The most frequently observed adverse drug reactions were injection site reactions, rhinitis, upper respiratory infection, abnormal laboratory test, and rash.

The rate of adverse events was approximately one AE per year and one serious event per 4 to 5 years among adalimumab-treated and placebo-treated patients. Adalimumab-treated patients experienced a higher incidence of laboratory AEs and serious infections (Table 57).

Table 57 : ISS :Overview of number (%) of patients with treatment-emergent AEs in patients treated with adalimumab during placebo-controlled and non-placebo-controlled periods, by treatment received – all studies in RA patients (safety set)

	Adalimumab 40 mg Q2w sc (N=1903)				All adalimumab doses sc and iv (N=2334)				Placebo-Treated Patients from the Adequate and Well-Controlled Studies (N=690)			
Patients with any[a]	N	(%)	E (E/100 pt-yrs)		N	(%)	E (E/100 pt-yrs)		N	(%)	E (E/100 pt-yrs)	
AE	1765	(93)	12172	(786)	2221	(95)	30775	(1042)	589	(87)	3304	(912)
Clinical AE	1675	(88)	9003	(582)	2180	(93)	19699	(667)	573	(83)	2769	(764)
Laboratory AE	886	(47)	3169	(205)	1201	(52)	11076	(375)	178	(26)	535	(148)
Fatal AE[b]	9	(1)	16	(1)	22	(1)	41	(1)	1	(0)	3	(1)
SAE	294	(15)	404	(26)	575	(25)	1022	(35)	60	(9)	75	(21)
AE leading to withdrawal	114	(6)	162	(11)	252	(11)	353	(12)	29	(4)	39	(11)
AE leading to dose interruption	340	(18)	522	(34)	614	(26)	1106	(37)	86	(13)	124	(34)
AE leading to dose reduction	2	(0)	2	(0)	23	(1)	43	(2)	0	(0)	0	(0)
Severe or life-threatening/intractable AE	372	(20)	610	(39)	734	(31)	1482	(50)	114	(17)	220	(61)
At least possibly drug-related AE	984	(52)	3214	(208)	1550	(66)	8620	(292)	280	(41)	850	(235)
Infection (serious and non-serious)	1061	(56)	2209	(143)	1573	(67)	4507	(153)	334	(48)	591	(163)
Serious infection	56	(3)	61	(4)	129	(6)	146	(5)	7	(1)	7	(2)
Malignancy	29	(2)	30	(2)	52	(2)	53	(2)	2	(0)	2	(1)
Immunologic reaction	16	(1)	19	(1)	38	(2)	49	(2)	4	(1)	4	(1)

Q2w = every other week sc = subcutaneous iv = intravenous
[a] More than one AE per patient possible.
[b] Can include more than one AE ongoing at time of death.

Increasing age among adalimumab-treated patients is associated with an increased frequency of occurrence of malignancies, SAEs, and AEs resulting in dose interruption (Table 58). These percentages increased as age increased over 65 and even higher over age 75 in both those patients treated with adalimumab and those receiving placebo. The percentage of patients with fatal AEs, which only occurred in the adalimumab–treated group, also increased in frequency with advancing age.

Table 58 : ISS : Overview of number (%) of patients with treatment-emergent AEs, by age - adequate and well controlled studies (safety set)

	Adalimumab 40 mg Q2w sc						Placebo					
	<65 (N=526)		≥65 (N=179)		≥75 (N=42)		<65 (N=520)		≥65 (N=170)		≥ 75 (N=34)	
	N	%	N	%	N	%	N	%	N	%	N	%
Patients with any[a] AE	475	(90)	163	(91)	39	(93)	457	(88)	141	(83)	25	(74)
Clinical AE	461	(88)	159	(89)	39	(93)	435	(84)	138	(81)	24	(71)
Laboratory AE	167	(32)	49	(27)	13	(31)	141	(27)	37	(22)	5	(15)
Fatal AE	0	(0)	5	(3)	3	(7)	0	(0)	1	(1)	0	(0)
SAE	31	(6)	30	(17)	9	(21)	40	(8)	20	(12)	5	(15)
AE leading to withdrawal	23	(4)	22	(12)	5	(12)	18	(4)	11	(7)	4	(12)
AE leading to dose interruption	67	(13)	36	(20)	11	(26)	64	(12)	22	(13)	6	(18)
AE leading to dose reduction	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(.0)
Severe or life-threatening/intractable AE	67	(13)	46	(26)	7	(17)	78	(15)	36	(21)	7	(21)
At least possibly drug-related AE	282	(54)	94	(53)	17	(41)	223	(43)	57	(34)	8	(24)
Infection (serious and non-serious)	303	(58)	95	(53)	21	(50)	258	(50)	76	(45)	14	(41)
Serious infection	7	(1)	11	(6)	2	(5)	4	(1)	3	(2)	1	(3)
Malignancy	7	(1)	3	(2)	2	(5)	1	(0)	1	(1)	0	(0)
Immunologic reaction	5	(1)	1	(1)	0	(0)	4	(1)	0	(0)	0	(0)

Q2w = every other week sc = subcutaneous
[a] More than one AE per patient possible.

C. Other Adverse Events

Table 59 demonstrates the most frequently reported treatment-emergent AEs, irrespective of relation to study drug, in patients treated with adalimumab during placebo-controlled and non-placebo-controlled study periods, by treatment received.

Table 59: ISS : Number (%) of patients with the most frequently reported treatment-emergent AEs, irrespective of relation to study drug, in patients treated with adalimumab during placebo-controlled and non-placebo-controlled study periods, by treatment received – all studies in RA patients

	Adalimumab 40 mg Q2w sc (N=1903)		All adalimumab doses, sc and iv (N=2334)		Placebo-Treated Patients from the Adequate and Well-Controlled Studies (N=690)	
Body system/AE[b]	**N (%)**	**E (E/100 pt-yrs)**	**N (%)**	**E (E/100 pt-yrs)**	**N (%)**	**E (E/100 pt-yrs)**
Abdominal pain	111 (6)	130 (8)	222 (10)	276 (9)	30 (4)	32 (9)
Accidental injury	183 (10)	221 (14)	309 (13)	396 (13)	56 (8)	59 (16)
Asthenia	104 (6)	114 (7)	224 (10)	269 (9)	40 (6)	41 (11)
Back pain	128 (7)	140 (9)	244 (11)	325 (11)	25 (4)	29 (8)
Clinical flare reaction	248 (13)	306 (20)	406 (17)	600 (20)	75 (11)	89 (25)
Fever	42 (2)	48 (3)	164 (7)	239 (8)	17 (3)	18 (5)
Flu syndrome	132 (7)	148 (10)	279 (12)	392 (13)	41 (6)	43 (12)
Infection	62 (3)	63 (4)	131 (6)	145 (5)	13 (2)	14 (4)
Surgery	108 (6)	122 (8)	208 (9)	270 (9)	23 (3)	25 (7)
Hypertension	99 (5)	106 (7)	218 (9)	287 (10)	18 (3)	18 (5)
Diarrhea	132 (7)	163 (11)	257 (11)	350 (12)	66 (10)	86 (24)
Nausea	134 (7)	158 (10)	265 (11)	350 (12)	54 (8)	63 (17)
Sore throat	98 (5)	124 (8)	190 (8)	244 (8)	39 (6)	45 (14)
Decreased hemoglobin	191 (10)	238 (15)	524 (23)	1077 (37)	44 (6)	49 (14)
Injection site pain	122 (6)	388 (25)	250 (11)	726 (25)	85 (12)	330 (91)
Injection site reaction	104 (6)	210 (14)	195 (8)	373 (13)	8 (1)	19 (3)
BUN increased	150 (8)	194 (13)	274 (12)	532 (18)	23 (3)	32 (9)
Peripheral edema	83 (4)	97 (6)	144 (6)	176 (6)	24 (4)	27 (8)
Arthralgia	84 (4)	92 (6)	185 (8)	228 (8)	43 (6)	48 (13)
Joint disorder	100 (5)	114 (7)	201 (9)	250 (9)	40 (6)	43 (12)
Dizziness	75 (4)	91 (6)	159 (7)	228 (8)	32 (5)	36 (10)
Headache	175 (9)	245 (16)	387 (17)	646 (22)	53 (8)	67 (19)
Depression	70 (4)	74 (5)	116 (5)	129 (4)	22 (3)	27 (8)
Bronchitis	116 (6.1)	133 (9)	242 (10)	324 (11)	35 (5)	42 (12)
Cough increased	109 (5.7)	127 (8)	242 (10)	294 (10)	42 (6)	45 (12)
Rhinitis	280 (15)	376 (24)	533 (23)	858 (29)	93 (14)	106 (29)
Sinusitis	178 (9)	234 (15)	275 (12)	389 (13)	61 (9)	78 (22)
Upper respiratory infection	294 (15)	373 (24)	430 (18)	585 (20)	86 (13)	96 (27)
Herpes simplex	65 (3)	77 (5)	131 (6)	183 (6)	15 (2)	21 (6)
Pruritus	72 (4)	80 (5)	237 (10)	310 (11)	10 (1)	11 (3)
Rash	205 (11)	237 (15)	432 (19)	600 (20)	43 (6)	49 (14)
Skin disorder	77 (4)	86 (6)	172 (7)	215 (7)	20 (3)	23 (6)
Hematuria	47 (3)	58 (4)	241 (10)	424 (14)	28 (4)	41 (11)
Urinary tract infection	129 (7)	160 (10)	195 (8)	251 (9)	36 (5)	50 (14)

Q2w = every other week sc = subcutaneous iv = intravenous
[a] Occurring in ≥5% of patients in the "all adalimumab" treatment group.

D. Deaths and Comparable Mortality Rates

Eight patients, 7 treated with adalimumab and 1 treated with placebo died, as a result of AEs during the adequate and well-controlled studies; the primary AE leading to death is presented by patient in Table 60. Deaths occurred at a rate of 0.3/100 patient-years (CI, 0.26, 0.82) among placebo-treated patients, 0.9/100 patient-years (CI, 0.23, 1.55) among all adalimumab-treated patients, and 1.3/100 patient-years (CI, 0.16, 2.35) among patients receiving the proposed recommended dose. Two additional deaths among adalimumab-treated patients (total of 9) are provided in supplementary final safety updates: 1.) diverticulitis with secondary sepsis and 2.) hepatic necrosis. The most frequent causes of death were sepsis (3) and malignancy (3) [carcinoma (2) and lymphoma (1)]. Two deaths related to infection are described in greater detail in Table 61.

Table 60 : ISS : Patients with fatal AEs – Adequate and Well-Controlled Studies

Study	Pt. No.	Age, sex	Treatment	Adverse event[a] (HARTS term)	Adverse event (Investigator's term)	Day on drug at onset	Duration (days)
DE011	2120	78, M	Adalimumab 40 mg wk	Gastrointestinal carcinoma	Metastatic adenocarcinoma	65	96
	4209	77, M	Adalimumab 40 mg eow	Carcinoma	Cholangiocarcinoma	13	116
	4217	73, F	Placebo	Intestinal obstruction	Intestinal obstruction	101	8
	4711	76, F	Adalimumab 40 mg eow	Myocardial infarction	Myocardial infarction[b]	157	3
DE019	1705	62, F	Adalimumab 20 mg wk	Lymphoma like reaction	B-cell lymphoma	147	96
	1706	73, F	Adalimumab 40 mg eow	Bone fracture (not spontaneous)	Multiple fractures	304	33
	8702	75, F	Adalimumab 40 mg eow	Sepsis	Septic shock	115	14
DE031	15106	70, M	Adalimumab 40 mg eow	Herpes zoster	Disseminated herpes	11	16

F = female M = male wk = weekly eow = every other week

[a] Primary AE leading to death; more than one AE with fatal outcome per patient possible.

