

**BACKGROUND INFORMATION  
FOR  
THE DERMATOLOGIC AND OPHTHALMOLOGIC DRUGS ADVISORY COMMITTEE  
(DODAC) MEETING**

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## List of Abbreviations and Definitions of Terms

Term/Abbreviation	Explanation
AAD	American Academy of Dermatology
ACR	American College of Rheumatology
ARISg	Adverse Reaction Information System global: software for adverse event management and reporting
BCC	basal cell carcinoma
BIW	twice per week
BMI	body mass index
BSA	body surface area
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
DLQI	Dermatology Life Quality Index
DMARDs	disease-modifying anti-rheumatic drugs
EAE	exposure-adjusted event
FDA	Food and Drug Administration
ICD	International Classification of Disease
JIA (JRA)	juvenile idiopathic arthritis (juvenile rheumatoid arthritis); in current accepted nomenclature and in the current etanercept label, JRA is referred to as JIA; juvenile rheumatoid arthritis will be used throughout the document
LT $\alpha$	lymphotoxin alpha (previously known as TNF beta)
MedDRA	Medical Dictionary for Regulatory Activities
NPF	National Psoriasis Foundation
NSAIDs	non-steroidal anti-inflammatory drugs
OTIS	Organization of Teratology Information Specialists
PASI	Psoriasis Area and Severity Index
PASI 50, PASI 75, and PASI 90	improvement of at least 50%, 75%, and 90%, respectively, in the Psoriasis Area and Severity Index
PedsQL	Pediatric Quality of Life Inventory
POSA	Pooled Observational Studies Analysis
PRO	patient-reported outcomes
PUVA	psoralen ultraviolet A
QOL	quality-of-life
QW	once per week

### List of Abbreviations and Definitions of Terms

Term/Abbreviation	Explanation
REMS	risk evaluation and mitigation strategy
SCC	squamous cell carcinoma
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results (United States-based data)
SIR	standardized incidence ratio
sPGA	Static Physician's Global Assessment of Psoriasis
Th	T helper cell
TNF	tumor necrosis factor, previously called TNF- $\alpha$
TNFR:Fc	TNF p75 receptor Fc fusion protein
US	United States
UVB	ultraviolet B

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## 1. EXECUTIVE SUMMARY

### KEY POINTS:

#### Background:

- Psoriasis is a chronic, inflammatory disease involving the skin that affects approximately 2% of the world's population. Psoriatic plaques are due to dysregulation of keratinocyte growth and differentiation in which tumor necrosis factor (TNF) appears to have a key role.
- Etanercept is a recombinant human TNF receptor that inhibits the activity of TNF.
- Etanercept has been approved for the treatment of adults with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis.
- Etanercept has been approved for polyarticular juvenile idiopathic arthritis in patients 2 years of age or older.

#### Unmet Medical Need:

- No systemic therapy is approved in the United States for children with plaque psoriasis.

#### Burden of Disease:

- Most children with psoriasis will have lifelong skin disease.
- Children with psoriasis are at increased risk for developing psoriatic arthritis.
- Psoriasis significantly impacts a child's physical and psychosocial functioning.

#### Efficacy:

- Study 20030211 was a 48-week trial of pediatric subjects (aged 4 to 17 years) with moderate to severe plaque psoriasis. The study consisted of 3 periods: a 12-week double-blind, randomized placebo-controlled period, a 24-week open-label period, and a 12-week double-blind randomized withdrawal/retreatment period.
- In the first period, 57% of etanercept-treated subjects achieved the primary endpoint of a PASI 75 response compared with 11% of placebo-treated subjects.
- During the 24-week open-label period, improvements in efficacy endpoints achieved at week 12 were maintained in the original etanercept group and were improved in the original placebo group once they began receiving open-label etanercept.
- During the randomized, double-blind withdrawal period, no subject had rebound (125% worsening from baseline) of their disease.

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**KEY POINTS:**

**Safety:**

- In Study 20030211, etanercept was well tolerated over the 48 weeks of the study with a favorable benefit-to-risk profile.
- Most adverse events in the etanercept group occurred at a similar exposure-adjusted rate to that seen in the placebo group.

**Potential Indication:**

Treatment of chronic moderate to severe plaque psoriasis in pediatric patients who are inadequately controlled with topical psoriasis therapy or who have received systemic therapy or phototherapy. In patients who respond, an initial response is generally apparent within 12 weeks. Safety beyond 1 year in pediatric patients with psoriasis has not been established; therefore, the benefits and risks of continuing treatment should be carefully considered.

**Risk Evaluation and Mitigation Strategy:**

Amgen proposes the following activities for risk evaluation and minimization:

- Continue ongoing extension Study 20050111 for 5 years to evaluate safety.
- Conduct 5-year prospective cohort study of 300 subjects to evaluate safety.
- Continue Organization of Teratology Information Specialists (OTIS) pregnancy registry (open to all ages).
- Conduct routine and/or enhanced pharmacovigilance of serious infections, malignancies, and demyelinating events through use of specific follow-up forms for standardized additional information.
- Implement educational programs for targeted healthcare providers, patients, and guardians focused on recognizing and managing risk.

**Conclusions:**

- Treatment with etanercept at a dose of 0.8 mg/kg once weekly (up to a maximum dose of 50 mg) for up to 48 weeks improved the measures of psoriasis compared with placebo and was well tolerated in pediatric subjects with moderate to severe plaque psoriasis.

## **2. Etanercept in the Treatment of Pediatric Plaque Psoriasis**

### **2.1 Potential Indication for Etanercept Use in Pediatric Patients with Plaque Psoriasis**

The potential indication for the use of etanercept in pediatric patients with plaque psoriasis is as follows:

*Treatment of chronic moderate to severe plaque psoriasis in pediatric patients who are inadequately controlled with topical psoriasis therapy or who have received systemic therapy or phototherapy. In patients who respond, an initial response is generally apparent within 12 weeks. Safety beyond 1 year in pediatric patients with psoriasis has not been established; therefore, the benefits and risks of continuing treatment should be carefully considered.*

### **2.2 Etanercept**

Etanercept is a recombinant human tumor necrosis factor receptor that binds both TNF and lymphotoxin alpha (LT $\alpha$ ) with high affinity (Smith et al, 1990) and competitively inhibits binding of TNF to cell surface receptors, thereby preventing TNF-mediated cellular responses. Etanercept also may modulate biologic responses controlled by additional downstream molecules (eg, other proinflammatory cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

### **2.3 Approved Indications for Etanercept in the United States**

Etanercept was originally approved in the United States in 1998 and has been approved for marketing in more than 70 countries worldwide including countries in Europe, Asia, Latin America, the Middle East, and the Pacific Rim. In the United States, etanercept is indicated for the following:

- Rheumatoid arthritis: initially approved in 1998 for reducing the signs and symptoms in patients with moderately to severely active rheumatoid arthritis, and subsequently approved for the additional indications of inducing major clinical response, inhibiting the progression of structural damage, and improving physical function.
- Polyarticular juvenile idiopathic arthritis: approved in 1999 for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age or older.
- Psoriatic arthritis: approved in 2002 for reducing the signs and symptoms and inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis.
- Ankylosing spondylitis: approved in 2003 for reducing the signs and symptoms in patients with active ankylosing spondylitis.

- *Plaque psoriasis: approved in 2004 for treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.*

## **2.4 Global Experience with Etanercept**

### **2.4.1 Clinical Experience**

#### **2.4.1.1 All Approved Indications**

Through 03 October 2007, 25,306 subjects from all indications had been exposed to etanercept in clinical trials and Amgen cohort studies, representing 34,034.3 subject-years of exposure.

#### **2.4.1.2 Plaque Psoriasis in the Adult Population**

Through 03 October 2007, 6844 subjects from adult plaque psoriasis had been exposed to etanercept in clinical trials and Amgen cohort studies, representing 5765 subject-years of exposure.

#### **2.4.1.3 Plaque Psoriasis in the Pediatric Population**

Through 25 April 2007 in clinical Study 20030211, 210 pediatric subjects with plaque psoriasis had been exposed to etanercept, representing 153.6 subject-years of exposure.

### **2.4.2 Postmarketing Experience**

Through 04 April 2008, cumulative worldwide postmarketing exposure to etanercept since product launch on 02 November 1998 was estimated at 496,900 patients, accounting for 1,502,400 patient-years. Assuming that etanercept use worldwide in pediatrics is similar to that in the United States, it is estimated that approximately 12,600 pediatric patients have been exposed globally, accounting for 37,200 subject-years of exposure.

In the United States, estimated exposure through 04 April 2008 is summarized in [Table 1](#).

**Table 1. Postmarketing Exposure to Etanercept in the United States**

Patient Population	Patients	Patient-Years
By Age:		
Pediatric (< 18 years)	9,400	27,900
Adult (18 – 64 years)	300,300	873,000
Elderly (≥ 65 years)	71,600	197,100
TOTAL	381,300	1,098,000
By Indication:		
Psoriasis	38,600	166,800
Psoriatic Arthritis	27,800	124,700
Other (includes RA, AS)	314,900	806,500
TOTAL	381,300	1,098,000

AS = ankylosing spondylitis

RA = rheumatoid arthritis

## 2.5 Etanercept Postmarketing Commitment Studies in Psoriasis and Juvenile Idiopathic Arthritis

As a condition for approval of etanercept in the adult psoriasis indication and pursuant to the Pediatric Research Equity Act, Amgen was required to conduct a study in pediatric patients with moderate to severe plaque psoriasis. The Pediatric Research Equity Act aims to improve the quality of pediatric information in drug labeling. This legislation provides the Food and Drug Administration (FDA) with explicit authority to require applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration to include pediatric studies. Pediatric studies may be deferred if the investigational product is ready for approval in adults before pediatric studies are completed. When such studies are deferred, they will be treated as required postmarketing study commitments under 21 CFR 314.81 and 601.70. See [Section 2.5.1](#) for details regarding the postmarketing commitment, and [Section 4.1](#) for details about the study design and results.

An etanercept biological license supplement was submitted 26 September 2007, and included a request for approval to market etanercept in the pediatric plaque psoriasis setting (ages 4 to 17).

### 2.5.1 Study 20030211: Placebo-controlled Multicenter Study with Etanercept to Determine Safety and Efficacy in Pediatric Subjects with Plaque Psoriasis (PEDS)

As a condition for approval of etanercept in the adult plaque psoriasis indication, pursuant to the Pediatric Research Equity Act, Amgen was required to conduct a study as follows:



*To conduct study protocol 20030211, a 48 week, 200 pediatric patient, multicenter placebo-controlled trial, to determine the safety and efficacy of etanercept in pediatric patients, 4 to 17 years of age, with chronic plaque psoriasis.*

The final clinical study report, with revised labeling, was submitted on 26 September 2007. Please see [Section 4.1](#) for a description of this study and its results.

**2.5.2 Study 20021626: Phase IV Registry of Etanercept (Enbrel®) In Children with Juvenile Rheumatoid Arthritis (JRA)**

As a condition for approval of etanercept in the juvenile rheumatoid arthritis indication in the United States, Amgen was required to conduct a study as follows:

*To collect safety and efficacy data on the long term use of etanercept (Enbrel®) in at least 500 JRA patients for a minimum of 3 years. The study will include detailed efficacy and safety data collection on 200 patients with more limited data collection in an additional 300 patients.*

The final clinical study report will be submitted in the fourth quarter of 2008. Please see [Section 5.1](#) for additional information about the study design and for a summary of results.

**2.5.3 OBSERVE-5™ (20040210): Observational Post-Marketing Safety Surveillance Registry of Enbrel® (etanercept) for the Treatment of Psoriasis**

As a condition for approval of etanercept for the treatment of adult patients with plaque psoriasis, Amgen was required to conduct a study as follows:

*To conduct a prospective, multicenter, surveillance study of 2500 adult patients with chronic plaque psoriasis who will be treated with commercial etanercept, but who have not been previously enrolled in an etanercept study. The surveillance study will be performed to assess the incidence of serious adverse events including all malignancies and serious infections. All enrolled study subjects will be evaluated twice yearly for a period of at least 5 years.*

Enrollment completed in the fourth quarter of 2007, and the 5-year patient follow-up is expected to occur by 29 November 2012.

### **3. Plaque Psoriasis**

#### **3.1 Description of the Disease**

Psoriasis is a common, chronic, inflammatory disease involving the skin and joints that affects approximately 2% of the world's population ([Nickoloff and Nestle, 2004](#)). A number of different forms of psoriasis exist; the discussion within this document will be focused on plaque psoriasis, which is the most common type of psoriasis, and is characterized by thin, silvery-white scales covering red, raised lesions, which can be very extensive ([Pariser et al, 2007](#); [Callen et al, 2003](#)). Most commonly involved areas include elbow, knees, scalp, and sacral areas, but highly troublesome areas that can be frequently affected include face, nails and feet ([Fisher, 2005](#); [Peters et al, 2000](#)).

The determination of severity is complex, as the disease can be localized and severe or widespread and mild. A uniform definition has not been agreed upon; experts suggest that body surface area (BSA) alone should not determine the severity of disease, but that disease location, response to previous therapies, and impact of disease should all be considered ([Pariser et al, 2007](#); [Feldman et al, 2005](#); [Callen et al, 2003](#)).

#### **3.2 Immunological Basis of the Disease**

Plaque psoriasis is a chronic inflammatory disease of the skin, with visible skin lesions that reflect the excessive growth and abnormal differentiation of keratinocytes. The underlying pathophysiology of the disease is immune dysregulation, characterized by increased activity of T lymphocytes, antigen-presenting cells (eg, dendritic cells), and Th-1 and Th-17 responses. Additionally, there is evidence for involvement of B lymphocytes and granulocytes, indicating broad immune activation of both innate and adaptive immunity ([Lowes et al, 2007](#); [Krueger and Bowcock, 2005](#)). The result of this involvement is infiltration of the dermis with activated T cells (CD45 RO+), abnormal keratinocyte proliferation, epidermal hyperplasia, and dilated dermal blood vessels.

The Th-1 cytokine, TNF, appears to have a key role in the pathology of plaque psoriasis ([Gaspari, 2006](#); [Krueger and Callis, 2004](#); [Mussi et al, 1997](#)). In patients with plaque psoriasis, elevated TNF concentrations are found in the sera, in the lesional skin and, to a lesser extent, in uninvolved skin ([Mussi et al, 1997](#); [Bonifati et al, 1994](#)). Serum and lesional TNF concentrations decrease after effective psoriasis therapy and correlate with clinical improvement, suggesting the important role of TNF in the disease ([Mussi et al, 1997](#); [Bonifati and Ameglio, 1999](#)).

### **3.3 Plaque Psoriasis in Pediatric Subjects**

#### **3.3.1 Incidence and Prevalence of Plaque Psoriasis in Pediatric Subjects**

Available literature suggests that the prevalence of pediatric psoriasis is approximately 1%. ([Gelfand et al, 2005](#); [Williams et al, 1994](#)) for pediatric psoriasis. Approximately one-third of adults with plaque psoriasis had the initial signs and symptoms during childhood and adolescence ([Benoit and Hamm, 2007](#); [Faber and Nall, 1974](#)).

Approximately 10% of patients with psoriasis are diagnosed before the age of 10 years, and in 2% of cases, onset of the disease occurs before the age of 2 years ([Leman and Burden, 2001](#); [Morris, et al 2001](#)). Children with plaque psoriasis are more likely to have a positive family history of psoriasis than those who develop the disease as adults. Childhood onset plaque psoriasis is comparable in extent and severity to adult psoriasis ([Raychaudhuri and Gross, 2000](#)). Remissions lasting a mean of 7 months occur in up to 39% of children with plaque psoriasis, but most continue to have persistent disease into adulthood ([Raychaudhuri and Gross, 2000](#)).

#### **3.3.2 Clinical Characteristics of Childhood Plaque Psoriasis**

Types or patterns of childhood psoriasis may vary; however, plaque psoriasis is the most common presentation of psoriasis in the pediatric population, representing up to 80% of pediatric psoriasis cases ([Fan et al, 2007](#); [Ferrandiz et al, 2002](#); [Morris et al, 2001](#); [Leman and Burden, 2001](#)). In children, plaque psoriasis can affect any part of the body; however, it is most commonly seen on the scalp (40% to 60% of patients), face (30% to 60% of patients), legs (60% of patients), arms (50% of patients), and nails (40% of patients) ([Fan et al, 2007](#); [Raychaudhuri and Gross, 2000](#)).

Although a proportion of patients only have facial rash or scalp manifestations of plaque psoriasis, disease at these sites can be quite visible and distressing ([Benoit and Hamm, 2007](#); [Morris et al, 2001](#)). Manifestations of psoriasis involving the nail may include pitting, onycholysis, oil spots, and subungual hyperkeratosis ([Ferrandiz et al, 2002](#); [Leman and Burden, 2001](#)). The effects of disease on physical appearance can have enduring effects on psychosocial functioning ([Mease and Menter, 2006](#)) ([Section 3.4.3](#)).

#### **3.3.3 Current Prescription Medications Used for Pediatric Plaque Psoriasis**

Currently, no systemic therapy has been approved in the United States for the treatment of pediatric plaque psoriasis. Topical treatments currently used to treat pediatric psoriasis are listed in [Table 2](#) though many additional topical corticosteroids are used off label. Systemic treatments for adult patients with psoriasis are presented in [Table 3](#).

**Table 2. Topical Agents**

Medication	Potency <sup>a</sup>	Adverse Events	Population (Restrictions on Dosing, Duration)
Corticosteroids			
Clobetasol fluocinolone	high	Extent and duration of treatment determine adverse events. Skin irritation, burning, erythema, atrophy and striae. Hypothalamic pituitary adrenal suppression	12 to 16 years of age (2 to 4 weeks)
mometasone furoate	medium		≥ 2 years of age (≤ 3 consecutive weeks)
desonide			≥ 3 months of age
aclometasone dipropionate	low to medium		≥ 1 years old (≤ 3 consecutive weeks)
fluticasone			≥ 3 months of age
			Pregnancy Category C
Vitamin D Analogs			
Calcipotriol		Skin Irritation, rare hypercalcemia.	Not approved for pediatric use Pregnancy Category C
Retinoid			
tazarotene 0.05 and 0.1%		Burning, itch, peeling, photosensitivity, teratogenicity	Stable plaques psoriasis < 20% body surface area ≥ 12 years Pregnancy Category X

<sup>a</sup> Steroids are tested for potency through a skin blanching assay

Pregnancy category definitions:

B is presumed safety based on animal studies; C is uncertain safety; no human studies and animal studies show an adverse effect; and X is highly unsafe; risk of use outweighs any possible benefit.

**Table 3. Systemic Therapies Approved for Adult (But Not Pediatric) Plaque Psoriasis**

Treatment	Adverse Events of Special Interest	Approvals in Pediatrics (Other Considerations)
<b>Folate inhibitor</b>		
methotrexate	Liver enzyme monitoring, biopsy; complete blood cell count monitoring; mucositis; teratogenicity	JRA Pregnancy Category X
<b>Calcineurin inhibitor</b>		
cyclosporine	Headache, nausea, hypertension, renal damage	Used ≥ 6 month old in transplant recipients Pregnancy Category C
<b>Retinoid</b>		
acitretin	Teratogenicity up to 3 years after discontinuation	No pediatric indications Pregnancy category X
<b>TNF soluble receptor</b>		
etanercept	TB, serious infection; no live vaccines	JRA ≥ 2 years of age <sup>a</sup> Pregnancy Category B
<b>Anti-TNF monoclonal antibody</b>		
infliximab	TB, serious infection, no live vaccines, hepato-splenic T cell lymphoma	Juvenile Crohn's disease ≥ 6 years of age <sup>a</sup> Pregnancy Category B
adalimumab	TB, serious infection No live vaccines	JRA ≥ 4 years of age <sup>a</sup> Pregnancy Category B
<b>Non-medication: phototherapy</b>		
ultraviolet B radiation, NB-UVB	Skin cancer, aging	Device (may require adult accompaniment for young children)

<sup>a</sup> All anti-TNF therapies require prescreening for mycobacterial infections, and immunizations should be up-to-date before initiating therapy. In the event of an infection, the agent should be withheld. Live vaccines are contraindicated.

JRA = juvenile rheumatoid arthritis; NBUVB = narrow band UVB radiation; TNF = tumor necrosis factor

For a comprehensive listing of adverse events, please refer to the package inserts

Pregnancy category definitions:

B is presumed safety based on animal studies; C is uncertain safety; no human studies and animal studies show an adverse effect; and X is highly unsafe; risk of use outweighs any possible benefit.

### **3.3.4 Unmet Medical Need in Pediatric Patients with Plaque Psoriasis**

Although there are no topical therapies approved for pediatric psoriasis, topicals are an accepted first line therapy by which many patients achieve symptomatic relief. In a subset of these patients with extensive chronic disease, it may be impractical to apply topical agents over a large BSA and for many topicals, use is not recommended beyond 2 to 4 weeks. Given these limitations, some patients who do not achieve adequate or sustained relief may require other treatment options. Many patients also achieve symptom relief from UV therapy, but this also may not be practical or sufficient for some patients ([Leman and Burden, 2001](#)). Currently, no systemic medication has been approved in the United States for children or adolescents with plaque psoriasis; however, there is use of systemic agents (approved in adult plaque psoriasis) in the pediatric population.

## **3.4 Burden of Disease**

### **3.4.1 Children with Plaque Psoriasis**

Studies suggest that 3% to 17% of children with psoriasis have joint involvement ([Fan 2007](#); [Ferrandiz et al, 2002](#)). Juvenile psoriatic arthritis accounts for 5% to 20% of all juvenile inflammatory arthritides ([Benoit and Hamm, 2007](#)). The impact on physical and psychosocial functioning will be discussed in [Section 3.4.3.1](#).

### **3.4.2 Adults with Plaque Psoriasis**

Up to one-third of adult patients with psoriasis will develop psoriatic arthritis. In most patients who develop psoriatic arthritis, skin manifestations precede joint symptoms by approximately 10 years on average ([Mease and Goffe, 2005](#)).

An increased incidence of metabolic syndrome and its components (obesity, insulin resistance, hypertension, and dyslipidemia), myocardial infarction and mortality have been demonstrated in the adult psoriasis population ([Gelfand et al, 2007](#); [Gelfand et al, 2006](#); [Neimann et al, 2006](#); [Sommer et al, 2006](#)). The risk of myocardial infarction and all cause mortality is highest in younger adults with severe psoriasis ([Gelfand et al, 2007](#), [Gelfand et al, 2006](#)). However, no study has been conducted that addresses whether treatment with etanercept impacts the risk of these conditions.

An increased risk of lymphoma has been observed in adults with plaque psoriasis, and has been associated with the severity of disease. Likewise, adults with plaque psoriasis appear to be at a higher risk for nonmelanoma skin cancer than the general population ([Gelfand et al, 2006](#); [Margolis et al, 2001](#)).

### **3.4.3 Effects of Plaque Psoriasis on Physical and Psychosocial Functioning**

Quality of life (QOL) is one component of patient-reported outcomes (PRO) that examines the impact of burden of disease or treatment on overall well-being ([VanBeek et al, 2007](#)). Patient-reported outcome is a broad term that involves a subjective assessment health status that is elicited directly from the patient ([Rothman et al, 2007](#)). Responses from the 1998 National Psoriasis Foundation (NPF) Survey provide “compelling evidence that individuals with psoriasis believe that disease has a profound emotional and social as well as physical impact on their quality of life” ([Krueger et al, 2001](#)) and recommend that clinicians focus equally on the impact of psoriasis on both psychosocial and physical functioning ([Pariser et al, 2007](#)). Patient-reported outcomes are an important metric in understanding the impact of the disease on the overall well-being of patients with psoriasis. As pediatric psoriasis usually persists through adulthood, it is important to understand the impact in both the pediatric and adult populations ([Ferrandiz et al, 2002](#); [Raychaudhuri and Gross, 2000](#), [Morris et al, 2001](#)). Studies have also shown that chronic dermatologic childhood diseases impact other family members ([Stein and Riessman, 1980](#); [Stein and Jessop, 2003](#); [Ben-Gashir et al, 2002](#)).

