Human platelets and megakaryocytes express surface CD11a and LFA-1, and the murine progenitor of the humanized antibody used in the psoriasis clinical trials has been reported to bind to human platelets. Therefore, there is a molecular basis for these adverse events of thrombocytopenia potentially linking it to the study drug. The delayed time course (at least 3 months in most cases) of the thrombocytopenia in addition to the response to systemic steroids suggests an immune-based mechanism of platelet depletion rather than direct toxicity. Furthermore, one patient (33203) tested positive for an anti-platelet antibody. It is unknown whether the other patients were tested.

Narratives for the patients with serious adverse events of thrombocytopenia are provided below.

Patient 44202:

The patient was a 73-year-old woman enrolled in Study 2601g, an open label-multicenter study for patients who previously participated in study 2600g. The patient received efalizumab (1 mg/kg/wk) for psoriasis in Study 2600g starting in September 25, 2002. On ——— her platelet count was noted to be 3,000/ mm3 without associated symptoms. She was admitted to the hospital. Her evaluation was positive for ANA>1:1280. She was treated with IV steroids and discharged with a platelet count of 60,000/ mm3 and oral prednisone. Her medical history and concomitant medications were not reported. The investigator assessed the event as not related to efalizumab. The sponsor's assessment of causality is possibly related.

Patient 10501

A 61 year-old man patient treated with efalizumab 2 mg/kg for approximately 12 weeks prior to the onset of the event. The patient's platelet count was within the normal range from March 21, 2000 to May 17, 2000. On June 14, 2000 his platelet count was 124, 000 cells/mm3. By July 19, 2000, it had dropped to 63,000 cells/mm3. He had no associated evidence of bleeding or hepatosplenomegaly. His bone marrow was normocellular on biopsy. His initial treatment was with systemic steroids. The event resolved after 112 days. The investigator's assessment was possibly related.

Patient 33203

41-year-old female treated with efalizumab 1 mg/kg for approximately 22 weeks prior to event onset. She presented with bruising and her platelet count was found to be 10, 000 cells/mm3. She was permanently discontinued from the study. On August 24, 2002, she was hospitalized with heavy vaginal bleeding and required a platelet transfusion of 10 units and RhoGam. The thrombocytopenia resolved after 41 days. The investigator assessed the event as possibly related.

Reviewer's comment: Although the event was reported to have resolved, the patient at last report was still receiving prednisone at a dose of 25 mg po per day. Therefore, more follow-up is needed to determine whether the patient remained prednisone-dependent for the treatment of her thrombocytopenia.

Patient 27103

A 29-year-old male subject with a past-medical history of thrombocytopenia and generalized seizures, controlled with medication (phenitoin and divalproex). The subject received

efalizumab 1 mg/kg for 17 months and the dose increased to 2 mg/kg 10 days prior to event onset. The subject required hospitalization for diminished oral intake and his platelet count was found to be 33,000 cells/mm^3. The event resolved after 35 days. The subject was permanently discontinued from the study. The investigator stated that the event was not related to efalizumab.

Based on available platelet count measurements, the onset of platelet decline was between 8 and 12 weeks after the first dose of efalizumab in 5 of the 8 patients. Onset was more delayed in 3 patients, occurring as late as one year in 1 patient. In these cases, the platelet count nadirs occurred between 12 and 72 weeks after the first dose of efalizumab.

7.2.8 Psoriasis Flares and Rebound

Of the 2589 subjects treated with SC efalizumab (Genentech or XOMA materials), 19 (0.7%) had a serious adverse event of psoriasis. These included psoriasis flares that occurred both during treatment and after treatment discontinuation.

The following were observed in subjects treated with the to-be-marketed efalizumab (i.e. Genentech material):

- In the first exposure of controlled clinical trials of efalizumab, adverse events of psoriasis occurred in more subjects receiving efalizumab (2.4%, n=22) than placebo (1.1%, n=5).
- Only subjects receiving efalizumab experienced psoriatic erythroderma, pustular psoriasis and palmoplantar psoriasis.
- In the FE studies, <1% of subjects experienced severe psoriasis and <0.5% discontinued efalizumab treatment because of psoriasis as an adverse event.
- In the EE studies, the incidence of adverse events of psoriasis was lower during Weeks 24–60 of continuous treatment compared with Weeks 12–24 of treatment.
- Adverse events of psoriasis were similar to FE during RE.
- Adverse events of psoriasis were approximately three times as common and more likely to be serious or severe during WO compared with FE.

Table 101 below shows the proportions of patients in the first exposure controlled period with psoriasis adverse events occurring during treatment. This table includes all psoriatic adverse events by morphology, both serious and non-serious.