[b] Patient had a gastrointestinal bleed (Hgb drop 11.8 – 6.0 mg/dL) followed by a myocardial infarction.

Table 61 : Deaths Related to Infections

Patient Number	Adverse Event	Relevant Medical History
8702	Urosepsis & septic shock	Onset fatigue and disturbance of equilibrium (incoordination), patient was withdrawn from study, and event resolved. Patient became febrile with urinary incontinence and a week later developed a urinary tract infection and a upper respiratory infection. Urosepsis (E. coli) was followed by septic shock and pancytopenia, cardiac arrest and death.
15106	Herpes zoster, dissemination, superinfection	Herpes zoster with dissemination, necrotizing fasciitis of upper extremity, superinfection with Group A streptococcus and death.

Table 62 lists all 22 fatal adverse events from among all patients treated with adalimumab in the clinical development program. Two additional deaths (total of 24), one each from diverticulitis with associated sepsis and hepatic necrosis are not shown on this table. Even though the majority (77%) of patients enrolled in these studies were females, the majority of deaths occurred in male subjects (58% [14/24]). The major categories for the deaths include cardiovascular (7), malignancy (6), infections (5), and gastrointestinal (3), [including the additional death from diverticulitis and associated sepsis not shown on this Table].

Table 62 : ISS : List of fatal adverse events during treatment with adalimumab. All patients treated with adalimumab. Study group: all studies in patients with RA (DE001/3, 004, 005/X, 010, 007, 009/X, 011, 019, 031, 018, 020).

	Category of Primary Cause of Death	Initial Study	Pt. No.	Age/ Sex	Adalimumab Treatment	Day on Drug at Onset	Fatal Adverse Event	Comments
1	Malignancy	DE010	209	56/M	1 mg/kg sc q2w	420	Small cell carcinoma lung	
2	Malignancy	DE003	22	67/M	3 mg/kg IV q4w	599	Prostate carcinoma	Metastatic
3	Malignancy	DE003	69	56/M	0.5 mg/kg IV q4w	812	Non-Hodgkin lymphoma	Pancytopenia & sepsis
4	Malignancy	DE011	2120	78/M	40 mg sc qw	65	Adenocarcinoma bowel	
5	Malignancy	DE011	4209	77/M	40 mg sc q2w	13	Cholangiocarcinoma	
6	Malignancy	DE019	1705	62/F	20 mg sc qw	147	B-cell lymphoma	
7	Gastrointestinal	DE001	23	54/M	0.5 mg/kg IV q4w	24	Necrotizing pancreatitis	Suspected abscess of spleen
8	Infection	DE019	8702	75/F	40 mg sc q2w	115	*E. coli* urosepsis	
9	Infection	DE007	2702	69/M	40 mg sc qw	420	Aspergilloma	Abcesses and granulomata
10	Infection	DE018	1808	58/F	40 mg sc q2w	240	Recurring foot infection	Septic myocarditis
11	Infection	DE018	801	43/F	80 mg sc qw	919	Possible septic shock	Pulmonary macro-infiltrates
12	Infection	DE031	15106	70/M	40 mg sc q2w	11	Necrotizing fasciitis	Herpes zoster arm; GA strep
13	Cardiovascular	DE009x	1906	61M	40 mg sc q2w	166	Abdominal aotic aneurysm	Surgery
14	Cardiovascular	DE010	215	38/F	1 mg/kg sc q4w	678	Myocardial infarction	
15	Cardiovascular	DE011	4711	76/F	40 mg sc q2w	157	Myocardial infarction	Gastrointestinal hemorrhage
16	Cardiovascular	DE003	105	55/M	10 mg/kg IV q2w	58	Heart failure	Sudden death
17	Cardiovascular	DE004	13	78/F	0.5 mg/kg sq q3w	726	Myocardial infarction	Sudden death
18	Cardiovascular	DE007	2015	65/M	40 mg sc qw	85	Myocardial infarction	
19	Cardiovascular	DE020	707	69/M	40 mg sc q2w	417	Heart failure	Dilated cardiomyopathy
20	Gastrointestinal	DE018	1417	72/F	40 mg sc q2w	322	Diverticular sigmoiditis	Complications of repair
21	Trauma	DE019	1706	73/F	40 mg sc q2w	304	Multiple fractures sec to fall	Complications of fall
22	Respiratory	DE003	19	71/M	3 mg/kg IV q4w	318	Respiratory insufficiency	Interstitial fibrosis

Because the adalimumab safety database includes a significant number of older patients, including a substantial portion aged 65 to 75 (22%) and over age 75 (5%), some deaths are expected. In addition, mortality has been reported to be increased in RA patients. To determine whether the death rate was higher than expected, the observed rate was compared to that expected among various populations (Table 63). Standardized Mortality Rate (SMR - ratio of observed death rate compared to age adjusted expected frequency) was 0.72 for all adalimumab-treated subjects (C.I., 0.46, 1.05), 1.38 for males (C.I., 0.72, 2.44) and 0.45 for females (C.I., 0.22, 0.83). The confidence interval for the male deaths overlaps 'one,' implying that the mortality rate observed was within the expected range. The mortality rate for the females was lower than expected. The SMR for adalimumab-treated patients did not exceed that observed in a variety of epidemiologic studies of RA patients

Table 63 : ISS : Comparable Mortality Rates Among RA Patients

Study	Population Base	SMR* (95% CI)
Wolfe et al (1994) [1]	Tertiary referral center (North America	1.98 - 3.08
	Community-based (North America)	1.98
Symmons et al (1998) [2]	Hospital-based referral center (England)	2.7 (2.4, 3.1)
Gabriel et al (1999) [3]	RA patients (All Rochester)	1.38 (1.22, 1.55)
Krause et al (2000) [4]	Methotrexate responders	1.47
	Methotrexate non-responders	4.11
Adalimumab clinical development program	Calculation using WHO mortality rates (22 adalimumab-treated patients that died)	0.72 (0.46, 1.05)
	Males (13)	1.38 (0.72, 2.44)
	Females (9)	0.45 (0.22, 0.83)

* Standardized Mortality Rate

Highest mortality rates associated with increased age, male sex, RF positivity, and continued signs of active inflammation

[1] Wolfe, F, Sibley TJ, et al. The mortality of rheumatoid arthritis. *Arthritis Rheum.* 1994; **37**: 481-494.

[2] Symmons DPM, Jones MA, Scott DL, Prior P. Long-term mortality outcome in patients with RA: rarly presenters continue to do well. *J Rheumatol.* 1998; **25**: 1072-7.

[3] Gabriel AE, Crowson CS, O'Fallon WM. Mortality in rheumatoid arthritis: have we made an impact in four decades. *J Rheumatol.* 1999; **25**: 2529-2533.

[4] Krause D, Schleusser B, Herborn G, Rau R. Response to methotrxate treatment is associated with reduced mortality in patients with severe RA. *Arthritis Rheum.* 2000; **43**: 14-21.

E. Serious Adverse Events

Overall the rate of SAEs was not higher among adalimumab-treated patients compared to placebo controls at the proposed recommended dose (Table 56). However, a higher rate of SAEs was observed among patients receiving 40 mg weekly.

To explore why SAEs were more frequent among patients receiving 40 mg weekly, the individual studies were examined. All 103 patients receiving that dose were in study DE011, the European monotherapy study. In that study, the rate of SAEs was lower among patients receiving adalimumab 40 mg weekly (22.6/100 patient–years) or adalimumab 40 mg biweekly (26.0/100 patient–years) than those receiving placebo (39.7/100 patient–years) [Table 64]. Thus, the rate of SAEs does not appear to be increased in patients receiving adalimumab 40 mg weekly.

For both adalimumab- and placebo-treated patients, the percentage of patients reporting SAEs was higher among patients >65 years of age than among patients <65 years of age, and higher still among the small group of patients >75 years of age (Table 95). Within each age group the overall percentage of SAEs was slightly higher among adalimumab-treated patients than among controls. During the double-blind placebo-controlled periods of the adequate and well-controlled studies, 151 adalimumab-treated patients (11% of 1380; 19 patients/100 pt-yrs) and 60 placebo-treated patients (9% of 690 ; 17 patients/100 pt-yrs) experienced one or more SAEs. SAEs reported slightly more frequently by adalimumab-treated patients included surgery, clinical flare reaction, bone fracture, and pneumonia.

The most commonly reported SAE was surgery, a HARTS term that encompassed arthroplasty and arthrodesis procedures (18 events in 17 patients), tendon repair, hernia repair, aneurysm repair, uterine prolapse repair, removal of fibroids, cholecystectomy, pacer placement revision, prostatectomy, and removal of a basal cell carcinoma (one patient each). Each of the five most commonly reported SAEs occurred more often among all adalimumab- than among placebo-treated patients. Ten percent of adalimumab-treated patients and 8 % of placebo-treated patients experiencd one or more SAEs other than planned surgeries

For both adalimumab- and placebo-treated patients, the percentage of patients reporting SAEs was not higher among patients taking corticosteroids at baseline than among patients not taking corticosteroids at baseline, and was not higher among patients taking concomitant MTX than among patients who were not (Table 97).

Table 64 : Study DE011 : Overview of number (%) of patients with treatment-emergent AEs (safety set)

	Adalimumab 40 mg Q2w 50.07 pt-yrs (N=113)		Adalimumab 40 mg Q2w 48.61 pt-yrs (N=103)		Placebo 40.34 pt-yrs (N=110)	
	N (%)	N/100 pt-yrs	N (%)	N/100 pt-yrs	N (%)	N/100 pt-yrs
Patients with any AE [a]	112 (99.1)	223.7	102 (99.0)	209.9	105 (95.5)	260.3
Serious AE (SAE)	13 (11.5)	26.0	11 (10.7)	22.6	16 (14.5)	39.7
Severe or life-threatening/intractable AE	27 (23.9)	53.9	21 (20.4)	43.2	25 (22.7)	62.0
At least possibly drug- related AE	74 (65.5)	147.8	69 (67.0)	142.0	49 (44.5)	121.5
AE leading to death	2 (1.8)	4.0	1 (1.0)	2.1	1 (0.9)	2.5
AE leading to permanent withdrawal	7 (6.2)	14.0	5 (4.9)	10.3	3 (2.7)	7.4
AE leading to temporary withdrawal	15 (13.3)	30.0	15 (14.6)	30.9	4 (3.6)	9.9
AE leading to dose reduction	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
AE leading to dose increase	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
AE leading to switch to rescue period	4 (3.5)	8.0	0 (0.0)	0.0	11 (10.0)	27.3
Infection	56 (49.6)	111.8	50 (48.5)	102.9	43 (39.1)	106.6
Serious infection	1 (0.9)	2.0	2 (1.9)	4.1	0 (0.0)	0.0
Malignancy	2 (1.8)	4.0	1 (1.0)	2.1	1 (0.9)	2.5
Immunologic reaction	1 (0.9)	2.0	1 (1.0)	2.1	0 (0.0)	0.0

[a] More than one AE per patient possible.

F. Malignancies and Comparative Expected Incidence Rates

Eight malignancies (excluding non-melanoma skin cancers) were observed in adalimumab-treated patients within the adequate and well controlled studies, and none were observed among placebo-treated patients. Thirty malignancies (excluding non-melanoma skin cancers) were observed in adalimumab-treated patients within the clinical development program, and none were observed among placebo-treated patients (Table 65). Six patients died of their malignancies. Adalimumab-treated patients had approximately an eight-fold greater safety observational exposure in the studies than did placebo-treated patients. Matching the data from the SEER database to the age and sex distribution seen in all patients treated with adalimumab, the expected number of cancers was 22.