Quality-of-life measures quantify the physical and psychosocial impact of chronic disease from the perspective of both the patient and the caregiver. Quality-of-life questionnaires can be classified as either generic or targeted. Generic health assessment questionnaires measure outcomes of nonspecific pediatric populations including those who are healthy and those with various diseases (eg, Pediatric Quality of Life Inventory (PedsQL) [[Varni et al, 1999](#)]). The pediatric and adolescent versions of PedsQL are also validated questionnaires and used in various age groups. Targeted health assessment questionnaires measure outcomes of patient's with specific disease states (eg, Dermatology Life Quality Index [DLQI] for adults [[Finlay and Kahn, 1994](#)] and the Children's Dermatology Life Quality Index [CDLQI] for children and adolescents [[Lewis-Jones and Finlay, 1995](#)] ([Appendix B](#)). The CDLQI was validated in a population of children and adolescents (ages 4 through 16 years).

#### **3.4.3.1 Physical and Psychosocial Functioning in Pediatric and Adolescent Plaque Psoriasis**

Few studies in the literature have examined the impact of psoriasis on the physical and psychosocial functioning in children with psoriasis ([Beattie and Lewis-Jones, 2006](#); [Lewis-Jones and Finlay, 1995](#)), and studies are limited by sample sizes. Furthermore,

no validated, “psoriasis-specific” instrument is available for children. Studies have used the “dermatology-specific” CDLQI for patients with various skin disorders, including psoriasis (Beattie and Lewis-Jones 2006; Lewis-Jones and Finlay, 1995). Despite these limitations, the available data suggest that psoriasis adversely impacts a child’s physical and psychosocial functioning (Beattie and Lewis-Jones 2006; Lewis-Jones and Finlay, 1995; Paller et al, 2008).

#### Physical Functioning

Symptoms associated with psoriasis include pruritis, irritation, redness, pain, soreness, bleeding, fatigue, and insomnia (Mease and Menter, 2006). Pruritis is a common and bothersome symptom among patients with psoriasis (Ikoma et al, 2006). Ikoma and colleagues (2006) state that “it is understood that chronic itch is a complex, unpleasant sensory experience with many similarities to pain. Both sensations are multidimensional with sensory discriminative, cognitive, evaluative and motivational components.” Pruritis and scratching may lead to sleep disturbances in children with inflammatory skin disease (Chamlin et al, 2005). Beattie and Lewis-Jones (2006) compared CDLQI responses of children with psoriasis to those with other chronic diseases and found that PRO of children with plaque psoriasis was comparable to children with asthma but worse than PRO in children with diabetes. Additionally the authors reported that the “itch and pain” item of the CDLQI demonstrated the greatest impairment from the psoriatic children’s perspective. Physical symptoms can also affect sleep, school work, and leisure activities, which are other domains captured in the CDLQI (Lewis-Jones and Finlay, 1995).

#### Psychosocial

Studies have demonstrated that a distorted self image, which may be associated with plaque psoriasis, along with the emotional burden of carrying a stigma can lead to an overall decline in patients’ perceptions of well-being (Mease and Menter, 2006). Beattie and Lewis-Jones (2006) reported that children with psoriasis frequently reported that they were “embarrassed or self-conscious, upset or sad resulting from the skin condition” illustrating the emotional impact of psoriasis. Additionally, studies have noted that stress is associated with exacerbations in children with psoriasis (Benoit and Hamm, 2007).

Data suggest that psoriasis affects a child’s social-functioning, but the impairment in this domain is not as strong as the impairment in the physical and emotional domains



([Lewis-Jones and Finlay, 1995](#)). Studies also suggest that plaque psoriasis may have a more significant impact in children and adolescents than adults as a result of their struggle with peer comparison and identity formation ([Perrott et al, 2000](#)) and because they are in a critical period of psychosocial development.

#### **3.4.3.2 Physical and Psychosocial Function in Adults with Plaque Psoriasis**

The evidence suggests that some of the physical and psychosocial impact of psoriasis on children is similar to the impact on adults. As with children, adults with plaque psoriasis have physical discomfort and limitations in daily activities, impaired emotional functioning (negative body image, negative self image), and social functioning. National Psoriasis Foundation surveys found that, among patients with plaque psoriasis, 79% indicated that the disease had a negative impact on their lives ([Krueger et al, 2001](#)). In a separate study, 40% of patients with plaque psoriasis reported problems with everyday life due to plaque psoriasis, and 25% of respondents were dissatisfied with their treatment for the disease ([Stern et al, 2004](#)).

Qualitative research conducted to elicit patients' perceptions of symptoms related to their psoriasis demonstrated that itch was a frequent and bothersome symptom (data on file). Additionally recent studies have demonstrated that the intensity of itch and pain is associated with decreased physical and social functioning, as well as feelings of frustration and depression ([Duque et al, 2005](#)). In the study by Duque et al (2005), subjects who reported being bothered by itch, burning, pain, irritation, and persistence of these symptoms also reported feelings of frustration and depression, and reduction in daily and recreational activities. In a qualitative study, psoriasis patients have also suggested that symptoms of itch and scratch are frequent and bothersome and have a negative impact on emotional-well being, including feelings of frustration, embarrassment, or irritability (data on file).

In a large population-based survey of 27,220 adults ages 18 or older, the prevalence of plaque psoriasis was 2.2%. In a 266-patient subsample of this population-based survey (mean age 47 years), the impact of psoriasis on physical and psychosocial functioning was found to be associated with extent of BSA affected by psoriasis ([Gelfand et al, 2004](#)). Even patients with only 1% to 2% of BSA affected had a significant decrease in PRO (as measured by psoriasis disability index) compared with patients with "none to little" BSA affected ( $p < 0.0001$ ). Younger age ( $p = 0.0075$ ) and female sex ( $p = 0.01$ ) are also associated with greater impairment (Gelfand et al, 2004). [Rapp and colleagues \(1999\)](#) reported impaired health-related PRO that was significantly impacted by the

severity of the skin lesions of patients with psoriasis and that their impairment in physical functioning was comparable to that reported by patients with other chronic conditions, including cancer, arthritis, hypertension, heart disease, diabetes, and depression.

### Psychosocial

Adult patients with psoriasis often deal with a variety of mental or emotional issues, including fatigue, depression and suicidal ideation ([Gupta and Gupta, 1998](#)), feelings of social isolation, and low self-esteem. Psoriasis also has been shown to be associated with low self-esteem and an increased prevalence of mood disorders, including depression ([Kimball et al, 2008](#); [Krueger et al, 2001](#)), and extensive data in the literature have implicated stress as precipitating and/or exacerbating psoriasis (Fortune et al, 1997; [Gupta et al, 1987](#)). Other studies have found that psychological distress ([Finzi et al, 2007](#)) and depression ([Sharma et al, 2001](#); [Devrimci-Ozguven et al, 2000](#)) were relatively frequent in patients with psoriasis, as were embarrassment and frustration (data on file).

In a randomized, double-blind, placebo-controlled study of etanercept in the treatment of moderate to severe psoriasis (n = 618), 33% of subjects in the etanercept group and 35% of subjects in the placebo group had mild or moderate to severe depression at baseline ([Tyring et al, 2006](#)) as measured by the Beck Depression Inventory ([Beck and Steer, 1984](#); [Beck and Steer, 1993](#)). At week 12, 55% of patients in the etanercept group had a  $\geq 50\%$  improvement from baseline in the Beck Depression Inventory compared with the 39% in the control group; this was statistically significant.

In a survey of patients with plaque psoriasis conducted by the NPF, approximately 51% of patients reported feeling depressed and having significant life disruptions and social withdrawal as a result of their disease ([Krueger et al, 2001](#)). Patients with psoriasis often have a number of social-related difficulties with: the workplace, socialization with family members and friends, exclusion from public facilities (eg, hair salons, gyms, public pools), embarrassment (eg, they are perceived as contagious or having a communicable disease), and negative self-image. The burden associated with psoriasis can also impact work productivity, absenteeism, and employment ([Pearce et al, 2006](#)).

#### **4. Etanercept Development Program for Pediatric Psoriasis**

As a condition for approval of etanercept in the adult psoriasis indication and according to the Pediatric Research Equity Act ([Section 2.5](#)), Amgen was required to conduct a study in pediatric patients with moderate to severe plaque psoriasis. Based on the results of this study (20030211), an etanercept biological license supplement was submitted 26 September 2007, and included a request for approval to market etanercept in the pediatric plaque psoriasis setting.

##### **4.1 Study 20030211: Placebo-controlled Multicenter Study with Etanercept to Determine Safety and Efficacy in Pediatric Subjects with Plaque Psoriasis (PEDS)**

###### **4.1.1 Study Design**

Study 20030211 was a randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and pharmacokinetics of etanercept 0.8 mg/kg once per week (QW) up to a maximum dose of 50 mg QW vs placebo in children (ages 4 to 11 years) and adolescents (ages 12 to 17 years) with moderate to severe plaque psoriasis.

Major inclusion criteria included: a Static Physician's Global Assessment of Psoriasis (sPGA) score  $\geq 3$  (moderate), BSA involvement  $\geq 10\%$ , and Psoriasis Area Severity Index (PASI) score  $\geq 12$ . Subjects must also have been treated with phototherapy or systemic psoriasis therapy and/or must have been considered poorly controlled with topical psoriasis therapy.

The study consisted of 3 treatment periods:

###### **4.1.1.1 Period 1: Double-blind**

The first phase of the trial was a 12-week double-blind, placebo-controlled treatment period. At or after week 4, an escape arm to active treatment (0.8 mg/kg QW, up to a maximum dose of 50 mg QW, which was the dose of etanercept used in all treatment periods) was available for all subjects who met the following criteria:

- > 50% worsening and absolute worsening of at least 4 points from baseline PASI at any single visit, or
- $\geq 25\%$  but  $\leq 50\%$  worsening at 2 consecutive visits with an absolute worsening of at least 4 points from baseline PASI at the second visit

###### **4.1.1.2 Period 2: Open Label**

Beginning at week 13, all subjects (including those in the escape arm) were to receive open-label treatment with etanercept through week 36.

At week 24, all subjects were evaluated to determine whether they had achieved PASI 50 ( $\geq 50\%$  improvement from baseline PASI). Those who did achieve PASI 50 were to continue open-label treatment through week 36. Those who did not achieve PASI 50 were to either discontinue the study or enter the incomplete responder arm.

Incomplete responders were eligible to receive topical psoriasis therapy according to the standard of care in addition to receiving open-label etanercept through week 48.

Incomplete responders were not eligible to enter the randomized withdrawal-retreatment period as described in [Section 4.1.1.3](#).

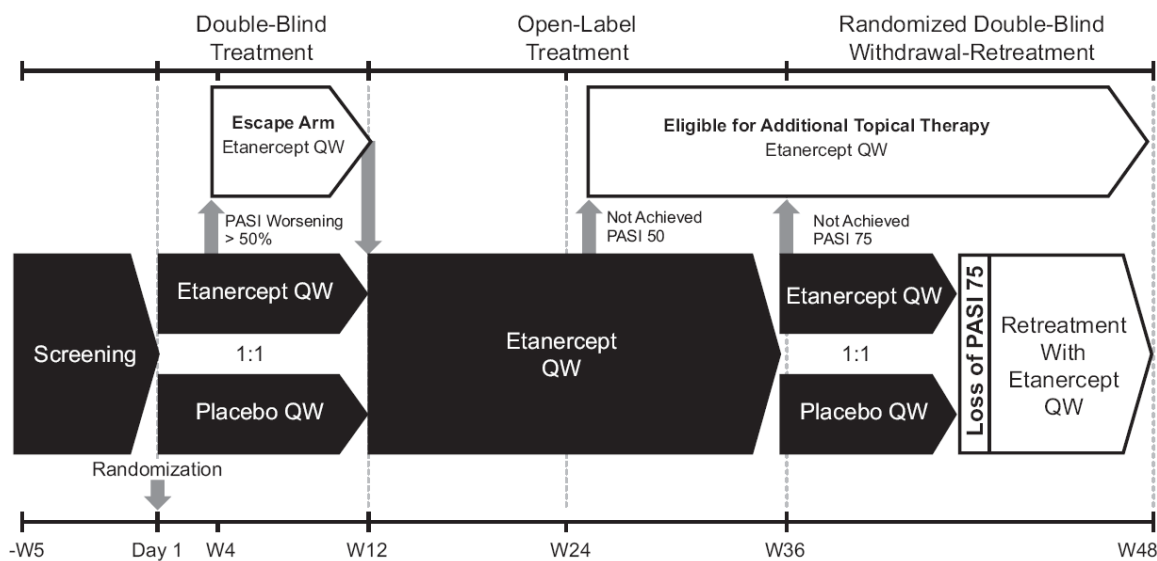
#### **4.1.1.3 Period 3: Randomized, Double-blind withdrawal-retreatment or Open-label Treatment for Incomplete Responders**

At week 36, all subjects (except those in the incomplete-responder arm) were evaluated to determine whether they had achieved a PASI 75 ( $\geq 75\%$  improvement from baseline PASI). Subjects who did achieve a PASI 75 at week 36 were to be randomized to receive etanercept or placebo through week 48. Subjects who did not achieve a PASI 75 at week 36 were to either discontinue the study or enter the incomplete responder arm described above (including eligibility for standard of care topical therapy) through week 48.

All subjects in the withdrawal-retreatment period were to be assessed for disease relapse ( $< 75\%$  improvement from baseline) every 4 weeks during blinded treatment. Upon relapse, subjects were to resume open label etanercept through week 48.

A schematic representation of the study design is shown in [Figure 1](#).

**Figure 1. Design for Study 20030211**



PASI = Psoriasis Area Severity Index; PASI 50/75 = 50%/75% improvement in PASI score from baseline; QW = once each week; W = week

#### 4.1.2 Demographics and Disposition

Baseline subject demographics were generally well balanced between the etanercept and placebo groups as were baseline disease characteristics, although a higher percentage of subjects in the placebo group had psoriatic arthritis at baseline than subjects in the etanercept group (13% vs 5%, respectively) (Table 4 and Table 5). Previous use of systemic or photo therapies was similar between the treatment groups.

A total of 211 subjects were randomized, and 210 of the subjects received at least 1 dose of etanercept. One placebo subject withdrew from the study before the open-label period and did not receive etanercept. Of these subjects, 194 (92%) completed the 48-week study. A figure summarizing subject disposition is provided in Figure 2.

**Table 4. Demographics for Double-blind Period Original Randomized Treatment**

	Placebo (N=105)	Etanercept 0.8 mg/kg QW (N=106)	All (N=211)
<b>Sex - n (%)</b>			
Female	52 (49.5)	51 (48.1)	103 (48.8)
Male	53 (50.5)	55 (51.9)	108 (51.2)
<b>Race - n (%)</b>			
White or Caucasian	75 (71.4)	83 (78.3)	158 (74.9)
Black or African American	8 (7.6)	3 (2.8)	11 (5.2)
Hispanic or Latino	14 (13.3)	8 (7.5)	22 (10.4)
Asian	6 (5.7)	9 (8.5)	15 (7.1)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.9)	1 (0.5)
Other	2 (1.9)	2 (1.9)	4 (1.9)
<b>Age Group (as stratified in randomization)</b>			
4 - 11	38 (36)	38 (36)	76 (36)
12 - 17	67 (64)	68 (64)	135 (64)
<b>Age (years)</b>			
n	105	106	211
Mean	12.61	12.78	12.70
SD	3.55	3.72	3.62
SE	0.35	0.36	0.25
Median	13.00	14.00	13.00
Min, Max	4.0, 17.0	4.0, 17.0	4.0, 17.0
<b>Weight (kg)</b>			
n	105	106	211
Mean	60.88	62.78	61.84
SD	26.53	29.56	28.04
SE	2.59	2.87	1.93
Median	59.80	59.55	59.80
Min, Max	17.2, 131.5	17.7, 168.3	17.2, 168.3
<b>Height (cm)</b>			
n	105	105	210
Mean	154.81	155.86	155.34
SD	18.89	19.80	19.31
SE	1.84	1.93	1.33
Median	157.48	159.00	157.49
Min, Max	104.0, 190.5	104.2, 188.0	104.0, 190.5

Treatment groups represent original randomized treatment

N = Number of subjects who received at least 1 dose of investigational product

Source: Table 14-2.1.1

**Table 5. Baseline Disease Summary for Double-blind Period Original Randomized Treatment**

	Placebo (N=105)	Etanercept 0.8 mg/kg QW (N=106)	All (N=211)
<b>Psoriasis Body Surface Area (%)</b>			
n	105	106	211
Mean (SD)	24.78 (14.97)	26.06 (15.93)	25.42 (15.43)
Median	20.00	21.00	20.00
Min, Max	10.0, 95.0	10.0, 90.0	10.0, 95.0
<b>Duration of Psoriasis (years)</b>			
n	105	106	211
Mean (SD)	5.77 (3.69)	6.30 (4.32)	6.03 (4.02)
Median	5.80	6.80	5.90
Min, Max	0.3, 15.8	0.3, 17.9	0.3, 17.9
<b>Previous Use of Systemic or Photo Therapies</b>			
No	43 (41)	48 (45)	91 (43)
Yes	62 (59)	58 (55)	120 (57)
<b>Psoriatic Arthritis</b>			
No	91 (87)	101 (95)	192 (91)
Yes	14 (13)	5 (5)	19 (9)
<b>Psoriasis Area and Severity Index</b>			
n	105	106	211
Mean (SD)	18.61 (6.75)	18.46 (6.72)	18.53 (6.72)
Median	16.40	16.70	16.40
Min, Max	12.0, 56.7	12.0, 51.6	12.0, 56.7
<b>Static Physician Global Assessment of Psoriasis</b>			
Unknown	0 (0)	0 (0)	0 (0)
0	0 (0)	0 (0)	0 (0)
1	0 (0)	0 (0)	0 (0)
2	1 (1)	1 (1)	2 (1)
3	68 (65)	69 (65)	137 (65)
4	33 (31)	33 (31)	66 (31)
5	3 (3)	3 (3)	6 (3)
<b>Total Children's Dermatology Life Quality Index</b>			
n	102	100	202
Mean (SD)	9.99 (6.37)	8.86 (5.99)	9.43 (6.20)
Median	9.50	7.00	8.00
Min, Max	0.0, 29.0	0.0, 26.0	0.0, 29.0

Page 1 of 2

Treatment groups represent original randomized treatment

N = Number of subjects who received at least 1 dose of investigational product

Source: Table 14-2.2.1



**Table 5. Baseline Disease Summary for Double-blind Period Original Randomized Treatment**

	Placebo (N=105)	Etanercept 0.8 mg/kg QW (N=106)	All (N=211)
Total Pediatric Quality of Life Inventory			
n	104	104	208
Mean (SD)	76.05 (16.93)	74.83 (17.77)	75.44 (17.32)
Median	79.90	77.20	77.20
Min, Max	30.4, 100.0	5.4, 100.0	5.4, 100.0
Stein Impact on Family Scale			
n	99	105	204
Mean (SD)	46.08 (8.40)	46.30 (9.55)	46.19 (8.99)
Median	45.00	46.00	46.00
Min, Max	17.0, 60.0	15.0, 60.0	15.0, 60.0
Total Harter's Self-Perception Profile for Children			
n	40	37	77
Mean (SD)	2.89 (0.48)	2.86 (0.50)	2.88 (0.49)
Median	2.90	3.00	2.90
Min, Max	2.0, 3.8	1.4, 3.7	1.4, 3.8
Total Harter's Self-Perception Profile for Adolescents			
n	53	60	113
Mean (SD)	2.88 (0.37)	2.86 (0.37)	2.87 (0.37)
Median	2.90	2.80	2.80
Min, Max	2.1, 3.7	1.9, 3.8	1.9, 3.8
Patient Assessment of Joint Pain			
n	33	19	52
Mean (SD)	2.82 (2.86)	1.89 (2.85)	2.48 (2.86)
Median	2.00	0.00	1.00
Min, Max	0.0, 8.0	0.0, 9.0	0.0, 9.0

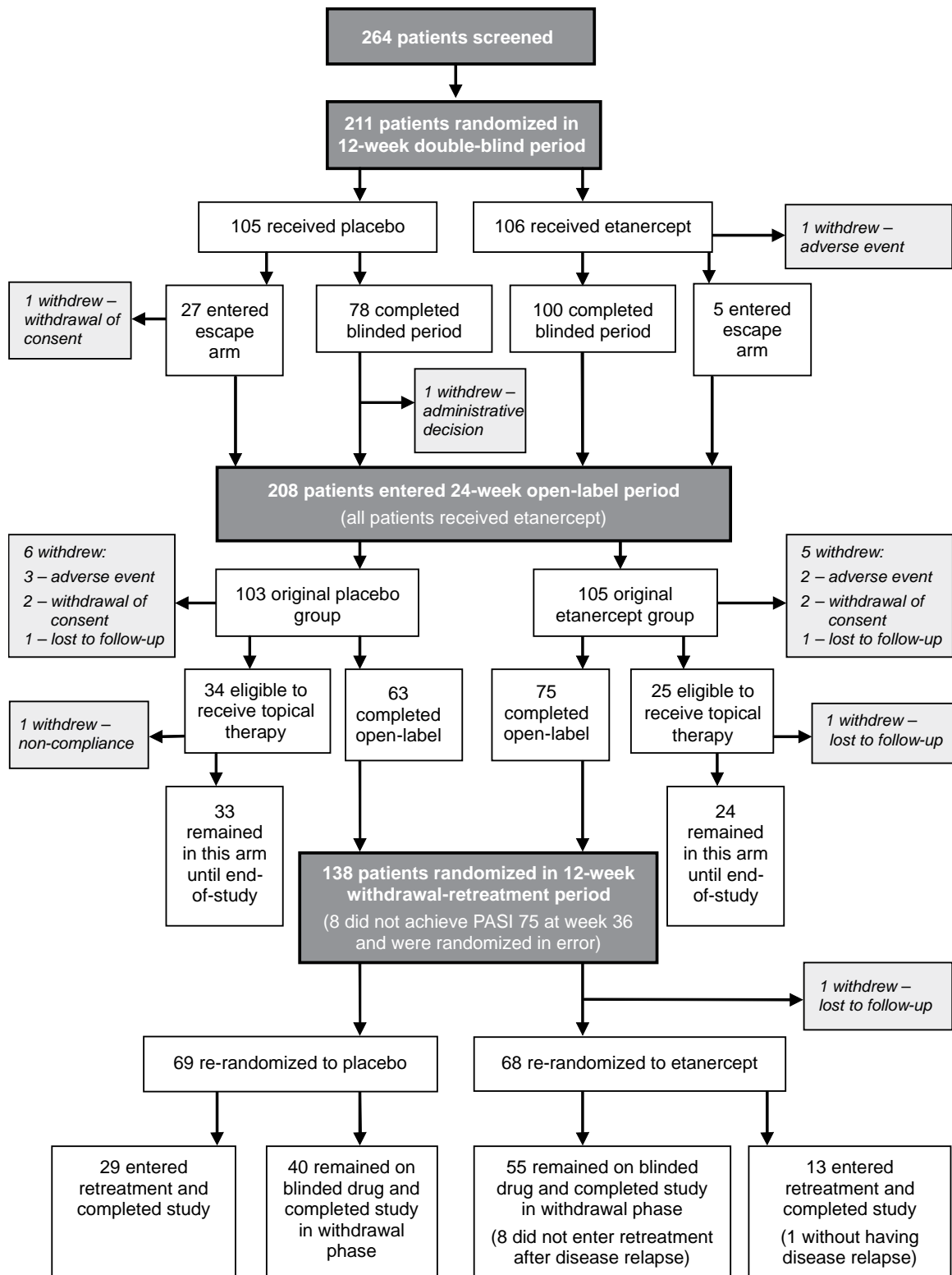
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Treatment groups represent original randomized treatment

N = Number of subjects who received at least 1 dose of investigational product

Source: Table 14-2.2.1

**Figure 2. Subject Disposition in Pediatric Plaque Psoriasis Study 20030211**



#### **4.1.3 Efficacy Results**

The primary objective of Study 20030211 was to determine the efficacy of etanercept in pediatric subjects with psoriasis. The primary efficacy endpoint for this study was the PASI 75 response at week 12. The secondary efficacy endpoints were PASI 50 response, PASI 90 response, a static physician global assessment (sPGA) of clear/almost clear status, and percent improvement from baseline in CDLQI at week 12. The overall significance level for the analyses of primary and secondary endpoints was controlled at 0.05 using a sequential testing scheme where endpoints at week 12 were evaluated in the following order: PASI 75 response, PASI 50 response, clear/almost clear status of sPGA, percent improvement from baseline in CDLQI, and PASI 90 response. Since the primary efficacy endpoint was significant, the secondary endpoints were tested sequentially at a significance level of 0.05.

