	Pneumonia (2), bronchitis, lower respiratory tract infection	4
	Upper respiratory tract infections	Tonsillitis, chronic tonsillitis, upper respiratory tract infection	3
	Abdominal and gastrointestinal infections	Appendicitis perforated, abdominal infection	2
	Ear infections	Ear infection, otitis media	2
	Dental and oral soft tissue infections	Tooth abscess, Gingival abscess	2
	Infections NEC	Infected bites, Purulent discharge	2
	Bone and joint infections	Osteomyelitis	1
Viral infectious disorders	Herpes viral infections	Herpes zoster (3), Varicella	4
	Viral infections NEC	Viral infection NEC (3)	3
	Epstein-Barr viral infections	Infectious mononucleosis	1
Bacterial infectious disorders	Streptococcal infections	Pharyngitis streptococcal, Toxic shock syndrome streptococcal	2
	Staphylococcal infections	Staphylococcal infection (3)	3
Fungal infectious disorders	Cryptococcal infections	Cryptococcal cutaneous infection	1
	Histoplasma infections	Histoplasmosis	1
Protozoal infectious disorders	Amoebic infections	Amoebiasis	1

HLT= high-level term; HLGT=high-level group term; NEC=not elsewhere classified
Source: Applicant table, Post-Marketing Experience, 5.3.6, Page 19.

Reviewer's comment:
Three cases of herpes zoster, and one case each of histoplasmosis, cutaneous cryptococcosis, amebiasis, and varicella reported as serious infections suggest immunodeficiency.

The fatal and serious opportunistic, bacterial, and viral infections cannot be mitigated. Fatal and serious infections are not features of psoriasis in children.

Malignancy

The Office of Surveillance and Epidemiology (OSE) has prepared annual reports summarizing the malignancy pharmacovigilance of all TNFα blockers in pediatric and young adult patients, from data provided by the applicant. The patient age range is defined as up to and including age 30 years at the time of diagnosis. The most recent report issued on February 10, 2016, included annual 2014 data, summary report for 2011 through December 31, 2014, and cumulative data since approval date November 2, 1998.

On February 10, 2016, the Office of Surveillance and Epidemiology (OSE) prepared a pharmacovigilance memorandum evaluating malignancies in pediatric and young adult patients exposed to TNF-α blockers. For the current review period (2014 interval) and cumulatively, patients age 30 years and younger receiving TNF-α blockers individually or with other medications were evaluated.

In the United States, three new malignancies were reported for etanercept in 2014: a histiocytic sarcoma in a 30 year-old woman with rheumatoid arthritis (RA); a skin cancer not otherwise specified (NOS) in a 12 year-old girl with juvenile idiopathic arthritis (JIA), and a "neoplasm" not otherwise specified in a 21 year-old with psoriasis.

Internationally, the sponsor reported 16 new malignancies with etanercept use in 2014. There were two cases of Hodgkin lymphoma, and three cases of cervical cancer. There were two cases of renal cell carcinoma in a 17 and a 24 year-old.

OSE stated the data suggest a new safety concern associated with cervical cancer. Cancers related to HPV causally represent 11 of 101 cases reported among ePV malignancy cases in 2014.

The Division of Pharmacovigilance has summarized cancer diagnoses reported with etanercept use. Between 2010 and 2014, twenty-one malignancies occurred in the U.S. in etanercept exposed patients ≤ 30 years of age. Those occurring in more than one patient were: cervical carcinoma (Ca) (4); Hodgkin lymphoma (2); thyroid carcinoma (2); Non Hodgkin lymphoma (2). Significantly, two patients with cervical Ca were 18 years and 22 years, younger than the age group (22-25 years) in which cervical Ca is among the five most common cancers.

Reviewer's Comment:
The HPV-related malignancies were unexpectedly high in number. Two cases of cervical Ca occurred at younger ages, which are rarely reported. This is of concern for adolescents who may be treated with etanercept. While the HPV vaccine series is recommended up to age 26 years, the effect of etanercept on the immune response to the HPV vaccine and the ability of the vaccine to prevent HPV-related malignancy are unknown and have not been evaluated in this application.

The postmarketing data is difficult to analyze or draw conclusions from due to incomplete reporting, the variable reporting periods reported by the applicant, and the lack of a denominator for analysis.