In the clinical development program, based on this smaller initial database, a higher SIR rate for malignancies was suggested (Table 65).

Table 65 : ISS : Malignancies in the Clinical Development Program

	Malignancy incidence		SIR (Standardized Incidence Ratio) [95% CI]	Exposure (patient-years)
	Observed incidence	Expected Incidence [1]		
Adequate and Well-Controlled Studies				
Malignancies in adalimumab-treated	8	6		
Malignancies in placebo-treated	0	0.8		
Clinical Development Program				
Malignancies in adalimumab-treated	30	22	1.33 [0.9, 1.9]	2,954
Malignancies in placebo-treated	0	2.9		385

[1] Matching data from NCI SEER database to calculate expected age-matched malignancy rate

for US population (SEER Program Public-Use Data 1973-1998)

These thirty malignancies (excluding non-melanoma skin cancers) were observed among 2334 adalimumab-treated patients over a median of 12 months during the clinical development program and were submitted with the BLA. The most frequently seen malignancies were breast (4), prostate (4), gastrointestinal (4), non-Hodgkin's lymphoma (4), uterine/endometrial (3), and melanoma (2) [Table 66].

Thirty-six non-melanoma skin cancers and 48 malignancies of various types were observed in 2468 RA patients treated in clinical trials with adalimumab for a median of 24 months and were submitted with the final safety update through August 31, 2002. The malignancies observed during use of adalimumab were neoplasms of the immune system (9), breast (7), colon-rectum (6), uterine-cervical (5), prostate (5), melanoma (3), gallbladder-bile ducts (2), and other carcinomas.

Table 66 : ISS : Cancer Incidence Analysis in Clinical Development Program

Cancer Site	Observed in BLA [1]	Observed in Interim Safety Update [2]	Observed in Final Safety Update [3]
Exposure	2334 patients median 12 months	2467 patients median 19.3 months	2468 patients median 24 months
All Sites	30	38	48
All lymphomas	4	8	10
NHL		7	
Hodgkin's D		1	
Breast	4	5	7
Colon – rectum	3	4	6
Cervix – Uteri	3	3	5
Prostate	4	4	5
Melanoma	2	2	3
Gallbladder – bile ducts	1		2
Adenocarcinoma (unknown origin)	2		2
Other	7	11	8
Non-melanoma skin cancers	24	32	36
Basal cell		23	
Squamous cell		9	

1 Data available through August 31, 2001
2 Data available through March 29, 2002
3 Data available through August 31, 2002

Based on 46 of the 48 malignancies observed in the final safety update, for which data was available to up-date the observed Standardized Incidence Ratio (SIR), the observed SIR (ratio of observed rate to age-adjusted expected frequency) for malignancies was 1.00 (95% CI, 0.7, 1.3)] [Table 67], implying that the observed frequency of malignancies among adalimumab-treated patients was within the expected incidence range.

Table 67: ISS : Comparative Expected Cancer Incidence Rates In the Adalimumab Clinical Development Program Through August 31, 2002

Cancer Type *	Observed	Expected	SIR	95% CI
All Sites	46	45.82	1.00	(0.7 – 1.3)
All Lymphomas	10	1.85	5.42	(2.6 – 10.0)
NHL	9	1.70	5.28	(2.4 – 10.0)
Hodgkin's Disease	1	0.14	7.09	(0.1 – 39.5)
Breast	7	11.15	0.63	(0.3 – 1.3)
Colon	5	4.75	1.05	(0.3 – 2.5)
Lung	1	6.67	0.15	(0.0 – 0.8)
Melanoma	3	1.53	1.97	(0.4 – 5.7)
Prostate	5	4.45	1.12	(0.4 – 2.6)
Uterine	4	2.30	1.74	(0.5 – 4.4)
Other sites	11	13.12	0.84	(0.4 – 1.5)
Non-Melanoma Skin Cancers **				
Basal Cell	23	20.12	1.14	(0.7 – 1.7)
Squamous Cell	9	3.79	2.37	(1.1 – 4.5)

* Cancer rates used were 1992-1999 SEER rates
** Skin cancer rates used were 1977-1978 NCI study rates

A total of ten lymphomas, primarily Non Hodgkin's lymphoma, were observed in patients treated with adalimumab. Based on these patients, the observed SIR (ratio of observed rate to age-adjusted expected frequency) for all lymphomas was 5.4 (95% CI, 2.6, 10.0). The wide confidence interval seen for Non Hodgkin's lymphoma did not allow an accurate determination of whether its frequency was greater than expected. An attempt was made to correlate the onset of the lymphomas and the duration of therapy with adalimumab. Analysis of the exposure interval between initiation of adalimumab treatment and time-to-onset of lymphoma did not provide clear evidence of a relationship between longer duration-of-therapy and incidence of lymphoma (Table 68).

Table 68 : ISS : Lymphoma Incidence Rates by Duration of Treatment with Adalimumab

Exposure Interval Until Time of Event - Months	Number/Total (%)	N(N/100 patient-years)
0 - < 6	2/2468 (0.08)	2 (0.2)
6 -< 12	1/2216 (0.05)	1 (0.1)
12 - <18	1/1867 (0.05)	1 (0.1)
18 - < 24	2/1395 (0.14)	2 (0.4)
24 - < 30	1/619 (0.16)	1 (0.4)
30 - < 36	0/375 (0.00)	0 (0.0)
36 - < 42	0/321 (0.31)	1 (0.8)

Table 69 summarizes the cases of lymphoma observed during the adalimumab clinical development program by type and concomitant therapy. Lymphomas that have occurred in the setting of impaired immune function have most often been large B cell, Non Hodgkin's lymphomas.[5] Similarly, the lymphoma type most often reported in this clinical development program was the large B cell, Non Hodgkin's lymphoma. Ninety percent of the lymphoma patients had received MTX (seven were receiving concomitant MTX and two had received prior MTX), and 80% were receiving concomitant corticosteroids.

Table 69 : ISS : Summary of Lymphoma Cases By Type and Concomitant Therapy

Subject/Study	Type of Lymphoma	Family History	Concomitant Therapy		
			Azathioprine/ Cyclophosphamide	MTX	CSTD
2204/DE007	Mantle zone B cell	Sister-leukemia		X	X
69/DE001	Diffuse Large B cell			X P	
1414/DE011	MALT cell B cell		X P	X P	X
8911/DE019	Follicular B cell			X	
10509?DE031	Large B cell				X
1705/De019	Mixed small and large B cell			X	
11601/DE031	T cell			X	X
8208/DE019	Small and large B cell			X	X
14605/DE031	Large B cell			X	X
4404/DE019	Hodgkin's			X	X
Total = 10		1	1	9	8

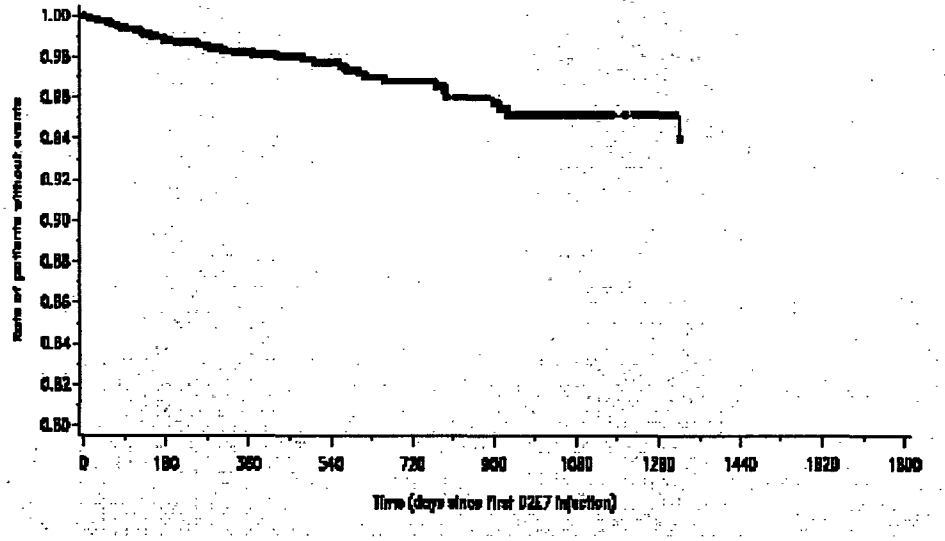
P = previous

[5] Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the FDA. *Arthritis and Rheumatism* 2002;**46**: 3151-3158

Among non- melanoma skin cancers, squamous cell carcinomas also occurred at a frequency greater than expected (Table 67). However, the data used to establish the expected rate were from 1977-1978, leading to some uncertainty of the comparison.

The Kaplan Meier plot in Figure 14 shows that the rate of detection of new malignancies (based on the August 31, 2001 data) was constant over the observation period for all patients treated with adalimumab. The plot does not support an association between increased development of malignancy and longer duration of exposure to adalimumab. If the risk had increased over time, the slope of the curve would become increasingly negative with time. Longer duration of observation will be required to determine whether exposure beyond 2 to 3 years is associated with a higher risk of malignancy.

Figure 14 : ISS : Kaplan Meier curve of time to first malignancy during treatment with adalimumab in all patients treated with adalimumab



In this clinical development program malignancies were observed at frequency rates approximating the expected rate, except for neoplasms of the immune system which were observed at a greater rate than expected. Since the introduction of TNF blocking agents which affect host defenses by modulating cellular immune responses, a major concern of the Agency has been the possibility of an increased risk of development of lymphomas among patients treated with TNF blocking agents. Published literature suggests that RA patients with highly active disease have a greater risk of lymphomas. Two published epidemiologic studies of 11,683 [6] and 1,767 [7] patients observed an approximately 4 to 5 fold increased incidence of lymphoma in patients with moderately active RA. The RA patients who participated in this clinical development program all had moderate to severe RA with mean duration of disease above 10 years.

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[6] Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis : nested case-control study. *BMJ* 1998; **517**: 180-1

[7] Abstract. Wolfe F. Inflammatory activity, but not methotrexate or prednisone use predicts Non-Hodgkin's lymphoma in rheumatoid arthritis: a 25-year study of 1,767 RA patients. *ACR Plenary II* 1998: **931**

Available data are insufficient to determine whether adalimumab increases the incidence of lymphomas above that expected in this patient population. Continued monitoring of adalimumab-treated patients is necessary to quantify the role of adalimumab, if any, in contributing to the high observed incidence of lymphomas.

G. Serious Infections

Since the introduction of TNF blocking agents like adalimumab that modulate cellular immunity, development of serious infections among patients treated with anti-TNF agents has been a major concern of the Agency. In the adalimumab clinical development program, serious infections were defined as infections associated with hospitalization or with use of parenteral antibiotics. Forty-one patients (34 [3%] of 1380 adalimumab-treated patients [4.3 patients/100 pt-yrs] and 7 [1%] of 690 placebo-treated patients [1.9 patients/100 pt-yrs]) experienced serious infections, as provided in the BLA data available through Aug 31, 2001. Four adalimumab-treated patients experienced two serious infections each; the remaining 37 patients experienced a single serious infection. Two patients died of infectious AEs, and 13 patients withdrew from the studies as a result of serious infections. The most common organs involved in the infections were the respiratory, skin, musculoskeletal, gastrointestinal, and genitourinary (Table 70).