Table 101 Psoriasis Flares and Variants Reported for First Exposure, Controlled Period (XOMA and GNE)

Adverse Event	Placebo 715	All Efalizumab 1620
Subjects with psoriasis AEs	10 (1.4%)	52 (3.2%)
Psoriatic erythroderma	0	9 (0.6%)
Pustular psoriasis	0	4 (0.2%)
Guttate psoriasis	2 (0.3%)	19 (1.2%)
Recurrence of plaque psoriasis	6 (0.8%)	9 (0.6%)
Unusual morphology	2 (0.3%)	6 (0.4%)
Inverse psoriasis	0	5 (0.3%)
Palmo-plantar psoriasis	0	4 (0.2%)

In this analysis, all the cases of psoriatic erythroderma and pustular psoriasis occurred in the efalizumab treatment arms. One patient with erythroderma in the first exposure controlled portion required hospitalization (25609).

Table 102 below shows the serious adverse events of psoriasis in efalizumab-treated patients by treatment period.

Table 102 Serious Adverse Events of Psoriasis Flares Experienced by Subjects Treated with Efalizumab

Subject ID	Event	Exposure Period	Response to Treatment	Admitted to Hospital
25609	Erythroderma	FE	NR	Yes
16513	Erythroderma	EE	NR	Yes
82009	Exfoliative erythroderma	EE	Initial R, then lost efficacy to NR	Yes
16517	Erythroderma	RE	PR	Yes
19515	Erythroderma	WO	NR	Yes
21505	Erythrodermic pustular	WO	R	Yes
25906	Pustular von Zumbusch	WO	NR	No
27708	Pustular	WO	PR initially then lost efficacy to NR	Yes
64006	Flare	WO	NR	Yes
82024	Erythroderma	WO	R	Yes
12516	Pustular	Post-WO	NR	Yes
16533	Erythroderma	NC [a]	NR	Yes
25914	Pustular von Zumbusch	Post-WO	PR initially then lost efficacy to NR	No
28615	Pustular	Post-WO	R	Yes
80002	Atypical flare	Post-WO	NR	Yes
16511	Erythroderma	NC [a]	NR	Yes
25601	Psoriasis Flare	WO	R	Yes
31614	Erythrodermic psoriasis	WO	NR	Yes
32802	Worsening of psoriasis	ET	NR	Yes

NC=not classified; NR=non-responder or non-response; PR=partial responder; R=responder.
WO= washout; FE= first exposure; EE= extended treatment
[a] The event occurred approximately 4 weeks after early discontinuation from FE. The subject had received three doses of efalizumab. The case was also counted during WO.

Most of the psoriasis adverse events that required hospitalization occurred in the extended treatment, washout or post-washout period. The two serious adverse events of psoriasis that did not result in hospitalization were deemed serious by the clinical investigator becaue they resulted in disability of the patient. Although most of the patients were classified as non-responders, some patients who were responders subsequently developed serious psoriasis-related complications.

Narratives of Psoriasis-related Adverse Events:

Subject No.: 12516

Events: Psoriasis (pustular psoriasis flare)
This 59-year-old man was randomized to 2.0 mg/kg/wk efalizumab in study ADC2058g and received his initial dose of 0.7 mg/kg on 15 May 2000. He also had had psoriasis for 6 years and had previously used systemic therapies. The patient's only medication at baseline was chlorpheniramine maleate/phenylpropanolamine hydrochloride, for sinus, since the 1960's. On FT Day 76, the patient was diagnosed with impetigo for which he was prescribed doxycycline. On FT Day 77, on the day his last dose of efalizumab, he began to experience a severe psoriasis flare accompanied by headaches, nausea and vomiting which lead to discontinuation from the study. The patient was treated with methotrexate and corticosteroid therapy. Approximately 10 days later, while on methotrexate and corticosteroid therapy, a severe diffuse pustular psoriasis flare was diagnosed for which he was hospitalized. The pustular psoriasis flare resolved in 8 days, and the headache, malaise, and vomiting continued beyond the subject's participation in the study. The investigator determined the psoriasis flare, headache, malaise, vomiting, and the serious adverse event of pustular psoriasis flare to be not related to study drug.

Reviewer's comment: Of note, the patient had severe flare of psoriasis during the first treatment period. This was followed by the episode of pustular psoriasis while on systemic corticosteroids and methotrexate. The fact that these events followed so closely and began within 1 day of dosing would make it seem unlikely that close observation with institution of alternative treatment could have prevented the sequence of events. In addition, according to the history, the patient developed "impetigo" within one day preceding the adverse event of psoriasis flare. Pustular impetigo is in the clinical differential diagnosis of pustular psoriasis and therefore, it is conceivable that the patient had pustular psoriasis rather than the impetigo. If this were the case, the pustular psoriasis diagnosis would have taken place during the first treatment period. It is also, worth noting that the patient demonstrated improvement in his psoriasis during the first treatment period his PASI improvement was up to 82% on FT day 42, approximately mid-way through his treatment course. This reviewer disagrees with the investigator's assessment of causality as the temporal relationship of this event as well as lack of an alternative explanation would indicate that the adverse event could possibly be related to use of the study drug.

Subject No.: 16517
This 30-year-old man had had psoriasis for 12 years and had a history of systemic therapy. He initially participated in the Genentech-sponsored study ACD2058g. He received placebo for the first 12 weeks followed by 2.0 mg/kg/wk SC efalizumab for the subsequent 12 weeks (ET), for a total of 12 doses of efalizumab. The patient showed clinical response to his first exposure to study drug in the ET period and ended the treatment with a PASI score of 3.9, an 85% improvement in PASI from baseline. Within one month of discontinuing therapy, during the follow-up period, however, his PASI increased to 25.7.

