U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Supplement Number:	103795 / 5552
Drug Name:	Enbrel (etanercept)
Indication(s):	Psoriasis in Pediatric Patients
Applicant:	Amgen
Dates:	Submitted: 1/5/2016 PDUFA: 11/4/2016
Review Priority:	Standard review
Biometrics Division:	Division of Biometrics III
Statistics Reviewer:	Kathleen Fritsch, Ph.D.
Concurring Reviewer:	Mohamed Alosh, Ph.D.
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Keywords: Pediatric subjects

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1 Executive Summary

Study 20030211 demonstrated the efficacy of Enbrel in subjects age 4 to 17 with moderate to severe plaque psoriasis. Subjects were followed for up to 48 weeks in Study 20030211 and for up to an additional 264 weeks in 20050111. Study 20030211 enrolled 76 subjects age 4 to 11 years and 135 subjects age 12 to 17 years. Subjects were to have at least 10% body surface area involvement, PASI ≥ 12, and a static Physician's Global Assessment score of moderate, marked or severe. Subjects must have been poorly controlled on topical therapy of have current or past treatment with phototherapy or systemic therapy. The primary efficacy endpoint of PASI 75 and the secondary endpoint of success on the static Physician's Global Assessment (sPGA) demonstrated statistical significance. See Table 1. Efficacy was consistent across different levels of baseline severity, as determined by both baseline sPGA and baseline PASI scores.

Table 1 – Efficacy Results at Week 12 in Study 20030211

	Etanercept N=106	Placebo N=105	P-value
PASI 75	60 (56.6%)	12 (11.4%)	<0.0001
sPGA 0 or 1 with 2 grades improvement	55 (51.9%)	14 (13.3%)	<0.0001

Although all subjects were supposed to have a baseline sPGA score of 3 or higher, two subjects entered the trial with a score of 2 (mild). One subject treated with etanercept with a baseline sPGA of 2 improved to a sPGA score of 1 at Week 12. The applicant treated this subject as a responder (their definition of sPGA success was to achieve a score of clear (0) or minimal (1)). This subject is treated as a failure in the FDA analyses as the subject did not improve by at least 2 grades.

In the long-term follow study (Study 20050111), the majority of subjects (77%) completed at least 2 years of follow-up and 35% completed the planned 5 years of follow-up.

Study 20030211 was originally reviewed when it was submitted to the BLA in 2007. The original statistical review conclusions are summarized in this review. Study 20050111 was submitted for the first time with this supplement.

2 Introduction

2.1 Overview

2.1.1 Regulatory History

Enbrel received approval for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy on April 30, 2004. Enbrel had previously received approval for rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, and ankylosing spondylitis. One of the post-marketing commitments included in the adult psoriasis approval letter was to "conduct protocol 20030211, a 48 week, 200 pediatric patient, multicenter placebo-

controlled clinical trial, to determine the safety and efficacy of Etanercept in pediatric patients, 4 to 17 years of age, with chronic plaque psoriasis."

The applicant completed Study 20030211 and submitted it as part of an efficacy supplement (Supplement 5350) on September 26, 2007 seeking to expand labeling for pediatric patients with psoriasis. Study 20030211 was fully reviewed during the review cycle by statistical reviewer Clara Kim, Ph.D. (see review dated April 29, 2008). On July 24, 2008, the Agency issued a Complete Response letter (b) (4)

Since 2009, the applicant has completed Study 20050111, the 5-year (264-week) long-term follow-up study of subjects originally randomized in Study 20030211. In Study 20050111, subjects continued to receive 0.8 mg/kg (up to 50 mg) of etanercept once weekly. At or after Week 96, subjects with a static Physician's Global Assessment (sPGA) of clear or almost clear were allowed to stop etanercept and the investigator could restart treatment at any time. Some subjects who have not yet turned 18 are continuing follow-up in Study 20050111 past 264 weeks. For these subjects only serious adverse events (including serious infections episodes) and sPGA scores are being collected.

For this efficacy supplement, the applicant has resubmitted the results for Study 20030211 and also submitted the results for Study 20050111 for the first time. The applicant has requested labeling for subjects age 4 to 17 years with chronic severe plaque psoriasis who are candidates for systemic therapy or phototherapy based on these studies. This review will summarize the relevant findings from the 2008 review of Study 20030211 and review the results of Study 20050111.

