Responses to ENBREL in Part 1: Open label.

Results of patients receiving open-label ENBREL for 3 months are summarized in Table 26. Last observation ·rried forward analysis is used, classifying dropouts as non-responders. In the second analysis, the JRA DOI ıdated by Giannini et. al. (Giannini 1997) is used (LOM, irrespective of pain or tenderness). In the final analysis, the 13 protocol violators are all categorized as non-responders.

Table 26: Number (%) of Patients Achieving 30%, 50% and 70% JRA Definition of Improvement (DOI) at Day 90.

JRA DOI	Immunex JRA DOI (n= 69)	Giannini JRA DOI (n = 69)	Protocol violators Categorized as Non responder (n = 69)
30%	52 (75)	48 (70)	41 (59)
50%	44 (64)	39 (56)	35 (51)
70%	25 (36)	21 (30)	21 (30)

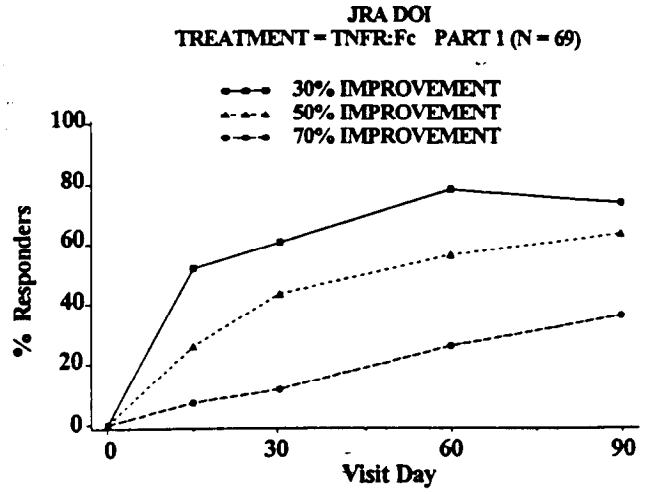
Median 90 day responses for the individual components of the JRA DOI, as well as other parameters of JRA disease activity, were also analyzed by CBER and are shown in Table 27.

Table 27: Disease Activity Measures at Baseline and Day 90 and Percent Improvement at Day 90 from Baseline (Median Values and [Interquartile Range]): Part 1, Enbrel

Parameter	Baseline (N = 69)	Day 90 (N = 64)	Percent Improvement (N = 69)
`A Core Set Criteria			
.al active joint count	28 [18, 37]	13 [6, 23]	56 [30, 76]
Joints w/ LOM + P/T	10 [4, 19]	2 [0, 8]	76 [24, 100]
MD global assessment	7 [5, 8]	2 [1, 5]	60 [29, 80]
Parent/pt global assess	5 [3, 7]	2 [1, 4]	50 [0, 100]
CHAQ	1.4 [1, 2.2]	0.88 [0.12, 1.5]	37 [15, 71]
ESR	35 [23, 62]	20 [8, 42]	50 [11, 70]
Additional Assessments			
CRP	3.5 [1.3, 9.3]	0.8 [0.1, 4.2]	60 [0, 93]
Articular Severity Score	88 [65, 133]	45 [26, 77]	50 [24, 67]
Morning stiffness duration	45 [25, 120]	30 [15, 30]	200 [0, 1800]
Pain (VAS)	3.6 [1.8, 5.4]	1.4 [0.2, 3.3]	63
Swollen joints	25 [16, 32]	9 [5, 12]	57 [24, 80]
Joints with LOM	23 [17, 35]	15 [10, 26]	22 [5, 54]

The time courses of responses for Part 1 of the study are shown in Figure 2. Clinical responses were evident as early as 2 weeks after initiating ENBREL therapy. The median time to JRA DOI 30% response was 17 days. The percent of patients achieving a JRA DOI 30% response peaked at month 2..

Figure 2: Percent of Patients with JRA Definition of Improvement 30%, 50% and 70% Responses in Part 1.



CBER also analyzed whether JRA DOI responses at 90 days varied by demographic factors or baseline disease activity. CBER found no differences in JRA 90 day response rates, using the JRA DOI, in any subset analysis (see Tables 28 - 40).

Table 28: 90 Day Responses in Part 1 by Disease Onset Subset.