Approximately 5 weeks after discontinuation of therapy, the subject entered Study ACD2062g in the Re-Exposure group with a PASI score of 61.2. The day after receiving his first dose of study drug, the subject was hospitalized for a severe erythrodermic psoriasis flare. The investigator determined the event of erythrodermic psoriasis flare to be not related to study drug.

Comments: Note, this patient's psoriasis quickly deteriorated within one month of discontinuation of therapy and the patient suffered an erythrodermic flare resulting in

hospitalization within 5 weeks of stopping therapy. Of note, this case meets the National Psoriasis Foundation's definition of rebound: a PASI of 125% of baseline or new generalized pustular, erythrodermic or more inflammatory psoriasis occurring within 3 months of stopping therapy.

Four subjects were receiving efalizumab at the time of the serious adverse event of psoriasis:

Subject No.: 25609
This 66-year-old woman had psoriasis for 15 years and a history of systemic therapy. She entered Study ACD2243g and was randomized to receive 2.0 mg/kg/wk SC efalizumab without topical corticosteroid therapy in the FT period. PASI at the time of the conditioning dose was 33. After receiving the fifth dose of study drug, the subject's PASI was 25. A total of seven doses of efalizumab were given.

Six weeks after her first dose, the subject began to develop a severe psoriasis exacerbation and discontinued efalizumab treatment and study participation. One week later, she developed a severe erythrodermic exacerbation of psoriasis and was hospitalized. PASI at this time was 31. Treatment included triamcinolone wraps, cyclosporine, and methotrexate. The subject was discharged in good condition in 4 days. The event resolved after 5 days. The investigator determined the psoriasis exacerbation and erythrodermic exacerbation of psoriasis to be related to efalizumab.

Comments: Of note, the patient's PASI score at the time of her erythrodermic flare, 31, was similar to her baseline PASI score of 33. The narrative does not address whether the patient had a positive anti-efalizumab antibody. It is unusual that the patient received both cyclosporin and methotrexate in the hospital.

Subject No.: 82009
54-year-old man. During the FT period, the subject's PASI scores had decreased from 13.6 to 2.8, and the percentage of psoriatic BSA had decreased from 12.9% to 3.0%.
On 4 September (ET Day 4), the subject reported that his psoriasis had worsened. Within 1 week, his body was covered with psoriatic lesions and he was erythrodermic. On 14 September 2000, he returned for evaluation and was noted to be erythrodermic with a PASI of 59.6 and a BSA of 90% involvement. According to the investigator, the psoriasis flare was not related to efalizumab.

Comments: This patient initially improved with efalizumab therapy. However, in this case, the patient developed clinically significant worsening requiring hospitalization despite continuing the treatment and negative anti-efalizumab antibody test results.

Table 103 below shows the severe non-serious psoriasis-related adverse events by treatment period.

Table 103 Severe Non-Serious Adverse Events of Erythrodermic or Pustular Psoriasis Reported for Efalizumab-Treated Subjects

Subject ID	Event	Exposure Period	Response to Treatment	Intensity
82026	Erythroderma	FE	NR	Severe
34229	Erythroderma	FE	NR	Severe
75610	Erythroderma	FE	NR	Severe
79202	Pustules in groin	FE	PR	Severe
69202	Erythroderma	WO	R	Severe
79208	Pustular lesions on groin/buttocks	WO	PR initially then lost efficacy to NR	Severe
80811	Erythroderma	WO	R	Severe
82003	Erythroderma	WO	PR	Severe
18503	Erythroderma	WO	NR	Severe
31403	Erythroderma	FE	NR	Severe
34229	Erythroderma	FE	NR	Severe
43409	Erythroderma	FE	NR	Severe
46410	Erythroderma	FE	NR	Severe

NR=non-responder or non-response; PR=partial responder; R=responder.

Each of these non-serious adverse events was listed as severe in intensity. They occurred both during treatment and after discontinuation with treatment. In some cases, the patient was classified as a responder and experienced rebound upon discontinuation of study drug. There were no cases of psoriasis variants in the control group.

Some of patients (e.g.11504, 17501) who discontinued from the study with psoriasis-related adverse events including (including some who had variants of psoriasis) were incorrectly classified as having discontinued for other causes i.e. "physician's decision."

7.2.9 Arthritis-Related Adverse Events

The incidence of arthritic adverse events by treatment group in shown in Table 104 below.