2.1.2 Clinical Studies

Study 20030211 randomized 211 subjects age 4 to 17 years with moderate to severe stable plaque psoriasis to etanercept (0.8 mg/kg once weekly up to 50 mg) or placebo. From Weeks 13 to 36, all subjects received etanercept (0.8 mg/kg once weekly up to 50 mg). At Week 36, subjects who had achieved at least PASI 50 at Week 24 and PASI 75 at Week 36 entered a randomized withdrawal period (continued etanercept or placebo). When PASI 75 response was lost, subjects resumed treatment with etanercept through Week 48. All subjects who had achieved at least a PASI 50 response in Study 20030211 at or after Week 12 and did not have a serious adverse event or other clinically significant adverse event considered related to investigational product were eligible to enroll in Study 20050111. In Study 20050111, 182 subjects who completed Study 20030211 were treated with etanercept (0.8 mg/kg once weekly up to 50 mg) for up to an additional 264 weeks. Subjects with an sPGA score of clear or almost clear at or after Week 96 were allowed to stop treatment with etanercept. The investigator was allowed to restart treatment with etanercept at any time, and subjects could stop and restart treatment more than once. The study designs are summarized in Table 2.

Table 2 – Clinical Studies Overview

Study Number and Title	20030211 Placebo-controlled Multicenter Study with Etanercept to Determine Safety and Efficacy in Pediatric Subjects with Plaque Psoriasis	20050111 An Open-label Extension Study to Evaluate the Safety of Etanercept in Pediatric Subjects with Plaque Psoriasis
Study Design	Weeks 0-12: Placebo-controlled Weeks 13-36: Open-label treatment Weeks 37-48: Randomized withdrawal/retreatment	Weeks 0-264: Open-label treatment (at or after Week 96, responding subjects could pause treatment)
Inclusion criteria	Age 4 – 17 years, sPGA of moderate/marked/severe, BSA ≥ 10%, PASI ≥ 12	Subjects who had achieved at least a PASI 50 response in Study 20030211 at or after Week 12 and did not have a serious adverse event or other clinically significant adverse event considered related to investigational product
Treatment regimen	0.8 mg/kg once weekly up to 50 mg	0.8 mg/kg once weekly up to 50 mg
Primary endpoint	PASI 75 at Week 12	Incidence of adverse events
Treatment arms and Sample Size	Stage 1: Etanercept – 106 Placebo – 105 Stage 2: Etanercept – 208 Stage 3: Etanercept – 68 Placebo - 69	Etanercept - 182
Study location	United States and Canada	United States and Canada
Study dates	Sept. 2004 – Nov. 2006	Aug. 2005 – Feb. 2012

2.2 Data Sources

This reviewer evaluated the applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. The submission was submitted in eCTD format and was entirely electronic. The applicant submitted analysis datasets in legacy format. The analysis datasets used in this review are archived at \\cdsesub1\evsprod\bla103795\0474\m5\datasets.

3 Statistical Evaluation

3.1 Data and Analysis Quality

The databases for Study 20030211 and 20050111 required minimal data management prior to performing the analyses, and no requests for information regarding the datasets were made to the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study 20030211

Study 20030211 was thoroughly reviewed by the statistical reviewer (Clara Kim, Ph.D) when the study report was submitted as part of Supplement 5350 in 2007 (see statistical review dated April 29, 2008). This review will summarize the key findings of Dr. Kim's review. For additional details, such as disposition, missing data handling, sensitivity analyses and subgroup analyses, refer back to the original statistical review.

3.2.1.1 Study Design and Subject Disposition

Study 20030211 had three parts. Part A (Weeks 0 to 12) was randomized and placebo-controlled (etanercept (0.8 mg/kg once weekly up to 50 mg) or placebo). At or after Week 4, subjects with at least 50% worsening in PASI and an absolute increase of at least 4 points in PASI were allowed to enter an escape arm to receive open-label etanercept through week 12. In Part B (Weeks 13 to 36) all subjects received open-label etanercept (0.8 mg/kg once weekly up to 50 mg). At Week 24, subjects who did not achieve PASI 50 response were given the option to discontinue the study or enter the incomplete-responder arm, where they continued to receive etanercept. At Week 36, subjects who had achieved at least PASI 50 at Week 24 and PASI 75 at Week 36 entered a randomized withdrawal period (continued etanercept or placebo). Subjects in the incomplete-responder arm continued treatment with etanercept. When PASI 75 response was lost in the randomized withdrawal period, subjects resumed treatment with etanercept through Week 48.