Onset Subset:	JRA DOI 30% Responses at Day 90 n (%)
Pauciarticular	3 / 7 (43%)
lyarticular	32 / 40 (80%)
,temic	17 / 22 (77%)

P = 0.11 by Chi Square

Table 29: 90 Day Responses in Part 1 by Age

Age (years)	JRA DOI 30% Responses at Day 90, n (%)
4 – 8	15/19 (79)
> 8 – 13	1320 (65)
> 13- 17	24/30 (80)

P = 0.44 by Chi Square test. Logistic Regression Analysis: OR = 0.996 ± 1.07, P = 0.96

Table 30: 90 Day Responses in Part 1 by Baseline Weight and Body Surface Area (Logistic Regression Analysis)

	Odds Ratio	P value
Weight	1.02 ± 1.02	0.23
Body Surface Area	2.3 ± 2.2	0.28

Table 31: 90 Day Responses in Part 1 by Gender

Gender	JRA DOI 30% Responses at Day 90, n (%)
Female	34/43 (79)
Male	18/26 (69)

= 0.36 by Chi Square. Logistic Regression Analysis: OR = 0.77 ± 1.33, P = 0.36

Table 32: 90 Day Responses in Part 1 by Study Site:

Study Site Number	JRA DOI 30% Responses at Day 90, n (%)
31	8/10 (80)
[illegible]	2/ 6 (33)
[illegible]2	4/ 7 (57)
242	4/ 5 (80)
502	3/ 5 (60)
503	14/15 (93)
504	7/ 9 (78)
506	2/ 2 (100)
514	8/10 (80)

P = 0.19 by Chi Square test.

Table 33: 90 Day Responses in Part 1 by Baseline Rheumatoid Factor status.

Rheumatoid factor status	JRA DOI 30% Responses at Day 90, n (%)
Positive	12/15 (80)
Negative	40/53 (76)

P = 0.20 by Chi Square

Table 34: 90 Day Responses in Part 1 by Race

Race	JRA DOI 30% Responses at Day 90, n (%)
Caucasian	14/52 (75)
Non-Caucasian	14/17 (82)

P = 0.44 by Chi Square.

ble 35: 90 Day Responses in Part 1 by Disease Duration (Logistic Regression Analysis)

	Odds Ratio	P value
Disease Duration	0.96 ± 1.08	0.64

Table 36: 90 Day Responses in Part 1 by Baseline Corticosteroid Use

Corticosteroid Use at Baseline	JRA DOI 30% Responses at Day 90, n (%)
Yes	33/44 (75)
No	19/25 (76)

P = 0.93 by Chi Square, Logistic Regression Analysis: OR = 1.03 ± 1.34, P = 0.93.

Table 37: 90 Day Responses in Part 1 by Baseline NSAID Use

NSAID Use at Baseline	JRA DOI 30% Responses at Day 90, n (%)
Yes	50/66 (76)
No	2/ 3 (67)

P = 0.72 by Chi Square

Table 38: 90 Day Responses in Part 1 by Baseline Active Joint Count

Baseline Active Joint Count	JRA DOI 30% Responses at Day 90, n (%)
9 – 23	20/25 (80)
24 – 33	16/21 (76)
[illegible]4	16/23 (70)

[illegible] = 0.70 by Chi Square test. Logistic Regression Analysis: OR = 0.99 ± 1.02, P = 0.60

Table 39: 90 Day Responses in Part 1 by Baseline CHAQ

Baseline CHAQ	JRA DOI 30% Responses at Day 90, n (%)
– 1	13/17 (76)
1 – 2	23/29 (79)
> 2 – 3	16/23 (70)

P = 0.71 by Chi Square test. Logistic Regression Analysis: OR = 0.98 ± 1.4, P = 0.94.

Table 40: 90 Day Responses in Part 1 by Baseline ESR and CRP (Logistic Regression Analysis)

	Odds Ratio	P value
ESR	0.98 ± 0.99	0.051
CRP	0.95 ± 1.03	0.119

Antibodies to Product.

None of the 69 JRA patients developed anti-ENBREL antibodies, detected by an ELISA.

D. Summary.

In a randomized withdrawal trial of Enbrel in polyarticular course JRA in which patients had moderate to severe disease activity and were intolerant of or failed therapy to MTX and responded to a 3 month trial of open-label Enbrel, patients continuing on Enbrel had a lower rate of flares compared to patients randomized to placebo. In addition, patients continuing on Enbrel had higher response rates from day 90 to day 120, as defined by the JRA DOI 30%, compared to patients receiving placebo during this period.

Overall, the results of the univariate and multple logistic regression analyses suggest that a higher baseline ESR is associated with a higher likelihood of disease flare, for both ENBREL and placebo-treated patients. Girls may be more likely to flare than boys, although this effect was stronger in the placebo arm and therefore has limited extrapolation to a clinical setting.

Differences in flare or response rates were not detected in any other clinical or demographic parameter examined, although the power to conduct such subset analyses is limited.

Specifically no differences were detected based upon disease onset type (pauciarticular, polyarticular or systemic JRA), or in rheumatoid factor status.

Enbrel appears to have comparable responses at 90 days for polyarticular course JRA as in adult RA, although the data are open-label.