##### **4.1.3.1 Period 1: Double-blind**

In the 12-week double-blind, placebo-controlled period of this study, etanercept provided statistically significant improvements to pediatric subjects with moderate to severe plaque psoriasis. A significantly higher percentage of subjects in the etanercept group achieved a PASI 50 and PASI 75 by week 4 and a PASI 90 by week 8 than did those treated with placebo (nominal  $p < 0.05$ ) ([Table 6](#)).

**Table 6. PASI Response During Double-blind Period<sup>a</sup>  
(ITT Subset with Treatment Failure Imputation)  
Subjects who Enter the Escape Arm Considered Treatment Failures at Time of  
Entering Escape Arm**

		Placebo	Etanercept 0.8 mg/kg QW	p-value <sup>b</sup>
≥ 50	Week 2	6/105 ( 6%)	9/106 ( 8%)	0.4323
	Week 4	12/105 ( 11%)	50/106 ( 47%)	<0.0001
	Week 8	20/105 ( 19%)	75/106 ( 71%)	<0.0001
	Week 12	24/105 ( 23%)	79/106 ( 75%)	<0.0001 <sup>c</sup>
≥ 75	Week 2	1/105 ( 1%)	1/106 ( 1%)	1.0000
	Week 4	3/105 ( 3%)	10/106 ( 9%)	0.0466
	Week 8	5/105 ( 5%)	47/106 ( 44%)	<0.0001
	Week 12	12/105 ( 11%)	60/106 ( 57%)	<0.0001 <sup>c</sup>
≥ 90	Week 2	0/105 ( 0%)	0/106 ( 0%)	N/A
	Week 4	1/105 ( 1%)	3/106 ( 3%)	0.3184
	Week 8	2/105 ( 2%)	14/106 ( 13%)	0.0019
	Week 12	7/105 ( 7%)	29/106 ( 27%)	<0.0001 <sup>c</sup>

<sup>a</sup> ITT subset with treatment failure imputation; subjects who enter the escape arm are considered treatment failures at the time of entering the escape arm.

<sup>b</sup> Two-sided Cochran-Mantel-Haenszel test stratified by age group

<sup>c</sup> Nominal p-value - Overall significance level for primary and secondary endpoints at week 12 will be controlled at 0.05 using a sequential testing scheme in the following order: PASI 75 response, PASI 50 response, clear/almost clear status of sPGA, percent improvement from baseline in CDLQI, and PASI 90 response.

#### **4.1.3.2 Period 2: Open-label**

During the 24-week open-label period, subjects who were originally randomized to the placebo group in the double-blind period achieved a similar PASI 75 at week 24 (after 12 weeks of open-label etanercept) as the original etanercept group had achieved at week 12 of the study (62% and 57%, respectively). Improvements in secondary efficacy endpoints (PASI 50 and PASI 90 response, sPGA of clear/almost clear status, and percent improvement from baseline in CDLQI at week 12) were maintained in the original etanercept group and were improved in the original placebo group once they began receiving open-label etanercept.

#### **4.1.3.3 Period 3: Randomized, Double-blind Withdrawal-retreatment or Open-label Treatment for Incomplete Responders**

During the withdrawal period, the placebo group lost the PASI 75 response more rapidly than the etanercept group. By week 48, more subjects re-randomized to placebo (29 of 69, 42%) had entered the retreatment period than subjects re-randomized to etanercept (13 of 69, 19%).

Of the subjects who had disease relapse and who entered the retreatment period from the placebo group, 27% (4 of 15) had regained a PASI 75 response by week 44, and 36% (10 of 28). These results were similar to those observed after subjects had received the initial treatment during the double-blind period. At week 4 of the double-blind period, 9% of subjects in the etanercept group had achieved PASI 75; by week 8, 44% of subjects had achieved PASI 75.

No subject had rebound of their disease, defined as a return to 125% of baseline PASI score within 3 months of treatment withdrawal.

#### **4.1.3.4 Patient-reported Outcomes in Pediatric Patients with Plaque Psoriasis Treated with Etanercept**

Patient-reported outcome data were evaluated at baseline and 12-weeks using the CDLQI and the PedsQL. Baseline results revealed poorer PRO in study subjects compared with those in healthy children reported from the literature ([Varni et al, 2002](#); [Lewis-Jones and Finlay, 1995](#)). Specifically, study subjects reported worse impairment on the CDQLI (mean score of 9) compared with healthy children (mean score of 0.4) in the validation study of the CDQLI (Lewis-Jones and Finlay, 1995) (higher scores represent more impairment). Study subjects also reported impaired PRO measured by the PedsQL (mean score 75) compared with those reported in healthy children (mean score of 88) in a comparative study of PRO of children with various health conditions (Varni et al, 2002) (higher scores on the PedsQL represent better PRO). At week 12 of Study 20030211, the mean percentage improvement from baseline in PRO as measured by the CDLQI was 52% in those who received etanercept compared with 17.5% in the placebo group ( $p < 0.0001$ ) ([Paller et al, 2008](#)). PedsQL total scores showed improvement in the etanercept group, but the results were not significant relative to placebo (82.2 and 81.4, respectively) (data on file). As a generic instrument, the PedsQL questionnaire has been shown to demonstrate significant differences in impairment in PRO among healthy patients and patients with various chronic conditions (Varni et al, 2007) as opposed to detecting differences in impairment between patients within a particular disease group.

#### **4.1.3.5 Efficacy Summary**

Etanercept at a dose of 0.8 mg/kg QW (up to a maximum dose of 50 mg QW) appeared to be efficacious in pediatric subjects with moderate to severe plaque psoriasis. At week 12 of the double-blind period, 57% of etanercept-treated subjects achieved the primary endpoint of a PASI 75 response compared with 11% of placebo-treated

subjects. During the open-label period, subjects originally randomized to the placebo group had similar responses in efficacy measures at week 24 (after 12 weeks of etanercept), compared with the original etanercept group at week 12 of the double-blind period. During the withdrawal period, more subjects who were re-randomized to the placebo group had disease relapse (loss of PASI 75 response) compared with subjects who were re-randomized to the etanercept 0.8-mg/kg QW group. However, after entering the retreatment period and receiving open-label etanercept, this placebo group again showed improvement in their PASI responses. Of note, no subject had a rebound of their disease. In addition, PRO measures demonstrated that scores generally improved over time as subjects continued to receive etanercept.

#### **4.1.4 Safety Results**

##### **4.1.4.1 Summary of Safety Results**

Overall, etanercept was well tolerated in the pediatric population of Study 20030211. No deaths occurred during the entire study. No serious adverse events or serious infections occurred during the 12-week double-blind period ([Table 7](#)). During the open-label period, 1 serious adverse event (benign ovarian mass) and 1 serious infection (lobar pneumonia) were reported. In addition, 2 serious infectious events (gastroenteritis and dehydration secondary to gastroenteritis) were reported for the same subject during the incomplete-responder arm. No subjects had a serious adverse event or infection during the randomized withdrawal or retreatment periods of the study. Six subjects withdrew from the study due to an adverse event or infection: 1 subject during the double-blind period and 5 subjects during the open-label period of the study. Three of these events were considered by the investigator to be related to investigational product: progression of disease (psoriasis) in the original placebo group; and skin infection and pneumonia in the original etanercept group. The pneumonia also was considered a serious infection.

##### **4.1.4.2 Safety Results During the 12-week Double-blind Period**

During the initial 12-week double-blind period, the proportion of subjects reporting 1 or more adverse events was generally similar between the etanercept and placebo groups (64.2% etanercept, 59.0% placebo) ([Table 7](#)). All events experienced prior to entering the escape arm were summarized in the treatment group that the subject was randomized to whereas all events experienced during the escape arm were summarized in a separate column.

**Table 7. Summary of Subject Incidence of Selected Adverse Events during Double-blind Period**

Types of Events	Escape Arm Etanercept 0.8 mg/kg QW (N=32) n (%)	Placebo (N=105) n (%)	Etanercept 0.8 mg/kg QW (N=106) n (%)
At least 1 Event	16 (50.0)	62 (59.0)	68 (64.2)
At least 1 Non-infectious Adverse Event	9 (28.1)	46 (43.8)	42 (39.6)
At least 1 Infection	9 (28.1)	33 (31.4)	50 (47.2)
At least 1 Serious Non-infectious Adverse Event	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
At least 1 Serious Infection	0 (0.0)	0 (0.0)	0 (0.0)
At least 1 Grade 3 Non-infectious Adverse Event	0 (0.0)	3 (2.9)	0 (0.0)
At least 1 Grade 3 Infection	0 (0.0)	0 (0.0)	0 (0.0)
At least 1 Non-infectious Adverse Event Leading to Withdrawal From Study	0 (0.0)	0 (0.0)	1 (0.9)
At least 1 Infection Leading to Withdrawal From Study	0 (0.0)	0 (0.0)	0 (0.0)
At least 1 Injection Site Reaction	1 (3.1)	5 (4.8)	7 (6.6)

Treatment groups represent actual treatment received

N = Number of subjects who were randomized and received at least 1 dose of investigational product

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The most commonly reported events occurred in similar proportions in the 2 groups, with the exception of (etanercept, placebo): upper respiratory tract infection (17.0% vs 11.4%), influenza (7.5% vs 1.9%), and gastroenteritis (5.7% vs 0%). Of these most common events, all were mild to moderate in severity. The most common adverse and infectious events ( $\geq 2\%$  in the etanercept-treated group) are summarized in [Table 8](#).

**Table 8. Subject Incidence of Adverse Events  $\geq$  2% by Preferred Term in Descending Frequency During Double-blind Period**

	Escape Arm Etanercept 0.8 mg/kg QW (N = 32)	Placebo (N = 105)	Etanercept 0.8 mg/kg QW (N = 106)
Preferred Term	n (%)	n (%)	N (%)
Number of Subjects Reporting Adverse Events	16 (50.0)	62 (59.0)	68 (64.2)
Upper Respiratory Tract Infection	4 (12.5)	12 (11.4)	18 (17.0)
Headache	1 (3.1)	13 (12.4)	14 (13.2)
Influenza	0 (0)	2 (1.9)	8 (7.5)
Nasopharyngitis	0 (0)	9 (8.6)	8 (7.5)
Gastroenteritis	1 (3.1)	0 (0)	6 (5.7)
Arthralgia	0 (0)	0 (0)	5 (4.7)
Dizziness	0 (0)	1 (1.0)	5 (4.7)
Cough	0 (0)	2 (1.9)	4 (3.8)
Vomiting	0 (0)	2 (1.9)	4 (3.8)
Abdominal Pain Upper	0 (0)	2 (1.9)	3 (2.8)
Nasal Congestion	1 (3.1)	3 (2.9)	3 (2.8)
Nausea	0 (0)	3 (2.9)	3 (2.8)
Pharyngitis Streptococcal	1 (3.1)	1 (1.0)	3 (2.8)
Rhinorrhoea	1 (3.1)	2 (1.9)	3 (2.8)

Treatment groups represent actual treatment received

N = Number of subjects who were randomized and received at least 1 dose of investigational product

Source: Table 14-6.2.1

#### **4.1.4.3 Safety Results during the Withdrawal Period**

Most adverse events that were reported during the withdrawal period occurred in similar proportions of etanercept-treated and placebo subjects, although the incidence of nasopharyngitis and headache was higher in the etanercept group (10.3% and 8.8%, respectively) than in the “placebo” group (2.9% and 2.9%, respectively). The “placebo” group here included subjects randomized to the placebo group during withdrawal.

#### **4.1.4.4 Safety Results during the Retreatment Period**

During the retreatment period, the most commonly reported adverse events were upper respiratory tract infection (14.3%) and sinusitis (7.1%) (all mild to moderate in severity). Safety results during the retreatment period should be interpreted with caution due to the small sample size and short duration of time.



#### **4.1.4.5 All Adverse Events and Infections – 48 week Exposure-adjusted Rates**

In the analysis of all adverse events during the entire 48 week study, the placebo treatment group only included placebo exposure during the initial 12-week double-blind period. Events occurring after subsequent exposure to etanercept were included in the etanercept treatment group.

Most events in the etanercept group occurred at a similar exposure-adjusted rate compared with the placebo group. Exceptions included streptococcal pharyngitis, skin papilloma, gastroenteritis, and arthralgia, which occurred at exposure-adjusted rates of 13.3, 9.7, 9.1, and 7.9 events per 100 subject-years, respectively, in the etanercept group, compared with 5.3, 0, 0, and 0 events per 100 subject-years, respectively, in the placebo group.

Seventeen subjects reported 23 events of streptococcal pharyngitis; 1 subject from placebo group reported 1 event. Pharyngitis and pharyngolaryngeal pain were reported at 26.6 and 31.9 events per 100 subject-years in the placebo arm, and 6.7 and 12.1 in the etanercept arm respectively.

There were 15 events of gastroenteritis in 13 subjects; all were exposed to etanercept. All cases were mild to moderate in severity with the exception of 1 case, which was assessed as severe.

Sixteen adverse events of skin papilloma were reported by 13 subjects. Two subjects reported adverse events  $\geq 2$  times during study. All cases of skin papilloma were reported after exposure to etanercept.

Thirteen events of arthralgia were reported in 10 subjects; all were exposed to etanercept. All events were mild to moderate in severity.

The most common adverse and infectious events ( $> 5$  events per 100 subject-years in the etanercept-treated group) are summarized in [Table 9](#).

**Table 9. All Events Through Week 48  
Exposure-adjusted Rates by Preferred Term in Descending Frequency with  
Etanercept Arm Exposure Adjusted Rate > 5.0**

Preferred Term	Placebo <sup>a</sup>		Etanercept 0.8 mg/kg QW <sup>a</sup>	
	(N = 105) (E = 18.8)		(N = 210) (E = 164.8)	
	n	r	n	r
Total Number of Events	144	(765.4)	914	(554.5)
Upper Respiratory Tract Infection	13	(69.1)	90	(54.6)
Headache	18	(95.7)	54	(32.8)
Nasopharyngitis	10	(53.2)	52	(31.5)
Influenza	3	(15.9)	23	(14.0)
Pharyngitis Streptococcal	1	(5.3)	22	(13.3)
Cough	2	(10.6)	20	(12.1)
Pharyngolaryngeal Pain	6	(31.9)	20	(12.1)
Vomiting	2	(10.6)	20	(12.1)
Nasal Congestion	3	(15.9)	17	(10.3)
Skin Papilloma	0	(0.0)	16	(9.7)
Gastroenteritis	0	(0.0)	15	(9.1)
Pyrexia	1	(5.3)	14	(8.5)
Arthralgia	0	(0.0)	13	(7.9)
Injection Site Bruising	4	(21.3)	13	(7.9)
Gastroenteritis Viral	3	(15.9)	12	(7.3)
Injection Site Pruritus	0	(0.0)	12	(7.3)
Nausea	3	(15.9)	12	(7.3)
Abdominal Pain Upper	2	(10.6)	11	(6.7)
Bronchitis	1	(5.3)	11	(6.7)
Injection Site Pain	0	(0.0)	11	(6.7)
Pharyngitis	5	(26.6)	11	(6.7)
Sinusitis	1	(5.3)	11	(6.7)
Acne	0	(0.0)	10	(6.1)
Dermatitis Contact	1	(5.3)	10	(6.1)
Skin Infection	1	(5.3)	10	(6.1)
Viral Upper Respiratory Tract Infection	1	(5.3)	10	(6.1)
Contusion	1	(5.3)	9	(5.5)
Ear Infection	1	(5.3)	9	(5.5)
Excoriation	1	(5.3)	9	(5.5)

<sup>a</sup> Placebo treatment group includes placebo exposure during the initial 12-week double-blind period only; events that occur during placebo exposure in the randomized withdrawal period are included in the Etanercept 0.8 mg/kg QW treatment group

N = Number of subjects who were randomized and received at least 1 dose of investigational product

E = Total number of exposure years

n = Number of adverse events

r = Exposure-adjusted event rate per 100 subject years (= n / E \* 100)

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#### **4.1.4.6 Clinical Laboratory Results**

Three transient grade 3 elevated hemoglobin concentrations were reported: 1 etanercept subject at baseline and 2 placebo subjects during the open-label period. No grade 4 laboratory abnormalities were reported during the study. None of the laboratory abnormalities were associated with any clinical reports of serious adverse events.

#### **4.1.4.7 Events of Medical Interest**

No events of medical interest (tuberculosis, congestive heart failure, opportunistic infection, lymphoma, or demyelination) were reported.

#### **4.1.4.8 Other Events of Medical Interest**

Other events that were considered by investigators and Amgen personnel to be of medical interest were reported by 15 subjects (8 etanercept, 7 placebo; some subjects had more than 1 event), and in the etanercept group included events considered neurologic in nature (dizziness, syncope vasovagal, hypoaesthesia), abdominal pain, and dysmenorrhoea. Most of these events were considered to be unrelated to investigational product; however, 7 events in those receiving etanercept were considered related: dizziness (3 events), syncope vasovagal (1 event), and hypoaesthesia (3 events). No malignancies were observed during the study.

#### **4.1.4.9 Antibody Results**

Of the 211 subjects who were randomized to the study, 208 had predose and postdose serum samples available for testing for antibodies to etanercept. Of these 208 subjects, 20 subjects (9.6%) had at least 1 sample that was positive for anti-etanercept antibodies at  $\geq 1$  time point. All samples were negative for neutralizing anti-etanercept antibodies.

There was no apparent relationship between anti-etanercept antibody status and adverse event profile.

#### **4.1.4.10 Safety Conclusions**

In general, etanercept was well tolerated in this 48-week study. The types of adverse events and infections reported in this study were similar to those seen in the studies of adults with chronic plaque psoriasis. More infectious adverse events were reported in pediatric psoriasis patients receiving etanercept than in adults receiving etanercept, such as streptococcal pharyngitis. Skin papillomas, gastroenteritis, and arthralgias were also reported more frequently in the etanercept group. Pharyngolaryngeal pain, viral gastroenteritis, and nasopharyngitis were more commonly reported in the placebo group.

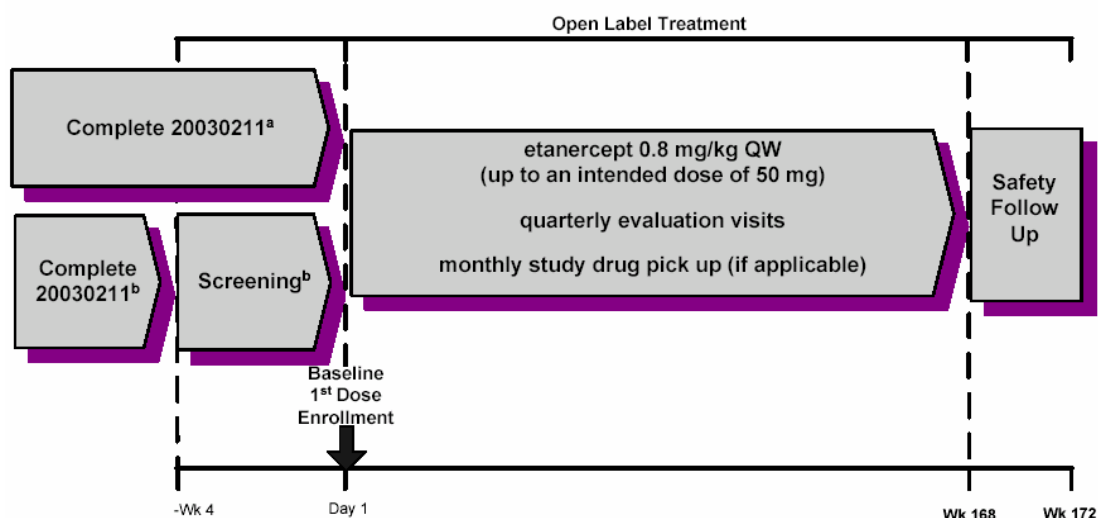
## 4.2 Study 20050111: An Open-label Extension Study to Evaluate the Safety of Etanercept in Pediatric Subjects with Plaque Psoriasis

Subjects who completed Study 20030211 or who received substantial benefit (achieved  $\geq$  PASI 50) from etanercept between week 12 and week 48 of the study, and who did not have a serious adverse event or other clinically significant adverse event considered related to investigational product were eligible to enroll into open-label extension Study 20050111.

### 4.2.1 Study Design

In this ongoing, multicenter, open-label extension study for subjects who participated in Study 20030211, subjects will receive etanercept 0.8 mg/kg (up to a maximum dose of 50 mg) once weekly by subcutaneous injection for 168 weeks. Subjects with a sPGA score of clear (0) or almost clear (1) may stop treatment with investigational product at week 96, 108, 120, 132, 144, or 156. Subjects who stop treatment with investigational product at or after week 96 will continue with safety evaluations every 12 weeks, but will not be evaluated for efficacy for the remainder of the study. The investigator may restart treatment with investigational product for the subject at any time. A subject may only stop and restart treatment with investigational product once. The study design is summarized in Figure 3.

Figure 3. Design for Study 20050111



<sup>a</sup> Subjects with  $\leq 4$  weeks investigational product interruption between last dose on 20030211 and first dose on this extension study do not require a screening visit. The end of treatment visit on the original study 20030211 may occur at the same time as the baseline visit for this extension study.

<sup>b</sup> Subjects with  $> 4$  weeks investigational product interruption between last dose on 20030211 and first dose on this extension study require a screening visit.

#### **4.2.2 Preliminary Demographics and Disposition**

A total of 181 of the 211 subjects who enrolled in 20030211 chose to enroll in the open-label extension Study 20050111 (86%). Out of the 181 subjects, 50.3% were girls, and 77.3% were white. At baseline of Study 20050111, the mean (SD) age was 13.7 (3.51) years; 27.6% of subjects were 4 to 11 years of age, while 72.4% were 12 to 17 years of age. At baseline of Study 20030211, mean (SD) weight was 62.03 (27.37) kg, and the mean duration of psoriasis was 6.05 years, with a range from 0.3 to 16.3 years.

As of 07 March 2008, an estimated 160 subjects had completed their 1-year visit, and an estimated 75 subjects had completed their 2-year visit. Thirty-three subjects (18.2%) had withdrawn from the study. Reasons for withdrawal included the following: consent withdrawn (10 subjects), lost to follow-up and noncompliance (6 subjects each), other (4 subjects), ineligibility determined (3 subjects), and adverse event and pregnancy (2 subjects each).

#### **4.2.3 Preliminary Safety Results**

##### **4.2.3.1 Summary of Preliminary Safety Results**

As of 07 March 2008, 3 subjects had withdrawn from the study due to an adverse event or infection: 1 subject withdrew due to Crohn's disease, 1 withdrew due to dehydration, and 1 withdrew due to sinusitis. None of these events was considered by the investigator to be related to investigational product. The event of dehydration also was considered a serious adverse event (see [Section 4.2.3.3](#)).

##### **4.2.3.2 Preliminary Adverse and Infectious Event Results**

As of 07 March 2008, 108 of the 181 enrolled subjects (59.7%) had reported adverse events. Events reported by > 5% of subjects (> 9 subjects) included: upper respiratory tract infection (15.5%); nasopharyngitis (13.3%); pharyngitis streptococcal (9.9%); headache (7.7%); sinusitis (6.6%); and cough, pharyngolaryngeal pain, and skin papilloma (5.5% each). Of these events, nasopharyngitis, pharyngitis streptococcal, sinusitis, and upper respiratory tract infection were infectious events.

##### **4.2.3.3 Preliminary Serious Adverse and Infectious Event Results**

As of 07 March 2008, 2 subjects (1.1%) had reported a total of 4 serious adverse events (preferred terms included abdominal tenderness, dehydration, and pregnancy for a 16-year-old girl, and anxiety for a 17-year-old boy); no serious infectious events were reported.