Study 20030211 randomized 211 subjects age 4 to 17 years with moderate to severe stable plaque psoriasis. Subjects were to have at least 10% body surface area involvement, PASI $\geq$ 12, and a static Physician's Global Assessment score of moderate, marked or severe. Subjects must have been poorly controlled on topical therapy of have current or past treatment with phototherapy or systemic therapy.

Three subjects (1%) discontinued the study during Part A. In Part B, approximately 6% of subjects discontinued the study. One subject discontinued during Part C. A greater number of placebo subjects than etanercept subjects entered the escape arm in Part A. In addition, a greater number of subjects who had treatment withdrawn (placebo arm) entered the re-treatment arm in Part C than those who were receiving etanercept. See Table 3.

Table 3 – Subject Disposition in Study 20030211

	Part A		Part B	Part C	
	Etanercept N=106	Placebo N=105	Etanercept N=208	Etanercept N=69	Placebo N=69
Subjects who discontinued study	1 (<1%)	2 (1.9%)	13 (6.3%)	1 (1.5%)	0 (0%)
Adverse event	1 (<1%)		5 (2.4%)		
Admin. Decision		1 (<1%)			
Lost to follow-up			3 (1.4%)	1 (1.5%)	
Consent withdrawn		1 (<1%)	4 (1.9%)		
Noncompliance			1 (<1%)		
Subjects who entered escape arm (Part A)	5 (4.7%)	26 (24.7%)			
Subjects who entered incomplete responders arm (Part B)			57 (27.9%)		
Subjects who entered retreatment arm (Part C)				13 (19.1%)	29 (42.0%)

Source: pg 117 of \\cdsesub1\evsprod\bla103795\0060\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5351-stud-rep-contr\20030211\csr-20030211.pdf and pg 10 of Clara Kim's Statistical Review dated 4/29/2008

Randomization was stratified by age (age 4 -11 years and 12-17 years). Approximately 36% of subjects were age 4-11 years and 64% of subjects were age 12-17 years at baseline. See Table 4.

Table 4 –Baseline Age Distribution in Study 20030211

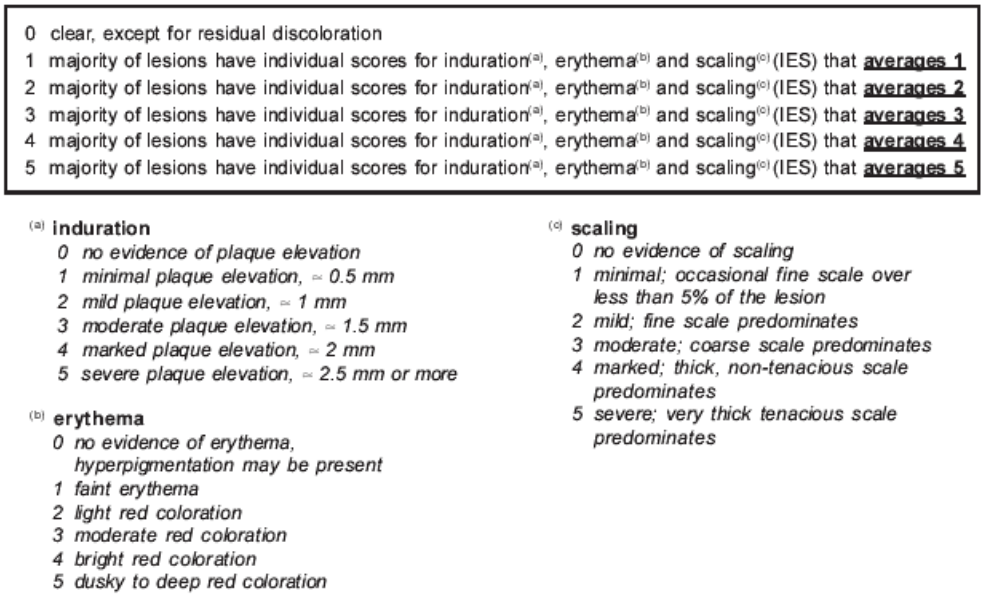
	Etanercept N=106	Placebo N=105
4-5	4 (3.8%)	5 (4.8%)
6-7	7 (6.6%)	3 (2.9%)
8-9	13 (12.3%)	15 (14.3%)
10-11	14 (13.2%)	15 (14.3%)
Total Age 4-11	38 (35.8%)	38 (36.2%)
12-13	14 (13.2%)	20 (19.0%)
14-15	19 (17.9%)	17 (16.2%)
16-17	35 (33.0%)	30 (28.6%)
Total Age 12-17	68 (64.2%)	67 (63.8%)

Source: reviewer analysis

3.2.1.2 Week 12 Efficacy Results

Efficacy was assessed using PASI, sPGA and the Children's Dermatology Life Quality Index (CLDQI). The sPGA was a 6-point scale with categories clear (0), minimal (1), mild (2), moderate (3), marked (4), and severe (5). The full scale is presented in Figure 1.