IV. SAFETY ANALYSIS.

Safety data are available from 69 JRA patients ages 4 – 17 years of age. Three-month data is available from all patients and 7-month data is available from the 25 patients who received ENBREL in part 2. One major difficulty in the adverse event analysis is that randomized adverse event data is only available in part 2 of the study, but the majority of adverse events occurred within the first 3 months of study in which no comparator arm is available. Adverse event (AE) data was obtained by review of patient diary and histories, physical examinations, laboratories (chemistries, hematology, urinalysis, and autoantibodies). The NCI Common Toxicity Criteria was modified for pediatric use to grade the severity of adverse events. A separate infectious disease questionnaire was used to capture infectious disease severity. Adverse events were classified using Modified Coding Symbols for a Thesaurus of Adverse Reaction Terms dictionary (COSTART 1990).

The extent of study drug exposure is shown in Table 41, and contrasts to 531 patients with adult RA exposed to ENBREL for 17,148 patient weeks. Analysis of JRA safety is focused on 3-month data available in 69 patients, because of the larger patient sample available in the open label phase of the study. Additional analyses included comparison of adverse events in the ENBREL arm (n=25) to the placebo arm (n=26) in part 2 (4 months); however, the incidence of adverse events was decreased in part 2 of the study compared to part 1. Finally, the number of adverse events and event rates are compared in the 69 JRA patients receiving 3 months of ENBREL to the 349 adult RA patients receiving ENBREL in placebo-controlled clinical trials. In this analysis, it is important to keep in mind that the duration of exposure in the JRA population is generally shorter (3 months) than the majority of patients with adult RA (6 months exposure), and thus event rate accounts for differences in time of exposure. The adult RA studies are also complicated by the fact that some patients received a dose equivalent that was lower (10 mg) than 0.4 mg/kg (adult equivalent 25 mg) administered to the JRA patients, and that 59 adult RA patients also received methotrexate in combination with ENBREL.

Table 41: Study Drug Exposure in JRA

	- Part 1 --	---------Part 2 ------	
Measurement	TNFR:Fc (n = 69)	Placebo[a] (n = 26)	TNFR:Fc (n = 25)
Patient-months on study	195	44	82
No. of doses (mean)	25	15	29
Mean cumulative dose (mg) per patient	354	254	361
Mean cumulative dose (mg/kg)	10	6	12
Mean days on study drug	86	51	100

a.For descriptive purposes only. Patients received placebo in Part 2.

A. Deaths and serious adverse events

No JRA patients died during the course of the clinical trial or in follow-up available in the open-label extension protocol, 16.0018. No children have developed a malignancy to date. Eight patients had a serious adverse event in the course of the study 16.0016, one patient was hospitalized for a procedure, and one patient discontinued ENBREL secondary to an adverse event (urticaria) [Table 42]. In the open-label extension protocol, 2 patients developed clinical symptoms consistent with aseptic meningitis secondary to varicella infection, and 7 other serious adverse events occurred.

Table 42: Severe Adverse Events (SAE), Safety Related Discontinuations, and Hospitalizations.

Dose Group (No. of pts)	Patient Number	SAE, Discontinuation or Hospitalization	Day	Grade
Part 1, 0.4 mg/kg Enbrel (n = 69)	—	Gastroenteritis and flu- required IV fluids in ER X 3 days	89	3
	—	Gastroenteritis X 2, required IV fluids in clinic and ER	50, 123	3, 3
	—	Urticaria (generalized); after first dose- pt discontinued trial	1	2

	—	Major depressive episode w/ aggressive/ violent behavior, personality disorder, situational - hospitalized	89	3
	—	Ulcer on face from scratch, ? spider bite, hyperpigmentation remains	50	3
	—	Vertebral compression fracture (unrelated)	61	3
	—	Fracture, right humerus, hospitalized (unrelated)	42	3
	—	Corticosteroid injection of Baker's cyst (unrelated)	66	
Part 2, Enbrel (n = 25)	—	Removal of preexisting tongue ulcer, biopsy benign (unrelated)	130	3
Protocol 16.0018 (Open Label Extension)	—	Aseptic meningitis 9 days after varicella.		3
		C1-C2 subluxation, vertebral artery compression and thrombosis (unrelated)		4
	—	Lethargy, HA, nausea, vomiting, and fever X 5 days, 9 d after varicella		1
	—	Epigastric pain and heme + stools X 25 days, preexisting. Hospitalized X 2	298	3
	—	Esophagitis and gastritis (bx), hospitalized X 2, preexisting recurrent peptic ulcer disease and GE reflux	282	3
	—	Appendicitis (unrelated)	113	
	—	Arthritis flare (unrelated)	320	

B. Non-Infectious Adverse Events.

The majority of non-infectious adverse events in the JRA trial were grade 1, with some grade events. Vomiting was more common in Enbrel-treated compared to placebo-treated patients in part 2 of the study (Table 43). No other differences between Enbrel and placebo-treated patients were observed; however the majority of adverse events occurred in part 1 of the study. In comparing adverse events from part 1 of the JRA trial (in 69 patients) to the 349 adult RA patients receiving Enbrel in controlled clinical trials, headache, rhinitis, nausea, vomiting, abdominal pain, and injection site hematomas were observed more frequently in JRA than adult RA patients. JRA patients had received 3 months on Enbrel exposure, whereas adult RA patients had more often received 6 months of Enbrel exposure, and 59 adult RA patients had received Enbrel in combination with MTX. When accounting for differences in time of exposure, using an event rate analysis, all the above mentioned adverse events, as well as somnolence, were observed more frequently in JRA patients compared to adult RA patients. The gastrointestinal adverse events did not correlate with the dose of naproxen sodium, the most common NSAID used in the JRA trial.