## 5. Safety of Etanercept in Pediatric Populations

### 5.1 Juvenile Rheumatoid/Idiopathic Arthritis

Amgen has conducted 5 studies (4 clinical, 1 prospective cohort study) that include subjects with juvenile rheumatoid arthritis (JRA). In current accepted nomenclature and in the current etanercept label, juvenile rheumatoid arthritis is referred to as juvenile idiopathic arthritis (Foeldvari et al, 2000; Petty et al, 1997; Fink et al, 1995). A list of these studies is provided in Table 10, and details from 3 of these studies are provided in the sections that follow. Because of slow enrollment, and in consultation with the FDA, 2 studies (16.0028 and 16.0031) were terminated early. These studies are discussed briefly in this document in terms of pharmacokinetics data (Section 6.3).

**Table 10. Amgen Studies in Subjects with Juvenile Rheumatoid/Idiopathic Arthritis**

Study Number	Study Title
16.0016	Safety, Population Pharmacokinetics, and Efficacy of Recombinant Human Tumor Necrosis Factor Receptor (p75) Fc Fusion Protein (TNFR:Fc) in Children with Juvenile Rheumatoid Arthritis
16.0018 <sup>a</sup>	Open-label Extension Treatment with TNFR:Fc for Participating Patients in Etanercept Clinical Trials
20021626	A Phase IV Registry of Etanercept (Enbrel®) in Children with Juvenile Rheumatoid Arthritis
16.0028 <sup>b</sup>	A Phase III Double Blind Randomized Study Comparing Etanercept (Enbrel®) Combined with Methotrexate vs Methotrexate Alone in Children with Polyarticular Course Juvenile Rheumatoid Arthritis
16.0031 <sup>c</sup>	A Phase 4 Safety and Efficacy Study of Etanercept in Children with Systemic Onset Juvenile Rheumatoid Arthritis

<sup>a</sup> This rheumatoid arthritis study included 58 subjects with juvenile rheumatoid arthritis

<sup>b</sup> Data from Study 16.0028 are not included in this document for comparison, except as part of the pharmacokinetic comparison in Section 6.3. Due to slow enrollment, and in consultation with the Agency, this study was terminated early with only 25 subjects enrolled, yielding insufficient statistical power for the planned safety and efficacy analysis.

<sup>c</sup> Data from Study 16.0031 are not included in this document for comparison. Because of slow enrollment (reluctance of parents to enroll their children in a clinical study with possible assignment to placebo rather than to etanercept since etanercept was commercially available), this study was terminated after 19 of the planned 75 subjects were enrolled; only 9 of these 19 subjects had entered the blinded phase.

**5.1.1 Study 16.0016: Safety, Population Pharmacokinetics, and Efficacy of Recombinant Human Tumor Necrosis Factor Receptor (p75) Fc Fusion Protein (TNFR:Fc) in Children with Juvenile Rheumatoid Arthritis**

**5.1.1.1 Study Design**

This was a multicenter study designed to determine the efficacy of etanercept (TNFR:Fc) in pediatric subjects with active polyarticular course juvenile rheumatoid arthritis, to monitor the safety of etanercept at a dose of 0.4 mg/kg (with maximum of 25 mg) administered twice weekly for up to 7 months, to determine the population pharmacokinetics for etanercept, and to evaluate the mean time to flare after randomization to placebo or etanercept.

The study included 2 parts:

- *Part 1 was a 3-month open-label run-in portion*
- *Part 2 was a 4-month randomized, double-blind, placebo controlled portion*

During the first part of the study, subjects received open-label 0.4 mg/kg etanercept by subcutaneous injection twice weekly for 3 months. At the end of the 3-month period, subjects who responded to treatment (Pediatric ACR30 criteria [[Gianni et al, 1997](#)]) were randomized to double-blind Part 2 of the study and received placebo or 0.4-mg/kg etanercept twice weekly until disease flare or until 4 months had elapsed.

Methotrexate and disease-modifying anti-rheumatic drugs (DMARDs) were discontinued 14 days and 28 days, respectively, before initiation of etanercept. Intraarticular and soft-tissue corticosteroid injections were not permitted during or for 1 month before the trial. Stable doses of NSAIDs, low doses of corticosteroids ( $\leq 0.2$  mg of prednisone per kilogram per day, with a maximum of 10 mg per day), or both were permitted.

**5.1.1.2 Demographics and Disposition**

A total of 69 subjects (43 girls and 26 boys) enrolled in the open-label portion of the study. Of these, 51 subjects (34 girls, 17 boys) continued to the double-blind portion of the study. At enrollment, the mean age was 10.5 years (range 4 to 17 years) and the mean duration of juvenile rheumatoid arthritis was 5.9 years. Baseline subject characteristics of age, race, and corticosteroid use were not equally distributed between the randomized etanercept and placebo groups in Part 2 of the study; this unequal distribution was not considered to have affected the study results.

Subject disposition during the 3-month open-label portion is summarized in [Table 11](#), and disposition during the 4-month double-blind portion is summarized in [Table 12](#). Only

1 subject discontinued either the open-label or double-blind portion of the study due to an adverse event (urticaria, which was not a serious adverse event).

**Table 11. Subject Disposition for the 3-month Open-label Portion of Study 16.0016**

Status	Etanercept 0.4 mg/kg BIW N = 69 n (%)
Completed Part 1	64 (93)
Continued to Part 2	51 (74)
Did not continue to Part 2 <sup>a</sup>	18 (26)
Adverse event <sup>b</sup>	1 ( 1)
Patient/parent refusal	2 ( 3)
Protocol issues	3 ( 4)
Response status: nonresponder	12 (17)

<sup>a</sup> 5 subjects prematurely discontinued the study during Part 1, the remaining subjects completed part 1, but did not continue to part 2

<sup>b</sup> urticaria, reported after the subject's first dose

BIW = twice per week

**Table 12. Subject Disposition for the 4-month Double-blind Portion of Study 16.0016**

Status	Placebo (n = 26) n (%)	Etanercept 0.4 mg/kg BIW (n = 25) n (%)
Completed Part 2	7 (27)	19 (76)
Discontinued Part 2	19 (73)	6 (24)
Patient/parent refusal	1 ( 4)	--
Response status: nonresponder	18 (69)	6 (24)

BIW = twice per week

### 5.1.1.3 Safety Results

Because of the relatively small sample size in this study, subject-years of exposure to etanercept were relatively low (part 1, 16.28 subject years; part 2, 6.87 subject years). Thus, results are presented by incidence.

Safety assessments included all 69 subjects who received  $\geq 1$  dose of etanercept. Subjects receiving placebo in the double-blind portion had previously received etanercept during the open label portion. The most common infectious events included upper respiratory infections and pharyngitis ([Table 13](#)). Two subjects reported adverse events that were serious, and included personality disorder and gastroenteritis. The case of gastroenteritis was also a serious infectious event. No deaths were reported.



**Table 13. Exposure-adjusted Event Rate of Infections in Study 16.0016**

System Organ Class Preferred Term	-- Part 1 -- Open Label ETAN (N=69) (Pt-yr=16.28) n (r)	----- Part 2 ----- Double-blind	
		PLA (N=26) (Pt-yr=3.63) n (r)	ETAN (N=25) (Pt-yr=6.87) n (r)
Number of Infections	74 (454.57)	12 (330.54)	27 (392.74)
Infections and infestations	74 (454.57)	12 (330.54)	27 (392.74)
Upper respiratory tract infection	34 (208.85)	6 (165.27)	13 (189.10)
Pharyngitis	12 (73.71)	0	3 (43.64)
Ear infection	8 (49.14)	2 (55.09)	1 (14.55)
Gastroenteritis	6 (36.86)	1 (27.55)	3 (43.64)
Sinusitis	3 (18.43)	1 (27.55)	0
Conjunctivitis infective	3 (18.43)	0	0
Influenza	2 (12.29)	2 (55.09)	2 (29.09)
Skin infection	2 (12.29)	0	1 (14.55)
Diarrhoea infectious	1 (6.14)	0	0
Gastroenteritis viral	1 (6.14)	0	0
Sialoadenitis	1 (6.14)	0	0
Vaginal infection	1 (6.14)	0	0
Tinea pedis	0	0	2 (29.09)
Bronchitis	0	0	1 (14.55)
Gastrointestinal infection	0	0	1 (14.55)

N = Number of subjects who enrolled and received at least 1 dose of investigational product in the specified study period

Pt-yr = Total subject years of exposure to investigational product

n = Number of Infections

r = Exposure-adjusted event rate per 100 subject-years ( $n/Pt\text{-}yr * 100$ )

Program: /stat/amg916/all/enbrel\_datamart/analysis/production/dodac\_apr2008/tables/t\_exp\_adj\_ae.sas

Output:

/stat/amg916/all/enbrel\_datamart/analysis/production/dodac\_apr2008/tables/output/t\_exp\_adj\_inf\_1616.  
rtf (Date Generated: 05MAY08:17:39:28)

Source Data:

/stat/amg916/all/enbrel\_datamart/analysis/production/dodac\_apr2008/statdata/crt/event.sas7bdat

#### **5.1.1.4 Conclusion**

Adverse events and infectious events were typically mild to moderate in intensity and did not result in interruption or discontinuation of etanercept.

### **5.1.2 Study 16.0018: Open-Label Extension Treatment with TNFR:Fc for Participating Patients in TNFR:Fc Clinical Trials**

#### **5.1.2.1 Study Design**

This ongoing 10 year open-label, multicenter extension study was designed to evaluate long-term safety of etanercept in adult and pediatric subjects with rheumatoid arthritis who had participated in randomized, controlled clinical trials of etanercept. Subjects with juvenile rheumatoid arthritis from Study 16.0016 (see [Section 5.1.1](#)) were eligible to enroll into Study 16.0018 provided they did not have clinically significant toxicity from investigational product. Subjects who had some response but did not meet the definition of improvement (Pediatric ACR30) during part 1, subjects with disease flare during Part 2, and subjects who completed 4 months of blinded therapy during Part 2 of the study were eligible to receive open-label treatment in Study 16.0018. Upon consent by the subject or subject's guardian, subjects could choose to enroll directly from the blinded portion of the initial study into this open-label extension. Methotrexate and other DMARDs were discontinued 2 weeks and 4 weeks, respectively, before subjects were permitted to enroll in Study 16.0018. Use of methotrexate and DMARDs was prohibited in the study. After 1 year of participation in Study 16.0018, methotrexate could be added, but dosing was limited to 10 to 20 mg/m<sup>2</sup>/week.

Data up to 8 years (including the 7 months of the 16.0016 study) from this ongoing study have been previously reported ([Lovell et al, 2008](#); [Lovell et al, 2006](#); [Lovell et al, 2003](#)). The data below include up to 9 years of etanercept exposure (data cutoff date of 06 June 2007).

#### **5.1.2.2 Demographics and Disposition**

A total of 69 subjects enrolled in the original randomized, controlled study (Study 16.0016), and 58 of these subjects (84%) enrolled in open-label extension Study 16.0018 and received weekly etanercept, for a total of 337.5 subject-years of etanercept exposure. Demographics for these subjects at baseline of Study 16.0016 are provided in [Table 14](#).

**Table 14. Demographic Characteristics of Subjects in Extension Study 16.0018 at Baseline of Study 16.0016**

Baseline Characteristic <sup>a</sup>	Subjects Enrolled in Study 16.0018 (N = 58)
Age, mean ± SD years	10.4 ± 3.8
Age range, min, max - years	4, 17
Sex, n (%)	
Female	39 (67)
Race, n (%)	
White	43 (74)
Black	4 (7)
Hispanic	9 (16)
Other	2 (3)
JRA onset type, n (%)	
Pauciarticular	5 (9)
Polyarticular	34 (59)
Systemic	19 (33)
Duration of JRA, Mean ± SD - years	5.9 ± 3.2

<sup>a</sup> Baseline of Study 16.0016

JRA = juvenile rheumatoid arthritis; NSAID = non-steroidal anti-inflammatory drugs; OLE = open-label extension; RF = rheumatoid factor; SD = standard deviation

Data cutoff date 06 June 2007

Of the subjects who enrolled in the open-label extension, as of the 9-year data cutoff date of this ongoing study, 19 of 58 subjects (33%) remain in the study. Interim subject disposition information is provided in [Table 15](#).

**Table 15. Subject Disposition at Year 9 of Ongoing Study 16.0018**

Withdrew from the Extension n = 39 of 58 subjects (67%)	
Reasons:	
Lack of efficacy	8 (14%)
Adverse event	4 (7%)
Physician decision	5 (9%)
Protocol issue	3 (5%)
Lost to follow-up	3 (5%)
Patient/parent refusal	7 (12%)
Other	9 (16%)
Remain on study	n = 19/58 (33%)

Data cutoff date 06 June 2007

source: enzweile - /mastat/enbrel/ra/lra/analysis/2007aug/tables/t\_finlast.sas (11oct2007,11:03)

### 5.1.2.3 Safety Results

The incidence and exposure-adjusted rate of safety events in Studies 16.0016 and 16.0018 are summarized in Table 16 by study year and in total. Safety data were reported for all 69 patients who enrolled in study 16.0016. Per protocol, only serious adverse events were reported during open-label extension Study 16.0018.

**Table 16. Exposure-adjusted rates of Serious Adverse Events and Serious Infections in Each Year of Etanercept Treatment**

		Serious Adverse Events				Serious Infectious Events			
		n	%	r	R	n	%	r	R
First Year <sup>a</sup>	(N=69, YR=57.4)	4	5.80	5	0.087	3	4.35	4	0.070
Second Year	(N=52, YR=49.8)	6	11.54	8	0.161	3	5.77	3	0.060
Third Year	(N=48, YR=44.9)	5	10.42	9	0.200	2	4.17	2	0.044
Fourth Year	(N=42, YR=39.9)	3	7.14	5	0.125	1	2.38	2	0.050
Fifth Year	(N=37, YR=36.1)	1	2.70	2	0.055	0	0.00	0	0.000
Sixth Year	(N=34, YR=33.2)	0	0.00	0	0.000	0	0.00	0	0.000
Seventh Year	(N=31, YR=28.3)	1	3.23	4	0.141	0	0.00	0	0.000
Eighth Year	(N=26, YR=25.3)	2	7.69	3	0.119	1	3.85	1	0.040
Ninth Year	(N=21, YR=18.5)	0	0.00	0	0.000	0	0.00	0	0.000
Tenth Year	(N=15, YR=4.1)	0	0.00	0	0.000	0	0.00	0	0.000
Subtotal	(N=69, YR=337.5)	16	23.19	36	0.107	9	13.04	12	0.036
Unknown	(N=69, YR=337.5)	1	1.45	3	0.009	0	0.00	0	0.000
Total	(N=69, YR=337.5)	16	23.19	39	0.116	9	13.04	12	0.036

<sup>a</sup> First year includes exposure from 16.0016.

N = total number of subjects; n = number of subjects with events, % =  $n \times 100 / N$

YR = total years on drug, r = number of events, R =  $r / YR$  + events beyond 30 days of last dose of etanercept are excluded

Unknown = the date of the reported event was not captured and therefore is unknown

Source: enzweile - /mastat/enbrel/ra/lra/analysis/2007aug/tables/t\_event\_rates.sas (16oct2007,16:10)

The rate of serious adverse events and serious infectious events did not increase with continued exposure to etanercept. The only serious adverse events that were reported more than once were arthritis flare (14 events), and abdominal pain (3 events) and macrophage activation (2 events). The 12 serious infections reported in 9 subjects included appendicitis, peritonitis, gastroenteritis, aseptic meningitis, varicella zoster infection, soft tissue infection, post-operative wound infection, sepsis syndrome, dental abscess periodontal, herpes zoster, fever, and pyelonephritis. Pyelonephritis was the only serious infection reported beyond year 4.

No deaths, malignancies, or opportunistic infections have been reported in Study 16.0018 as of 06 June 2007.

#### **5.1.2.4 Conclusion**

The rate of serious adverse events and serious infectious events did not increase over a 9-year follow-up period (through 2007).

#### **5.1.3 Study 20021626: Phase IV Registry of Etanercept (Enbrel®) In Children with Juvenile Rheumatoid Arthritis (JRA)**

As stated in [Section 2.5.2](#), this study was conducted as a condition for approval of etanercept in the juvenile rheumatoid arthritis indication. The final clinical study report will be submitted no later than fourth quarter of 2008.

##### **5.1.3.1 Study Design**

Study 20021626 was an open-label, non-randomized multicenter prospective cohort study conducted in the United States and Canada that was designed to determine the long-term safety of etanercept administered with or without other DMARDs in pediatric subjects with polyarticular course or systemic juvenile rheumatoid arthritis compared with a control cohort of subjects with polyarticular or systemic juvenile rheumatoid arthritis receiving methotrexate (with or without other DMARDs). The final subject's last follow-up visit was completed on 31 January 2008. Subjects in the prospective cohort study were followed for a total of 36 months. Subjects completed the study at the end of their 36-month visit or when etanercept was discontinued in the etanercept arm, or when methotrexate was discontinued in the methotrexate arm. Some subjects in the methotrexate arm who discontinued methotrexate and started etanercept, or who added etanercept to methotrexate were re-enrolled in the etanercept arm or the etanercept plus methotrexate arm, provided the subject had not been on the methotrexate arm of the prospective cohort study for more than 30 months. Subjects from the etanercept arm who added methotrexate or subjects from the etanercept plus methotrexate arm who discontinued etanercept but remained on methotrexate were discontinued from the study. Safety and other exploratory endpoints were assessed at baseline, months 3, 6, 9, 12, 18, 24, 30, and at end of study (month 36).

##### **5.1.3.2 Demographics and Disposition**

Subject demographic information is provided in [Table 17](#). Baseline characteristics data revealed that 73% to 91% of subjects were receiving NSAIDs at baseline and 18% to 27% were receiving prednisone (data not shown).

**Table 17. Baseline Demographic Characteristics for Subjects in Etanercept Juvenile Rheumatoid/Idiopathic Arthritis Study 20021626**

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

Page 1 of 2

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

Program: /userdata/stat/amg916/ra/20021626/analysis/final/tables/t\_demog.sas

Output: t\_02\_001\_demog.rtf (Date Generated: 30APR08:15:17:56) Source Data: sdf.dem sdf.rahx

**Table 17. Baseline Demographic Characteristics for Subjects in Etanercept Juvenile Rheumatoid/I idiopathic Arthritis Study 20021626**

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

Page 2 of 2

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

Program: /userdata/stat/amg916/ra/20021626/analysis/final/tables/t\_demog.sas

Output: t\_02\_001\_demog.rtf (Date Generated: 30APR08:15:17:56) Source Data: sdf.dem sdf.rahx

Subject disposition for this 3-year prospective cohort study is provided in [Table 18](#). Out of the 594 subjects who enrolled, 6 withdrew from the study due to adverse events (1.0%).

**Table 18. Disposition for Subjects in Juvenile Rheumatoid Arthritis Prospective Cohort Study 20021626**

	Methotrexate Only n (%)	Etanercept Only n (%)	Etanercept + Methotrexate n (%)
Subjects enrolled	197	103	294
Subjects who completed study	66 (33.5)	47 (45.6)	132 (44.9)
Subjects who discontinued study	131 (66.5)	56 (54.4)	162 (55.1)
Adverse event	3 (1.5)	2 (1.9)	1 (0.3)
Refusal - subject	8 (4.1)	4 (3.9)	13 (4.4)
Refusal - parent/guardian	9 (4.6)	5 (4.9)	11 (3.7)
Protocol issues	17 (8.6)	10 (9.7)	14 (4.8)
Remission	24 (12.2)	8 (7.8)	12 (4.1)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Physician decision	4 (2.0)	3 (2.9)	4 (1.4)
Insufficient therapeutic effect	36 (18.3)	8 (7.8)	59 (20.1)
Other	30 (15.2)	16 (15.5)	48 (16.3)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages based on subjects enrolled

Program: /userdata/stat/amg916/ra/20021626/analysis/final/tables/t\_disp.sas

Output: t\_01\_001\_disp.rtf (Date Generated: 30APR08:15:17:30) Source Data: sdf.dem, sdf.fin



### 5.1.3.3 Safety Results

A summary of exposure-adjusted rates of selected adverse events is provided in Table 19. Overall, the safety profiles of the subjects from the methotrexate, etanercept, and etanercept plus methotrexate group were similar, with no significant difference in exposure-adjusted rates of adverse events between the groups (Table 19). No cases of lymphoma, tuberculosis, malignancy, or death were reported during the study.

**Table 19. Summary of Exposure-adjusted Rates for Selected Adverse Events in Juvenile Idiopathic/Rheumatoid Arthritis Study 20021626**

	Methotrexate Only	Etanercept Only or Etanercept + Methotrexate	p-value <sup>a</sup>
	(Pt-yr = 387.80) (N=197)	(Pt-yr = 859.28) (N=397)	
	n (r)	n (r)	
Non-infectious Adverse Events	74 (19.1)	188 (21.9)	0.7595
Infectious Episodes	6 (1.5)	18 (2.1)	0.8723
Non-infectious AEs Leading to Withdrawal from Drug	8 (2.1)	13 (1.5)	0.9826
All Serious Adverse Events	19 (4.9)	58 (6.7)	0.7633
Death	0 (0.0)	0 (0.0)	N/A
Grade 3 and 4 Non-infectious Adverse Events	22 (5.7)	76 (8.8)	0.2849
Cancers	0 (0.0)	0 (0.0)	N/A
Serious Non-infectious Adverse Events	14 (3.6)	44 (5.1)	0.7283
Serious Infectious Episodes	5 (1.3)	14 (1.6)	0.9968
All Adverse Events	80 (20.6)	206 (24.0)	0.7372

<sup>a</sup> From Poisson regression adjusted for age, sex, baseline disease characteristics and treatment crossover

Pt-yr = Total subject years of exposure to investigational product

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

n = Number of adverse events

r = Exposure-adjusted event rate per 100 subject-years (n/Pt-yr \*100)

Program: /userdata/stat/amg916/ra/20021626/analysis/dodac2008apr/stats/t\_aesum2\_expos.sas

Modified from: t\_06\_020\_002\_aesum3\_expos.rtf (Date Generated: 13MAY08:18:04:29) Source Data:

sdf.dem sdf.aemeddra sdf.afamedra sdf.dthsum sdf.ramedhx sdf.rahx sdf.asmtscor

Overall, the exposure-adjusted rates of adverse events (in events per 100 subject-years) for subjects in the methotrexate only arm, etanercept only arm, and the etanercept plus methotrexate arm were similar (20.63, 21.42, and 24.88, respectively). The only adverse event with an exposure-adjusted rate > 1.0 event per 100 subject-years for subjects who received etanercept (with or without methotrexate) were included depression, anxiety, arthritis, and headache. These events, and all others with an exposure-adjusted rate of > 0.5 events per 100 subject-years in any of the 3 treatment arms, are summarized in Table 20.