Table 104 Arthritis-Related Adverse Events Studies ACD2058g, ACD2059g, ACD2390g, and ACD2600g (FT Period): All Subjects

COSTART Preferred Term	Classification	Placebo (N=715)		Efalizumab 1.0 mg/kg/wk (N=1213)		Efalizumab 2.0 mg/kg/wk (N=407)		Efalizumab All Subjects (N=1620)	
Subjects with completed forms		715		1213		407		1620	
- Total -		16	(2.2%)	29	(2.4%)	16	(3.9%)	45	(2.8%)
Arthritis NOS		7	(1.0%)	8	(0.7%)	9	(2.2%)	17	(1.0%)
Exacerbation/flare psoriatic arthritis		2	(0.3%)	13	(1.1%)	4	(1.0%)	17	(1.0%)
Worsening/increasing psoriatic arthritis		3	(0.4%)	5	(0.4%)	2	(0.5%)	7	(0.4%)
Psoriatic arthritis		3	(0.4%)	2	(0.2%)	1	(0.2%)	3	(0.2%)
Osteoarthritis		1	(0.1%)	1	(<0.1%)	1	(0.2%)	2	(0.1%)

During the first treatment period, a higher proportion of patients in the combined efalizumab-treated group experienced exacerbation/ flares in psoriatic arthritis than placebo (1.1% vs. 0.3%). The incidence of arthritis not otherwise specified and osteoarthritis was the same in the combined efalizumab groups as in the placebo group. The incidence of arthritis-related adverse events was 2.2% in placebo, 2.4% in the 1-mg/kg/wk and 3.9% in the 2-mg/kg/wk groups.

There have been 15 cases of serious adverse events for arthritis, 0.6% of the studied population. None of the serious adverse events occurred within the first treatment period of placebo controlled studies.

Some of the serious adverse events for inflammatory arthritis are notable for occurring in association with other findings of inflammation, including neuritis, peripheral edema and bilateral cellulitis, fever and positive ANA. See the narratives below.

New onset inflammatory arthritis, accompanied by fever, peripheral edema, and neuritis: patient (28336)

The subject, a 49-year-old man, with a three-year history of psoriatic arthritis, previously treated with systemic corticosteroids, but negative history for psoriatic arthritis entered Study ACD2243g and was randomized to receive 2.0 mg/kg/wk SC efalizumab. After receiving, four doses of efalizumab, the patient experienced severe inflammatory arthritis, characterized by left ankle pain, followed by moderate bilateral lower leg peripheral edema and cellulitis of both feet. The patient was treated with nonsteroidal antiinflammatory medications and antibiotics without improvement, and continued to receive efalizumab. Approximately 7 weeks after the first dose, the subject complained of arthralgias, neuritis to feet, total body joint inflammation, and severe right knee pain associated with a right knee effusion, and increasing bilateral lower extremity peripheral edema. The patient was unable to ambulate subsequently hospitalized for further evaluation. Evaluation was negative for a deep vein thrombosis. An antinuclear antibody test done previously was positive and chemistries revealed an elevated sedimentation rate and creatine kinase. The patient received systemic corticosteroids and IV antibiotics. By the following day, the edema had markedly decreased and the subject was discharged on methylprednisolone, cephalexin, gabapentin. By 8 weeks after the first dose and 1 week after discontinuation of efalizumab, the subject experienced intermittent fevers lasting 45 days. He was re-hospitalized for three days for increased ankle edema and lower extremity pain. He underwent aspiration of a left knee effusion twice following discharge. He was hospitalized for left knee debridement, lavage, and antibiotic therapy. Laboratory results revealed an elevated sedimentation rate. During hospitalization, the subject experienced intermittent fevers, but an infectious etiology was ruled out. The subject continued to have an elevated sedimentation rate, and steroid therapy was initiated. A rheumatologist made the diagnosis of inflammatory arthritis and initiated methotrexate. The subject continued to have intermittent pain and edema to his lower extremities, while his arthritis was improved by 7 months after the onset of the adverse event. The event remains ongoing. The investigator determined the inflammatory arthritis and bilateral lower extremity cellulitis to be related to efalizumab.

Reviewer's comment: This adverse event is unusual because it resulted in hospitalization on three occasions and (as of the most recent report to the Agency) failed to resolve after discontinuation of therapy. After examining the clinical database, it was determined that the patient tested negative to anti-efalizuamab antibodies during and after treatment discontinuation.

Psoriatic Arthritis and psoriasis flare (25601)

A 24-year-old Asian female assigned to 1.0 mg/kg/wk efalizumab enrolled in Study ACD2243g and received the first dose of 2.0 mg/kg/wk efalizumab on 22 March 2001.
The subject's medical history was significant for adequately controlled type 1 diabetes (since 1996) and psoriatic arthritis in the knees (since 1997). The subject experienced two events of a psoriatic arthritis flares. On [redacted], the subject was evaluated by her physician for left-knee pain. Treatment included celecoxib. Within a few days she noted swelling in both knees and an X-ray of the left knee revealed a small joint effusion. One week later, the subject was unable to ambulate. She was admitted to the hospital where she was treated for 3 days. An arthrocentesis was performed, which revealed a white blood cell (WBC) count of 41,000/μL,

with 87% segmented neutrophils, and no crystals and no organisms identified on Gram stain. The subject's Rhesus factor was 30, erythrocyte sedimentation rate was 40 mm/hr, and an antinuclear antibody test was positive. The subject noted her psoriasis started to worsen during hospitalization and continued to worsen despite having initiated treatment with methotrexate. She was subsequently hospitalized with an erythrodermic psoriasis flare. The psoriatic arthritis flare was noted to resolve on December 17, 2002. The investigator determined the psoriatic arthritis flare to be related to study drug and the psoriasis flare not to be related to study drug.