Figure 1 – Static Physician's Global Assessment (sPGA)



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The primary endpoint specified in the protocol was PASI 75 at Week 12. The secondary endpoints, which were analyzed sequentially, were PASI 50 at Week 12, success on the sPGA at Week 12 (where success was defined as clear or minimal (0 or 1)), percent improvement from baseline to Week 12 on CLDQI, and PASI 90 at Week 12. PASI 75, PASI 50, PASI 90 and sPGA success were analyzed with the Cochran-Mantel-Haenszel (CMH) test stratified on age group stratum. Subjects with missing Week 12 data or who had entered the open-label escape arm were counted as non-responders. Percent change in CLDQI was analyzed with a van Elteren stratified rank test adjusting for age group stratum. Missing data for CLDQI was handled with baseline observation carried forward.

Success on the sPGA was defined as achieving a score of 0 or 1. The inclusion criteria specified that subjects were to have sPGA ≥ 3 at baseline, thus subjects achieving a score of 0 or 1 would have a reduction of at least 2 units from baseline. However, two subjects enrolled in the study had baseline sPGA scores of 2 (mild), one on the etanercept arm and one on the placebo arm. The subject on the etanercept arm with a baseline sPGA of 2 improved to an sPGA score of 1 at Week 12 and was included in the applicant's analyses as a responder. The statistical reviewer in 2008 recommended defining responders as subjects who achieved clear or minimal on the sPGA with at least 2 grades reduction from baseline, as is typically recommended by the Division for success on physician's global assessment endpoints. Under this definition, a subject moving from sPGA 2 to 1 would not be counted as a responder. Thus the sPGA analysis where success is defined as 0 or 1 with 2 grades improvement from baseline has one fewer responders on the etanercept arm than the definition defining success as 0 or 1. The statistical analysis plan stated that the pre-specified primary and secondary endpoints would be analyzed in sequential order. All of the p-values for the primary and secondary endpoints were

<0.0001 and met the statistical significance criteria under the sequential analysis. See Table 5.

Table 5 – Efficacy Results at Week 12 in Study 20030211

	Etanercept N=106	Placebo N=105	P-value
PASI 75	60 (56.6%)	12 (11.4%)	<0.0001
PASI 50	79 (74.5%)	24 (22.9%)	<0.0001
sPGA 0 or 1	56 (52.8%)	14 (13.3%)	<0.0001
CLDQI percent improvement [mean (SD)]	52.3 (61.0)	17.5 (84.1)	<0.0001
PASI 90	29 (27.4%)	7 (6.7%)	<0.0001
sPGA 0 or 1 with 2 grades improvement	55 (51.9%)	14 (13.3%)	<0.0001

Source: pg 126-128 of \\cdsesub1\evsprod\bla103795\0060\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5351-stud-rep-contr\20030211\csr-20030211.pdf and pg 13 of Clara Kim's Statistical Review dated 4/29/2008

3.2.1.3 Efficacy Results by Baseline Severity

The applicant has requested an indication for the treatment of pediatric patients age 4 to 17 years with chronic severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The baseline disease severity is presented in Table 6.

Table 6 –Baseline Disease Severity in Study 20030211

	Etanercept N=106	Placebo N=105
sPGA		
Mild	1 (1%)	1 (1%)
Moderate	69 (65%)	68 (65%)
Marked	33 (31%)	33 (31%)
Severe	3 (3%)	3 (3%)
PASI		
Mean (SD)	18.5 (6.7)	18.6 (6.8)
Median	16.7	16.4
≤20	75 (71%)	72 (69%)
>20	31 (29%)	33 (31%)
Range	12-51.6	12-56.7
%BSA		
Mean (SD)	26.1 (15.9)	24.8 (15.0)
Median	21	20
Range	10-90	10-95

Source: pg 121 of \\cdsesub1\evsprod\bla103795\0060\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5351-stud-rep-contr\20030211\csr-20030211.pdf and pg 12 of Clara Kim's Statistical Review dated 4/29/2008 and reviewer analysis