**Table 20. Adverse Events with an Exposure-adjusted Rate > 0.50 Events per 100 Subject-years in Study 20021626**

Preferred Term	Methotrexate Only (Pt-yr = 387.80) (N = 197) n (r)	Etanercept Only (Pt-yr = 224.11) (N = 103) n (r)	Etanercept + Methotrexate (Pt-yr = 635.17) (N = 294) n (r)
Total Number of All Adverse Events	80 (20.63)	48 (21.42)	158 (24.88)
Depression	3 (0.77)	3 (1.34)	12 (1.89)
Anxiety	3 (0.77)	6 (2.68)	3 (0.47)
Headache	0 (0.0)	1 (0.45)	7 (1.10)
Arthritis	3 (0.77)	0 (0.0)	11 (1.73)
Abnormal Behaviour	3 (0.77)	2 (0.89)	3 (0.47)
Alanine Aminotransferase Increased	8 (2.06)	0 (0.0)	1 (0.16)
Aspartate Aminotransferase Increased	5 (1.29)	0 (0.0)	1 (0.16)
Hepatic Enzyme Increased	5 (1.29)	0 (0.0)	0 (0.0)
Rheumatoid Arthritis	1 (0.26)	1 (0.45)	4 (0.63)
Viral Infection	0 (0.0)	2 (0.89)	0 (0.0)
Complex Regional Pain Syndrome	0 (0.0)	2 (0.89)	0 (0.0)
Fatigue	1 (0.26)	1 (0.45)	5 (0.79)
Asthma	2 (0.52)	0 (0.0)	1 (0.16)
Vesicoureteric Reflux	2 (0.52)	0 (0.0)	0 (0.0)
Autoimmune Thyroiditis	2 (0.52)	0 (0.0)	0 (0.0)
Anger	2 (0.52)	0 (0.0)	0 (0.0)
Agitation	4 (1.03)	1 (0.45)	0 (0.0)
Insomnia	0 (0.0)	2 (0.89)	3 (0.47)

Pt-yr = Total subject years of exposure to investigational product

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

n = Number of adverse events

r = Exposure-adjusted event rate per 100 subject-years ( $n/Pt\text{-}yr * 100$ )

Program: /userdata/stat/amg916/ra/20021626/analysis/dodac2008apr/tables/t\_ae\_expos.sas

Modified from: t\_06\_024\_allae\_expos.rtf (Date Generated: 25APR08:15:42:30) Source Data: sdf.dem  
sdf.aemeddra

The exposure-adjusted rate per 100-subject years for all infectious adverse events was 1.55, 2.23, and 2.05 for the methotrexate-only, etanercept-only, and etanercept-plus-methotrexate groups, respectively. The only preferred term that was reported more than once in any treatment arm was pyelonephritis (3 events; 1 in the methotrexate-only and 2 in the etanercept-plus-methotrexate groups). The only serious adverse events with an exposure-adjusted rate > 0.50 events per 100-subject years for subjects who received etanercept included viral infection, arthritis, and headache. No serious infectious adverse event was reported more than once in any treatment arm.

#### **5.1.3.4 Postmarketing Experience in Pediatric Patients (< 18 Years old) through 04 April 2008**

This section reviews all pediatric postmarketing safety reports for all approved and unapproved indications from launch through 04 April 2008 from worldwide reports in the Adverse Reaction Information System global (ARISg); Amgen's serious adverse event management and reporting. In order to capture all etanercept pediatric reports of adverse events received by Amgen worldwide, a search was conducted of the ARISg database for all formulations and dosage forms of etanercept in patients <18 years of age for Medical Dictionary for Regulatory Activities (MedDRA) preferred terms under all MedDRA system organ classifications. The search included worldwide reports, medically confirmed and unconfirmed, serious and non-serious, in the safety database where etanercept (or Enbrel®) was identified as a suspect, co-suspect, or suspect-interacting medication. The search include reports from all clinical studies, postmarketing studies, and registry studies; spontaneous reports including those from consumers, health care professionals, literature, other companies and health-authorities; and, consumer solicited reports (see [Appendix D](#)) that were received by Amgen from launch of etanercept in 02 November 1998 through 04 April 2008. Generally, clinical study reports are entered in the ARISg database only if they are categorized as serious. Because reports are classified as serious or non-serious at the case level and at the event level, some spontaneous cases may have the designation of serious, while the particular event of interest was not considered serious. All cases were retrieved independently of the reporter's relationship to causality.

### Pediatric Postmarketing Safety Reports

In the pediatric postmarketing setting, a total of 2821 reports were in the database with 5833 reported events. Of the postmarketing reports, approximately two thirds were non-medically confirmed and approximately 50% were consumer-solicited ([Appendix D](#)).

The distribution of pediatric reports was as follows: juvenile arthritis (n = 1707), followed by psoriasis (n = 294), rheumatoid arthritis (n = 277), other (n = 197), psoriatic arthropathy (n = 141), ankylosing spondylitis (n = 104), and unknown (n = 101). A majority of the patients were girls (n = 2041), with an overall mean age of 11.7 years.

Across all pediatric reports, the most frequent events occurred within the following system organ classes:

- General disorders and administrative site conditions (2209 events):
  - injection site pain (497 events)
  - injection site reaction (413 events)
  - injection site bruising (184 events)
- Infections and infestations (679 events):
  - nasopharyngitis (91 events)
  - upper respiratory tract infection (52 events)
  - sinusitis (47 events)
- Musculoskeletal and connective tissue disorders (433 events):
  - arthralgia (75 events)
  - juvenile arthritis (67 events)
  - rheumatoid arthritis (63 events)

Of the pediatric psoriasis reports there were 10 medically confirmed serious and 25 medically confirmed non-serious. Of these, 22 were girls, 11 were boys, and 2 were unknown. The mean age of these patients was 13.5 years.

There were 10 serious, medically confirmed, psoriasis reports that included the following preferred terms: eosinophilia, splenomegaly, cryptococcal cutaneous infection, pneumonia, varicella, cachexia, dysaesthesia, hypoaesthesia, optic neuritis, and lymphoma. Lymphoma will be discussed in [Section 7.1](#). No deaths were reported.

Among the 25 nonserious, medically confirmed, psoriasis reports, the most frequent were injection site reaction, psoriasis, and abdominal pain.

Of the pediatric juvenile rheumatoid arthritis/rheumatoid arthritis reports, there were a total of 402 medically confirmed, serious (205) and non-serious (197) reports. Of these, 285 were girls, 104 were boys and 13 were unknown.

Among the 205 medically confirmed, serious reports, the most frequent adverse events were condition aggravated (65 events), juvenile arthritis (28 events), and pyrexia and uveitis (21 events each). The frequency of the rest of the serious reported events appeared to be low. Of note, the following events are assessed as adverse drug reactions and included in the USPI as such: infections (viral, bacterial, fungal), optic neuritis, pyrexia, convulsion, leukopenia, pancytopenia, lupus-like syndrome, injection site pain, transaminases increased, agranulocytosis, leukocytoclastic vasculitis, thrombocytopenia, rash, pruritus, hypersensitivity, Henoch-Schonlein purpura, demyelination, cutaneous vasculitis, aplastic anaemia. The rest of the events continue to be closely monitored and evaluated through routine safety surveillance.

Among the 197 medically confirmed, non-serious reports, the most frequent adverse events were injection site pain (51 events), pharmaceutical product complaint (26 events), and injection site erythema (17 events).

#### Registry Reports

Amgen JRA Registry Study 20021626 is presented in [Section 5.1.3](#). In the European registries (German JIA Registry, United Kingdom JIA Registry, and Swedish Rheumatic Disease Registry), a total of 416 reports were in the database with 416 reported events. The largest indication for etanercept use was for juvenile arthritis (n = 227), followed by other (n = 90), unknown (n = 50), psoriatic arthropathy (n = 23), rheumatoid arthritis (n = 22), psoriasis (n = 3), and ankylosing spondylitis (n = 1).

The most frequent adverse events within the most frequent MedDRA system organ classes in the prospective cohort study reports were:

- Infection and infestations (109 total events):
  - upper respiratory tract infections (18 events)
  - varicella (7 events)
  - herpes zoster (6 events)
  - impetigo (6 events)
  - infection (unspecified) (6 events)

- Musculoskeletal and connective tissue disorders (56 total events):
  - juvenile arthritis (20 events)
  - arthritis (18 events)
  - rheumatoid arthritis (3 events)
  - synovial cyst (3 events each)
- Gastrointestinal disorders (27 total events):
  - nausea (6 events)
  - abdominal pain (4 events)
  - colitis (2 events)
  - ulcerative colitis (2 events)

## 6. Etanercept use in Adults with Plaque Psoriasis

### 6.1 Clinical Study Experience in Adults with Plaque Psoriasis

Data were integrated from the double-blind, placebo-controlled portions of adult plaque psoriasis Studies 20021639 and 20021642 (phase 3), and phase 3 long-term Study 20030117 and compared with the three year extension study (20030115). A summary of the double-blind studies and dosing groups is provided in [Table 21](#).

**Table 21. Studies and Dose Groups Used for Integrated Analysis of Controlled Data for Adult Plaque Psoriasis Studies**

Study Number	Study Title	Dosing During Double-blind Period
20021639 <sup>a</sup>	Study 20021639 - Phase 3 Multicenter, Dose-ranging Study of the Safety and Efficacy of ENBREL® in Psoriasis	placebo, or etanercept 25 mg BIW, or etanercept 50 mg BIW
20021642 <sup>a</sup>	Phase 3 Multicenter Study of the Safety and Efficacy of ENBREL® in Psoriasis	placebo, or etanercept 25 mg BIW, or etanercept 50 mg BIW
20030117	A Phase 3 Multicenter Study to Assess the Efficacy and Safety of Etanercept 50 mg Twice Weekly in Psoriasis	placebo or etanercept 50 mg BIW

<sup>a</sup> Subjects from Studies 20021639 and 20021642 were eligible to enroll into the open-label extension Study 20030115, which did not include a double-blind period.

BIW = twice per week

#### 6.1.1 Long-term Safety Data

Integrated long-term safety results were calculated for subjects who received  $\geq 50$  mg QW of etanercept in Studies 20021639, 20021642, 20030115 and 20030117. The mixed-dose group includes those subjects enrolled in Studies 20021639 and 20021642 who subsequently enrolled in Study 20030115 (long-term extension). Subjects could have been on various etanercept doses (25 mg twice per week [BIW], 50 mg QW, or 50 mg BIW) and may have had gaps in dosing due to study design. The majority of exposures were  $< 50$  mg BIW. Long-term results are presented for: years 1, 2, and 3; and cumulative dosing through last dose.

##### 6.1.1.1 Summary of Adverse Events in Long-term Safety Analysis

In the mixed-dose group, the exposure-adjusted event rates for all adverse events, infections, and noninfectious adverse events declined as the study progressed ([Table 22](#)). Serious infections remained infrequent during long-term therapy, with exposure-adjusted event rates comparable to the rate of 1.4 events per 100 subject-years seen in the placebo group during double-blind therapy. The exposure-adjusted event rate for serious infections did increase from 0.8 in year 1 to 2.0 in year 2 before declining to 1.0 in year 3; however, due to the low number of events, these rates should

be interpreted with caution. The increase in exposure-adjusted event rates for noninfectious serious adverse events in the mixed-dose group from year 2 (5.4) to year 3 (8.6) was not the result of an increase in any specific event; of the 18 events observed in year 3, only myocardial infarction was reported more than once (2 reports). The total exposure data available for year 3 was limited in comparison with previous years and should be interpreted with caution.



**Table 22. Overall Summary of Adverse Events Over Time (Exposure-adjusted Event Rate per 100 Subject-years),  
12-week Double-blind and Long-term Mixed-dose Group**

Type of Adverse Events	12-week Placebo-controlled Safety Profile						Long-term Safety Profile - Group A <sup>a</sup> Etanercept ≥ 50 mg QW <sup>e</sup>							
	Placebo <sup>b</sup> (N = 665) (E = 141.8)		Etanercept 25 mg BIW <sup>c</sup> (N = 358) (E = 77.5)		Etanercept 50 mg BIW <sup>d</sup> (N = 670) (E = 147.2)		1st Year (N = 1160) (E = 1038.8)		2nd Year (N = 913) (E = 808.2)		3rd Year (N = 663) (E = 209.8)		All <sup>f</sup> (N = 1160) (E = 2052.4)	
	n	r	n	r	n	r	n	r	n	r	n	r	n	r
All Events	828	(583.9)	483	(623.3)	812	(551.6)	4278	(411.8)	1971	(243.9)	410	(195.4)	6664	(324.7)
All Serious Events	9	(6.3)	2	(2.6)	11	(7.5)	74	(7.1)	60	(7.4)	20	(9.5)	154	(7.5)
Infections	201	(141.7)	112	(144.5)	221	(150.1)	1540	(148.3)	818	(101.2)	152	(72.4)	2510	(122.3)
Serious Infections	2	(1.4)	0	(0.0)	2	(1.4)	8	(0.8)	16	(2.0)	2	(1.0)	26	(1.3)
Non-infectious AEs	627	(442.2)	371	(478.8)	591	(401.5)	2738	(263.6)	1153	(142.7)	258	(123.0)	4145	(202.4)
Non-infectious SAEs	7	(4.9)	2	(2.6)	9	(6.1)	66	(6.4)	44	(5.4)	18	(8.6)	128	(6.2)

BIW = twice per week; E = total number of exposure years; N = number of subjects; n = number of adverse events;

r = exposure-adjusted event rate per 100 subject-years (= n / E \* 100)

<sup>a</sup> Mixed-dose group data includes Studies 20021639, 20021642 and 20030115

<sup>b</sup> Includes 12-week double-blind portions of Studies 20021639, 20021642, and 2003117

<sup>c</sup> Includes double-blind portions of Studies 20021639 and 20021642

<sup>d</sup> Includes first 12 weeks of Studies 20021639, 20021642, and 20030117

<sup>e</sup> Etanercept at 25 mg BIW, 50 mg QW, or 50 mg BIW

<sup>f</sup> Includes events that occurred on or after a subject's first dose of ≥ 50 mg per week (25 BIW or 50 QW or 50 BIW) through end of dosing

Source: ISS Tables: 6.13.1, 6.14.1, 6.15.1, 6.16.1, 6.17.1, 6.18.1, 6.25.1, 6.25.2, 6.25.3, 6.25.4, 6.26.1, 6.26.2, 6.26.3, 6.26.4, 6.27.1, 6.27.2, 6.27.3, 6.27.4, 6.28.1, 6.28.2, 6.28.3, 6.28.4, 6.29.1, 6.29.2, 6.29.3, 6.29.4, 6.30.1, 6.30.2, 6.30.3, and 6.30.4

#### 6.1.1.2 All Adverse Events in Long-term Safety

The most commonly reported adverse events for all years combined were in the system organ classes of infections and infestations and musculoskeletal and connective tissue disorders. Adverse event rates in all system organ classes (rate  $\geq 10.0$  per 100 subject-years in any single system organ class or dose group) tended to decline as etanercept exposure increased in the mixed-dose group ([Table 23](#)). The cumulative exposure-adjusted event rate for infections was 112.7 (mixed-dose group) and for musculoskeletal and connective tissue disorders was 29.5 (mixed-dose group), which were lower than the exposure adjusted event rates seen in the placebo group during controlled therapy (137.4 infections, 70.5 musculoskeletal and connective tissue disorders).

During the 12-week placebo-controlled portion of the study, there appeared to be an imbalance in system organ class nervous system disorders (headache most common) across treatment groups (59.2 per 100 subject-years in the placebo group, 104.5 per 100 subject-years in the etanercept 25 mg BIW group, and 67.3 per 100 subject-years in the etanercept 50 mg BIW group) ([Table 23](#)). The exposure-adjusted rate of headache in the placebo, etanercept 25 mg BIW and etanercept 50 mg BIW was 38.1, 68.4 and 43.5 respectively.

Nervous system disorders declined with increased etanercept exposure. This was apparent by year 1 ([Table 23](#)).

**Table 23. All Adverse Events (Infectious and Non-infectious) Over Time By System Organ Class  
(Exposure-adjusted Event Rate of  $\geq 10$  in any single Treatment Group/System Organ Class)  
(12-week Double-blind and Long Term Mixed-dose Group)**

System Organ Class	12-week Placebo-controlled Safety Profile						Long-term Safety Profile - Group A <sup>a</sup> Etanercept $\geq 50$ mg QW <sup>e</sup>							
	Placebo <sup>b</sup> (N = 665) (E = 141.8)		Etanercept 25 mg BIW <sup>c</sup> (N = 358) (E = 77.5)		Etanercept 50 mg BIW <sup>d</sup> (N = 670) (E = 147.2)		1st Year (N = 1160) (E = 1038.8)		2nd Year (N = 913) (E = 808.2)		3rd Year (N = 663) (E = 209.8)		All <sup>f</sup> (N = 1160) (E = 2052.4)	
	n	r	n	r	n	r	n	r	n	r	n	r	n	r
Eye disorders	5	(3.5)	8	(10.3)	8	(5.4)	55	(5.3)	25	(3.1)	5	(2.4)	85	(4.1)
Gastrointestinal disorders	67	(47.2)	43	(55.5)	73	(49.6)	309	(29.7)	148	(18.3)	35	(16.7)	492	(24.0)
General disorders & administration site conditions	110	(77.6)	62	(80.0)	104	(70.6)	322	(31.0)	61	(7.5)	11	(5.2)	394	(19.2)
Infections / infestations	191	(137.4)	108	(139.4)	216	(146.7)	1428	(137.5)	757	(93.7)	129	(61.5)	2314	(112.7)
Injury, poisoning, & procedural complications	56	(39.5)	23	(29.7)	57	(38.7)	294	(28.3)	130	(16.1)	36	(17.2)	460	(22.4)
Musculoskeletal & connective tissue	100	(70.5)	32	(41.3)	78	(53.0)	378	(36.4)	199	(24.6)	28	(13.3)	605	(29.5)
Nervous system disorders	84	(59.2)	81	(104.5)	99	(67.3)	421	(40.5)	96	(11.9)	22	(10.5)	540	(26.3)
Psychiatric disorders	18	(12.7)	9	(11.6)	25	(17.0)	110	(10.6)	47	(5.8)	10	(4.8)	167	(8.1)
Respiratory, thoracic, & mediastinal disorders	41	(28.9)	32	(41.3)	37	(25.1)	211	(20.3)	114	(14.1)	21	(10.0)	346	(16.9)
Skin & subcutaneous tissue disorders	76	(53.6)	40	(51.6)	49	(33.3)	263	(25.3)	110	(13.6)	30	(14.3)	405	(19.7)
Vascular disorders	12	(8.5)	10	(12.9)	13	(8.8)	78	(7.5)	45	(5.6)	9	(4.3)	132	(6.4)

N = number of subjects; E = total number of exposure years; n = number of adverse events; r = exposure-adjusted event rate per 100 subject-years ( $= n / E * 100$ )

<sup>a</sup> Mixed-dose group data includes studies 20021639, 20021642 and 20030115

<sup>b</sup> Includes 12-week double-blind portions of studies 20021639, 20021642, and 2003117

<sup>c</sup> Includes double-blind portions of 20021639 and 20021642

<sup>d</sup> Includes first 12 weeks of 20021639, 20021642, and 20030117

<sup>e</sup> Etanercept at 25 mg BIW, 50 mg QW, or 50 mg BIW

<sup>f</sup> Includes events that occurred on or after a subject's first dose of  $\geq 50$  mg per week (25 mg BIW or 50 QW or 50 BIW) through the end of dosing

Source: ISS Tables: 6.21.1, 6.33.1, 6.33.2, 6.33.3, and 6.33.4

#### **6.1.1.3 All Infections in Long-term Safety**

The most common infections reported were upper respiratory tract infections and nasopharyngitis, both of which declined over time in the study ([Table 24](#)).

**Table 24. Infections Over Time by Preferred Term  
(Exposure-adjusted Event Rate of  $\geq 5.0$  in any single Treatment Group/Preferred Term)  
(12-week Double-blind and Long Term Mixed-dose Group)**

Preferred Term	12-week Placebo-controlled Safety Profile						Long-term Safety Profile - Group A <sup>a</sup> Etanercept $\geq 50$ mg QW <sup>e</sup>							
	Placebo <sup>b</sup> (N = 665) (E = 141.8)		Etanercept 25 mg BIW <sup>c</sup> (N = 358) (E = 77.5)		Etanercept 50 mg BIW <sup>d</sup> (N = 670) (E = 147.2)		1st Year (N = 1160) (E = 1038.8)		2nd Year (N = 913) (E = 808.2)		3rd Year (N = 663) (E = 209.8)		All <sup>f</sup> (N = 1160) (E = 2052.4)	
	n	r	n	r	n	r	n	r	n	r	n	r	n	r
Total number of events	201	(141.7)	112	(144.5)	221	(150.1)	1540	(148.3)	818	(101.2)	152	(72.4)	2510	(122.3)
Upper respiratory tract infection	44	(31.0)	23	(29.7)	38	(25.8)	315	(30.3)	179	(22.1)	23	(11.0)	517	(25.2)
Nasopharyngitis	26	(18.3)	15	(19.4)	25	(17.0)	195	(18.8)	142	(17.6)	18	(8.6)	355	(17.3)
Sinusitis	10	(7.1)	11	(14.2)	21	(14.3)	108	(10.4)	60	(7.4)	10	(4.8)	178	(8.7)
Influenza	9	(6.3)	12	(15.5)	12	(8.2)	107	(10.3)	41	(5.1)	5	(2.4)	153	(7.5)
Pharyngitis	5	(3.5)	5	(6.5)	9	(6.1)	52	(5.0)	15	(1.9)	3	(1.4)	70	(3.4)
Bronchitis	5	(3.5)	3	(3.9)	9	(6.1)	50	(4.8)	28	(3.5)	5	(2.4)	83	(4.0)
Herpes Simplex	3	(2.1)	6	(7.7)	6	(4.1)	51	(4.9)	25	(3.1)	4	(1.9)	80	(3.9)
Urinary tract infection	5	(3.5)	3	(3.9)	5	(3.4)	36	(3.5)	15	(1.9)	11	(5.2)	62	(3.0)
Viral upper respiratory infection	3	(2.1)	4	(5.2)	3	(2.0)	26	(2.5)	13	(1.6)	0	(0.0)	39	(1.9)
Cellulitis	10	(7.1)	1	(1.3)	5	(3.4)	19	(1.8)	6	(0.7)	5	(2.4)	30	(1.5)
Gastroenteritis	13	(9.2)	1	(1.3)	3	(2.0)	53	(5.1)	15	(1.9)	0	(0.0)	68	(3.3)

N = number of subjects; E = total number of exposure years; n = number of adverse events;

r = exposure-adjusted event rate per 100 subject-years ( $= n / E * 100$ )

<sup>a</sup> Mixed-dose group data includes studies 20021639, 20021642 and 20030115

<sup>b</sup> Includes 12-week double-blind portions of studies 20021639, 20021642, and 2003117

<sup>c</sup> Includes double-blind portions of studies 20021639 and 20021642

<sup>d</sup> Includes first 12 weeks of 20021639, 20021642, and 20030117

<sup>e</sup> Etanercept at 25 mg BIW, 50 mg QW, or 50 mg BIW

<sup>f</sup> Includes events that occurred on or after a subject's first dose of  $\geq 50$  mg per week (25 mg BIW or 50 QW or 50 BIW) through the end of dosing

Source: ISS Tables 6.14.1, 6.26.1, 6.26.2, 6.26.3, and 6.26.4

#### **6.1.1.4 Serious Infections in Long-term Safety**

The rates of serious infections were low in all 3 years of etanercept exposure. The exposure-adjusted event rates remained stable and were similar to those seen in the placebo group.

The most frequently reported serious infection was cellulitis with a total of 5 reports in the mixed-dose (mixed-dose group) subjects. The majority of serious infections had only 1 report.