Table 70 : ISS : Organ involvement for serious infections excluding tuberculosis and Opportunistic infections – (Data Available through August 31, 2001)

Body system	Type of Infection	Number
Respiratory	Pneumonia	29
	Bronchitis	6
	Laryngitis	2
	Flu-Syndrome	2
	Sinusitis	1
	Cough Increased	1
Skin	Cellulitis	10
	Wound Infection	7
	Herpes Zoster	6
	Abscess	6
	Digit Infection	3
	Necrotizing Fasciitis	1
Genitourinary	Urinary Tract Infection	10
	Pyelonephritis	4
	Cystitis	3
Musculoskeletal	Septic Arthritis	9
	Infected Prosthesis	2
	Osteomyelitis	2
	Bursitis	1
	Spondylodiscitis	1
Gastrointestinal	Diverticulitis	7
	Appendicitis	4
	Viral Gastroenteritis	2
	Infectious Diarrhea	1
Other	Sepsis	4
	Otitis Media	1
	Bacteremia	1
	Bacterial Infection	1
	Endocarditis	1

Table 71 presents the different kinds of serious infections observed during the adequate and well-controlled studies.

Table 71 : ISS : Patients with serious infections – adequate and well-controlled studies

Study	Pt. No.	Age, sex	Treatment	Adverse event (HARTS term)	Adverse event (Investigator's term)	Day on drug at onset	Duration (days)
DE009	2301	68, M	Adalimumab 40 mg eow	Pneumonia	Pneumonia	150	18
	3006	78, F	Adalimumab 40 mg eow	Gastrointestinal disorder	Diverticulitis	113	8
	3421	63, M	Adalimumab 80 mg eow	Pneumonia	Pneumonia	147	17
DE011	114	45, F	Adalimumab 40 mg wk	Arthritis[a]	Septic arthritis	95	11
	305	73, M	Adalimumab 40 mg eow	Pneumonia	Pneumonia	109	23
	524	76, F	Adalimumab 20 mg wk	Pneumonia	Pneumonia	48	25
	1402	35, F	Adalimumab 20 mg wk	Flu syndrome	Flu-like syndrome	130	2
	1420	33, F	Adalimumab 40 mg wk	Cystitis	Cystitis	126	4
	1910	48, M	Adalimumab 20 mg wk	Pyogenic arthritis[a]	Septic arthritis	54	41
	2820	58, F	Adalimumab 40 mg wk	Sinusitis	Right maxillary sinusitis	79	124
	3501	61, F	Adalimumab 20 mg eow	Sepsis	Urosepsis	162	29
				Cough increased	Cough	180	38
	4009	64, F	Adalimumab 20 mg wk	Urinary tract infection	Urinary tract infection	30	unk
	4411	61, F	Adalimumab 20 mg eow	Sepsis[a]	Sepsis	90	11
	4913	73, F	Adalimumab 20 mg wk	Infection	Erysipelas	18	13
DE019	1110	41, F	Placebo	Pneumonia	Pneumonia	192	10
	2205	71, F	Adalimumab 40 mg eow	Gastrointestinal disorder[a]	Diverticulitis	73	20
				Pneumonia[a]	Pneumonia	73	20
	2405	63, M	Adalimumab 40 mg eow	Urinary tract infection	Urinary tract infection	112	4
	2419	50, F	Adalimumab 40 mg eow	Pneumonia[a]	Pneumonia	214	NA
	2704	67, F	Adalimumab 20 mg wk	Gastroenteritis	Viral gastroenteritis	26	3
	2902	73, F	Adalimumab 40 mg eow	Pneumonia[a]	Bilateral pneumonitis	48	8
	3205	58, F	Adalimumab 20 mg wk	Pyelonephritis	Pyelonephritis	131	31
	3416	66, M	Adalimumab 40 mg eow	Herpes zoster[a]	Disseminated herpes zoster	85	68
	3813	28, F	Adalimumab 40 mg eow	Tuberculosis reactivated[a]	Tuberculosis	106	NA
	3901	70, M	Adalimumab 40 mg eow	Pneumonia	Pneumonia	58	3
	5503	59, M	Adalimumab 40 mg eow	Pneumonia	Pneumonia	348	73
	5706	79, M	Adalimumab 20 mg wk	Urinary tract infection	E. coli urosepsis	149	5
	6210	71, F	Adalimumab 40 mg eow	Infection[a]	Histoplasmosis	77	NA
	7811	73, F	Adalimumab 40 mg eow	Bronchitis	Bronchitis	308	22
	8702	75, F	Adalimumab 40 mg eow	Urinary tract infection	E. coli urosepsis	115	14
				Sepsis	Septic shock	115	14
	8910	70, F	Adalimumab 20 mg wk	Pneumonia	Pneumonia	262	5
	9606	53, M	Adalimumab 20 mg wk	Infection[a]	Foot infection	113	5
DE031	10706	78, F	Placebo	Bronchitis	Acute bronchitis	5	5
	10711	66, F	Placebo	Colitis	Colitis	116	4
	10712	72, F	Placebo	Bronchitis	Acute bronchitis	163	4
	11613	61, M	Adalimumab 40 mg eow	Infection[a]	Foot infection	81	45
	11614	62, M	Placebo	Pneumonia[a]	Pneumonia	82	5
	12001	43, F	Adalimumab 40 mg eow	Gastrointestinal disorder	Appendicitis	34	5
	12603	23, M	Adalimumab 40 mg eow	Gastrointestinal disorder	Appendicitis	3	2
	15006	58, F	Placebo	Abscess[a]	Epidural abscess	72	NA
	15106	70, M	Adalimumab 40 mg eow	Herpes zoster	Disseminated herpes	11	16
				Tendon disorder	Necrotizing fasciitis	11	16
	15714	44, F	Placebo	Pneumonia	Pneumonia	84	10

F = female M = male wk = weekly eow: every other week
unk: = unknown NA = not applicable
[a] Resulted in permanent withdrawal

Infections that were associated with sepsis during the clinical development program are listed in Table 72. Skin, musculoskeletal and urinary infections were among those infections most frequently associated with sepsis.

Table 72 : ISS : Infections Associated with Sepsis During the Adalimumab Clinical Development Program

Body system	Type of Infection	Number
Genitourinary	Urinary Tract Infection	3
Musculoskeletal	Spondylodiscitis	1
	Infected Prothesis	1
Skin	Cellulitis	1
	Abscess	1
	Necrotizing fasciitis	1
Other	Bacteremia	1
	Sepsis	3

Table 73 summarizes all patients who experienced serious infections, including the 4-month interim and final safety up-dates.

Table 73 : ISS : Overview of Serious Infections of Clinical Interest As Reported in the ISS, Interim 4-Month Safety Update, and Final Safety Update

Patients with Any	Safety Data and Up-Dates			Total
	ISS BLA Submission [1]	4-Month Interim Up-Date [2]	Final Up-Date [3]	
SAE	575	241	160	976
Serious infection	129	35	38	202
Tuberculosis	9	1	3	13
Opportunistic Infection	2	1	3	6

[1] The ISS reported safety data through 31-Aug-2001 included in the original submission
[2] The 4-month safety update data from 31-Aug-2001 through 29-March-2002 and data that had not been reported in the original submission
[3] This safety update reported data from 29-March-2002 through 31-Aug-2002

A total of 202 adalimumab-treated patients (includes the final safety up-date of 31-Aug-2002) experienced serious infections during the clinical development program. Review of information provided on 186 subjects with serious infections, revealed a wide assortment of serious infections. Based on this larger safety database, the order of frequency remains similar; the serious infections observed were pulmonary, musculoskeletal (including post-surgical), skin, gastrointestinal, and genitourinary.

Representative serious pulmonary infections included various pneumonias, some with empyema; musculoskeletal infections included septic arthritis, post-surgical infections, and infected prostheses; infections of the skin included erysipelas, cellulitis, and disseminated herpes zoster; gastrointestinal infections included diverticulitis, appendicitis, and diarrhea; genitourinary infections included pyelonephritis, and chronic pyelonephritis.

Table 74 compares the serious infection incidence rates among RA patients within the adalimumab clinical development program and comparable population bases from published studies. There is considerable variation in the reported rates for SAEs per 100 patient years, varying from 3.1 to 9.5 events per 100 patient years. The incidence rate for adalimumab-treated patients at the proposed dosage of 40 mg biweekly is at the lower end of that range, but is higher than the rate for placebo-treated patients.

Table 74 : ISS : Comparable Serious Infection Incidence Rates Among RA Patients

Study/Publication	Population Base	Events/ 100 patient-yrs	
Doran (2000) [8]	Mayo Clinic	3.1-9.5	
Singh (1999) [9]	ARAMIS database		
Adalimumab clinical development program		4.9	
Adalimumab 40 mg q2w treatment group		3.9	
Adalimumab Trials (AWC)		Adalimumab	Placebo
		4.8	1.9

For both adalimumab- and placebo-treated patients, the rate of serious infections was lower among patients <65 years of age than for older patients. (See Table 95 and Table 96.) Both of the patients who died of serious infections were > 65 years of age (70 and 75 years), and both patients with herpes zoster infections were > 65 years of age (66 and 70 years). Of note, both patients with fatal infections and both patients with herpes zoster infections were among the patients taking concomitant MTX.

[8] Abstract. Doran MF, Crowson CS, O'Fallon WM, Gabriel SE. Infections in rheumatoid arthritis. *Arthritis Rheum.* 2000; **43**, No. 9 (suppl) 606.
[9] Abstract. Singh G, Ramey DRUG-RELATED, Rausch PL, Schettler JD. Serious infections in rheumatoid arthritis: Relationship to immunosuppressive use. *Arthritis Rheum.* 1999; **42**, No 9 (suppl) 1029.

H. Tuberculosis and Other Opportunistic Infections

Nine cases of tuberculosis were observed during the clinical development program (Table 76), five of which occurred among patients over age 65. An additional four cases were provided with the Safety Update of August 31, 2002, yielding a total of thirteen cases. Infections included miliary, lymphatic, peritoneal, and pulmonary tuberculosis. Most of the cases of tuberculosis occurred within the first few months after initiation of therapy and may reflect recrudescence of latent disease.

Occurrence of seven cases of tuberculosis out of 542 patients treated (1.7%) early in the clinical trials prompted discussions between the Agency and the sponsor and consideration of placing the clinical program on hold. Thorough analysis of those 7 cases determined that ¾ of the cases had baseline chest x-rays consistent with tuberculosis, suggesting that screening might be an effective way to identify patients at risk. At the recommendation of the FDA, the sponsor instituted measures for screening and prophylaxis for all patients prior to enrollment. The sponsor adopted screening procedures consisting of chest x-ray in Europe and PPD plus chest x-ray in the U.S. and initiation of appropriate prophylactic tuberculosis treatment in accordance with the CDC Guidelines (Table 75).

The incidence of cases of reactivation tuberculosis promptly decreased after initiation of this program, and the proposed labeling supports these recommendations.

Six cases of invasive opportunistic infections caused by histoplasma, aspergillus, and nocardia were also reported in clinical trials.

Table 75 : ISS : Screening prophylaxis methodology employed and maximum dose administered during the adalimumab clinical development program

	Europe		North America	
Year	Screening used	Maximum wk dose[a]	Screening used	Maximum wk dose[a]
1997	Phase I – No screen	10 mg/kg	NA	NA
1998	Phase II – Screen with CXR; no prophylaxis	1 mg/kg	Phase I – Screen only	2.5 mg/kg
1999-2001	Phase III – Screen and exclude if positive CXR	0.5 mg/kg	Phase II/III and III – Screen and recommend prophylaxis if PPD skin test positive	0.5 mg/kg

CXR = chest x-ray NA = Not applicable

[a] 40 mg is assumed to be similar to 0.5 mg/kg and every other week doses are assumed to be similar to one-half the same dose given weekly.