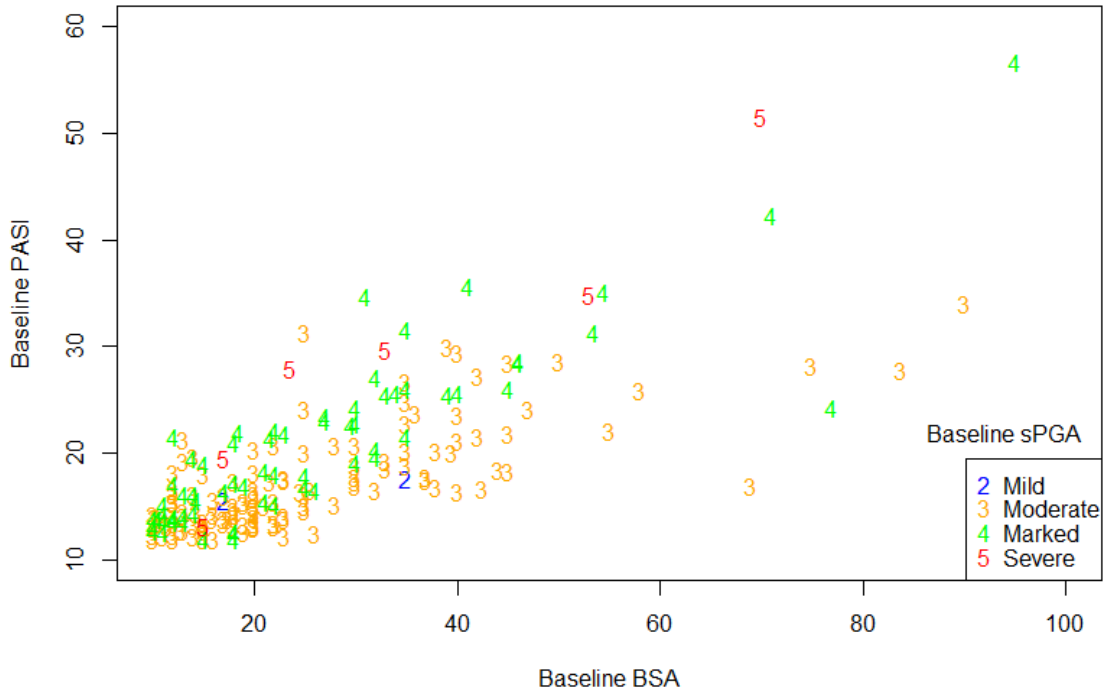
Although the Agency typically recommends that sponsors use a 5-point PGA scale for assessing psoriasis (clear, almost clear, mild, moderate, severe), the applicant's sPGA scale has an additional category (marked) that falls between moderate and severe. Thus a 'severe' score on the applicant's 6-point sPGA is not equivalent to a score of severe on a

5-point sPGA, as presumably the 'marked' category includes some subjects who would have been categorized as moderate on a 5-point scale and some who would have been categorized as severe.

A comparable sPGA scale was used in the applicant's adult psoriasis studies. According to the Enbrel labeling (http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103795s5548lbl.pdf, accessed 8/31/2016), adult psoriasis Studies I and II enrolled subjects with chronic stable psoriasis with BSA ≥ 10%, PASI ≥ 10 and who had received or were candidates for systemic antipsoriatic therapy or phototherapy. The inclusion criteria did not include a minimum score on the sPGA. Subjects in the two studies had a median baseline PASI scores ranging from 15-17 and baseline sPGA classifications ranging from 54% to 66% for moderate, 17% to 26% for marked, and 1% to 5% for severe. The inclusion criteria in Study 20030211 were slightly stricter than in Studies I and II, requiring PASI ≥ 12 rather than 10, and a minimum requirement of sPGA ≥ 3. The median PASI scores across all three studies are comparable (approximately 16) and the distributions of baseline sPGA scores are similar.

The inter-relationships of the baseline PASI, BSA, and sPGA scores in Study 20030211 are displayed in Figure 2. From this plot we can see that higher PASI scores are associated with higher BSA values, and that for a given BSA value, higher PASI scores are associated with higher sPGA values, though there is considerable overlap. The sPGA scale does not include BSA as part of the assessment.

Figure 2 – Inter-relationships between Baseline PASI, BSA, and sPGA Scores in Study 20030211 (Combined Treatments)



Source: Reviewer analysis.