**Table 25. Serious Infections Over Time by Preferred Term**  
**(Exposure-adjusted Event Rate Reports  $\geq 1.0$  in any single Treatment Group/Preferred Term in the First Year)**  
**(12-week Double-blind and Long Term Mixed-Dose Group)**

Preferred Term	12-week Placebo-controlled Safety Profile						Long-term Safety Profile - Group A <sup>a</sup> Etanercept $\geq 50$ mg QW <sup>e</sup>							
	Placebo <sup>b</sup>		Etanercept 25 mg BIW <sup>c</sup>		Etanercept 50 mg BIW <sup>d</sup>		1st Year		2nd Year		3rd Year		All <sup>f</sup>	
	(N = 665)	(E = 141.8)	(N = 358)	(E = 77.5)	(N = 670)	(E = 147.2)	(N = 1160)	(E = 1038.8)	(N = 913)	(E = 808.2)	(N = 663)	(E = 209.8)	(N = 1160)	(E = 2052.4)
	n	r	n	r	n	r	n	r	n	r	n	r	n	r
Total number of events	2	(1.4)	0	(0.0)	2	(1.4)	8	(0.8)	16	(2.0)	2	(1.0)	26	(1.3)
Cellulitis	1	(0.7)	0	(0.0)	1	(0.7)	3	(0.3)	1	(0.1)	1	(0.5)	5	(0.2)
Facial Palsy	0	(0.0)	0	(0.0)	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonia	1	(0.7)	0	(0.0)	0	(0.0)	2	(0.2)	1	(0.1)	0	(0.0)	3	(0.1)
Gastroenteritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)	2	(0.1)
Abdominal Abscess	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)

N = number of subjects; E = total number of exposure years; n = number of adverse events;

r = exposure-adjusted event rate per 100 subject-years ( $= n / E * 100$ )

<sup>a</sup> Mixed-dose group data includes studies 20021639, 20021642 and 20030115

<sup>b</sup> Includes 12-week double-blind portions of studies 20021639, 20021642, and 2003117

<sup>c</sup> Includes double-blind portions of studies 20021639 and 20021642

<sup>d</sup> Includes first 12 weeks of 20021639, 20021642, and 20030117

<sup>e</sup> Etanercept at 25 mg BIW, 50 mg QW, or 50 mg BIW

<sup>f</sup> Includes events that occurred on or after a subject's first dose of  $\geq 50$  mg per week (25 mg BIW or 50 QW or 50 BIW) through the end of dosing

Source: ISS Tables 6.17.1, 6.29.1, 6.29.2, 6.29.3, and 6.29.4

#### **6.1.1.5 Serious Noninfectious Adverse Events in Long-term Safety**

Serious noninfectious adverse events were infrequent and exposure-adjusted event rates generally remained stable throughout long-term therapy. Exceptions in the mixed-dose group were in the system organ classes of injury, poisoning, and procedural complications (year 1 exposure-adjusted event rate = 1.0); cardiac disorders (year 1 exposure-adjusted event rate = 0.9); and nervous system disorders (year 1 exposure-adjusted event rate = 0.5), with each category more than doubling their exposure-adjusted event rates by year 3 (injury exposure-adjusted event rate = 2.4; cardiac exposure-adjusted event rate = 1.9; nervous system exposure-adjusted event rate = 1.4). However, the small number of events makes interpretation difficult. An increase in the exposure-adjusted event rates for total serious noninfectious events in the mixed-dose group from 5.4 in year 2 to 8.6 in year 3 was not the result of any single event; only 1 event, myocardial infarction, was seen more than once (2 reports).

#### **6.1.1.6 Noninfectious Adverse Events in Long-term Safety**

Like infections, noninfectious exposure-adjusted event rates typically decreased with increasing exposure to etanercept. Cumulative exposure-adjusted event rates during long-term etanercept exposure were lower than rates seen in the placebo group with the exception of the system organ class of eye disorders, which was slightly higher for the mixed-dose group (3.2) than placebo (2.1).

#### **6.1.1.7 Antibody Data and Safety Relationship in Long-term safety**

The overall safety profile of the mixed-dose group subjects was similar regardless of the number of times a subject tested positive for non-neutralizing anti-etanercept antibodies. No samples tested positive in the mixed-dose group subjects for neutralizing anti-etanercept antibodies.

### **6.2 Conclusions Regarding Etanercept Adverse Event Profile in Adults with Plaque Psoriasis**

Etanercept was well tolerated during the 12-week, double-blind therapy.

When comparing the long term overall (years 1 to 3) exposure-adjusted event rates to those for the 12 week period, no apparent trends in the reporting of adverse events were seen with higher doses of etanercept or over time.

Although there was an increase in the number of subjects who tested positive for anti-etanercept antibodies, no subjects tested positive for neutralizing antibodies to



etanercept. There was no increase in reports of lack of efficacy in the subjects with anti-etanercept antibodies.

### **6.2.1 Overall Safety Conclusion**

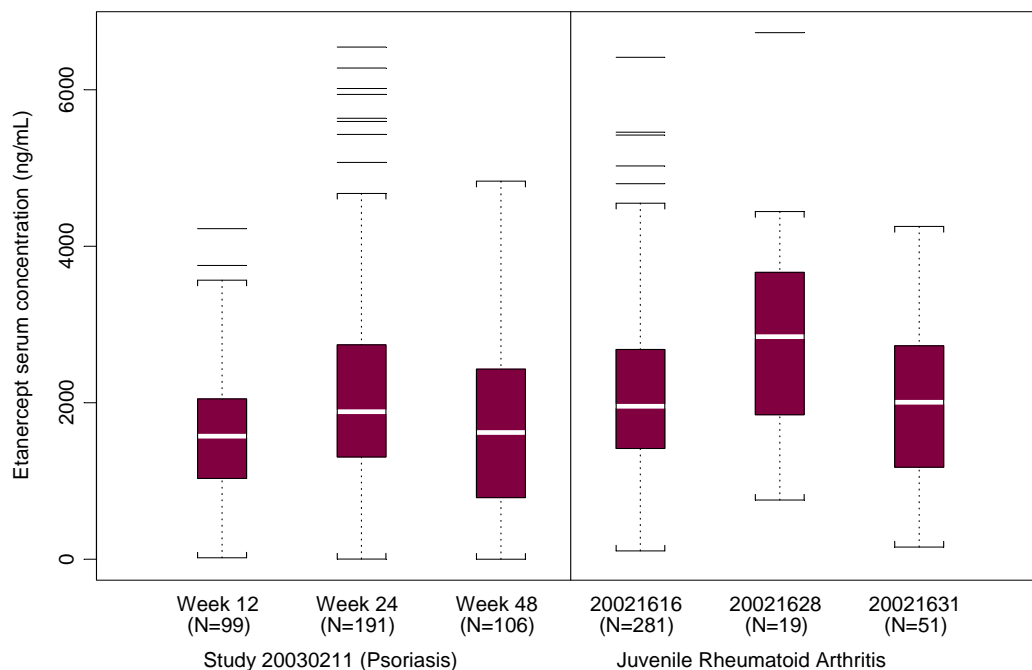
In summary, the benefit-to-risk ratio for etanercept treatment in the pediatric psoriasis population remains favorable in the 48 weeks studied, as has been previously demonstrated for other indications (including juvenile rheumatoid arthritis and adult psoriasis). In the pediatric psoriasis population, the potential risks related to response to immunizations, effects on growth and development, development of malignancies, and demyelination, are not known with certainty, and will be addressed in the Risk Evaluation and Mitigation Strategy (REMS).

### **6.3 Pharmacokinetic Data**

#### **6.3.1 Pharmacokinetic Data in Children with Plaque Psoriasis versus Children with Juvenile Rheumatoid/Idiopathic Arthritis**

Steady-state trough etanercept concentrations were compared between subjects in pediatric plaque psoriasis Study 20030211 (0.8 mg/kg etanercept, up to 50 mg QW) and average concentrations in juvenile rheumatoid arthritis Studies 16.0016, 16.0028, and 16.0031 (0.4 mg/kg up to 25 mg BIW). No notable differences were noted in exposure to etanercept in these 2 pediatric patient populations ([Figure 4](#)).

**Figure 4. Comparison of Etanercept Concentrations in Pediatric Subjects with Plaque Psoriasis Versus Pediatric Subjects with Juvenile Rheumatoid Arthritis (Studies 20020211 and Studies 16.0016, 16.0028, and 16.0031, Respectively)**



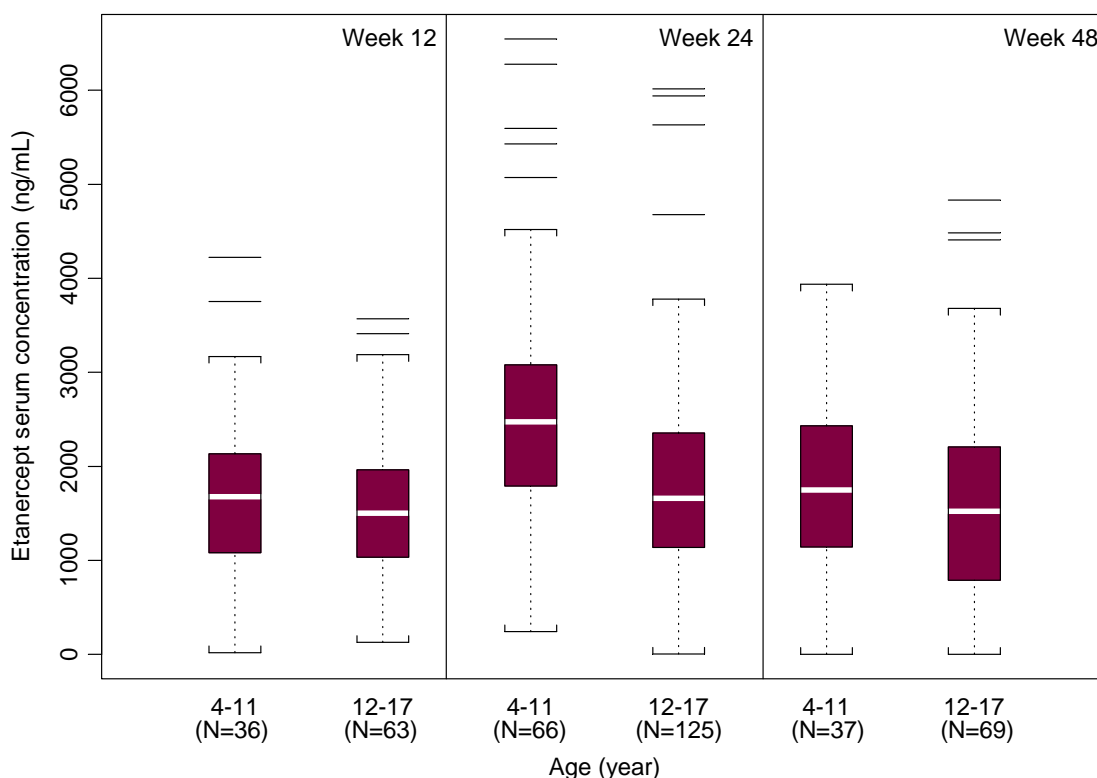
Source: documentum\Docbases\usddms\R&D Candidates\Development\Enbrel - 4506 Psoriasis\Preclinical Non-Study Specific\PKDM\Pre-Submission\BLA-NDA\Spreadsheets\FDA response-ped psoriasis\JRA\_r1.sgr (Splus script "JRA.ssc")

### 6.3.2 Comparison of Pharmacokinetic Data in Children and Adults with Plaque Psoriasis

#### 6.3.2.1 Stratification by Age (4 to 11 Years Versus 12 to 17 Years)

In pediatric plaque psoriasis Study 20030211 (etanercept 0.8 mg/kg up to 50 mg QW as described in [Section 4.1](#)), trough concentrations of etanercept were obtained predose, and at weeks 12, 24, and 48. When steady-state serum etanercept concentrations were stratified by age group (4 to 11 years vs 12 to 17 years), no apparent differences in exposure were noted between the groups ([Figure 5](#)).

**Figure 5. Comparison of Etanercept Concentrations by Age in Pediatric Subjects with Plaque Psoriasis (Study 20020211)**

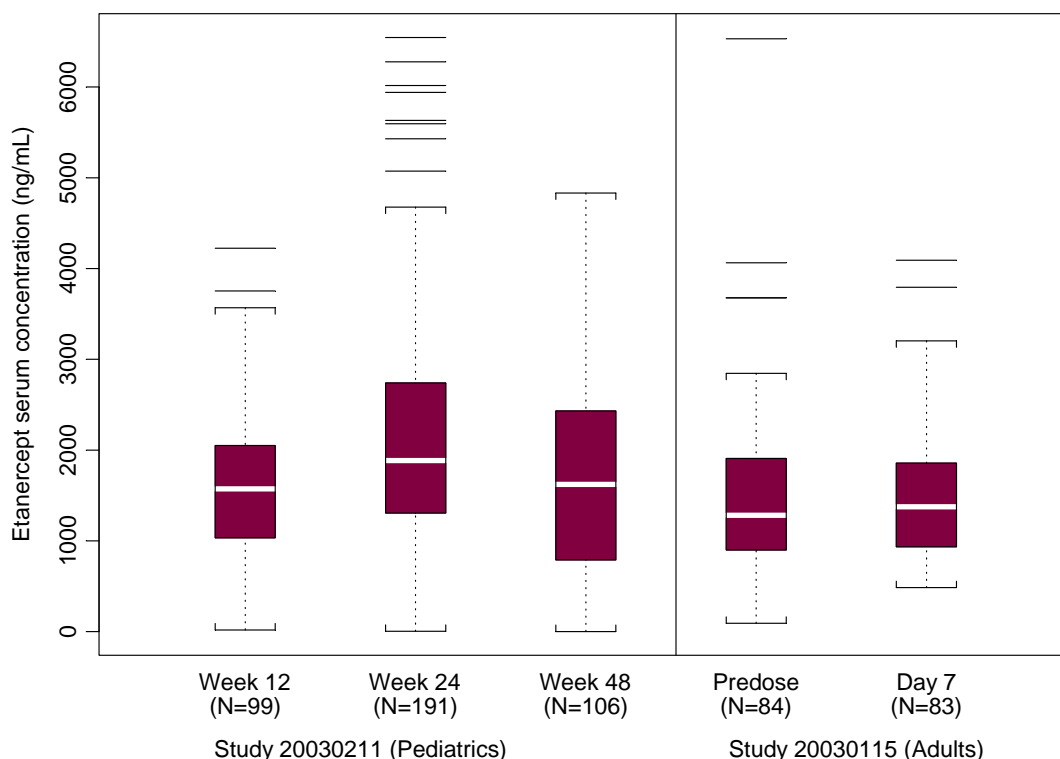


Source: documentum\Docbases\usddms\R&D Candidates\Development\Enbrel - 4506 Psoriasis\Preclinical Non-Study Specific\PKDM\Pre-Submission\BLA-NDA\Spreadsheets\FDA response-ped psoriasis\PK211box.sgr (Splus script "CrtPK211.ssc")

### 6.3.2.2 Adults versus Children with Plaque Psoriasis

Trough etanercept concentrations from pediatric Study 20030211 (0.8 mg/kg etanercept, up to 50 mg QW) were compared with trough concentrations taken at baseline and day 7 of adult plaque psoriasis Study 20030115 (50 mg etanercept QW) (see [Section 6.1](#)). No notable differences were noted in exposure to etanercept ([Figure 6](#)).

**Figure 6. Comparison of Etanercept Concentrations in Pediatric and Adult Subjects with Plaque Psoriasis (Studies 20020211 and 20030115, Respectively)**



Source: documentum\Docbases\usddms\R&D Candidates\Development\Enbrel - 4506 Psoriasis\Preclinical Non-Study Specific\PKDM\Pre-Submission\BLA-NDA\Spreadsheets\FDA response-ped psoriasis\CmprAdult\_r1.sgr (Splus script "CrtPK115.ssc")

## **7. Special Considerations for Etanercept Use**

### **7.1 Malignancy in the Pediatric Population**

Cancer is relatively rare among children. In 2005, an estimated 14,085 children < 20 years old were diagnosed with cancer. Although malignancy has been identified as an event of medical interest in ongoing safety studies among adults receiving etanercept, no malignancies were seen in pediatric patients receiving etanercept in clinical trials. Malignancies identified in pediatric postmarketing safety reports worldwide for all approved and unapproved indications through 04 April 2008 are discussed in [Section 7.1.2](#). Age-adjusted and age-specific cancer incidence rates for select tumors in the pediatric population in the United States between the years 2000 to 2005 are presented in [Table 26](#). These rates provide background cancer incidence rates in the general pediatric population and may be useful in helping interpret risk of malignancy in pediatric patients exposed to etanercept relative to the general population.

**Table 26. Age-adjusted and age-specific cancer incidence rates (per million)<sup>a</sup> for select tumors in the pediatric population<sup>b</sup>, United States, 2000-2005<sup>c</sup>**

	Age at Diagnosis (years)				
	4 – 11	12 – 17	4 – 17	18 – 22	4 – 22
Leukemia (includes myelodysplastic syndromes)	41.1	31.2	36.9	25.0	33.8
Lymphoid leukemia	34.5	20.0	28.4	11.3	24.0
Acute myeloid leukemia	4.8	9.1	6.7	9.6	7.4
Chronic myeloproliferative diseases	0.6	1.3	0.9	3.0	1.4
Myelodysplastic syndrome and other myeloproliferative	0.2 <sup>d</sup>	0.0 <sup>e</sup>	0.1 <sup>d</sup>	0.0 <sup>e</sup>	0.1 <sup>d</sup>
Unspecified and other specified leukemias	1.0	0.8	0.9	1.1	0.9
Lymphomas and reticuloendothelial neoplasms	14.7	35.0	23.3	59.7	32.7
Hodgkin lymphoma	5.0	19.3	11.0	38.5	18.1
Non-Hodgkin lymphoma (except Burkitt lymphoma)	6.4	12.4	8.9	18.1	11.3
Burkitt lymphoma	2.9	2.7	2.8	1.7	2.5
Miscellaneous lymphoreticular neoplasms	0.4	0.2 <sup>d</sup>	0.3	0.4	0.3
Unspecified lymphomas	0.1 <sup>d</sup>	0.5	0.3	1.1	0.5
Malignant melanomas	1.9	9.0	4.9	32.0	11.9
Skin carcinomas	0.1 <sup>d</sup>	0.2 <sup>d</sup>	0.1	0.1 <sup>d</sup>	0.1
Renal carcinomas	0.2	1.0	0.6	1.6	0.8
Thyroid carcinomas	1.4	10.0	5.0	32.6	12.1
Urinary bladder cancer <sup>f</sup>	0.3	0.6	0.4	1.5	0.7
Yolk sac tumor <sup>f</sup>	0.1 <sup>d</sup>	0.2 <sup>d</sup>	0.1	0.8	0.3

<sup>a</sup> Rates are per million and are age-adjusted to the 2000 United States Standard Population (single ages to 84 – Census P25-1130) standard.

<sup>b</sup> Unless otherwise noted, cancers are classified according to the International Classification of Childhood Cancer (ICCC) as described in: Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, Third Edition. *Cancer* 2005;103(7):1457-67.

<sup>c</sup> Data source: Surveillance, Epidemiology, and End Results (SEER) Program ([www.seer.cancer.gov](http://www.seer.cancer.gov)) SEER\*Stat Database: Incidence - SEER 17 Regs Limited-Use + Hurricane Katrina Impacted Louisiana Cases, Nov 2007 Sub (2000-2005) <Single Ages to 85+, Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2005 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2008, based on the November 2007 submission.

<sup>d</sup> Estimate based on fewer than 10 cases reported for the time interval (2000-2005).

<sup>e</sup> No cases reported for the time interval (2000-2005).

<sup>f</sup> Bladder cancer (C670-679) and yolk sac tumor (C620-C629, histologic type 9071) are classified according to International Classification of Diseases oncology (ICD-O) codes (3<sup>rd</sup> Edition), as these are not tumor types recognized by the International Classification of Childhood Cancer.

### 7.1.1 Malignancies in Pediatric Clinical Trials

In an analysis of the 3 completed Amgen juvenile rheumatoid arthritis clinical trials (16.0016, 16.0028, and 16.0031) and 2 ongoing clinical trials (16.0018, 16.0026), no malignancies had been reported as of 03 May 2006, examining 486 subjects and 1128.92 subject-years of etanercept exposure. Study 16.0026 has since completed and no malignancies were reported. Study 16.0018 is an ongoing 10-year extension trial. As of the data cut (06 June 2007) through the study's ninth year, no malignancies have been reported examining 337.5 subject-years.

There were no reported malignancies in the 48 week pediatric psoriasis trial, nor have there been any reported malignancies in the ongoing 3-year extension as of 07 March 2008. Based on SEER data, 1998 to 2002, 0.024 cases would be expected given the number of patient-years of exposure in the pediatric psoriasis population. Given the patient-years of exposure in the JRA population, 0.17 malignancy cases would be expected.

### 7.1.2 Malignancies in Pediatric Postmarketing

This section reviews pediatric postmarketing safety reports for all approved and unapproved indications from launch entered into the ARISg database through 07 May 2008 from worldwide reports. In order to improve case ascertainment (to include cases in subjects exposed to etanercept before the age of 18 years), the database was searched for all patients for whom a possible malignancy (neoplasm) was reported by age 22 years (14 total cases). The 14 cases are broken down into the following 3 tables: [Table 27](#) shows a summary of the 6 cases where the malignancy was reported before the age of 18; [Table 28](#) shows a summary of the 6 cases where etanercept was initiated before the age of 18 and a malignancy was reported from 18 to 22 years; [Table 29](#) shows a summary of the 2 cases where etanercept was initiated before the age of 18 years and a report where malignancy could not be excluded before the age of 22 years.

**Table 27. Patients Treated with Etanercept with Reported Malignancy at < 18 Years of Age**

Country/Source	Adverse Event by Preferred Term	Age at Event (years)	Time from Etanercept Initiation to Onset	Indications	Comments/Confounders
<b>Hematological</b>					
Germany/ Registry	Diffuse large B-cell lymphoma	14	7 years	Juvenile arthritis	Methotrexate
United States/ Healthcare provider	Leukemia	10	5 months	Juvenile arthritis, Seronegative arthritis	Juvenile rheumatoid arthritis
United States/ Healthcare provider	Lymphoma	17	- -	Psoriasis	Insufficient information
<b>Solid tumors</b>					
United States/ Literature	Progression of renal cancer <sup>a</sup>	14	- -	Idiopathic pneumonia syndrome	history of renal cell carcinoma transplant patient
United States/ Consumer	Bladder cancer <sup>b</sup>	17	- -	Drug use for unknown indication	Minimal information
Germany/ Registry	Yolk sac tumor site unspecified	16	29 days	Juvenile arthritis	1 month Rx methotrexate

<sup>a</sup> Renal cancer was pre-existing.

<sup>b</sup> Bladder cancer was not medically confirmed.



There were 6 reported postmarketing cases of malignancies in the pediatric population (4 in the United States and 2 ex-United States). Two reports included prior exposure to methotrexate. The patient with renal cancer was being treated for idiopathic pneumonia syndrome secondary to stem cell transplant because of an existing renal cell carcinoma. The yolk sac tumor occurred after 29 days of treatment with etanercept and the patient had previously received methotrexate. Two reports (1 report of bladder cancer, and 1 report of lymphoma in a 17-year-old) contained insufficient information to make a definitive assessment.

**Table 28. Patients Who Began Etanercept Treatment at < 18 Years of Age with Reported Malignancy 18 to 22 Years of Age**

Country/Source	Adverse Event by Preferred Term	Age at Event (years)	Time from Etanercept Initiation to Onset	Indications	Comments/Confounders
Hematological					
Great Britain/ Healthcare provider	B-cell lymphoma	18	3 years	Juvenile arthritis	Pediatric exposure unclear Smoker
United States/ Healthcare provider	Acute myeloid leukaemia, lymphoma	19	1.5 years	Ankylosing spondylitis	
Solid tumors					
Great Britain/ Registry	Malignant melanoma	19	11 months	Psoriatic arthropathy	Methotrexate
Great Britain/ Healthcare provider	Malignant melanoma	19	14 months	Psoriatic arthropathy, Juvenile arthritis	Methotrexate Cosuspect
United States/ Healthcare provider	Papillary thyroid cancer	18	4 years	Juvenile arthritis	
Germany/ Registry	Thyroid cancer	18	10 months	Spondyloarthropathy	

Another 6 reports of malignancies were in patients who were 18 to 22 years of age (but exposed to etanercept prior to the age of 18 years); this included 2 United States cases and 4 ex-United States. Of these, 2 had confounding factors, including exposure to immunosuppressive drugs (methotrexate in 1 patient with malignant melanoma and 1 with thyroid cancer).

**Table 29. Patients Who Began Etanercept at < 18 Years of Age and Reported Event at ≤ 22 Years of Age Where Malignancy Could Not be Excluded**

Country/Source	Adverse Event by Preferred Term	Age at Event (years)	Time from Etanercept Initiation to Onset	Indications	Comments/Confounders
Germany/Registry	Myelodysplastic syndrome	17	4 years	Juvenile arthritis	Unclear diagnosis Pre-malignant condition
Great Britain/Registry	Thyroid neoplasm	18	6 months	- -	Uncertain diagnosis Methotrexate

Two of the reports in [Table 29](#) include reports of neoplasia where the possibility of a malignancy could not be excluded, based on the available data. However, no clear diagnosis of malignancy was reported.