Table 43: Non-Infectious Adverse Events

	Frequency of Non-Infectious Adverse Events in Protocol 16.0016, n (%)		Percent of JRA vs. Adult RA Patients with Non-Infectious Adverse Events N, %, [Event Rate per Year]*	
Event	Part 2, 16.0016 N = 26 N (%) [Pt yrs]	Part 2, 16.0016 N = 25 N (%) [Pt yrs]	Part 1, 16.0016, JRA N = 69 N (%) [Pt years] [16.25 patient years]	Adult RA N = 349 N (%) [Pt years] [117 patient years]
None	18 (69)	12 (48)	13 (19)	
Any	8 (31)	13 (52)	37 (81)	
Headache	3 (12) [0.09]	5 (20) [0.09]	**28 (41)[1] [1.66][1]**	**59 (17)[1] [0.68][1]**
Rhinitis	1 (4) [0.02]	5 (20) [0.06]	**19 (28)[2] [1.23][1]**	**42 (12)[2] [0.45][1]**
Nausea	0	2 (8) [0.04]	**15 (22)[3] [0.98][1]**	**35 (10)[3] [0.30][1]**
Vomiting	**0 (0)[1]**	**5 (20)[1] [0.06]**	**12 (17)[1] [0.74][1]**	**10 (3)[1] [0.09][1]**
Rash	3 (12) [0.07]	1 (4) [0.07]	10 (14) [0.43]	25 (7) [0.21]
Abdominal pain	1 (4) [0.06]	3 (12) [0.04]	**10 (14)[4] [0.74][1]**	**20 (6)[4] [0.17][1]**
Asthenia	2 (8) [0.05]	1 (4) [0.01]	6 (9) [0.37]	19 (5) [0.16]
Accidental Injury	6 (9) [0.03]	1 (4) [0.02]	6 (9) [0.37]	12 (3) [0.10]
Diarrhea	5 (7) [0.03]	0	**5 (7) [0.31]**	32 (9) [0.27]
Cough	4 (6) [0.02]	1 (4) [0.02]	4 (6) [0.25]	21 (6) [0.18]
Hematoma, injection site	3 (4) [0.02]	0	**4 (6)[1] [0.18][2]**	**0 (0)[1] [0.00][2]**
Mouth ulcer	4 (6) [0.02]	0	4 (6) [0.18]	10 (3) [0.09]
Pharyngitis	4 (6) [0.02]	0	4 (6) [0.31]	28 (8) [0.24]
Dizziness	3 (4) [0.02]	0	3 (4) [0.18]	25 (7) [0.21]
Edema	3 (4) [0.02]	0	3 (4) [0.12]	3 (1) [0.03]
ack pain	2 (3) [0.01]	0	2 (3) [0.12]	10 (3) [0.09]
Fever	2 (3) [0.01]	1 (4) [0.02]	2 (3) [0.12]	9 (3) [0.08]
Somnolence	2 (3) [0.01]	0	2 (3) **[0.12][5]**	1 (0.3) **[0.01][5]**

* Frequency of adverse events may be higher than percent of patients with a particular event, since in the latter calculation patients with more than one event are counted only once.
b. Malaise was not coded in adults; events of malaise were coded to asthenia.

[1]P < 0.001, [2]P = 0.002, [3]P = 0.011, [4]P = 0.020, [5]P = 0.041

C. Infectious Adverse Events.

Sixty-two percent of 69 JRA patients receiving Enbrel developed an infection during the first 3 months of study (Table 44). Ninety-percent of the infectious adverse events were grade 1, with remainder scored as grade 2 (Table 44, 46). There was a trend towards more frequent upper respiratory infections (URI) in the Enbrel-treated patients compared to placebo in part 2 of the study. There was no significant difference in event rates of any infection between placebo and Enbrel-treated JRA patients in part 2 of the study. However, the majority of infectious adverse events occurred in the first 3 months (open-label) phase of the study. In comparing the 25 JRA patients who received 6 months of Enbrel at 0.4 mg/kg to the 78 adult RA patients receiving the same duration and equivalent dose of Enbrel (25 mg), JRA patients had more infectious episodes per patient during 6 months of Enbrel therapy than adult RA patients (Table 46). Pharyngitis and gastroenteritis were more frequent in the JRA than adult RA patients receiving equivalent exposures to Enbrel, and there was a trend towards more URI in the JRA than adult RA patients (Table 44,45). Differences in season of exposure and frequency of these events in normal children compared to normal adults are not accounted for in this analysis.