The key efficacy results by baseline sPGA and baseline PASI group (≤ 20, > 20) are presented in Table 7 and Table 8. The efficacy results are generally consistent across the baseline sPGA categories, though the severe category has few subjects. The efficacy results are also consistent across the baseline PASI groups, though the PASI 75 response in subjects on the etanercept arm with higher baseline PASI scores is higher.

Table 7 – Efficacy Results at Week 12 by Baseline sPGA in Study 20030211

	Baseline sPGA	Etanercept N=106	Placebo N=105
PASI 75	Mild	1/1 (100%)	0/1 (0%)
	Moderate	36/69 (52%)	9/68 (13%)
	Marked	20/33 (61%)	3/33 (9%)
	Severe	3/3 (100%)	0/3 (0%)
sPGA 0 or 1 with 2 grades improvement	Mild	0/1 (0%)	0/1 (0%)
	Moderate	38/69 (55%)	12/68 (18%)
	Marked	16/33 (49%)	2/33 (6%)
	Severe	1/3 (33%)	0/3 (0%)

Source: pg 126-128 of \\cdsesub1\evsprod\bla103795\0060\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5351-stud-rep-contr\20030211\csr-20030211.pdf and pg 23 of Clara Kim's Statistical Review dated 4/29/2008

Table 8 – Efficacy Results at Week 12 by Baseline PASI Group in Study 20030211

	Baseline PASI	Etanercept N=106	Placebo N=105
PASI 75	≤ 20	38/75 (51%)	8/72 (11%)
	>20	22/31 (71%)	4/33 (12%)
sPGA 0 or 1 with 2 grades improvement	≤ 20	37/75 (49%)	10/72 (14%)
	>20	18/31 (58%)	4/33 (12%)

Source: reviewer analysis

3.2.1.4 Maintenance of Response in Randomized Withdrawal Period

From Weeks 13 to 36, all subjects received etanercept (0.8 mg/kg once weekly up to 50 mg). At Week 36, subjects who had achieved at least PASI 50 at Week 24 and PASI 75 at Week 36 entered a randomized withdrawal period. Subjects who met the PASI criteria were randomized 1:1 to either continue treatment with etanercept or switch to placebo. When PASI 75 response was lost, subjects resumed treatment with etanercept through Week 48. Four subjects on each treatment arm entered the randomized withdrawal period without meeting the protocol-specified efficacy response (achieving PASI 75 at Week 36). A higher proportion of subjects who continued treatment with etanercept maintained PASI 75 response than subjects who withdrew treatment through Week 48 (65% vs. 49%). See Table 9.

Table 9 – Maintenance of Response during Randomized Withdrawal Period in Study 20030211

	Etanercept N=68	Placebo N=69
Week 36	64 (94.1%)	65 (94.2%)
Week 40	54 (79.4%)	52 (75.4%)
Week 44	49 (72.1%)	40 (58.0%)
Week 48	44 (64.7%)	34 (49.3%)

Source: pg 136 of \\cdsesub1\evsprod\bla103795\0060\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5351-stud-rep-contr\20030211\csr-20030211.pdf and pg 18 of Clara Kim's Statistical Review dated 4/29/2008

3.2.2 Study 20050111

3.2.2.1 Study Design and Subject Disposition

Study 20050111 is 264-week, open-label, long-term follow-up study of subjects who completed Study 20030211. Subjects less than 18 years of age could continue follow-up past 264 weeks until their 18th birthday. Subjects received treatment with etanercept (0.8 mg/kg once weekly up to 50 mg) for at least 96 weeks. After 96 weeks, subjects with sPGA score of 0 or 1 were allowed to stop treatment. Subjects could restart treatment at the investigator's discretion. Subjects were evaluated every 12 weeks for safety and efficacy outcomes.

Of the 194 subjects who completed Study 20030211, 182 entered Study 20050111. Of these subjects, 63 (35%) completed the study through Week 264. Twenty-eight subjects remain on the study past Week 264 for subjects are not yet 18 years of age. See Table 10 and Table 11.

Table 10 – Disposition of Subjects in Study 20050111

Subjects enrolled in Study 20030211	211
Subjects completing Study 20030211	194
Completed in incomplete responders arm	*57*
Completed withdrawal/retreatment period	*137*
Subjects enrolled in Study 20050111	182
Subjects receiving treatment in Study 2005011	181
Completed Week 48	168 (92%)
Completed Week 96	140 (77%)
Completed Week 264	63 (35%)

Source: pg 59 of \\cdsesub1\evsprod\bla103795\0474\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5352-stud-rep-uncontr\20050111\csr-20050111.pdf and reviewer analysis.