Continued monitoring of adalimumab-treated patients for additional examples of serious and opportunistic infections is needed.

Table 76 : ISS : Listing of tuberculosis cases observed in the adalimumab clinical development program

Study grouping	Initial Study	Patient number	Sex	Country	Age (yrs)	Day on drug at onset	Dose and schedule at onset	Protocol requires screening[a]/ exclusion	Comments
Open-label continuation studies	DE001	114	F	Germany	67	100	10 mg/kg q4wk iv	No/No No screening done [c]	Recovered.
	DE004	16	F	Germany	71	116	1 mg/kg wk sc	No/No No screening done [c]	Recovered.
	DE001	111	F	Germany	67	202	5 mg/kg q4wk iv	No/No No screening done [c]	Recovered.
	DE010	305	M	Germany	63	183	1 mg/kg eow sc	No/No No screening done [c]	Recovered.
	DE011	3511	F	Germany	67	351	40 mg eow sc	Yes/Yes PPD-not done Chest X-ray neg	Recovered. Case entered into database after clinical cut-off of 31- Aug-01.
	DE001	106	F	Germany	45	431	3 mg/kg q4wk iv	No/No No screening done [c]	Recovered.
	DE007	2110	F	UK	68	219	40 mg wk sc	Yes/No No screening done [c]	Recovered.
	DE007	2506	F	Spain	57	241	80 mg wk sc	Yes/No No screening done [c]	Recovered.
Adequate and well-controlled studies	DE019	3813	F	US	28	106	40 mg eow sc	Yes/No[b] PPD- neg Chest X-ray neg	Not resolved. Primary case. Patient had recent family exposure to tuberculosis.
Long-term post-study follow-up	DE011	4801	M	Italy	45	--	Post-study	Yes/Yes PPD-not done Chest X-ray neg	Off adalimumab for 4 months.
	DE011	3408	F	Germany	28	--	Placebo	Yes/Yes PPD-not done Chest X-ray neg	Placebo-treated patient (ie, did not receive adalimumab).
	DE007	1507	F	Germany	70	184	Post-study	Yes/No No screening done [c]	Recovered. Seventy (70) days post adalimumab treatment. Prior treatment was 40 mg weekly.

F = female M = male wk = weekly eow = every other week q4wk = every 4 weeks sc = subcutaneous iv = intravenous

[a] Screening by chest x-ray in EU/Australia and PPD skin test in US/Canada

[b] Prophylaxis recommended but not mandatory

[c] For the eight patients that had no screening tests performed, retrospective review of previous chest x-rays by two radiologists revealed that 6 of the 8 patients had some finding consistent with possible old tuberculosis infection

I. ANA and Anti-dsDNA

In the controlled trials, increases in ANA and anti-dsDNA titers were observed more frequently in adalimumab-treated patients than in placebo-treated patients. At Week 24, 12% of adalimumab-treated patients and 7% of placebo-treated patients shifted from ANA negative at baseline to positive (Table 77).

Table 77 : ISS : ANA Shift – Baseline To LOCF Weeks 12 and 24 [a] –

Adequate and well-Controlled Studies by randomized treatment (safety set)

	20 mg q2w	20 mg qw	40 mg q2w		40 mg qw	80 mg q2w	All adalimumab N = 1289		Placebo N =640	
	Baseline negative patients									
				%				% [1]		% [1]
Baseline negative/ negative at Week 12	124	221	475	86	72	42	934	88	484	90
Baseline negative/ negative at Week 24 [b]	127	213	455	82	76	43	914	86	493	92
Baseline negative/ positive at Week 12	13	25	51	9	15	0	104	10	42	8
Baseline negative/ positive at Week 24 [b]	11	33	77	14	11	0	132	12	39	7

[1] Percentage of maximal number of observations among patients with negative ANA at baseline

[a] Data from Study De031 reports maximum ANA at Weeks 12 and 24 instead of LOCF Week 12 and 24; baseline positive to Week 12 or 24 positive determined by subtraction.

[b] Data from Study De011 substitutes Week 26 for Week 24.

J. Lupus-Like Syndromes

A few cases of lupus-like syndromes with skin rash, serositis, and positive serologies were seen (Table 78). One patient treated with adalimumab developed clinical signs suggestive of new-onset lupus-like syndrome. The patient improved following discontinuation of therapy.

A worldwide search of the safety database (reported November 26, 2002) revealed 4 cases of pleural effusion, 3 cases of pericarditis, and 1 case of pericarditis and pleuritis among adalimumab-treated patients. Information on these cases is still sketchy. Therefore, the role of adalimumab usage in the occurrence of these cases is currently unclear. One case of pleuritis was attributed to be manifestations of the underlying rheumatoid arthritis by biopsy, and one case of pleural effusion was later attributed to tuberculosis. Several of these cases were evaluated for drug-induced lupus erythematosus, but no evidence was found.

The impact of long-term treatment with adalimumab on the development of autoimmune diseases is unknown

Table 78 : ISS : Listing of the lupus-like cases observed during the adalimumab clinical development program

Initial study	Patient number	Sex	Age (yrs)	Day on drug at onset	Dose and schedule at onset	Comments
DE001	94	F	48	1428	40 mg q2w sc	Skin rash and positive serologies
DE007	1526	F	70	168	40 mg wk sc	Serositis and positive serologies
DE010	103	F	49	418	1 mg/kg q2w sc	Undocumented serositis and positive serologies
DE011	113	F	45	107	20 mg wk sc	Probable lupus before study, exacerbation with neutropenia and elevated serologies

F = female wk = weekly q2w = every other week sc = subcutaneous

K. Immunologic Reactions

Table 79 lists the immunologic reactions observed during the clinical development program. They were primarily allergic rashes (14), infusion reactions (7), urticarial reactions (6), and anaphylactic reactions (4).

L. Demyelinating Disease

Table 80 lists the three cases of possible demyelinating disease observed during the clinical development program of adalimumab. Demyelinating disease has been observed in studies of many TNF blockers, including etanercept, infliximab, and lenercept.[10] Of note, one normal volunteer developed demyelinating disease after a single dose of adalimumab. Two of the 3 patients had complete recovery, the other has residual leg numbness.

[10] Mohan N, Edwards ET, Cupps TR, Oliverio PJ, Crayton H, Rickert JR, Siegel JN. Demyelination occurring during anti-tumor necrosis factor α therapy for inflammatory arthritis. *Arthritis & Rheumatism* 2001; 44: 2862-2869.

M. AEs Leading to Withdrawal, Interruption, and Reduction of Study Drug

The most frequent reasons for withdrawal were adverse events, lack of efficacy, and withdrawal of consent. At the recommended dose (40 mg biweekly), AEs among adalimumab-treated patients leading to temporary withdrawal occurred in 18% and permanent withdrawal in 6% of adalimumab-treated patients. The most common adverse events leading to discontinuation of adalimumab were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%). The incidence of temporary withdrawal was higher with weekly dosing and intravenous administration (Table 81).

Table 79 : ISS :Listing of the immunologic reactions observed during the adalimumab clinical development program

Type	Initial study	Patient number	Sex	Age (yrs)	Day on drug at onset	Dose and schedule at onset	SAE Yes/No	Comments
Infusion reaction	DE001	28	F	48	27	1 mg/kg Q4wk iv	Yes	Repeat administration at slower rate.
	DE001	43	F	63	27	1 mg/kg Q4wk iv	No	Repeat administration at slower rate.
	DE001	21	F	26	43	1 mg/kg Q4wk iv	Yes	Discontinued from study.
	DE001	53[a]	F	24	296	3 mg/kg eow iv	Yes	Vasovagal event. Discontinued from study.
	DE001	82	F	76	857	3 mg/kg eow iv	No	No comments.
	DE001	85	F	47	143	3 mg/kg eow iv	No	Two episodes. Discontinued from study.
	DE001	123	F	45	265	3 mg/kg Q4wk iv	Yes	No comments.
Anaphylactoid reaction	DE007	2201	F	36	407	40 mg wk sc	No	No comments.
	DE007	2415	M	53	315	80 mg wk sc	No	No comments.
	DE007	2423	F	51	21	20 mg wk sc	No	Flu-symptoms, three episodes.
	DE019	9903	F	39	22	20 mg wk sc	No	No comments.
								No comments.
Other systemic reaction	DE007	1526	F	70	168	40 mg wk sc	Yes	Lupus-like illness.
	DE019	4814	M	65	118	40 mg eow sc	Yes	Immunosuppression.
Allergic rash	DE001	95	F	40	14	5 mg/kg q4w iv	No	No comments.
	DE007	414	F	64	518	40 mg wk sc	No	No comments.
	DE007	1610	M	67	84	80 mg wk sc	No	No comments.
	DE007	1701	F	58	79	80 mg wk sc	No	No comments.
	DE007	2205	F	67	797	40 mg eow sc	No	No comments.
	DE007	2208	F	46	957	40 mg eow sc	No	No comments.
	DE007	2325	F	71	962	40 mg eow sc	No	No comments.
	DE010	109	F	67	1322	40 mg eow sc	No	No comments.
	DE011	1404	F	36	101	40 mg eow sc	No	Two episodes.
	DE011	3020	F	50	103	20 mg wk sc	No	No comments.

Type	Initial study	Patient number	Sex	Age (yrs)	Day on drug at onset	Dose and schedule at onset	SAE Yes/No	Comments
	DE011	3809	F	37	10	20 mg eow sc	No	Two episodes, 232 days apart.
	DE011	3816	F	54	11	40 mg eow sc	No	No comments.
	DE011	4401	F	70	314	40 mg wk sc	No	No comments.
	DE011	5031	F	58	14	40 mg wk sc	No	No comments.
Urticaria-type reactions	DE007	2101	F	62	733	40 mg q6w sc	No	No comments.
	DE019	5904	F	50	14	40 mg eow sc	No	Two episodes.
	DE019	9305	F	43	20	40 mg eow sc	No	No comments.
	DE019	9604	F	49	56	40 mg eow sc	No	No comments.
	DE031	11908	F	61	265	40 mg eow sc	No	Two episodes.
	DE031	12810	F	68	57	40 mg eow sc	No	No comments.
Fixed drug eruption	DE001	53[a]	F	24	28	3 mg/kg q4w iv	No	No comments.
	DE031	9003	F	24	86	40 mg eow sc	No	No comments.
Lupus-skin reaction	DE010	103	F	49	418	1 mg/kg eow sc	Yes	No systemic symptoms.
Allergic reaction unspecified	DE001	7	F	27	41	1 mg/kg q4w iv	No	No comments.
	DE007	2507	M	53	880	40 mg eow sc	No	No comments.
	DE009	802	F	60	340	40 mg eow sc	No	No comments.