Reviewer's comment:
This case was notable for a flare in both psoriasis and psoriatic arthritis.

7.2.10 Serious Vascular and Thrombotic Events

Table 105 below presents serious cardiovascular events experienced by subjects within the first treatment period of placebo controlled studies.

Table 105 Serious Cardiovascular Adverse Events First Exposure Controlled Studies

Adverse Event n	Placebo 715	Efalizumab (combined) 1620
Subjects with at least one event	1 (0.1%)	4 (0.2%)
Coronary artery disorder	0	2 (0.1%)
Angina pectoris	0	0
Arteriosclerosis	0	0
Arteriospasm	0	1(<0.1%)
Myocardial infarct	1 (0.1%)	1(<0.1%)
Deep thrombophlebitis	0	0
Cerebral ischemia	0	0
Pulmonary embolus	0	0
Peripheral vascular disorder	0	0

The incidence of these serious cardiovascular events was low and was similar between efalizumab- and placebo-treated subjects. There was no apparent increase in incidence in serious cardiovascular events associated with efalizumab treatment. However, the numbers are too small to draw any definitive conclusions.

All cardiovascular adverse events (serious and non-serious) were also analyzed (see Table 106).

Table 106 All Cardiovascular Adverse Events First Treatment Period

Group of Cardiovascular Adverse Events		Placebo (N=715)	Efalizumab 1.0 mg/kg/wk (N=1213)	Efalizumab 2.0 mg/kg/wk (N=407)	Efalizumab All Subjects (N=1620)
Subjects with completed forms		715	1213	407	1620
Subjects with at least one cardiovascular adverse event*		19 (2.7%)	38 (3.1%)	7 (1.7%)	45 (2.8%)
Arrhythmia	- Total -	4 (0.6%)	6 (0.5%)	2 (0.5%)	8 (0.5%)
Cardiovascular Disease	- Total -	1 (0.1%)	6 (0.5%)	1 (0.2%)	7 (0.4%)
	CARDIOVASCULAR DISORDER	(0.0%)	2 (0.2%)	(0.0%)	2 (0.1%)
	CORONARY ARTERY DISORDER	(0.0%)	1 (<0.1%)	1 (0.2%)	2 (0.1%)
	ANGINA PECTORIS	(0.0%)	1 (<0.1%)	(0.0%)	1 (<0.1%)
	ARTERIOSPASM	(0.0%)	1 (<0.1%)	(0.0%)	1 (<0.1%)
	MYOCARDIAL INFARCT	1 (0.1%)	1 (<0.1%)	(0.0%)	1 (<0.1%)
Congestive Heart Failure and Cardiomegaly	- Total -	(0.0%)	2 (0.2%)	(0.0%)	2 (0.1%)
	CONGESTIVE HEART FAILURE	(0.0%)	2 (0.2%)	(0.0%)	2 (0.1%)
	CARDIOMEGALY	(0.0%)	1 (<0.1%)	(0.0%)	1 (<0.1%)
Hypertension	- Total -	6 (0.8%)	12 (1.0%)	2 (0.5%)	14 (0.9%)
Hypotension	- Total -	2 (0.3%)	1 (<0.1%)	1 (0.2%)	2 (0.1%)

No signals were seen with respect to arrhythmia, congestive heart failure and cardiomegaly, hypertension and hypotension. The proportion of patients with cardiovascular disease was numerically slightly higher in the efalizumab-treated patients; however, the numbers were very small and no firm conclusions can be made regarding efalizumab and cardiovascular risk from these data.

7.2.11 Serious Inflammatory and Autoimmune Reactions

Two cases of pneumonitis occurred in clinical development (See narratives below). One case was classified as eosinophilic pneumonitis. In addition, search of the sponsor's safety database was performed which revealed another case of pneumonitis in a 38 year old-man. One patient presented with adenopathy, fever, and arthritic symptoms which her clinician indicated was a diagnosis of a serum-sickness like reaction.

Eosinophilic pneumonitis

The patient (40011) is a 66-year-old male with a history of hypertension enrolled in trial ACD2601g. His history was negative for previous autoimmune disease, methotrexate use or lung disease. He received efalizumab 1 mg/kg/wk SC for 6 months. Concomitant medications included aspirin, hydrochlorothiazide and propranolol (dates unknown). The patient was diagnosed after having presented with flu-like symptoms and shortness of breath beginning on 31-Jan-2003, three months after his first dose of efalizumab in trial ACD2600g. The drug was

temporarily stopped on 21-Feb-2003 but then resumed on 27-Feb-2003. The patient had an increased white blood cell count of $19.9x10^3$/mm3 and notable for an eosinophil count of 13%. Chest radiography and follow-up CT scan both showed cardiomegaly and bilateral diffuse interstitial lung disease. Pulmonary function tests showed significant restrictive lung disease with gas transfer defect. Lung biopsy showed mild, non-specific, chronic inflammation and interstitial thickening without atypia. The patient was treated by permanent discontinuation of efalizumab (last dose April 23, 2003) and systemic corticosteroids. The patient's symptoms resolved after the drug was discontinued. The investigator classified the event as possibly related to study drug.