9 Appendices

9.1 Literature Review/References

Becker L, Tom WL, Eshagh K, Benjamin LT, Paller AS. Excess adiposity preceding pediatric psoriasis. JAMA Dermatol. 2014 May;150(5):573-4.

Bronckers IM, Paller AS, van Geel MJ, van de Kerkhof PC, Seyger MM. Psoriasis in Children and Adolescents: Diagnosis, Management and Comorbidities. Paediatr Drugs. 2015;17:373–384.

Cohen BE, Martires KJ, Ho RS. Psoriasis and the Risk of Depression in the US Population: National Health and Nutrition Examination Survey 2009-2012.
JAMA Dermatol. 2016;152(1):73-79.

DeFoor W, Tackett L, Minevich E, Wacksman J, Sheldon C. Risk factors for spontaneous bladder perforation after augmentation cystoplasty. Urology. 2003 Oct;62(4):737-41.

Flytström I, Stenberg B, Svensson A, Bergbrant IM. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. Br J Dermatol 2008 Jan;158(1):116-21.

Global report on Psoriasis, World Health Organization, WHO Press, Geneva, Switzerland, 2016.

Helmick CG, Lee-Han H, Hirsch SC, Baird TL, Bartlett CL. Prevalence of psoriasis among adults in the U.S.: 2003-2006 and 2009-2010 National Health and Nutrition Examination Surveys. Am J Prev Med. 2014 Jul;47(1):37-45.

Heydendael VM, Spuls PI, Opmeer BC, de Borgie CA, Reitsma JB, Goldschmidt WF, Bossuyt PM, Bos JD, de Rie MA. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med. 2003 Aug 14;349(7):658-65.

Kanerva M, Nissinen J, Moilanen K, Mäki M, Lahdenne P, Pitkäranta A.
Microbiologic findings in acute facial palsy in children. Otol Neurotol. 2013 Sep;34(7):e82-7.

Langley, RG, Ellis CN Evaluating psoriasis with Psoriasis Area and Severity Index, Psoriasis Global Assessment, and Lattice System Physician's Global Assessment, J Am Acad Derm, (51):4, October 2004, Pages 563–569.

Raychaudhuri SP, Gross J. A comparative study of pediatric onset psoriasis with adult onset psoriasis. Pediatr Dermatol. 2000 May-Jun;17(3):174-8.

Saurat JH, Langley RG, Reich K, Unnebrink K, Sasso EH, Kampman W. Relationship between methotrexate dosing and clinical response in patients with moderate to severe psoriasis: subanalysis of the CHAMPION study. Br J Dermatol. 2011 Aug;165(2):399-406.

Schlomer BJ, Copp HL. Cumulative incidence of outcomes and urologic procedures after augmentation cystoplasty. J Pediatr Urol. 2014 Dec;10(6):1043-50.

Thomson L, Paton J. Oxygen toxicity. Paediatr Respir Rev. 2014 Jun;15(2):120-3.

www.cdc.gov/nceh/lead/

9.2 Labeling Recommendations

Labeling recommendations are in progress.

9.3 Advisory Committee Meeting

During the first review cycle, a Dermatologic and Ophthalmic Drug Advisory Committee (DODAC) meeting was held June 18, 2008 to comment on the efficacy and adequacy of the safety database from RCT Study 20030211, and to make recommendation regarding future studies in the pediatric population.

After presentations from the Agency, a majority of the committee voted in the affirmative that the benefits of etanercept outweigh the risks for children with moderate to severe plaque psoriasis, and that the drug should be approved. The lack of data impeded the discussion. The committee deliberated psoriasis severity as a critical issue, including the lack of consensus or definition of severity for physicians and professional organizations. DODAC recommended that the moderate psoriasis patient population not be considered for approval.

9.4 Regulatory Briefing

A CDER internal regulatory briefing was held regarding etanercept use in pediatric psoriasis on July 22, 2016. After the presentation the panel agreed that efficacy was established primarily in pediatric subjects with moderate psoriasis. There was discussion regarding extrapolation of adult psoriasis data to children. The postmarketing data presented malignancies and opportunistic infections; though the reports of malignancies were limited in number, the limitations of postmarketing data including the lack of denominator and incomplete reporting were discussed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROSELYN E EPPS
09/23/2016
Clinical Review

SNEZANA TRAJKOVIC
09/27/2016