F = female M = male
wk = weekly
eow = every other week
qxwk = every x weeks
sc = subcutaneous
iv = intravenous
[a] This patient had two different and separate allergic type reactions

Table 80 : ISS : Listing of cases of possible demyelinating disease observed in the adalimumab clinical development program

Initial study	Patient number	Sex	Age (yrs)	Day on drug at onset	Dose and schedule at onset	Comments	Post Study Follow-up
DE009	2508	F	50	243	40 mg eow sc	Optic neuritis and subsequent positive MRI.	Patient treated acutely for optic neuritis with high dose corticosteroids, improved and continued on adalimumab. MRI consistent with demyelinating disease. The patient remains asymptomatic and has stopped taking adalimumab
DE024C	77	M	30	8	1 mg/kg iv	Paresthesias in healthy volunteer.	Patient had mild to moderate paresthesias of the upper and lower extremities. MRI consistent with old demyelinating disease (no lesions enhanced with contrast material). Treated with high dose corticosteroids and has recovered off any medications.
DE019	9710	F	52	28	20 mg wk sc	Paresthesias treated with Copaxone.	Patient had episodes of lower extremity numbness. MRI consistent with demyelinating disease. Treated with glatiramer acetate and improved. Jan-02 the glatirarner acetate was discontinued secondary to headaches and the patient was placed on interferon beta-1b. The interferon beta-1b was discontinued in May-02. At this time the patient has intermittent right leg numbness and is able to perform all activities of daily living.

F = female M = male wk = weekly eow = every other week
sc = subcutaneous iv = intravenous

Table 81 : ISS : Adverse Events Leading to Withdrawal, Temporary Interruption , and Reduction of Study Drug

	Adalimumab													
	20 mg sc q2w		20 mg sc qw		40 mg sc q2w		40 mg sc qw		All sc		All IV		All Adalimumab	
	N= 175		N=397		N=1903		N=466		N=2263		N=197		N=2334	
Any adverse event	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
AEs leading to permanent withdrawal [1]	11	6	29	7	114	6	29	6	211	9	42	21	252	11
AEs leading to temporary interruption [2]	16	9	91	23	340	18	103	22	576	26	53	27	614	26
AEs leading to dose reduction [3]	0	0	2	1	2	<1	1	<1	7	<1	16	8	23	1

Reviewer's Table
1 Source of data: sponsor's Table 5.3.11
2 Source of data: sponsor's Table 5.3.12
3 Source of data: sponsor's Table 5.3.13

N. Laboratory Abnormalities

1. Hematologic Changes

Adalimumab-treated patients demonstrated elevations of red blood cells, hemoglobin, and hematocrit levels and reductions in leucocytes, primarily neutrophils (Table 82). To a great extent this represents normalization of abnormal deviations associated with their chronic disease.

Table 82 : ISS : Hematology Changes From Baseline in Adequate and Well-Controlled Studies by Randomized Treatment

	Adalimumab-Treated Patients		Placebo-Treated Patients
Hematological Parameter	**Mean change LOCF Week 24**	**Comment**	**Mean change LOCF Week 24**
Hemoglobin	↑ 4.2 g/L *	Changes greater with higher doses	↑ 0.7 g/L
WBC	↓ 0.6 x 10^9/L *	Neutaphils decreased ; lymphocytes increased	↑ 0.1 x 10^9/L
	WBC ↓ 0.8x 10^9/L * Neutrophils ↓ 8% Lymphocytes ↑ 7%		
Basophils	Mean changes in percentages were very small		
Eosinophils			
Monocytes			
Platelet count	↓ 33.2 x 10^9/L	Changes greater with higher doses	↑ 3.3 x 10^9/L
	↓ 33.5 x 10^9/L		
Hematocrit	Similar to hemoglobin		
RBC			

* $p \leq 0.001$

2. Laboratory Changes

Many subjects (5% to 13 %) had uric acid levels higher than the upper limit of normal (ULN) at baseline. Hyperuricemia was only graded as 1 (>ULN to ≤ 10 mg/DL) or 4 (≥10 mg/DL) with no grading in-between. Adalimumab-treated patients demonstrated a higher frequency of Grade 4 hyperuricemia than placebo-treated patients during the

clinical trials (Table 83). However, nineteen of these twenty subjects demonstrated elevation of uric acid at baseline (10 had Grade 1, and 9 had Grade 4). One adalimumab-treated patient developed an episode of gout and another an episode of nephrolithiasis.

Table 83 : ISS : CTC Grade 3 and 4 Laboratory Changes from Baseline Recorded During Clinical Development Program

Study Group & Test Abnormality	Adalimumab-Treated			Placebo-Treated		
Clinical Pharmacology HV	**Grade 3**	**Grade 4**	**Total/ N**	**Grade 3**	**Grade 4**	**Total/ N**
Hypophosphatemia	5		5/176			
Hyperuricemia		1	1/235			20
Clinical Pharmacology RA						
Hypercholesterolemia	3					
Hyponatremia	1			3		
Hypokalemia	1			1		
Hyperkalemia	1	3		2	2	
Hyperuricemia		2				
Hypercreatinine	1					
Hypophosphatemia					1	
Adequate and Well-controlled						
Low hemoglobin	8			1		
Leukopenia	3			1		
Lymphocytopenia	15			12		
Neutropenia		1			1	
AST elevation	1			2		
ALT elevation	1			2		
CK elevation	2			1		
Hypercholesterolemia						
Hyponatremia		1				
Hypernatremia		1				
Hypokalemia						
Hyperkalemia		1				
Hyperuricemia		20*			7*	
Hypercreatinine						
Hypophosphatemia						

* Among these 27 patients with hyperuricemia, 12 patients had grade 1 hyperuricemia (>ULN – ≤10 mg/dl) and 13 had grade 4 hyperuricemia (≥10 mg/dl) at screening or baseline. Six patients had hyperuricemia classified as an adverse event. One patient had an episode of gout and one patient had a kidney stone possibly related to hyperuricemia. There was no grade 3 hyperuricemia.

3. Liver Enzymes

During the adequate and well-controlled studies, sixteen patients (nine treated with adalimumab and seven treated with placebo) developed AST and ALT liver enzyme elevations greater than twice the ULN. Overall between one and four percent of adalimumab-treated patients developed $\geq$ 2 fold elevation of liver enzymes. This was similar to the percent of placebo-treated patients with liver enzyme elevations (Table 84; Table 85).

Four patients with these elevations did not return to normal by the end of the study or during the open-label continuation studies. Bilirubin levels were always within normal range and albumin and GGT levels were not determined for these patients. In two patients, ALT and AST elevations returned to normal ranges during follow-up periods (one was taking concomitant MTX). In a third patient, taking concomitant MTX, these liver enzymes were elevated at baseline and remained elevated. The fourth patient was eventually diagnosed with primary biliary cirrhosis. None of these four patients received leflunomide.

One patient with a history of fatty liver developed hepatic necrosis and died while receiving adalimumab. This patient never had elevation of AST or ALT. Given the history of liver disease, it is uncertain whether adalimumab was contributory. Nonetheless, vigilance for additional cases of hepatotoxicity is warranted.

Table 84 : ISS : Percentage of Patients with AST Elevation Greater Than Two Times ULN on At Least One Occasion

		Adalimumab Dosage				
Study	**Placebo**	**20 mg q2w**	**20 mg qw**	**40 mg q2w**	**40 mg qw**	**80 mg q2w**
DE009 [1]	0	3		3		1
DE011 [2]	1	4	3	2	0	
DE019 [3]	4		2	3		
DE031 [4]	3			4		

[1] In this study, all patients were on concomitant MTX.
[2] In this study, all patients were on no concomitant DMARDs.
[3] In this study, all patients were on concomitant MTX.
[4] In this study, all patients were on concomitant standard of care which could include any combination of DMARDs.

Table 85 : ISS : Percentage of Patients with ALT Elevation Greater Than Two Times ULN on At Least One Occasion

Study	Placebo	Adalimumab Dosage				
		20 mg q2w	20 mg qw	40 mg q2w	40 mg qw	80 mg q2w
DE009 [1]	2	1		8		4
DE011 [2]	2	1	2	3	2	
DE019 [3]	7		5	3		
DE031 [4]	2			6		

[1] In this study, all patients were on concomitant MTX.
[2] In this study, all patients were on no concomitant DMARDs.
[3] In this study, all patients were on concomitant MTX.
[4] In this study, all patients were on concomitant standard of care which could include any combination of DMARDs.

O. Immunogenicity

Concern has been raised about the ability of HAHAs (human anti-human antibody) to reduce the beneficial effects of biological therapeutic agents, as well as increase the likelihood of adverse effects. Therefore, patients were tested at multiple time-points for antibodies to adalimumab during the 6 to 12 month period of the trials (Table 86). Six percent of adalimumab-treated patients and less than one percent of placebo-treated patients developed low-titer neutralizing HAHAs at titers > 20 ng/ml at least once during treatment.

Table 86 : ISS : Development of HAHAs by randomized treatment in the adequate and well-controlled studies with (DE009, DE019) and without (DE011) background MTX

	20 mg eow (N=175)		20 mg wk (N=324)		40 mg eow (N=387)		40 mg wk (N=103)		80 mg eow (N=73)		All adalimumab (N=1062)		Placebo (N=372)	
	HAHA		HAHA		HAHA		HAHA		HAHA		HAHA		HAHA	
	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)
Study	N	N	N	N	N	N	N	N	N	N	N	N	N	N
DE009[a]	0	89	NA	NA	0	67	NA	NA	1	72	1	208	1	61
DE011[b]	19	87	11	101	20	93	4	99	NA	NA	54	380	0	110
DE019[a]	NA	NA	1	211	2	205	NA	NA	NA	NA	3	416	1	199
All Studies	19	156	12	312	22	385	4	99	1	72	58	1004	2	370

wk = weekly eow = every other week

[a] With concomitant methotrexate.

[b] Without concomitant methotrexate.

Patients receiving biweekly dosing developed antibodies more frequently than those receiving weekly dosing (Table 87).

Table 87 : ISS : Relationship of HAHA Positivity Status to Adalimumab Frequency

	Adalimumab Administration Frequency						Placebo N =372	
	Weekly N = 427		Q2 weeks N = 635		All N =1062			
	n	%	n	%	n	%	n	%
HAHA (+)	16	4	42	7	58	5	2	0.5
	20 mg:	4	20mg:	11				
	40 mg:	4	40mg:	6				

Patients treated with concomitant methotrexate had a lower rate of antibody development than patients on adalimumab monotherapy (1% versus 12%) (Table 88).

Table 88 : ISS : Relationship of HAHA Positivity Status to Adalimumab Concomitant MTX Therapy

	Adalimumab						Placebo N =372	
	Monotherapy N = 434		With MTX N = 628		All N =1062			
	n	%	n	%	n	%	n	%
HAHA (+)	54	12	4	1	58	5	2	1

HAHA-positivity was higher among patients treated biweekly with adalimumab at 20 mg than at 40 mg (Table 89). The long-term immunogenicity of adalimumab is unknown.

Table 89 : ISS : Relationship of HAHA Positivity Status to Adalimumab dosage

	Adalimumab Dosage									
	20 mg N = 499		40 mg N = 490		80 mg N = 73		All N =1062		Placebo N =372	
	n	%	n	%	n	%	n	%	n	%
HAHA (+)	31	6	26	5	1	1	58	5	2	0.5
	Qw	4	Qw	4						
	Q2w	11	Q2w	6						

At the proposed dosage of 40 mg the ACR 20 response was lower among antibody-positive patients (30%) than among antibody-negative patients (50%).