Table 44: Frequency of Infectious Adverse Events, n (%) [Events per patient month].

	Part 1, 16.0016	Part 2, 16.0016	Part 2, 16.0016	Part 1 & 2, 16.0016	16.0009
ent	N=69 195 patient months N (%) [Pt yrs]	Placebo N=26 44 patient months N (%) [Pt yrs]	Enbrel N=25 82 patient months N (%) [Pt yrs]	6 months Enbrel, JRA (0.4 mg/kg) N=25 N (%)	6 months Enbrel, Adult RA (25 mg) N=78 N (%)
None	26 (38)	18 (69)	12 (48)	6 (24)	33 (42)
Any	43 (62) [0.38]	8 (31) [0.28]	13 (52) [0.33]	19 (76)	45 (58)
URI	33 (48) [0.17]	**6 (23)[1] [0.14]**	**13 (52)[1] [0.16]**	**14 (56)*[2]**	**26 (33)[2]**
Pharyngitis	11 (16) [0.06]	0	3 (12) [0.04]	**6 (24)[3]**	**2 (3)[3]**
Gastroenteritis	9 (13) [0.04]	1 (4) [0.02]	4 (16) [0.05]	**7 (28)[4]**	**1 (1)[4]**
Otitis media	8 (12) [0.04]	2 (8) [0.05]	1 (4) [0.01]	0	2 (3)
Sinusitis	3 (4) [0.02]	1 (4) [0.02]	0	0	9 (12)
Conjunctivitis	3 (4) [0.02]	0	0	0	2 (3)
Flu	1 (1) [0.01]	2 (8) [0.05]	1 (4) [0.01]	2 (8)	3 (4)
Skin infection	1 (1) [0.01]	0	0	0	2 (3)
Salivary Gland	1 (1) [0.01]	0	0	0	1 (1)
Vaginitis	1 (1) [0.01]	0	0	0	4 (5)
Viral stomatitis	1 (1) [0.01]	0	0	0	0
Bronchitis	0	0	1 (4) [0.01]	0	3 (4)
nea pedis	0	0	2 (8) [0.02]	2 (8)	0

[1] = 0.065 [2] P = 0.074 [3] P = 0.002, [4] P < 0.001.

*Number of patients with URI; each patient counted once per event. Total number of URIs = 30.

** Cystitis, abscess, gingival/dental, herpes zoster, pneumonia, prostatitis, cellulitis, tracheitis, urethritis are infections seen in adult RA (16.009), but not JRA (16.0016).

Table 45: Frequency and Grade of URIs.

	Part 1, 16.0016	Part 2, 16.0016	Part 2, 16.0016	Part 1 & 2, 16.0016	16.0009
Parameter	N=69 n (%)	Placebo N=26 n (%)	Enbrel N=25 n (%)	6 months Enbrel, JRA (0.4 mg/kg) N=25 n (%)	6 months Enbrel, Adult RA (25 mg) N=78 n (%)
None	45 (65)	22 (84)	14 (56)	10 (40)	52 (67)
Any	24 (35)	**6 (23)[1]**	**13 (52)[1]**	**14 (56)[2]**	**26 (33)[2]**
Number / Patient					
1	16 (23)	2 (8)	9 (36)	8 (32)	18 (23)
2	5 (7)	2 (8)	1 (4)	5 (20)	7 (9)
3	1 (1)	0	1 (4)	0 (0)	1 (1)
4	1 (1)	0	0	1 (4)	0
5	0	0	0	1 (4)	0
Intensity					
Grade 1	31 (94)	6 (100)	12 (86)	27 (96)	25 (96)
ade 2	2 (6)	0	2 (14)	1 (4)	1 (4)
ade 3 or 4	0	0	0	0	0

[1] P = 0.065 [2] P = 0.074

Table 46: Frequency and Grade of Infections.

	Part 1, 16.0016	Part 2, 16.0016	Part 2, 16.0016	Part 1 & 2, 16.0016	16.0009
Parameter	**N=69** **n (%)**	**Placebo N=26** **n (%)**	**Enbrel N=25** **n (%)**	**6 months Enbrel, JRA (0.4 mg/kg) N=25** **n (%)**	**6 months Enbrel, Adult RA (25 mg) N=78** **n (%)**
None	26 (38)	18 (69)	12 (48)	6 (24)	33 (42)
Any	43 (62)	8 (31)	13 (52)	19 (76)	45 (58)
Number / Patient					
1	24 (35)	4 (15.5)	8 (32)	**10 (40)**[1]	**26 (33)**[1]
2	11 (16)	4 (15.5)	1 (4)	**3 (12)**	**11 (14)**
3	4 (6)	0	2 (8)	**1 (4)**	**6 (8)**
4 – 6	3 (5)	0	2 (8)	**5 (20)**	**0**
7 – 10	0	0	0	**0**	**2 (2)**
Intensity					
Grade 1	63 (90)	11 (92)	22 (92)	40 (91)	41 (91)
Grade 2	7 (10)	1 (8)	2 (8)	4 (9)	4 (9)
Grade 3 or 4	0	0	0	0	0