Reviewer's comment: The patient continued to receive efalizumab for several months despite having had continued symptoms of a flu-like illness and dyspnea, an important protocol violation to note. If licensed, the label should advise to withhold dosing in the presence of unexplained pulmonary symptomatology suchas shortness of breath.

Pneumonitis

The second patient is a 38 year-old man who was enrolled in study ACD2059g. The patient had no previous history of systemic therapy for psoriasis and was a nonsmoker. The subject received placebo 1.0 mg/kg/wk in the first treatment course (first dose received on August 8, 2000). The patient received 4.0 mg/kg/wk efalizumab during the extended treatment period. The onset of the adverse event occurred 2 days after the patient received his 9th dose of study drug on December 29, 2000. The patient failed outpatient treatment with levofloxacin. After home dosing on January 3, 2001 the patient experienced worsening of symptoms and study drug was permanently discontinued. On ——— the patient was hospitalized for a fever and ongoing dry cough and was noted to be hypoxic (pO2 level of 52). Chest X ray revealed diffuse parenchymal changes consistent with drug-induced hypersensitivity. Bronchoscopy results were unremarkable with all cultures and diagnostic tests negative. The patient received supplemental oxygen, trimethoprim/sulfamthoxazole and methylprednisolone. The pneumonitis resolved after 60 days. Test results for antiefalizumab antibodies were negative. The investigator indicated the final diagnosis was pneumonitis of unknown etiology and assessed the event as related to study drug.

Serum-sickness-like reaction

The patient (42004) is a 35year-old female who received treatment with efalizumab 1.0 mg/kg/wk in study ACD2600g. Three and half weeks after receiving the first dose of efalizumab, the patient presented to the emergency room with tender cervical lymphadenopathy, fever and slight chest pressure. She was admitted to the hospital and the following laboratory evaluations were negative: chest x-ray, blood cultures, EBV titer, CMV titer, monospot. The patient had psoriatic arthritis at baseline and while in the hospital she experienced febrile episodes and an exacerbation of her psoriatic arthritis accompanied with an elevation of the erythrocyte sedimentation rate. She responded to prednisone at a dose of 60 mg per day with an improvement in her lymphadenopathy and psoriatic arthritis symptoms. The investigator's assessment of relationship to study medication was potentially related while the physician responsible for the patient's care in the hospital reported the relationship as causal and advised the patient not to receive efalizumab in the future. Follow-up information revealed that the patient's adenopathy had resolved without evidence of recurrence. Similar adverse events

involving adenopathy and fever of unknown origin are in the efalizumab safety database. This event possibly represents a serum sickness-like reaction to the study drug.

7.3 Severe Adverse Events

During the first treatment period of controlled clinical trials, the proportion of patients with at least one severe adverse event was higher among efalizumab-treated (11.8%) patients than placebo-treated patients (6.9%).

Severe adverse events seen in higher proportions of efalizumab-treated patients included: headache, chills, pain, fever, neck rigidity, migraine, nausea, arthritis, dizziness thrombocytopenia, psoriasis and kidney calculus (Table 2.7.4.2.1/37 of amendment 23 of the BLA submission, data not shown).

The incidence overall of kidney calculus was 0/715 placebo treated patients, 9/1213 efalizumab (1 mg/kg) treated patients and 2/407 (1 mild and 1 moderate) efalizumab (2 mg/kg) patients. Six of the 9 cases of kidney calculus in the 1-mg/kg/wk efalizumab group were classified as severe.

Reviewer's comment:
The finding of kidney calculus is unexplained. This observation will be monitored in spontaneous post-marketing database. It is not known whether there is a causal relationship with efalizumab.

7.4 Common Adverse Events

Adverse events with a ≥ 1% higher incidence among the efalizumab-treated patients compared to placebo-treated patients in the first exposure in controlled studies are shown below.

Table 107 Adverse Events that Occurred in ≥ 1% of Subjects Treated with Efalizumab (1 or 2 mg/kg/wk) Compared with Placebo