Seven percent (4/58) of HAHA-positive adalimumab-treated patients withdrew prematurely from Studies DE009, DE011, and DE019 (Table 90). One of these four patients withdrew due to an AE. The other patients withdrew due to lack of efficacy (2 patients) and withdrawal of consent (1 patient). There is no evidence for an increase in incidence of withdrawals related to the occurrence of HAHA-positivity

Table 90 : ISS : Withdrawal by reason in Studies DE009, DE011 and DE019 by randomized treatment and HAHA status (101)

	Adalimumab												Placebo	
	20 mg eow		20 mg wk		40 mg eow		40 mg wk		80 mg eow		All doses			
	HAHA (+) N=19	HAHA (-) N=156	HAHA (+) N=12	HAHA (-) N=312	HAHA (+) N=22	HAHA (-) N=385	HAHA (+) N=4	HAHA (-) N=99	HAHA (+) N=1	HAHA (-) N=72	HAHA (+) N=58	HAHA (-) 1004	HAHA (+) N=2	HAHA (-) N=370
Withdrawal/reason	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Total withdrawals	0	17	2	52	2	64	0	8	0	2	4	143	0	86
Planned selection criterion	0	0	0	0	0	1	0	0	0	0	0	1	0	0
Adverse event	0	8	1	18	0	32	0	3	0	1	1	62	0	16
Lost to follow-up	0	0	0	3	0	3	0	0	0	1	0	7	0	4
Protocol violation	0	2	0	5	0	5	0	1	0	0	0	13	0	1
Death	0	0	0	0	0	2	0	0	0	0	0	2	0	1
Withdrawal of consent	0	3	0	12	1	9	0	1	0	0	1	25	0	20
Lack of efficacy	0	4	1	9	1	10	0	3	0	0	2	28	0	37
Administrative reason	0	0	0	5	0	3	0	0	0	0	0	8	0	7

wk = weekly eow = every other week

Treatment-emergent AEs were reported in $\geq$ 5% of all adalimumab-treated patients during Study DE011 (Table 91). HAHA-positivity occurred more frequently in this monotherapy study without concomitant MTX, but HAHA-positivity was not associated with clinically meaningful differences in the incidence of treatment-emergent AEs.

Table 91 : ISS : Overview of treatment-emergent adverse events by HAHA status in Study DE011

	All Adalimumab		Placebo
	HAHA (+) (N=54)	HAHA (-) (N=380)	(N=110)
	N (%)	N (%)	N (%)
Patients with any			
AE	53 (98)	376 (99)	105 (96)
Clinical AE	47 (87)	350 (92)	92 (84)
Laboratory AE	49 (91)	342 (90)	98 (89)
Fatal AE	0 (0)	3 (1)	1 (1)
SAE	8 (15)	54 (14)	18 (16)
Planned surgery	5 (9)	11 (3)	3 (3)
SAE except planned surgeries	4 (7)	47 (12)	15 (14)
AE leading to withdrawal	2 (4)	25 (7)	3 (3)
AE leading to dose interruption	6 (11)	55 (15)	6 (6)
AE leading to dose reduction	1 (2)	0 (0)	0 (0)
At least severe AE	13 (24)	96 (25)	25 (23)
At least possibly drug-related AE	36 (67)	257 (68)	50 (46)
Infection	29 (54)	178 (47)	43 (39)
Serious infection	0 (0)	11 (3)	0 (0)
Malignancy	0 (0)	5 (1)	1 (1)
Immunologic reaction	1 (2)	3 (1)	0 (0)

P. Impact of Dose on Safety

Based on data from Study DE011, the monotherapy trial, adalimumab 40 mg administered weekly showed a higher ACR20 than when administered biweekly, 54% compared to 47%, respectively. The AE rate observed with the two interim dosing schedules did not show an increased adverse event rate in patients treated weekly compared to those treated every other week (Table 92).

Table 92 : ISS : Overview of number (Percentage) of patients with treatment-emergent AEs Subsetted by Dosage (safety set)

	Adalimumab							
	20 mg eow 44.24 pt-yrs (N=106)		20 mg weekly 49.58 pt-yrs (N=112)		40 mg eow 50.07 pt-yrs (N=113)		40 mg weekly 48.61 pt-yrs (N=103)	
Patients with any *	N (%)	N/100 pt-yrs	N (%)	N/100 pt-yrs	N (%)	N/100 pt-yrs	N (%)	N/100 pt-yrs
AE	105 (99.1)	237.4	110 (98.2)	221.9	112 (99.1)	223.7	102 (99.0)	209.9
Serious AE (SAE)	11 (10.4)	24.9	18 (16.1)	36.3	13 (11.5)	26.0	11 (10.7)	22.8
Severe or life-threatening/intractable AE	30 (28.3)	67.8	28 (25.0)	56.5	27 (23.9)	53.9	21 (20.4)	43.2
At least possibly drug- related AE	73 (68.9)	165.0	73 (65.2)	147.2	74 (65.5)	147.8	69 (67.0)	142.0
AE leading to death	0 (0.0)	0.0	0 (0.0)	0.0	2 (1.8)	4.0	1 (1.0)	2.1
AE leading to permanent withdrawal	5 (4.7)	11.3	6 (5.4)	12.1	7 (6.2)	14.0	5 (4.9)	10.3
AE leading to temporary withdrawal	13 (12.3)	29.4	14 (12.5)	28.2	15 (13.3)	30.0	15 (14.6)	30.9
AE leading to dose reduction	0 (0.0)	0.0	1 (0.9)	2.0	0 (0.0)	0.0	0 (0.0)	0.0
AE leading to dose increase	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
AE leading to switch to rescue period	7 (6.6)	15.8	7 (6.3)	14.1	4 (3.5)	8.0	0 (0.0)	0.0
Infection	48 (45.3)	108.5	51 (45.5)	102.9	56 (49.6)	111.8	50 (48.5)	102.9
Serious infection	2 (1.9)	4.5	5 (4.5)	10.1	1 (0.9)	2.0	2 (1.9)	4.1
Malignancy	1 (0.9)	2.3	0 (0.0)	0.0	2 (1.8)	4.0	1 (1.0)	2.1
Immunologic reaction	1 (0.9)	2.3	1 (0.9)	2.0	1 (0.9)	2.0	1 (1.0)	2.1

* More than one AE per patient possible.
* Comparison *versus* placebo (Pearson's χ^2 test): p≤0.05.

Q. Impact of Dose Interruption on Safety

The impact of dose interruption on loss of efficacy and safety was evaluated in a small group of patients who had single dose interruptions of either >70 to ≤ 140 days or > 140 days (Table 93). The majority of patients demonstrating an ACR20 prior to an interruption for >70 to ≤ 140 days maintained their ACR20-response. With only four cases with interruption of > 140 days, the numbers are too small to draw any definite conclusion.

Table 93 : ISS : Impact of Dose Interruption on Efficacy

Duration of Dose Interruption During Therapy in Days	ACR20 Response in Relation to Interruption			
	Response Prior to Interruption		Response Within First Two Time points After Restarting	
	Negative	Positive	Positive	Negative
Dose Interruptions During Therapy - Single				
>70 to ≤ 140 [a] (N with data=101)	[redacted]	40	[redacted]	6 (15%)
			34 (85%)	[redacted]
	61	[redacted]	21 (34%)	[redacted]
			[redacted]	40 (66%)
>140 [b] (N with data=20)	[redacted]	4	[redacted]	2 (50%)
			2 (50%)	[redacted]
	16	[redacted]	9 (56%)	[redacted]
			[redacted]	7 (44%)

[a] approximately 5 to 10 half-lives
[b] approximately 10 half-lives

The types of AEs that occurred before and after dose interruption appeared to be comparable. In the intravenous portion of the clinical development program, two patients had systemic infusion reactions associated with dose interruptions of >70 to ≤140 days (Table 94). Of 20 patients having longer dose interruptions (i.e. >140 days), both in the intravenous portion and subcutaneous portions of the clinical development program, they did not have systemic immunologic reactions.

Table 94 : ISS : Impact of Dose Interruption on Safety

Patients	Type of Immunologic Reaction (Systemic Anaphylactoid Reaction or Urticaria)	
	Before Interruption	After Interruption
Intravenous Portion of Clinical Development Program Interruption >70 to ≤ 140 Days		
Patient # 53	Fixed drug reaction	Two separate infusion reactions Patient remained on study drug
Patient # 85		Two infusion reactions on days 143 and 380. Following second reaction study drug was discontinued.
Intravenous Portion of Clinical Development Program Interruption >140 Days		
None		
Subcutaneous Portion of Clinical Development Program		
None		

R. Impact of Age on Safety

In the AWC studies, the exposure-weighted frequency of AEs increased with increasing age among the elderly in both adalimumab- and placebo-treated groups (Table 95; Table 96). The rate of SAEs, AEs leading to withdrawal, AEs leading to dose interruption, severe or life-threatening/intractable AEs, and serious infections were higher among patients over age 65 compared to patients under 65 in both the adalimumab– and placebo-treatment groups. However, the frequency of patients with serious infections was highest among adalimumab–treated patients over age 65. The frequency of patients with malignancies and fatal AEs, which mainly occurred in the adalimumab-treated group, also increased with increasing age. Due to the relatively small number of patients involved, firm conclusions cannot be reached regarding whether adalimumab increases the relative risk of older patients for these events.

Table 95: ISS - Overview of Number (Number/100 Patient Years) of Patients with Treatment – Emergent AEs Subsetted By Age – Adequate and Well-Controlled Studies (Safety Set)

	Adalimumab 40 mg eow sc						Placebo					
	<65 (N=526)		≥65 (N=179)		≥75 (N=42)		<65 (N=520)		≥65 (N=170)		≥75 (N=34)	
Patients with any[a]	N	(N/100PY)	N	(N/100PY)	N	(N/100PY)	N	(N/100PY)	N	(N/100PY)	N	(N/100PY)
AE	475	(161.7)	163	(155.6)	39	(174.9)	457	(164.3)	141	(167.6)	25	(157.8)
Clinical AE	461	(156.9)	159	(151.8)	39	(174.9)	435	(156.3)	138	(164.0)	24	(151.5)
Laboratory AE	167	(56.8)	49	(46.8)	13	(58.3)	141	(50.7)	37	(44.0)	5	(31.6)
Fatal AE	0	(0.0)	5	(4.8)	3	(13.5)	0	(0.0)	1	(1.2)	0	(0.0)
SAE	31	(10.6)	30	(28.6)	9	(40.4)	40	(14.4)	20	(23.8)	5	(31.6)
AE leading to withdrawal	23	(7.8)	22	(21.0)	5	(22.4)	18	(6.5)	11	(13.1)	4	(25.2)
AE leading to dose interruption	67	(22.8)	36	(34.4)	11	(49.3)	64	(23.0)	22	(26.1)	6	(37.9)
AE leading to dose reduction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Severe or life-threatening/intractable AE	67	(22.8)	46	(43.9)	7	(31.4)	78	(28.0)	36	(42.8)	7	(44.2)
At least possibly drug-related AE	282	(96.0)	94	(89.8)	17	(76.3)	223	(80.2)	57	(67.7)	8	(50.5)
Infection (serious and non-serious)	303	(103.1)	95	(90.7)	21	(94.2)	258	(92.7)	78	(90.3)	14	(88.4)
Serious infection	7	(2.4)	11	(10.5)	2	(9.0)	4	(1.4)	3	(3.6)	1	(6.3)
Malignancy	7	(2.4)	3	(2.9)	2	(9.0)	1	(0.4)	1	(1.2)	0	(0.0)
Immunologic reaction	5	(1.7)	1	(1.0)	0	(0.0)	4	(1.4)	0	(0.0)	0	(0.0)

eow = every other week sc = subcutaneous

[a] More than one AE per patient possible.