[1] P = 0.007 for overall distribution

D. Injection Site Reactions and Immune-Mediated Adverse Events.

Thirty-nine percent of Enbrel-treated JRA patients developed an injection site reaction within the first three months of exposure to Enbrel (Table 47). Seventy-percent of injection site reactions were grade 2, with the remainder scored as grade 1. The average number of injection site reactions was 4.5 per patient in the first 3 months of study. The mean time to first occurrence was 16 days, and mean duration of an injection site reaction was 2 days. In part 2 of the JRA study, injection site reactions were more common in Enbrel treated JRA patients than placebo (part 2), when examining event rates. However, most injection site reactions occurred within the first 3 months. The frequency injection site reactions does not differ between JRA and adult RA patients receiving equivalent exposures of Enbrel (6 months at 0.4 mg/kg, 25 mg maximum). JRA patients were more likely to have grade 2 injection site reactions compared to patients with adult RA, which were more often grade 1 in intensity (Table 47). - Two patients developed urticaria: one patient developed grade 2 urticaria after the first dose of Enbrel and withdrew from the study; a second patient developed grade 1 urticaria on day 9, which did not recur.

ble 47. Frequency and Grade of Injection Site Reactions.

	Part 1, 16.0016	Part 2, 16.0016	Part 2, 16.0016	Part 1 & 2, 16.0016	16.0009
Parameter	**N=69 195 patient months N (%) [Pt yrs]**	**Placebo N=26 44 patient months N (%) [Pt yrs]**	**Enbrel N=25 82 patient months N (%) [Pt yrs]**	**6 months Enbrel, JRA (0.4 mg/kg) N=25**	**6 months Enbrel, Adult RA (25 mg) N=78**
None	42 (61)	25 (96)	24 (96)	14 (56)	40 (51)
Any	27 (39) [0.62]	1 (4) [0.16]	1 (4)[0.39]	11 (44)	38 (49)
Mean No./Patient	4.5	7.0	3.2		
No. events/ no. doses	0.07	0.02	0.04		
Mean event duration (days)	2.1	2.6	1.3		
Number / Patient					
1 – 5	21 (30)	0	0	9 (36)	24 (31)
6 – 10	3 (4)	1 (4)	0	1 (4)	4 (5)
> 10	3 (4)	0	1 (4)	1 (4)	10 (13)
ɛensity					
Grade 1	39 (30)	0	0	**6 (9)[1]**	**14 (37)[1]**
Grade 2	89 (70)	7 (100)	27 (100)	**63 (91)[1]**	**24 (63)[1]**
Grade 3 or 4	0	0	0	0	0

[1]P< 0.001

E. Autoantibodies and autoimmune disease.

Several patients developed new positive anti- ds-DNA, ANA, rheumatoid factor, or caridiolipin antibodies, tested by ELISA assays, while receiving Enbrel (Table48). One patient developed anti-U1RNP autoantibodies. The frequency of new positive autoantibodies did not differ between placebo and Enbrel patients (part 2), or between JRA and adult RA patients receiving equivalent exposures of Enbrel. – None of the patients with these new autoantibodies have demonstrated signs of a related connective tissue disease (SLE, MCTD, thrombotic events). Nine patients testing positive for anti-ds-DNA antibodies in an ELISA assay were negative for anti-ds-DNA using more specific testing with a Crithidia assay.

Three patients developed vasculitic rashes, not associated with the development of autoantibodies. Two patients had rashes that were clinically consistent with the rash of systemic JRA and were associated with flares of arthritis. A third patient developed a vasculitic rash on day 113, which upon examination of the patient's chart, was described further as hyperhydrosis at the site of a wrist splint. Skin biopsies were not performed in these patients.

Table 48. Frequency of autoantibodies, n (%) in Protocol 16.0016.