	Placebo (n=715)	Efalizumab 1 mg/kg/wk (n=1213)	Efalizumab 2 mg/kg/wk (n=407)
Headache	159 (22%)	391 (32%)	151 (37%)
Infection	188 (26%)	350 (29%)	114 (28%)
Chills	32 (4%)	154 (13%)	53 (13%)
Nausea	51 (7%)	128 (11%)	56 (14%)
Vomiting	12 (1.7%)	26 (2.1%)	17 (4.2%)
Pain	38 (5%)	122 (10%)	45 (11%)
Back pain	14 (2%)	50 (4%)	25 (6%)
Abdominal pain	6 (0.8%)	25 (2.1%)	11 (2.7%)
Chest pain	4 (0.6%)	20 (1.6%)	9 (2.2%)
Myalgia	35 (5%)	102 (8%)	32 (8%)
Flu Syndrome	29 (4%)	83 (7%)	19 (5%)
Arthralgia	19 (2.7%)	52 (4.3%)	14 (3.4%)
Arthritis	16 (2.2%)	29 (2.4%)	16 (3.9%)
Fever	24 (3%)	80 (7%)	46 (11%)
Acne	4 (1%)	45 (4%)	11 (2.7%)
Peripheral edema	18 (2.5%)	47 (3.9%)	17 (4.2%)
Pharyngitis	47 (6.6%)	88 (7.3%)	31 (7.6%)
Dizziness	21 (2.9%)	41 (3.4%)	17 (4.2%)
Psoriasis	10 (1.4%)	39 (3.2%)	13 (3.2%)
Herpes Simplex	24 (3.4%)	49 (4.0%)	25 (6.1%)
Conjunctivitis	10 (1.4%)	28 (2.3%)	13 (3.2%)
Deafness	5 (0.7%)	13 (1.1%)	15 (3.7%)
Migraine	2 (0.3%)	16 (1.3%)	4 (1.0%)
Urticaria	3 (0.4%)	16 (1.3%)	6 (1.5%)
Fungal Dermatitis	1 (0.1%)	5 (0.4%)	9 (2.2%)

Adverse events with a 5% or higher incidence among efalizumab-treated patients compared to placebo-treated patients were headache and chills. The incidence of adverse events appears to be higher in the 2 mg/kg group compared to the 1 mg/kg group.

7.5 Hypersensitivity Reactions (serious and non-serious)

The following table provides a placebo-controlled comparison of the hypersensitivity-related adverse events predefined in the clinical protocol.

Table 108 Hypersensitivity-Related Adverse Events Studies ACD2058g, ACD2059g, ACD2390g, and ACD2600g (FT Period): All Subjects Treated with Combined Materials

COSTART Body System	COSTART Preferred Term	Placebo (N=715)		Efalizumab 1.0 mg/kg/wk (N=1213)		Efalizumab 2.0 mg/kg/wk (N=407)		Efalizumab All Subjects (N=1620)	
Subjects with completed forms		715		1213		407		1620	
Subjects with at least one hypersensitivity-related adverse event		49	(6.9%)	95	(7.8%)	37	(9.1%)	132	(8.1%)
Body as a Whole	TOTAL	13	(1.8%)	26	(2.1%)	10	(2.5%)	36	(2.2%)
	Allergic reaction	6	(0.8%)	14	(1.2%)	5	(1.2%)	19	(1.2%)
	Face edema	6	(0.8%)	6	(0.5%)	3	(0.7%)	9	(0.6%)
	Injection site hypersensitivity	1	(0.1%)	6	(0.5%)	2	(0.5%)	8	(0.5%)
Respiratory	TOTAL	14	(2.0%)	15	(1.2%)	7	(1.7%)	22	(1.4%)
	Dyspnea	3	(0.4%)	9	(0.7%)	3	(0.7%)	12	(0.7%)
	Asthma	6	(0.8%)	4	(0.3%)	3	(0.7%)	7	(0.4%)
	Laryngismus	5	(0.7%)	1	(<0.1%)	1	(0.2%)	2	(0.1%)
	Bronchiolitis		(0.0%)	1	(<0.1%)		(0.0%)	1	(<0.1%)
Skin/Appendages	TOTAL	26	(3.6%)	59	(4.9%)	20	(4.9%)	79	(4.9%)
	Rash	20	(2.8%)	37	(3.1%)	11	(2.7%)	48	(3.0%)
	Urticaria	3	(0.4%)	16	(1.3%)	6	(1.5%)	22	(1.4%)
	Maculopapular rash	3	(0.4%)	8	(0.7%)	2	(0.5%)	10	(0.6%)
	Angioedema		(0.0%)	1	(<0.1%)	3	(0.7%)	4	(0.2%)
	Erythema multiforme		(0.0%)	1	(<0.1%)		(0.0%)	1	(<0.1%)

The proportions of patients who experienced at least one hypersensitivity-related adverse event in the combined efalizumab group and the placebo group were similar, 8.1% vs. 6.9%.

A single case of erythema multiforme and four cases of angioedema took place in efalizumab-treated patients. Urticaria was at least three times more common in efalizumab-treated patients than in control (1.4% vs. 0.4%).

7.6 Immunogenicity

7.6.1 Anti-efalizumab Antibodies

The screening test for anti-efalizumab antibodies (HAHA) is less sensitive during treatment with efalizumab, due to interference by the drug with the assay. Therefore, the preferred analysis is one using the data from screening done after patients have undergone drug washout. The incidence of anti-efalizumab antibodies is shown in Table 109.