Data source: Appendix 3, Table 3.3.1.1d

Table 96 : ISS : Overview of Number (Number of Events/100 Patient Years) of Patients with Treatment –Emergent AEs Subsetted By Age – Adequate and Well-Controlled Studies (Safety Set)

	Adalimumab 40 mg eow sc						Placebo					
	<65 (N=526)		≥65 (N=179)		≥75 (N=42)		<65 (N=520)		≥65 (N=170)		≥75 (N=34)	
Patients with any[a]	E	(E/100PY)	E	(E/100PY)	E	(E/100PY)	E	(E/100PY)	E	(E/100PY)	E	(E/100PY)
AE	3019	(1027.6)	1144	(1092.3)	236	(1054.1)	2484	(892.8)	820	(974.5)	131	(828.8)
Clinical AE	2443	(831.5)	976	(931.9)	198	(879.1)	2098	(754.1)	671	(797.4)	108	(869.0)
Laboratory AE	576	(196.1)	169	(160.4)	39	(174.9)	386	(138.7)	149	(177.1)	25	(157.8)
Fatal AE	0	(0.0)	9	(8.6)	6	(26.9)	0	(0.0)	3	(3.6)	0	(0.0)
SAE	35	(11.9)	45	(43.0)	13	(58.3)	50	(18.0)	25	(29.7)	6	(37.9)
AE leading to withdrawal	32	(10.9)	42	(40.1)	16	(71.8)	27	(9.7)	12	(14.3)	5	(31.6)
AE leading to dose interruption	110	(37.4)	62	(59.2)	19	(85.2)	90	(32.3)	34	(40.4)	7	(44.2)
AE leading to dose reduction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Severe or life-threatening/intractable AE	103	(35.1)	113	(107.9)	20	(89.7)	139	(50.0)	81	(96.3)	19	(119.9)
At least possibly drug-related AE	935	(318.3)	371	(354.2)	73	(327.4)	616	(221.4)	234	(278.1)	47	(296.6)
Infection (serious and non-serious)	561	(191.0)	176	(168.0)	35	(157.0)	469	(168.6)	122	(145.0)	24	(151.5)
Serious infection	7	(2.4)	14	(13.4)	3	(13.5)	4	(1.4)	3	(3.6)	1	(6.3)
Malignancy	7	(2.4)	3	(2.9)	2	(9.0)	1	(0.4)	1	(1.2)	0	(0.0)
Immunologic reaction	6	(2.0)	1	(1.0)	0	(0.0)	4	(1.4)	0	(0.0)	0	(0.0)

eow = every other week sc = subcutaneous

[a] More than one AE per patient possible.

S. Impact of Concomitant Methotrexate on Safety

In order to determine whether concomitant MTX would increase the incidence of AEs associated with adalimumab, a comparison was made of the incidence of AEs with and without concomitant MTX (Table 97). At the proposed adalimumab dosage of 40 mg biweekly, concomitant MTX did not appear to increase the incidence of AEs, SAEs, serious infections, infections, malignancies, or laboratory AEs. However, caution should be used in interpreting these figures since many of the patients treated with concomitant MTX were from different trials than the patients not receiving concomitant MTX. The monotherapy trials were performed in Europe and the MTX combination trials were performed in the US. Differences in the overall incidence of adverse events in the different trials could influence the relative rates shown in Table 97.

Table 97 : ISS : Overview of Adverse Events During Treatment With 40 mg Every Other Week Adalimumab With and Without MTX (All studies in patients with RA through March 29, 2002)

	Adalimumab 40 mg Every Other Week					
	With MTX N=1195			Without MTX N=1005		
Patients with Any	N	%	N/100PY	N	%	N/100PY
AE	1092	91	89	972	97	96
Clinical AE	1080	90	88	918	91	91
Laboratory AE	292	24	19	730	73	72
Fatal AE	8	1	1	7	1	1
SAE	208	17	13	245	24	24
AE leading to withdrawal	81	7	5	78	8	8
AE leading to interruption	258	22	16	242	24	24
AE leading to dose reduction	3	<1	<1	1	<1	<1
Severe/Life-threatening/Intractable AE	250	21	16	306	30	30
At least possibly drug-related AE	585	49	37	615	61	61
Infections (serious and non-serious)	754	53	48	601	60	59
Serious infections	45	4	3	38	4	4
Malignancy	32	3	2	21	2	2
Immunologic reaction	8	1	1	12	1	1

VII. Financial Disclosure

The effect of potential financial conflicts of interest on clinical study results was assessed. Analysis of the financial disclosure forms provided by sponsor listed no participation in financial arrangements or financial interests by clinical investigators of adalimumab in the following clinical studies: DEOO1, DEOO3, DEOO4, DEOO5, DE005X, DEOO7, DEOO9, DEOO9X, DEO11, DEOI5, DEO18, DEOI9, DEO20, DEO24, DEO29 and DE031. In conclusion, results of these studies did not appear to be influenced by potential financial conflicts of interest.

VIII. Overall Summary of Efficacy and Safety

The clinical development of adalimumab focused on establishing the therapeutic indications of 1) reducing the signs and symptoms, 2) inhibiting the progression of structural damage, and 3) improving health-related quality of life and reducing disability in adult patients with moderately to severely active RA who have had an incomplete response to one or more DMARDs. Adalimumab was evaluated in four clinical studies: DE009, a dose ranging trial, DE011, a monotherapy trial, DE019, a background MTX trial, and DE031, a background DMARDs trial (use in a setting comparable to standard rheumatologic care). The results of the randomized efficacy studies are consistent in showing efficacy of adalimumab in reducing the signs and symptoms of rheumatoid arthritis as measured by the ACR20 response. Efficacy of adalimumab was observed in all patient subsets based on baseline demographics, baseline disease activity and baseline prognostic factors. ACR50 and ACR70 responses higher than with placebo were also achieved.

Efficacy of adalimumab was seen both for monotherapy (study DE011), combination therapy with MTX (study DE019), and combination with a variety of other DMARDs that patients were already receiving (study DE031). The optimal dose of adalimumab is 40 mg sc every other week when given in combination with MTX. Higher doses were not more effective (study DE009). In contrast, for monotherapy, although adalimumab 40 mg every other week was effective (43% ACR20 responses at 6 months), 40 mg weekly was associated with higher response rates (54% ACR20 responses at 6 months) (study DE011). Of note, the point estimates of the response rates for adalimumab 40 mg every other week with MTX were higher (63% ACR20 responses at 6 months – study DE019) than with monotherapy (46 % ACR20 responses at 6 months – study DE011). Although comparing results between studies must be done with caution, the higher responses with the adalimumab-MTX combination may be due to inhibition of anti-adalimumab antibody formation by MTX.

Improvement was seen on all the components of the ACR response criteria. Separation between the responses of adalimumab- and placebo-treated patients occurred as early as Week 2 and was maintained through Week 52. In study DE019, adalimumab-treated patients experienced a lower rate of progression in structural damage as measured by the modified Sharpe score than placebo-treated patients. In addition, adalimumab-treated

patients experienced improvement in physical function as measured by the disability index of the HAQ compared to placebo over 52 weeks. However, as stated in the RA Guidance Document, attaining a claim of Improvement in Physical Function requires data demonstrating sustained improvement in the HAQ out to 2 years.

Overall, the short- and long-term safety and tolerability of adalimumab has been demonstrated in a large database of RA patients exposed to the drug for up to 4 years. Adalimumab, at the proposed dosage of 40 mg biweekly, was generally well tolerated, except for the increased occurrence of injection site reactions and pain, upper respiratory infections, abnormal laboratory tests, and rashes. Three categories of events of special interest were observed to occur at a higher frequency among adalimumab-treated patients compared to placebo: deaths, lymphomas, and infections (serious and non-serious).

Twenty-four deaths were observed among the adalimumab-treated patients in the clinical development program. Since the trials included a significant number of older patients, 22% age 65 to 75 and 5% over age 75, some deaths were expected Even though the majority of patients enrolled in these studies were females, the majority of the deaths occurred in male subjects. The most frequent categories of death were cardiovascular, malignancy, infections, and gastrointestinal.

Since most of the patient exposure was from open-label extension studies, there are no concurrent controls for comparison. To provide an estimate as to whether the mortality rate is higher than expected, the mortality rate was compared to that predicted based on sex and age-matched rates in the general US population.

Determination of the Standardized Mortality Rate (SMR) for comparison of the observed death rate to the age-adjusted expected frequency of deaths for this population suggested that the death rate for males was higher (SMR 1.38 [CI, 0.72,2.44]) and the death rate for females was lower than expected (SMR 0.45 [CI, 0.22, 0.83]). Whereas the confidence interval for male deaths overlapped 'one,' the male mortality rate and overall mortality rate were within the expected range. The SMR for the whole group of adalimumab-treated patients was 0.72 [CI, 0.46, 1.05]. These data do not indicate a higher death rate with adalimumab treatment. Collection of additional data with longer-term exposure is warranted, particularly for male patients.

A total of ten lymphomas, primarily Non Hodgkin's lymphoma, was observed in patients treated with adalimumab. The observed SIR (ratio of observed rate to age-adjusted expected frequency) for all lymphomas was 5.4 (95% CI, 2.6, 10.0) compared to the general population. The increased incidence of lymphomas observed among these adalimumab-treated patients has raised concerns about whether adalimumab increases the risk of development of lymphomas. Published literature suggests that RA patients have an approximately 2-fold higher risk of lymphoma than the general population. Furthermore, RA patients with highly active disease have an even greater risk of lymphomas, irrespective of their treatment, in the same range as the SIR reported for adalimumab-treated patients. Analysis of the time-to-onset of the cases of lymphoma seen with adalimumab did not provide evidence of a relationship to duration of

adalimumab therapy. Available data are insufficient to determine whether adalimumab increases the incidence of lymphomas. Continued monitoring of adalimumab-treated patients is necessary to quantify the role of adalimumab, if any, in contributing to the observed higher incidence of lymphomas than in the general population.

Since the introduction of TNF blocking agents, which affect host defenses by modulating cellular immune responses, the Agency has been concerned about an increased risk of serious infections among anti-TNF-treated patients. Patients treated with adalimumab experienced more frequent serious infections than did placebo-treated patients (4.2 vs. 1.9 per 100 patient-years). The most common organs affected by serious infections among adalimumab-treated patients were pulmonary, musculoskeletal, skin, gastrointestinal, and genitourinary. Two patients died and 13 patients withdrew from studies as a result of serious infections. In addition, thirteen cases of tuberculosis (TB) and six cases of invasive opportunistic fungal infections were observed. Implementation of pre-treatment screening with intradermal PPD in the US, chest x-rays in Europe, and appropriate prophylactic anti-tuberculosis treatment in accordance with CDC Guidelines was associated with a reduction in the rate of active TB. However, other variables may have also contributed to the lower rate of TB later in the clinical development program, including less exposure to higher doses of adalimumab and possibly recruitment of fewer patients at high risk of latent TB infection.

For both adalimumab- and placebo-treated patients, the rate of serious infections and deaths due to serious infections were lower among patients <65 years of age. Increasing age among adalimumab-treated patients was associated with an increased occurrence of malignancies, SAEs, AEs leading to withdrawals, and AEs resulting in dose interruption compared to age-matched placebo-treated patients. The percentage of patients with fatal AEs, which only occurred in the adalimumab–treated group, was also higher with advancing age.

In summary, adalimumab treatment has demonstrated substantial efficacy, both for signs and symptoms as well as for progression of structural damage to joints and for improvement in disability for up to 12 months. Uncommon, but serious adverse events were observed in adalimumab-treated patients. Overall, adalimumab has shown a favorable benefit to risk profile when administered subcutaneously at the recommended dose of 40 mg every other week, and the higher dose of 40 mg weekly, either alone or in combination with methotrexate or other DMARDs.