	Part 1, 16.0016	Part 2, 16.0016	Part 2, 16.0016	Part 1 & 2, 16.0016	16.0009
·ameter	N=69	Placebo N=26	Enbrel N=25	7 months Enbrel, JRA (0.4 mg/kg) N=25	6 months Enbrel, Adult RA (25 mg) N=78
	N (%)	N (%)	N (%)	N (%)	N (%)
ds-DNA*					
New pos ds-DNA	2 (3)	1 (4)	2 (8)	2 (8)	9 (12)
Positive ds-DNA	4 (6)	2 (8)	2 (8)	3 (12)	15 (19)
ANA					
New pos ANA	3 (4)	3 (11)	2 (8)	3 (12)	9 (12)
Positive ANA	11 (16)	3 (11)	5 (25)	6 (24)	27 (35)
ENA					
New pos ENA	1** (1)	0	0	0	
Positive ENA	2 (3)	0	0	1 (4)	
RF					
New pos RF	5 (7)	1 (4)	1 (4)	2 (8)	
Positive RF	18 (26)	5 (25)	5 (32)	8 (32)	
Cardiolipin					
New pos ACLA IgG	3 (4)	0	1 (4)	2 (8)	
sitive ACLA IgG	8 (12)	0	3 (12)	4 (16)	
w pos ACLA IgM	0	0	0	0	
Positive ACLA IgM	2 (3)	1 (4)	0	1 (4)	

* 9 patients positive for ds-DNA are all negative on Crithidia testing
** Positive U1RNP

F. Laboratory Toxicities.

There was no significant difference in laboratory abnormalities occurred between placebo and Enbrel treated patients. Grade 3 toxicities were due to active JRA, or in the case of a rise in bilirubin due to underlying Gilbert's syndrome, and were generally preexistent. In patients not receiving prednisone, five episodes of Grade 2 lymphopenia occurred; one was persistent.

Table 49. Laboratory Toxicities – Part 2 (Placebo and TNFR:Fc Patients)

Parameter	Grade	Range	Placebo n = 25 n (%)	TNFR:Fc n = 25 n (%)
Hematology				
ANC low	1	≥ 1.5 to < 2.0 x 1000 cells/cmm	1 (4)[a]	3 (12)
Hemoglobin low	1	≥ 10 to < N g/dL	5 (21)[a]	5 (20)
	2	≥ 8.0 to < 10 g/dL	2 (8)[a]	6 (24)
	3	≥ 6.5 to < 8.0 g/dL	1 (4)[a]	0
Lymphocytes low	1	≥ 1.0 to < 1.5 x 1000 cells/cmm	5 (21)[a]	1 (4)

	2	≥ 0.5 to < 1.0 x 1000 cells/cmm	3 (13)[a]	3 (12)
WBC low	1	≥ 3.0 to < 4.0 x 1000/cmm	0[a]	3 (12)
Blood chemistry				
Albumin low	1	≥ 3.0 to ≤ 3.5 g/dL	6 (24)	2 (8)
	2	≥ 2.6 to < 3.0 g/dL	1 (4)	4 (16)
Creatinine high	1	> N to < 1.5 x N	0	1 (4)
SGOT (AST) high	1	> N to ≤ 2.5 x N IU/L	0	4 (16)
SGPT (ALT) high	1	> N to ≤ 2.5 x N IU/L	1 (4)	2 (8)
Total bilirubin high	3	≥ 1.5 x N to ≤ 3.0 x N mg/dL	1 (4)[b]	0

Note: N = upper or lower limit of normal.

a. n = 24. (Laboratory tests were not done during Part 2 on Patient No. — parental consent was withdrawn for the patient's participation in the study, and the patient was prematurely discontinued on Day 99 after three doses of placebo.)

b. Patient had Gilbert's Syndrome.

Table 50. Patients with Grade 3/4 Laboratory Toxicities at Baseline or During Study

		Toxicity Grade			
	Patient		Part 1	Part 2	
Parameter	No.	Baseline	TNFR:Fc	Placebo	TNFR:Fc
Low hemoglobin		3	4	--	2
		1	3	N/A	N/A
		3	2	2	--
		2	2	3	--
		3	3	N/A	N/A
Low albumin		3	3	--	2
		2	3	N/A	N/A
		3	3	2	--
High total bilirubin		2	3	3	--

Note: N/A = not applicable. Patient Nos — were not randomized to Part 2 of the study.

G. Additional Safety Information.

Responses to Immunizations: Two patients received during the trial (day 15 and day 76, respectively). Both patients had greater than 4 fold rise in antibody titer compared with baseline and convalescent serum results of greater than 40 Units to all 3 antigens in the vaccine.

Subset analyses for adverse events.

The proportion of patients with headaches, gastrointestinal intolerance,or certain infections (URIs, pharyngitis, gastroeneteritis) does not differ by age, weight, JRA onset type or RF status (Tables 51, 52).