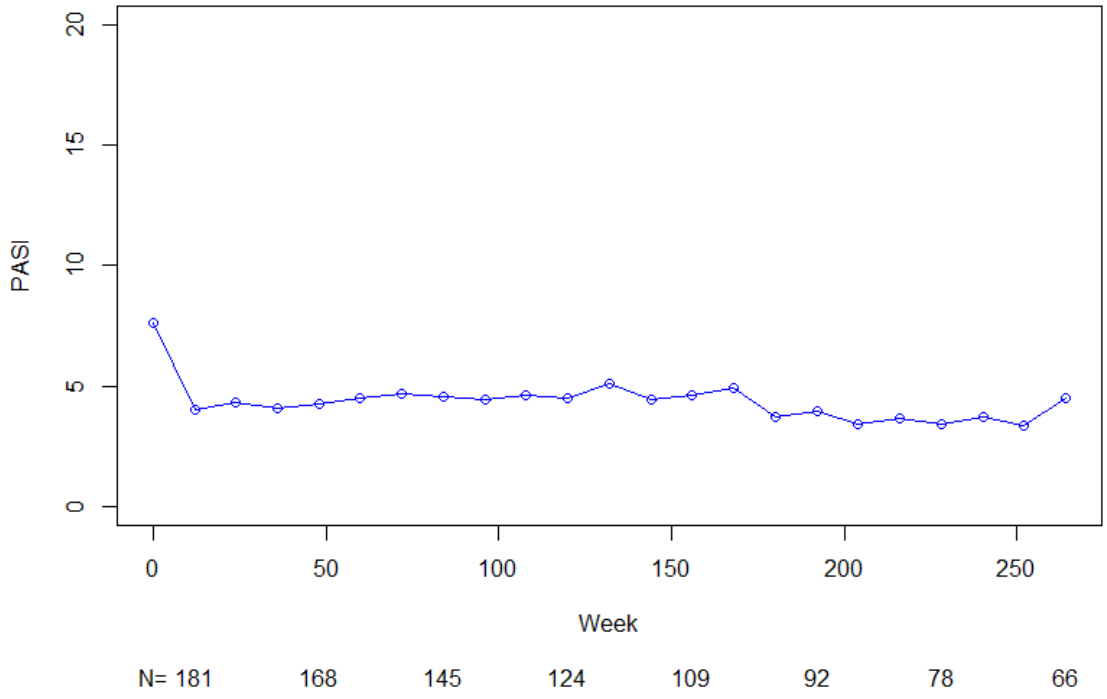
Table 11 – Reasons for Study Discontinuations in Study 20050111

	N=182
Remain on study	28 (15.4%)
Completed study	41 (22.5%)
Discontinuations	
Consent withdrawn	42 (23.1%)
Lost to follow-up	19 (10.4%)
Noncompliance	17 (9.3%)
Disease progression	7 (3.8%)
Protocol deviation	7 (3.8%)
Adverse event	5 (2.7%)
Pregnancy	4 (2.2%)
Administrative decision	2 (1.1%)
Ineligibility determined	2 (1.1%)
Other	8 (4.4%)

Source: pg 59 of \\cdsesub1\evsprod\bla103795\0474\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5352-stud-rep-uncontr\20050111\csr-20050111.pdf and reviewer analysis.

As an open-label, single-arm study, Study 20050111 did not have any pre-specified efficacy endpoints. In the study, the percent improvement in PASI and response rates like PASI 75 were calculated relative to the baseline value in Study 20030211. Because of the long duration of Study 20050111, this review will summarize the raw PASI scores over time, rather than using PASI 75, as reference to a single baseline value several years in the past may not be meaningful. The mean PASI scores by study visit (every 12 weeks) are presented in Figure 3. Mean PASI scores remained relatively constant over the course of the study among subjects who remained in the study. However, these results do not account for subjects who discontinued the study and whose outcomes are unknown. Due to the large amount of subject dropout over the course of the study, these results should be interpreted with caution.

Figure 3 – Mean PASI Score by Study Visit (Observed Cases)



Source: Reviewer analysis

3.3 Evaluation of Safety

3.3.1 Study 20030211

Refer to Clara Kim's statistical review dated April 29, 2008 for the evaluation of safety in Study 20030211.