## **7.2 Malignancies in the Adult Population**

### **7.2.1 Background**

An increased risk of lymphoma has been observed in adults with plaque psoriasis, and has been associated with the severity of disease. Likewise, adults with plaque psoriasis appear to be at a higher risk for nonmelanoma skin cancer than the general population ([Gelfand et al, 2006](#); [Margolis et al, 2001](#)). The increased risk for these diseases may be associated with plaque psoriasis treatment itself: Psoralen ultraviolet A (PUVA) phototherapy may increase the risk for melanoma and nonmelanoma skin cancer ([Lindelo et al, 1999](#); [Stern et al, 1998](#); [Stern et al, 1997](#); [Stern and Laird, 1994](#)); methotrexate use in psoriasis has been associated with development of lymphoma ([Stern, 2006](#)); and cyclosporine use has been associated with nonmelanoma skin cancer ([Paul et al, 2003](#)).

Reports suggest that rates of lymphoma are elevated in the rheumatoid arthritis population ([Askling et al, 2005](#); [Thomas et al, 2000](#); [Mellemkjaer et al, 1996](#)). Additionally, the risk of lymphoma has been shown to be associated with disease activity ([Baecklund et al, 1998](#)).

### **7.2.2 Malignancies in Etanercept Clinical Trial Data in Adults with Psoriasis**

An expanded analysis of all psoriasis clinical studies with a completed clinical study report (20021632, 20021639, 20021642, 20030115, 20030117, 20030190), encompassing 4278 subject-years of etanercept exposure was performed. The standardized incidence ratio (SIR) for all malignancies (excluding non-melanoma skin cancer and in situ malignancies except bladder) was 1.31 (95% CI: 0.88, 1.88) based on incidence in the general United States population (SEER), adjusted for age and sex. The age- and sex-adjusted SIR for lymphoma based on incidence in the general population (SEER) was also within the expected range (1.86, 95% CI: 0.23, 6.73) as was the SIR for melanoma (2.99, 95% CI: 0.62, 8.73).

The SIRs for non-melanoma skin cancers were calculated applying sex- and age-specific rates from well-established databases. Gray et al, 1997 gives rates for the general population from Arizona with high sun exposure and Harris et al, 2001 gives rates for the general population from Minnesota with low sun exposure. Compared with

the general population with high (SIR = 1.93; 95% CI: 1.18, 2.98) or low sun exposure (SIR = 4.59; 95% CI: 2.81, 7.09), the incidence of SCC in etanercept-treated patients with psoriasis was higher than expected. The incidence of BCC for psoriasis patients with high sun exposure was lower than expected (SIR = 0.60; 95% CI: 0.39, 0.88).

However, of those patients who reported non-melanoma skin cancers in psoriasis studies, the percentage who received any phototherapy at any time was 70% (SCC) and 65% (BCC) and the percentage who received PUVA was 45% (SCC) and 31% (BCC).

### **7.3 Meta-analyses of Malignancies**

#### **7.3.1 Meta-analyses of All TNF Inhibitors Approved in Rheumatoid Arthritis**

It is difficult to evaluate the risk of rare events in clinical trials, as an individual trial may not be powered to detect a rare event. Meta-analysis is one method employed to combine evidence from several clinical trials in order to assess risk of rare events. Two recent meta-analyses have examined the risk of malignancy in rheumatoid arthritis patients treated with TNF inhibitors (adalimumab, etanercept, infliximab).

In a meta-analysis of 9 etanercept trials in rheumatoid arthritis by [Bongartz et al \(2008\)](#), a Cox's Proportional Hazards, fixed-effect model stratified by trial yielded a hazard ratio of 1.84 (95% CI: 0.79, 4.28) for malignancy for the etanercept group compared to the control group. In a secondary analysis based on aggregate study-level data using Mantel-Haenszel methods with a continuity correction designed for sparse data, the pooled odds ratio was 1.93 (95% CI: 0.85, 4.38).

In 2006, Bongartz et al reported results from a meta-analysis of 9 randomized, placebo-controlled trials of infliximab and adalimumab in rheumatoid arthritis. The Mantel-Haenszel method with a continuity correction designed for sparse data yielded a pooled odds ratio for malignancy of 3.3 (95% CI: 1.2, 9.1). A follow-up that included data from a subsequent clinical study yielded a pooled odds ratio for malignancy of 2.4 (95% CI: 1.2, 4.8) (Bongartz et al, 2006).

#### **7.3.2 Amgen Conducted Pooled Analysis of Etanercept Clinical Trial Data**

For all malignancies based on the SEER definition, which excludes non-melanoma skin cancer and in situ malignancies except bladder, in patients in the double-blind periods of the 23 controlled trials of subjects with rheumatoid arthritis, psoriasis, juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and pediatric psoriasis the relative risk (etanercept groups vs placebo control groups) was 0.88 (95% CI: 0.43, 1.81). Compared to the general population (SEER), the SIR for all indications combined

from all 45 clinical studies used in this analysis was 1.00 (95% CI: 0.83, 1.19). No cases of lymphoma were reported in ankylosing spondylitis, psoriatic arthritis, juvenile rheumatoid arthritis patients, and pediatric psoriasis. Thirteen cases of lymphoma were reported in rheumatoid arthritis studies (SIR = 3.45; 95% CI: 1.83, 5.89), and 2 cases were reported in psoriasis studies (SIR = 1.86; 95% CI: 0.23, 6.73). The total SIR for lymphomas across all studies was 2.85 (95% CI: 1.59, 4.70).

There were no SCCs reported in subjects with juvenile rheumatoid arthritis, psoriatic arthritis, and pediatric psoriasis patients and the incidence of SCC was similar to expected (SIRs <1) for rheumatoid arthritis and ankylosing spondylitis, regardless of sun exposure. The overall incidence of SCC for all patients receiving etanercept over all indications, including psoriasis, was below the expected rate when compared with the general population with high sun exposure (SIR = 0.55; 95% CI: 0.36, 0.79) and the SIR was 1.24 when compared with the general population with low sun exposure (95% CI: 0.82, 1.79). The incidence of BCC was low for all patients receiving etanercept for all indications (SIR = 0.26; 95% CI: 0.19, 0.33). The SIR for melanoma for clinical studies including all indications was 2.01 (95% CI: 0.92, 3.82).

#### 7.4 Immunizations

The NPF recommends that immunizations be updated before initiating a biologic agent, and that live or live-attenuated vaccines not be given to patients receiving biologics (Lebwohl et al 2008). Limited data exist to describe the efficacy and safety of immunizations in children receiving etanercept. Consistent with the package insert, children in all etanercept juvenile rheumatoid arthritis studies and pediatric psoriasis Study 20030211 were required to have updated immunizations before etanercept was initiated, as live vaccines were not permitted while subjects were receiving etanercept on study. In Study 20030211, subjects who received immunizations with non-prohibited vaccines had them recorded as concomitant medications, with on-study vaccinations recorded on a designated case report form; no adverse events were reported that related to immunizations. Two children who had baseline adequate titers for varicella acquired limited zoster. Anti-varicella titers drawn at the time of the zoster were within the immune range (> 1.0 mg/mL).

Limited data are available that describe patients' response to immunization while taking etanercept. Responses to pneumococcal vaccination have been reported for etanercept in psoriatic arthritis (Mease et al, 2004) and etanercept and infliximab in rheumatoid arthritis (Elkayam et al, 2007; Kapetonovic et al, 2006). Patients receiving these

anti-TNF agents generally achieved adequate responses to the vaccine. Antibody titers tended to be lower in patients receiving methotrexate, with or without an anti-TNF agent (Mease et al, 2004). Responses to influenza vaccine have been studied in patients with Crohn's disease (van der Bijl et al, 2005) and rheumatoid arthritis (Kapetonovic et al, 2007). Antibody responses were lower in the anti-TNF-treated patients, but 79% achieved protective levels. In a small group of patients receiving etanercept for rheumatoid arthritis, only one third achieved an adequate antibody response at 6 months (Ravikumar et al, 2006).

## **7.5 Effect of Etanercept on Growth and Development in Pediatric Patients**

While children with juvenile rheumatoid arthritis are commonly known to have growth retardation relative to healthy children (Bernstein et al, 1977), which can be further compounded by treatment with corticosteroids (Wang et al, 2002), data are not available that demonstrate a similar impact of disease upon development in pediatric psoriasis subjects.

Analyses of growth parameters have been performed in all available pediatric subjects treated with etanercept in clinical trials (Studies 016.0016, 016.0018, and 20030211) or the cohort study (Study 20021626). Height and weight data were available for variable amounts of etanercept exposure, from a year up to 7.3 years. As placebo exposure relative to etanercept was minimal, analyses are not presented by treatment group with the exception of Study 16.0026.

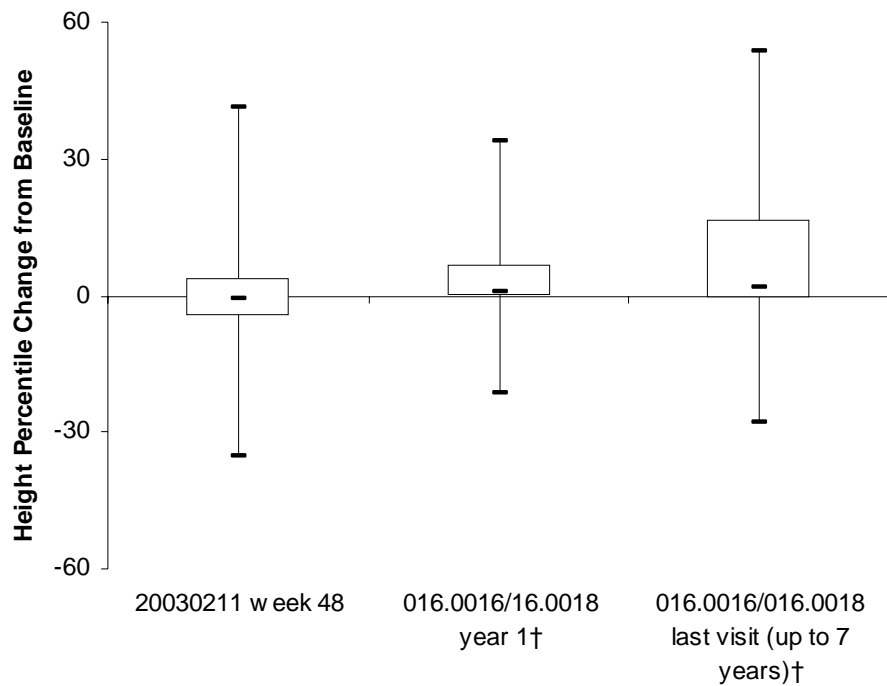
In the analyses presented here, etanercept was associated with a modest increase in height, weight, and body mass index (BMI) percentile in subjects with juvenile rheumatoid arthritis, and with a slight decrease in height percentile and increase in BMI percentile in pediatric subjects with psoriasis. While these studies were not primarily designed to study growth velocity, these data suggest that etanercept does not have an adverse effect on height, weight, or BMI in this pediatric population.

### **7.5.1 Height**

Over the 48-week period, a slight, non-significant decrease in height percentile was seen in the subjects with pediatric plaque psoriasis (Figure 7); in contrast, a modest increase was seen in height percentiles in subjects with juvenile rheumatoid arthritis over a longer time period (Figure 7 and Figure 8).



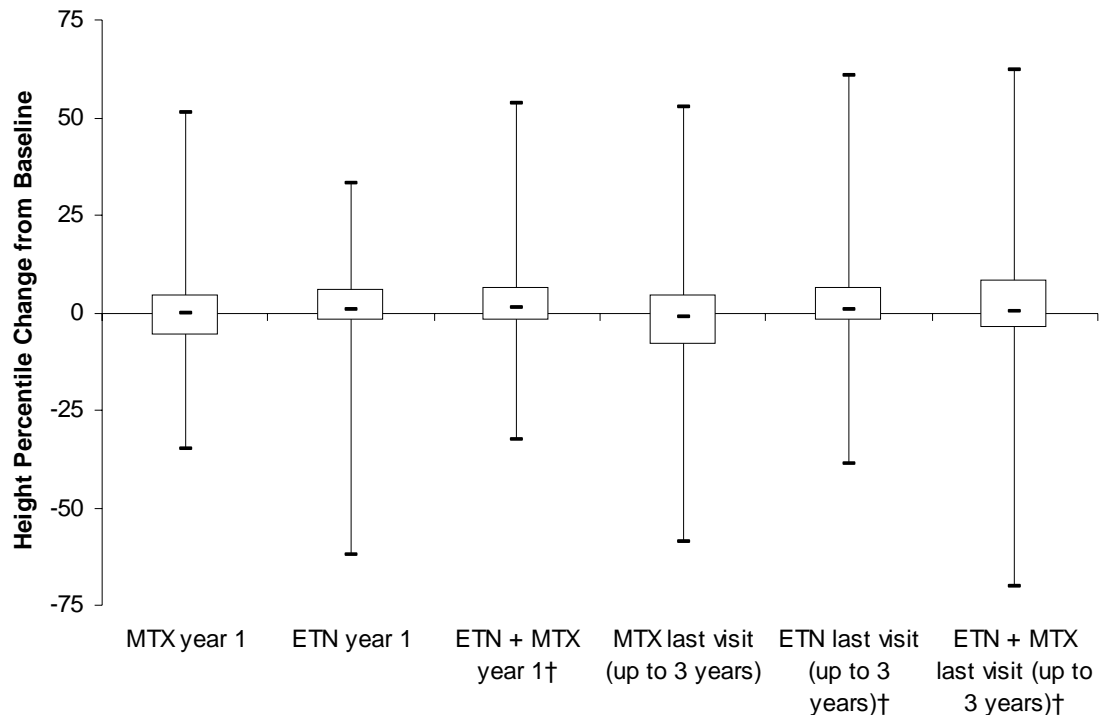
**Figure 7. Height Percentile Change From Baseline in Pediatric Subjects in Etanercept Clinical Trials (20030211, 016.0016, 016.0018)**



Note: no stadiometer was used

† p < 0.05 relative to baseline

**Figure 8. Height Percentile Change From Baseline in Etanercept Juvenile Idiopathic Arthritis (JIA) Cohort Study Subjects (016.0026)**



Note: no stadiometer was used

† p < 0.05 relative to baseline

Despite the slight decrease in height percentile in the pediatric psoriasis study, most subjects remained close to their baseline height percentile (146 of 188 subjects were between >-10% and <+10% of their baseline height percentile). Overall, few pediatric psoriasis subjects were at either height percentile extreme (below the 3rd or above the 97th percentile) at baseline or week 48: the same number of subjects (6) was below the 3rd percentile at baseline and week 48; 11 subjects were above the 97th percentile at baseline and 9 were above it at week 48.

Slight decreases in median height percentile from baseline were seen regardless of age (4 to 11 vs 12 to 17), sex, or previous corticosteroid use in pediatric psoriasis subjects (all median changes  $\leq 2.05$ ).

### 7.5.2 Weight

Modest increases were seen in weight percentiles in the pediatric juvenile rheumatoid arthritis population over a year or longer (median increase of 4.7 at year 1 and 5.9 at last visit for clinical trial subjects and median increase of 4.57 at year 1 and 2.1 at last visit

for cohort study subjects receiving etanercept only); pediatric psoriasis subjects did not demonstrate a significant weight percentile change over 48 weeks (median change of 0).

### **7.5.3 Body Mass Index**

Pediatric psoriasis subjects showed a slight increase in BMI percentile over 48 weeks (median increase of 0.75), though the change was not significant. Modest increases were seen in BMI percentiles in the pediatric juvenile rheumatoid arthritis population over a year or longer (median increase of 4.3 at year 1 and 6.3 at last visit for clinical trial subjects and median increase of 4.69 at year 1 and 2.43 at last visit for cohort study subjects receiving etanercept only).

## **7.6 Pregnancy**

### **7.6.1 Pregnancy in Women in the United States**

Pregnancy and birth rates in the United States can be used to assess the risk that an adolescent female will become pregnant or have a live birth. In 2002, pregnancy and birth rates per 1000 women aged 14 and under were 8.6 and 3.6, respectively.

Pregnancy and birth rates per 1000 women among those aged 15 to 17 years were 42.3 and 23.2, respectively, and pregnancy and birth rate per 1000 women aged 18 to 19 years were 125.8 and 72.8, respectively

([www.guttmacher.org/pubs/state\\_pregnancy\\_trends.pdf](http://www.guttmacher.org/pubs/state_pregnancy_trends.pdf), accessed April 30, 2008).

### **7.6.2 Pregnancy in Women Receiving Etanercept**

#### **7.6.2.1 Background**

Limited data is available regarding the use of etanercept by pregnant women. To monitor planned and unplanned pregnancies the Organization of Teratology Information Specialists (OTIS), a North American network of hospital- and university-based pregnancy risk counseling services, is conducting an observational study. The Rheumatic Diseases and Psoriatic Pregnancy Registry is a prospective, observational, exposure cohort study of pregnancy outcomes in women with rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, and ankylosing spondylitis who were exposed to etanercept during pregnancy. Pregnancy outcomes of women receiving etanercept during pregnancy are compared with disease-matched women who have not been exposed to etanercept during pregnancy, and to an historic cohort of women without rheumatic diseases or exposure to etanercept.

Endpoints for the prospective cohort study include the incidence of major structural defects; the frequency and patterns of minor malformations; spontaneous and elective abortions; still birth; preterm delivery; and pre and postnatal fetal and infant weight,

length, and head circumference. In addition, in the first year of life, developmental milestones will be monitored, as well as the incidence of malignancies, and serious and opportunistic infections. An overall sample size of 900 subjects across all 3 cohorts is planned: 300 etanercept-exposed subjects, 300 disease-matched subjects, and 300 unexposed historic subjects.

#### 7.6.2.2 Results

The Rheumatic Diseases and Psoriasis Pregnancy Registry - OTIS Autoimmune Diseases in Pregnancy Study is an ongoing study that was established in March 2005, with the first subject recruited in April 2005. As of 04 April 2008, 213 subjects were enrolled (144 etanercept-exposed subjects and 69 disease-matched subjects). Of the enrolled subjects, 100 etanercept-exposed subjects (69%) and 53 disease-matched subjects (77%) gave birth (live or otherwise) (Table 30). Data from the unexposed historic cohort are not available at this time, and will therefore not be presented.

**Table 30. Enrolled Subjects with Pregnancy Outcomes (Births)  
by Disease Category**

	Etanercept (N = 144) n (%)	Diseased Controls (N = 69) n (%)
Number Enrolled with Outcome	100 (69.44)	53 (76.81)
Number Enrolled Pending Outcome	44 (30.56)	15 (21.74)
Number Enrolled Lost to Follow-up		
Withdrawals	0 (0)	1 (1.45)
No contact	0 (0)	0 (0)
Total	144 (100)	69 (100)

The maternal age (mean [SD]) at the estimated due date was similar between etanercept-exposed (32 years [4.81]) and disease-matched controls (33 years [5.34]). A total of 34% and 43% had a maternal age at the estimated due date > 34 years of age for etanercept-exposed and disease-matched subjects, respectively. Most enrolled subjects were white (80% to 86%).

The outcome of the pregnancies is summarized by outcome type in Table 31. Live births were reported in 94 etanercept-exposed subjects and 47 disease-matched subjects.

**Table 31. Outcome of Pregnancies**

	Etanercept (N = 100) n (%)	Disease-Matched Controls (N = 54) n (%)
Live birth	94 (94.00)	47 (87.04)
Spontaneous Abortion	6 (6.00)	5 (9.26)
Stillbirth	0 (0)	0 (0)
Termination	0 (0)	1 (1.85)
Social	0 (0)	0 (0)
Medical	0 (0)	1 (1.85)
Lost to Follow-up	0 (0)	1 (1.85)

Major birth defects are summarized in [Table 32](#).

**Table 32. Major Birth Defects**

	Etanercept n/N (%)	Disease-matched Controls n/N (%)
Number of infants with major birth defects among all pregnancies with outcome	8/100 (8.00)	3/53 (5.66)

#### **7.6.2.3 Conclusion**

The percentage of pregnancies resulting in live births was similar between patients receiving etanercept and disease-matched control. The incidence of major malformations was similar between the etanercept and disease –matched controls, though the preliminary data from this ongoing study are too limited at this time to allow for meaningful conclusions.

## **8. Potential Use of Etanercept in Pediatric Patients with Plaque Psoriasis**

### **8.1 Target population**

The target population for etanercept use is pediatric (aged 4 to 17 years) patients with chronic moderate to severe plaque psoriasis who are inadequately controlled with topical psoriasis therapy or who have received systemic therapy or phototherapy.

### **8.2 Proposed Dose**

The proposed dosing for etanercept in pediatric patients with plaque psoriasis is the dosing regimen that was used in Study 20030211: 0.8 mg/kg etanercept administered by subcutaneous injection once weekly up to a maximum dose of 50 mg. In patients who respond, an initial response is generally apparent within 12 weeks. Safety beyond 1 year in pediatric patients with psoriasis has not been established; therefore, the benefits and risks of continuing treatment should be carefully considered.

### **8.3 Proposed Risk Evaluation and Mitigation Strategy**

In order to minimize known and potential risks, including risk of serious infections, demyelinating disease, immunization and growth-related risks, and malignant diseases, we will target prescriber education. This will be targeted to ensure that only the appropriate population is treated with this systemic therapy (ie, those in whom topical therapy has not been successful or who are on systemic or phototherapy), and that the risk related prescribing recommendations are followed. Another goal will be to ensure that patients are adequately immunized, that the patient has not been recently exposed to infections that may pose a serious risk prior to starting therapy, and that patients are treated for the appropriate duration. We will also target education of guardians and patients with risk related information. The effectiveness of these activities will be assessed prior to implementation and on an ongoing basis to ensure that the goals of REMS are met. The inputs of these assessments, and additional prospectively collected risk and utilization data, will be utilized to make appropriate changes to the program to achieve its goals.

The proposed goals of REMS are:

- Use of etanercept only in the target population
- Mitigate identified and potential risks for this new pediatric population

Amgen is committed to using a combination of REMS tools to further assess and manage these identified and potential risks for etanercept.

It is proposed to meet the goals using the following:

- Provider and Parent/ Patient Education
- Reminder Systems: Prescriber Checklist
- Active surveillance
- Utilization and prospective cohort studies
- Long-term follow up in extension studies

A comprehensive risk mitigation program for the targeted pediatric psoriasis population, including instructions in the prescribing information, a Patient Medication Guide, Patient Starter Kit; educational activities for patients, parents, and prescribers; active surveillance; a database utilization study; and a prospective cohort study, is proposed. Amgen believes these actions are appropriate and adequate to manage the known and potential risks of etanercept use in the potential indication.

The risk-management program for etanercept is based on the assessment of risk described in the sections that follow.

### 8.3.1 Additional Risk Assessment for Identified and Potential Risks

As a part of continued risk assessment, additional data on the potential and identified risks of etanercept in the pediatric psoriasis population will be collected and analyzed. Lists of events of interest and proposed actions for the monitoring and evaluation of all identified and potential risks are provided in [Table 33](#) and [Table 34](#). The proposed studies will be further described in [Section 8.3.4](#).