Table 51. Percent (n/N) of Patients with Adverse Events by Demographic Subsets (All Patients in Part 1 of the Study; N = 69)

	Age Group (years)			Weight (kg)			
Event	< 10	≥ 10	p-value[a]	< 21	21 – 35	> 35	p-value[a]
Headache	11 (3/28)	27 (11/41)	0.11	5 (1/20)	29 (6/21)	25 (7/28)	0.12
Gastrointestinal[b]	36 (10/28)	34 (14/41)	0.89	30 (6/20)	38 (8/21)	36 (10/28)	0.71
URI	43 (12/28)	29 (12/41)	0.25	50 (10/20)	19 (4/21)	36 (10/28)	0.40
URI or pharyngitis	54 (15/28)	39 (16/41)	0.24	60 (12/20)	24 (5/21)	50 (14/28)	0.64
Gastroenteritis	14 (4/28)	10 (4/41)	0.57	10 (2/20)	19 (4/21)	7 (2/28)	0.68

a. P-value from Mantel-Haenszel chi-square test (1 degree of freedom test). The p-value indicates whether the adverse event rate increases (or decreases) with changing values of the covariates.

b. May include nausea, vomiting, abdominal pain, and/or diarrhea.

Table 52. Percent (n/N) of Patients with Adverse Events by Disease Subsets (All Patient in Part 1 of the Study; N = 69)

	JRA Onset				Rheumatoid Factor		
Event	Pauciarticular	Polyarticular	Systemic	p-value[a]	Negative	Positive	p-value[a]
Headache	0 (0/7)	28 (11/40)	14 (3/22)	0.98	19 (10/54)	27 (4/15)	0.49
Gastrointestinal[b]	14 (1/7)	35 (14/40)	41 (9/22)	0.25	39 (21/54)	20 (3/15)	0.18
URI	14 (1/7)	40 (16/40)	32 (7/22)	0.75	35 (19/54)	33 (5/15)	0.90
URI or pharyngitis	29 (2/7)	53 (21/40)	36 (8/22)	0.77	41 (22/54)	60 (9/15)	0.19
Gastroenteritis	14 (1/7)	10 (4/40)	14 (3/22)	0.87	15 (8/54)	0 (0/15)	0.12

a. P-value from Mantel-Haenszel chi-square test (1 degree of freedom test). The p-value indicates whether the adverse event rate increases (or decreases) with changing values of the covariates.

b. May include nausea, vomiting, abdominal pain, and/or diarrhea.

Summary.

From a database of 69 JRA patients with detailed adverse event data and a comparison to 349 adult RA patients treated with equivalent exposures to Enbrel, the frequency of adverse events in JRA appears to be comparable to adult RA, except for an increase in headache, rhinitis, gastrointestinal intolerance (nausea, vomiting, abdominal pain), and injection site hematomas in JRA patients. Adverse events were predominantly mild to moderate in intensity. JRA patients had more infectious episodes per patient during 6 months of Enbrel therapy than adult RA patients, particularly more episodes of pharyngitis and gastroeneteritis. Increased frequencies of certain infections in JRA patients are expected based on the natural history of these infections in pediatric vs. adult populations. The role of TNFR:Fc in mediating aseptic meningitis following varicella infection is unclear. Thirty-nine percent of JRA patients developed injection site reactions within the first three months of Enbrel treatment, and 70% were grade 2, which was more severe than those seen in adult RA patients. Three percent of JRA patients developed urticaria. The development of anti-dsDNA autoantibodies, measured by ELISA, occurred in 3% of JRA patients, but none tested positive in a more specific Crithidia assay. One to seven

percent of patients developed new positive rheumatoid factor, ANA or ENA (anti-U1RNP) autoantibodies. No specific autoimmune events have been observed related to these autoantibodies. No specific laboratory toxicity was observed following treatment with Enbrel. In summary, the safety profile of Enbrel in children 4 – 18 rs of age with polyarticular JRA appears to be comparable to adult RA and most adverse events are mild to derate in intensity, although the safety database is limited by exposure in only 69 JRA patients for 3 – 7 months duration. Conclusions about the comparison of Enbrel treated patients versus placebo in part 2 of the study cannot be easily interpreted, due to the fact that most adverse events occurred in part 1 (the non-randomized portion) of the study, and that exposure to placebo was much briefer in part 2 compared to exposure to Enbrel.

V. OVERALL SUMMARY.

The data in the application provide evidence of efficacy of Etanercept in polyarticular-course JRA patients who have been refractory or intolerant of MTX, based on a randomized withdrawal trial with disease flare as the primary endpoint. Overall, the safety of Etanercept appears to be comparable to the safety profile in adult RA. Several cases of aseptic meningitis following varicella infection were seen in the JRA trial. JRA patients experienced headaches, gastrointestinal intolerance, and certain infections (URI, pharyngitis, otitis media) more frequently than adult RA patients, some of which is expected based on the more frequent occurrence of these events in a healthy population with the same age distribution. Postlicensure commitments include establishment of a large registry of JRA patients of a minimum duration of 3 years, focusing on collection of serious adverse events, as well as examination of serious infections, malignancies, autoimmune diseases, and the effects of Etanercept on normal growth and development in children. Other commitments include additional examination of pharmacokinetic data, pK studies in children — years of age, a study of the combination of MTX and Enbrel, a study in systemic-onset JRA, and the

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