3.3.2 Study 20050111

3.3.2.1 Extent of Exposure

The mean duration of dosing was 1224.1 days (3.4 years) out of 1848 scheduled study days. See Table 12.

Table 12 – Duration of Dosing in Study 20050111 (Days)

	Etanercept N=181
Mean (SD)	1224.1 (608.1)
Median	1304
Min, Max	56, 1927

Source: pg 98 of \\cdsesub1\evsprod\bla103795\0474\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5352-stud-rep-uncontr\20050111\csr-20050111.pdf and reviewer analysis.

At Week 96, subjects who achieved an sPGA score of 0 or 1 were permitted to pause dosing. Six subjects paused dosing. Two subjects did not restart dosing, and were followed for an additional 85 and 176 weeks respectively. Four subjects paused dosing for between 8 and 13 weeks, including one subject who paused dosing prior to Week 96 (Week 94) against the protocol.

Table 13 – Subjects who Paused Dosing at or after Week 96 due to sPGA Response

Subject ID	Week Stopped	Week Re-started
502007	135	NA (followed through Week 220)
508002	116	124
532001	98	NA (followed through Week 274)
555004	94	103
556007	96	109
556010	96	109

Source: reviewer analysis

3.3.2.2 Adverse Events

The majority of subjects experienced at least one adverse event in Study 20050111. Three percent of subjects had a grade 3 infection and 1% of subjects had a serious infection. Nine percent of subject had an injection site reaction. See Table 14.

Table 14 – Adverse Events in Study 20050111

	Etanercept N=181
At least 1 adverse event	161 (89%)
At least 1 non-infectious adverse event	149 (82%)
At least 1 infection	140 (77%)
At least 1 grade 3 non-infectious adverse event	14 (8%)
At least 1 grade 3 infection	5 (3%)
At least 1 serious non-infectious adverse event	5 (3%)
At least 1 serious infection	2 (1%)
At least 1 non-infectious adverse event leading to withdrawal from study	5 (3%)
At least 1 infection leading to withdrawal from study	1 (<1%)
At least 1 injection site reaction	16 (9%)

Source: pg 73 of \\cdsesub1\evsprod\bla103795\0474\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5352-stud-rep-uncontr\20050111\csr-20050111.pdf and reviewer analysis.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, Age, and Geographic Region

Refer to Clara Kim's statistical review dated April 29, 2008 for the subgroup evaluation in Study 20030211.

4.2 Other Special/Subgroup Populations

Refer to Clara Kim's statistical review dated April 29, 2008 for the subgroup evaluation in Study 20030211.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The applicant has evaluated the safety and efficacy of Enbrel in 211 pediatric psoriasis subjects age 4 to 17 years. The subjects were followed for up to 48 weeks in Study 20030211 and for up to an additional 264 weeks in Study 20050111. Efficacy relative to placebo was demonstrated in Study 20030211 for PASI 75 and response on the sPGA at Week 12 ($p<0.0001$). Study 20030211 enrolled 76 subjects age 4 to 11 years and 135 subjects age 12 to 17 years. Although all subjects were supposed to have a baseline sPGA score of 3 or higher, two subjects entered the trial with a score of 2 (mild). One subject treated with etanercept with a baseline sPGA of 2 improved to a sPGA score of 1 at Week 12. The applicant treated this subject as a responder (their definition of sPGA success was to achieve a score of clear (0) or minimal (1)). This subject is treated as a failure in the FDA analyses as the subject did no improve by at least 2 grades.

5.2 Conclusions and Recommendations

Study 20030211 demonstrated the efficacy of Enbrel in subjects age 4 to 17 years with moderate to severe plaque psoriasis. Subjects were followed for up to 48 weeks in Study 20030211 and for up to an additional 264 weeks in 20050111. The efficacy results for PASI 75 and sPGA success at Week 12 are presented in Table 15. Efficacy was consistent across different levels of baseline severity, as determined by both baseline sPGA and baseline PASI scores.

Table 15 – Efficacy Results at Week 12 in Study 20030211

	Etanercept N=106	Placebo N=105	P-value
PASI 75	60 (56.6%)	12 (11.4%)	<0.0001
sPGA 0 or 1 with 2 grades improvement	55 (51.9%)	14 (13.3%)	<0.0001

In the long-term follow study (Study 20050111), the majority of subjects (77%) completed at least 2 years of follow-up and 35% completed the planned 5 years of follow-up.

Signatures/Distribution List

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