**Table 33. Summary of Proposed Risk Assessment Plan for Identified Risks of Etanercept in the Pediatric Plaque Psoriasis Population**

Identified Risks	Proposed Risk Evaluation Approach
Serious Infections (eg, viral, bacterial, fungal)	Monitor in extension study 20050111 Monitor in the proposed prospective cohort study Routine pharmacovigilance
Injection-site reactions	Monitor In extension study 20050111 Monitor In the proposed prospective cohort study Routine pharmacovigilance,
Demyelinating events	Monitor in extension study 20050111 Monitor in the proposed prospective cohort study Continue enhanced surveillance using questionnaire for demyelination expanded for pediatric use, plus periodic assessment of reports
Hematologic events	Monitor in extension study 20050111 Monitor in the proposed prospective cohort study Routine pharmacovigilance
Hepatitis B reactivation	Monitor in extension study 20050111 Monitor in the Proposed Prospective cohort study Routine pharmacovigilance
Allergic reactions	Monitor in extension study 20050111 Monitor in the proposed prospective cohort study Routine pharmacovigilance
Autoimmune hepatitis or Lupus-like syndrome	Monitor in extension study 20050111 Monitor in the proposed prospective cohort study Routine pharmacovigilance
Changes in morphology or severity of psoriasis	Monitor in extension study 20050111 Monitor in the proposed prospective cohort study Routine pharmacovigilance



**Table 34. Summary of Proposed Risk Assessment Plan for Potential Risks of Etanercept in the Pediatric Plaque Psoriasis Population**

Potential Risks	Proposed Evaluation
Malignancies	Routine and additional pharmacovigilance with use of specific questionnaire for follow-up of spontaneously reported malignancies in patients up to 22 years of age. Monitor in extension Study 20050111 Monitor in the proposed prospective cohort study Complete protocol 20030249 (POSA)
Reaction to immunizations (live vaccines) and related infections (varicella); response to immunizations	Monitor in extension Study 20050111 Monitor in the proposed prospective cohort study Routine pharmacovigilance
Impairment of growth and development	Monitor in extension Study 20050111 monitor in the proposed prospective cohort study
Response to immunizations	Monitor in extension Study 20050111 Monitor in the proposed prospective cohort study Routine pharmacovigilance
Pregnancy-related disorders (birth defects)	Pregnancy Cohort Study 20040246 (OTIS); In addition, reports of pregnancy or pregnancy related events for patients that are not eligible for inclusion in OTIS are automatically included in an Amgen registry for follow-up and reporting

Except for the potential impact on growth and development, all identified risks in [Table 33](#) and all potential risks in [Table 34](#) are described in current prescribing information and in warnings and precautions where appropriate.

### **8.3.2 Ongoing Pediatric Studies**

#### **8.3.2.1 Open-label Pediatric Psoriasis Extension Study (20050111)**

A description of this study is provided in [Section 4.2](#). This study will be extended to follow currently enrolled pediatric psoriasis patients for up to a total of 5 years and will examine the risk of infections, injection site reactions, immunogenicity, and impact of etanercept treatment on growth and vaccinations.

### **8.3.3 Other Ongoing Studies**

#### **8.3.3.1 Pregnancy Cohort Study (Study 20040246)**

A description of the study by the Organization of Teratology Information Specialists is provided in [Section 7.6.2](#). This study is open to pediatric patients who meet enrollment criteria upon parent or guardian consent.

#### **8.3.3.2 Study 20030249**

An annual interim (progress) report is due every July 31 for “A Pooled Analysis of Observational Studies on Lymphoma Incidence Among Rheumatoid Arthritis Patients

Initiating Enbrel® Therapy: Pooled Observational Studies Analysis (POSA)” (Amgen protocol 20030249). A final study report will include interval and cumulative analyses and will be submitted by July 31, 2009 (as described in the protocol).

#### **8.3.3.3 Study 20021618**

Open-label Extension Treatment with TNFR:Fc for Participating Patients in TNFR:Fc Clinical Trials (includes subjects with JRA) (20021618). A description of this study is provided in [Section 5.1.2](#).

#### **8.3.3.4 Study 20021623**

Open-label Extension Treatment with TNFR:Fc for Participating Patients in TNFR:Fc Clinical Trial 016.0012 (20021623).

### **8.3.4 Proposed Additional Clinical Studies**

#### **8.3.4.1 Prospective Cohort Study of Patients with Pediatric Plaque Psoriasis Treated with Etanercept**

Amgen proposes to discuss with the Agency the goals and objectives for a prospective cohort study of pediatric patients with moderate to severe plaque psoriasis treated with etanercept. The population of pediatric patients with moderate to severe psoriasis that may be treated with etanercept is estimated to be small and, consequently, may be too small for the evaluation of rare events. The extension Study 20050111 will continue to monitor growth and the proposed prospective cohort study will monitor growth and development; both will evaluate the nature of infections and other adverse events of interest over time ([Table 33](#) and [Table 34](#)).

It is proposed that the primary objective of the open-label etanercept-treated prospective cohort study be the estimation of the overall rate of serious infection and secondarily an exploratory examination for any increase in the rate of serious infections with duration of exposure. The rate of serious infections observed in the prospective cohort study will be compared to the exposure-adjusted rate (per 100 patient-years) of serious infections in other etanercept-treated populations, including adults psoriasis (1.3 [[Section 6.1](#)]), in juvenile rheumatoid arthritis (2.1 – 3.6), and in pediatric psoriasis (1.8). A 300 patient study with a cumulative observation of 1000 subject-years and an observed rate of 2.0 serious infections per 100 person-years would have 95% CI: 1.2, 3.1 per 100 subject-years (Poisson, STATA 9.2).

This proposed study will enroll 300 patients aged 4 to 17 years with moderate to severe plaque psoriasis treated with etanercept and follow them for up to 5 years (depending upon age at enrolment, this could be up to age 22). The study will evaluate growth and

development, the incidence of allergic and injection site reactions, responses to any immunizations, and monitor for the occurrence of serious adverse events including serious infections. Other medical events of interest, including tuberculosis, opportunistic infections, malignancies, and demyelinating events as well as any deaths that may occur in the study cohort will also be collected. Annual reports will be provided to the Agency.

#### **8.3.5 Risk Minimization Activities**

Current prescribing information describes the known and potential risks for use of etanercept and provides precautions and warnings for patients, including those of pediatric age, who have been diagnosed with juvenile rheumatoid arthritis.

In summary, etanercept treatment has been studied in the pediatric psoriasis population (up to 48 weeks). It was previously studied for the currently approved indication of juvenile rheumatoid arthritis and adult psoriasis and rheumatoid arthritis. Treatment related risks were described in [Table 33](#) and [Table 34](#).

Postmarketing surveillance indicates that there is current off-label use of etanercept in the pediatric population. Amgen believes that the risks and potential risks associated with use of etanercept in the pediatric psoriasis population are best minimized by appropriate labeled use rather than off-label use. Amgen recognizes that potential serious long-term risks, while unproven, are of concern and need to be addressed through educational efforts. Although the prescribing population will be relatively small ([Section 8.1](#)), restricting distribution would be difficult. Amgen's approach will be to educate the prescribing population of physicians.

Amgen will optimize the benefit-risk of etanercept use in this population, by addressing the key identified and potential risks described in [Table 33](#) and [Table 34](#). This will be accomplished by educational activities directed to prescribers, patients, and parents/guardians regarding proper patient selection and adherence to REMS. The proposed tools include a prescribing checklist, a patient medication guide, and a starter kit.

Promotional materials and sales force activities will be designed to meet risk-management objectives:

- Amgen sales representatives will only promote etanercept for this indication to targeted specialists (eg, dermatologists) and their office staff
- No direct-to-consumer media advertising will be used to promote the use of etanercept for pediatric psoriasis

#### **8.3.5.1 Approach of Risk Minimization Activities**

The overall approach of the REMS is proposed to include:

- Optimization of use in targeted population where better therapeutic alternatives are not available
- Targeting prescriber awareness of the appropriate population of pediatric psoriasis patients
- Adherence to risk minimization:
  - Prescriber use of checklist for ensuring:
    - appropriate patients are started on etanercept therapy
    - immunizations are completed prior to starting patients on etanercept
    - screening for tuberculosis and hepatitis B
  - Starter Kit and Patient Medication Guide to ensure patient and guardian are fully educated in appropriate product risk related information
- Gather additional information to better define the risk profile of etanercept use in pediatric psoriasis in order to optimize the benefit–risk during future use of the product

#### **8.3.5.2 Educational Component of Risk Evaluation and Mitigation Strategy**

##### **8.3.5.2.1 Patient Medication Guide and Starter Kit for Pediatric Psoriasis Patients**

The current Patient Medication Guide for etanercept will be modified to reflect and explain any changes in the prescribing information to include relevant information for pediatric psoriasis use. A Patient Medication Guide and starter kit will be provided to all pediatric psoriasis patients at the initiation of etanercept therapy with the objective of ensuring the appropriate use of etanercept and to explain its risks and benefits. This tool will work in coordination with physician education tools to ensure patient-physician dialog on the approved indication and risks associated with etanercept use. The Medication Guide and starter kit will address each risk that is relevant for pediatric psoriasis patients and that the parent or guardian should know.

##### **8.3.5.2.2 Targeted Physician Education and Outreach**

Education will be provided through various online or written sources and will be made available on a voluntary basis to all dermatologists and pediatricians (and to other

healthcare providers, as needed) and in association with professional organizations. The main purpose will be to ensure that healthcare providers are aware of the following risks, and are provided with education about prevention of these risks:

Identified risks for pediatric psoriasis:

- serious infections
- demyelination

Potential risks for pediatric psoriasis:

- malignancies
- impairment of growth and development
- response to immunizations
- pregnancy-related disorders (birth defects)

The educational tools in this category include specific, targeted education and outreach efforts regarding safety risks, with the main goal to provide information to different audiences (healthcare practitioners) to ensure appropriate product use. All tools will be driven by the United States Prescribing Information, which describes the approved indication, risks, warnings, and precautions associated with use of etanercept.

Planned initiatives to educate physicians and other healthcare providers on the known and theoretical risks of etanercept and ensure appropriate use include the following:

- Training and education program for health care professionals
- Continuing education for healthcare practitioners
- Dissemination of safety information to prescribers (through Regional Medical Liaisons and sales force)
- Education through Medical and Scientific Associations (American Academy of Dermatology [AAD], etc.)

Healthcare associations and professional organizations are another means by which healthcare providers keep current on new developments regarding various treatment options. Amgen has been engaged and will continue to be so with relevant organizations (eg, AAD and NPF) to determine how to best communicate and educate their membership.

### **8.3.5.3 Reminder System**

A reminder system will be made available using a prescribing checklist including the following to target the goals of treatment of the appropriate population and optimize the benefit-risk ratio of etanercept for pediatric patients with moderate to severe psoriasis:

- Patient has moderate to severe psoriasis
- Patient is poorly controlled on topicals and is a candidate for systemic agents
- Vaccines are up-to-date for age
- No recent varicella exposure
- Not at risk for tuberculosis and/or evaluated for existing infection
- Not at risk for hepatitis B virus and/or evaluated for existing infection
- No existing active infection
- Applicable risks of etanercept therapy have been discussed with the patient and/or guardian

### **8.3.6 Pre-testing of Risk Minimization Elements**

Prior to implementation, Amgen plans to conduct market research studies to assess the comprehension and ease of use of the proposed REMS elements, specifically:

- Comprehension of the etanercept Medication Guide and Starter kit by parent or guardian.
- Comprehension and utility of the physician educational materials and prescribing checklist.

### 8.3.7 Evaluation of Risk Minimization Activities

Post-implementation, Amgen is committed to evaluating the risk minimization program on a continuing basis. Results of these assessment activities will be reviewed with FDA to evaluate both the appropriate labeled use and off-label use of etanercept.

Activity	Evaluation
Education and training of prescribers	Monitor process measurements Conduct survey of knowledge
Appropriate use as defined in prescribing information	Conduct survey of prescribing behavior Inspect prescribing patterns in a large external database
Effectiveness of precautions and warnings in prescribing information (risk of TB, HBV reactivation, live vaccine use, serious infections)	Examine frequency of selected outcomes in spontaneously reported adverse events
Patient Medication Guide and Starter Kit	Evaluate comprehension and usefulness of the language in communicating the concepts of risk and the nature of the described events to a group of parents or guardians of pediatric patients with moderate to severe psoriasis
Use of prescriber checklist	Conduct survey of use

### 8.3.8 Risk Evaluation and Mitigation Strategy Summary

[Table 35](#) provides a summary of the REMS.

**Table 35. Summary of Proposed Risk Minimization Activities in Association with Safety Concerns for Pediatric Psoriasis Indication**

Safety Concern	Routine Risk Minimization Communication, and Education	Post-Marketing Safety Surveillance	Safety Monitoring in Ongoing and Future Clinical Studies	Post-Approval Studies	Risk Minimization Tools proposed
Identified Risks for Pediatric Psoriasis					
Serious Infections (Eg, Viral, Bacterial, Fungal)	X	X	X	X	Medication Guide and Starter Kit Prescriber Checklist. Targeted clinician education and outreach Safety registry
Demyelinating Events	X	X	X	X	Medication Guide and Starter Kit Prescriber Checklist Targeted clinician education and outreach Safety registry
Potential Risks for Pediatric Psoriasis					
Malignancies	X	X	X	X	Prescriber Checklist Targeted clinician education and outreach Safety registry
Impairment of growth and development	X	X	X	X	Targeted clinician education and outreach Safety registry
Response to immunizations	X	X	X	X	Medication Guide and Starter Kit Prescriber Checklist Targeted clinician education and outreach Safety registry
Pregnancy-related disorders (birth defects)	X	X	X		Medication Guide and Starter Kit Targeted clinician education and outreach Pregnancy registry



Amgen is committed to establishing a comprehensive REMS program including appropriate instructions in the prescribing information, pharmacovigilance (both routine and proactive), additional studies, and risk minimization activities. These include an educational program targeted at dermatologists and pediatricians, a reminder system (prescriber checklist to facilitate adherence to risk mitigation activities), a medication guide and starter kit to educate patients and parents. Amgen also proposes an evaluation of the Patient Medication Guide and Starter kit. Additional risk information will be collected in a long-term follow-up in the extension study (20050111) and a proposed prospective cohort study, and specific follow-up questionnaires for selected spontaneous reports. Surveys of prescribing behavior in dermatologists, studies of prescribing patterns in health care databases, and examination of the indications in spontaneously reported adverse events will contribute to the assessment of the effectiveness of the risk minimization activities. Results of these assessment activities will be reviewed with FDA to evaluate both the appropriate labeled use and off-label use of etanercept. The inputs of these assessments will be utilized to make appropriate changes to the program to achieve its goals.

Amgen believes these actions are appropriate and adequate to manage and minimize the safety risks of etanercept in pediatric patients with moderate to severe plaque psoriasis.

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**10. Appendices**

## Appendix A. Description of Clinical Measures of Disease

The following is a list of measures that have been used to assess clinical disease and response to therapy:

Body Surface Area (BSA): Approximately 1 of the patient's handprints is considered to represent 1% of the patient's BSA. Thus, 10 handprints would correlate to 10% affected BSA ([Finlay, 2005](#)).

Psoriasis Area and Severity Index (PASI): The PASI is a composite measure performed by physicians and involves scoring the severity of erythema, induration, and desquamation and area of involvement for each body area (head, upper extremities, trunk, and lower extremities) ([Fredriksson and Petersson, 1978](#); validation in [Berth-Jones et al, 2006](#)). Total PASI scores are calculated by multiplying the area of involvement score, the sum of the severity scores for erythema, induration, and scaling, and a weight factor for that body area (0.1, 0.2, 0.3, and 0.4 for head, upper extremities, trunk, and lower extremities, respectively), and then summing across all 4 body areas. The total range of the PASI score is 0 to 72, where 0 = no psoriasis and 72 = severe disease. PASI 50, 75, and 90 represent 50%, 75%, and 90%, improvement from baseline PASI scores, respectively ([Carlin 2004](#)).

Static Physician's Global Assessment of Psoriasis (sPGA): The sPGA includes a static assessment of psoriasis severity averaged over all lesions. The static assessment is rated on a scale from 0 to 5, where 0 represents "clear" or "no evidence" and 5 represents the most severe ([Feldman and Krueger, 2005](#)).

ACR Pediatric 30: The definition of improvement for ACR Pediatric 30 requires both of the following: 1) at least 30% improvement from baseline in at least 3 of the 6 variables in the core set (number of joints with active arthritis; number of joints with limitation of motion [LOM]; physician's assessment of disease activity; parent's assessment of the patient's overall well-being; a validated measure of physical function; and a laboratory measure of inflammation), and 2) no more than 1 of the remaining variables worsening by >30% ([Giannini et al, 1997](#)).

## **Appendix B. Description of Patient-reported Outcome Measures Used to Determine Physical and Psychosocial Functioning**

These PRO questionnaires have been cited in the text.

### **Questionnaires for Children and Adolescents**

Children's Dermatology Life Quality Index (CDLQI): The CDLQI is an established disease specific questionnaire for children (ages 4 to 16) with chronic skin disease (Lewis-Jones and Finlay, 1995). The recall period is last week. The CDLQI 10-item questionnaire covers 6 subscales, including symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and treatment. The 4 item response categories include, "very much," "quite a lot," "quite a little," and "none at all." The total score ranges from 0 to 30 with lower scores representing better QOL. The CDLQI can also be expressed as a percentage of the maximum score of 30. There are separate versions of the questionnaire for children ages 4 to 12 (cartoon version) and children ages 13 to 17 (text version). The CDLQI has been used in a number of studies to evaluate QOL of children and adolescents with various inflammatory skin diseases (Beattie and Lewis-Jones 2006; Lewis-Jones and Finlay, 1995), and the CLQI has been used to compare QOL in children with various health conditions (Beattie and Lewis-Jones, 2006)

Pediatric Quality of Life Inventory (PedsQL): The PedsQL is a generic measure used to assess health-related quality of life in children in various disease areas (Varni et al, 1999). The PedsQL is applicable for healthy school and community populations, as well as pediatric populations with acute and chronic health conditions. The multidimensional scales include physical, emotional, social, and school functioning. The PedsQL includes 23 items (21 items for toddlers 2 to 4 years old). The 5 item responses include, "never," "almost never," "sometimes," "often," and "almost always." The time recall is past month for the standard version and past seven days for the acute version. The summary scores include total score, physical health summary score, and psychological health summary score. Possible scores range from 0 to 100, with higher scores indicating better QOL. The PedsQL is developmentally appropriate (child self report for ages 5 to 7, 8 to 12, 13 to 18 and parent proxy-report for ages 2 to 4, 5 to 7, 8 to 12, 3 to 18). The instrument can distinguish between healthy children and children with acute and chronic health conditions and can also distinguish severity within a chronic health condition (Varni et al, 1999)

## Questionnaires for Adults

Beck Depression Inventory (BDI): The BDI is a subject-administered questionnaire that measures the severity of depression. The BDI global score (range 0 to 63) is calculated from an equal-weight summary of 21 symptoms and attitudes, each of which is rated from 0 to 3 for severity, and higher total scores indicate more severe depression. The recall period is the past two weeks ([Beck and Steer, 1993](#); [Beck and Steer, 1984](#))

Dermatology Life Quality Index (DLQI): The DLQI is a validated subject-reported outcome questionnaire for adults that consists of 10 items that assess how much a skin problem has affected the subject over the past week. The 4-item responses include, “very much,” “not at all,” “a little,” “not at all.” The DLQI score is calculated as an equal-weighted summary of the items (range 0 to 30), and higher scores indicate poorer outcomes. This score is composed of 6 subscales that measure symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment ([Finlay and Kahn, 1994](#)).

Dermatitis Family Impact (DFI) Questionnaire: The DFI measures the impact of atopic dermatitis on the family over the previous 7 days and is based on 10 items: housework, food preparation, sleep of others in the family, leisure activities such as swimming, time spent on shopping, cost related to treatment or clothes, tiredness or exhaustion, emotional distress, relationships in the family, and the impact of helping with treatment on the life of the main caregiver. Each question has four answers, including “not at all,” “a little,” “a lot,” and “very much.” The overall summary score aggregates the score of each item and ranges between 0 (the best score) and 30 (the worst score). The higher the score, the poorer the quality of life for the family. ([Lawson et al, 1998](#)).

Stein Impact on Family Scale: The Stein Impact on Family Scale is a generic instrument to measure the effects of chronic illness on parents and families of children with chronic diseases at the time of questionnaire administration. The IOF Scale uses a 24-item Likert scale to measure the impact of each subject’s illness on the family ([Stein and Jessop, 2003](#); [Stein and Reissman, 1980](#)). The 4-item response categories include, “strongly agree,” “agree,” “disagree,” and “strongly disagree.” The four subscales of impact include economic (changes in the financial status of the family), social/familial (quality and quantity of interaction outside and within the home), personal strain (subjective burden experienced by the primary caretaker), and mastery or coping. Results of the IOF can be represented by the total score representing overall impact and 4 component scores ([Stein, 1980](#)). The Total IOF Score has been revisited and is

calculated by summing a subset of 15 items that reflect the social and familial impact of chronic childhood illness ([Stein and Jessop, 2003](#))

## **Appendix C. Background Rates of Common Pediatric Infections**

### **Potential for Tuberculosis**

Between 1993 and 2001, in the general population, a total of 11,480 cases of tuberculosis were reported to the national tuberculosis surveillance system in the United States among children age < 15 years. In 2001, the annual proportion of tuberculosis cases reported among children was approximately 5.8% (931 cases reported), with an incidence rate of 1.5 per 100,000 population. The annual incidence rates (per 100,000 population) of tuberculosis were 2.8 among children < 5 years old, 1.0 among children aged 5 to 9 years, and 0.9 among children aged 10 to 14 years ([Nelson et al, 2004](#)).

### **Potential for Other Infections**

In 1995, the number of cases of severe sepsis requiring hospitalization among children < 19 years of age was 42,364 (with 4400 associated deaths). The annual incidence of severe sepsis per 1000 population was estimated to be 0.56 for all ages < 19 years; 5.16 for ages < 1 year old (largely due to neonatal sepsis); 0.49 for ages 1 to 4 years; 0.22 for ages 5 to 9 years; 0.20 for ages 10 to 14 years; and 0.37 for ages 15 to 19 years ([Watson et al, 2003](#)).

### **Other Infections**

Acute nasopharyngitis (ICD-9 Code 460): In 1996, incidence of the common cold among children aged less than 5 years and between 5 and 17 years of age was reported as 48.6 and 33.8 per 100 persons, respectively ([Adams et al, 1999](#)). Up to 10% to 15% of preschool children will have ≥ 12 infections per year ([Turner, 1998](#)). Children younger than 18 years may experience an average of 3-4 non-influenza-related viral respiratory tract infections per year ([Fendrick et al, 2003](#); [Gwaltney et al, 2004](#)).

Acute sinusitis (ICD-9 Code 461): Acute community-acquired bacterial sinusitis reportedly complicates 5% to 10% of common colds in children ([Gwaltney et al, 2004](#); [Aitken, 1998](#)).

Streptococcal sore throat (ICD-9 Code 034): Sore throat accounted for approximately 18 million office visits in 1996. From 15% to 30% of sore throats can be attributed to streptococcal infection, varying with season, geography and age ([Tsevat, 1999](#)).

Pneumococcal pneumonia (ICD-9 Code 481): In 2004, the annual average rate of invasive pneumococcal disease among children aged less than 5 years was 22.6 cases per 100,000 population, with infections due to non-vaccine serotypes accounting for approximately 19.9 cases per 100,000 population ([Hicks et al, 2007](#)). In

December 2004, the seasonally adjusted hospital admission rates (cases per 100,000 population) for pneumococcal pneumonia were estimated to be 9.2 among those <2 years old; 7.3 for 2 – 4 year olds; and 1.9 for 5 – 17 year olds ([Grijalva et al, 2007](#)). The seasonally adjusted estimated hospital admission rates (cases per 100,000 population) for all-cause pneumonia were 790.9 among those <2 years old; 344.6 among 2 – 4 year olds, and 74.3 among those 5 – 17 years old ([Grijalva et al, 2007](#)).

Candidiasis (ICD9 Code 112.5): The estimated annual incidence of candidiasis among children aged 13 months to 19 years is 2 cases per 100,000 ([Kao et al, 1999](#)).

Human papillomavirus (HPV) (ICD9 Code 079.4): Among children age 0 – 20 years, HPV is found in the oral cavity/oropharynx in approximately 1.9% ([Smith et al, 2007](#)). The prevalence of genital HPV infection among sexually active females age 14 – 19 years is approximately 40% based upon data from the 2003-2004 National Health and Nutrition Examination Survey ([Dunne et al, 2007](#)).

#### **Appendix D. Consumer-Solicited Reports**

From the Council for International Organizations of Medical Sciences (CIOMS) V:

Solicited reports are those derived from organized data collection systems, which include clinical trials, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance. Adverse event reports obtained from any of these should not be considered spontaneous.

For the purposes of safety reporting, solicited reports should be handled as if they were study reports, and therefore should have an appropriate causality assessment. In the case of a consumer solicited report, a 'confirmation' by a healthcare professional requires not just verification of the patient, the exposure, the reported medical event (s), and the drug, but also the healthcare professional's opinion that the event(s) may have been causally linked to drug exposure.