Table 109 Incidence of Anti-Efalizumab Antibodies in Genentech Sponsored Studies by Manufacturer

	Efalizumab Manufacturer			
	Genentech	XOMA	Both [a]	All Subjects
No. of HAHA-positive subjects/no. of subjects tested (all available data)	28/904 (3.1%)	38/716 (5.3%)	17/302 (5.6%)	83/1922 (4.3%)
No. of HAHA-positive /no. of subjects with follow-up samples [b]	12/173 (6.9%)	38/623 (6.1%)	17/267 (6.4%)	67/1063 (6.3%)

[a] Subjects exposed to Genentech efalizumab in Study ACD2062g after prior exposure to XOMA efalizumab (subjects who are not included in manufacturer-specific columns).
[b] Only includes data from completed studies for subjects who tested positive or who had a negative sample at least 56 days after last dose.

The incidence of anti-efalizumab antibodies was 6.3% (67/1063) among patients treated with either Genentech or XOMA-manufactured, 56 days after discontinuation of treatment. There was little difference in the incidence of HAHA antibodies by efalizumab manufacturer.

Six subjects with local injection-site reactions tested positive for HAHA. The adverse events coded to injection-site mass, hypersensitivity reaction, or inflammation and were described as irritation, inflammation, redness, lump, or urticaria. These adverse events resolved despite continued efalizumab therapy. A potential a relationship between presence of HAHA and local cutaneous reactions exists.

Of the HAHA-positive patients, 20% achieved a PASI 75 and 53.3% achieved a PASI 50. These data are consistent with the response rate, overall. However, the response was on the low side of the range of observed values in the dose groups tested in the phase 3 and open-label studies. Titers of the antibodies were generally low.

The long-term immunogenicity of efalizumab is not known.

Reviewer's comment: The association of arthritic and other inflammatory adverse events with HAHA positivity may be underestimated given that some of the patients may have discontinued the study prematurely due to their adverse event and thus, have missing data with regard to anti-efalizumab antibody screening.

7.6.2 Other Laboratory Changes and Adverse Events Associated with Efalizumab Therapy:
7.6.2.1 Effects on Total White Blood Cell Counts
During the FE/Controlled studies, mean WBC counts increased by approximately 30%–40% relative to baseline among subjects receiving Genentech efalizumab compared with no increase in placebo-treated subjects. Table 86 below shows the absolute change in WBC counts by treatment group. Leukocytosis was sustained throughout efalizumab treatment, including the EE and RE treatment periods, and subsequently resolved during WO after efalizumab discontinuation.

Table 110 Change in White Blood Cell Counts (K/cmm) from Baseline to Day 84 of Each Period for Subjects Treated with Genentech Efalizumab

		Genentech Efalizumab, Mean			
Type of Study/Period	Placebo	2.0 mg/kg/qow	1.0 mg/kg/wk	2.0 mg/kg/wk	3.0–4.0 mg/kg/wk
FE/Controlled	-0.09	NA	2.53	3.20	NA
FE	NA	2.17	2.51	2.54	2.53
EE-1	NA	3.03	2.66	2.71	2.72
EE-2	NA	NA	2.71	3.27	2.84
EE-3	NA	NA	2.66	2.72	4.92
EE-4	NA	NA	2.23	2.94	5.23
RE-1	NA	NA	2.40	2.97	NA
WO	NA	0.20	0.06	0.32	0.09

NA=not applicable.

The maximal WBC count observed in any efalizumab-treated subject was 26.0 K/cmm during the first 12 weeks of efalizumab treatment, 24.1 K/cmm during extended treatment, and 21.5 K/cmm during retreatment. The increase in WBC count appeared to be dose dependent. Among patients who received 1 mg/kg/wk of efalizumab (GNE or XOMA) and had low or normal baseline total WBC counts, 31% (213/676) experienced a shift to high total WBC counts during the first 12 weeks of therapy compared to 2.4% (10/414) of placebo-treated patients.

7.6.2.2 Lymphocyte Counts

Table 111 shows the change in absolute lymphocyte counts from baseline by treatment group.

Table 111 Change in Absolute Lymphocyte Counts (K/cmm) from Baseline to Day 84 of First Treatment

		Baseline				Change			
Treatment Group	N	Mean	Mdn	Min	Max	Mean	Mdn	Min	Max
Placebo	664	1.9	1.8	0.4	4.2	0.05	0.0	-2.6	2.5
Efalizumab	1538	1.9	1.8	0.5	5.1	2.10	1.9	-1.2	9.4

A mean doubling of absolute lymphocyte counts took place at the end of the first treatment period in the efalizumab group compared to negligible changes in the placebo group. Among patients who received 1 mg/kg/wk of efalizumab (GNE or XOMA) and had low or normal baseline absolute lymphocyte counts, 46% (324/701) experienced a shift to high total lymphocyte counts during the first 12 weeks of therapy compared to 1% (4/434) of placebo-treated patients. The clinical significance of this finding is unknown. The changes are reversible upon discontinuation of therapy.

7.6.2.3 Segmented Neutrophils

With the emergence of adverse events of low platelets and given that segmented neutrophils (among other WBC subsets) express CD11a, it is important to consider carefully any changes that are occurring in neutrophils. Mean decreases occur in the percentages of segmented

neutrophils. The percentage change is –13.6% in the efalizumab 1.0 mg/kg/wk group the minimum percentage change is –55%.

In contrast to percentage changes in neutrophil counts, mean absolute neutrophil counts increased somewhat with treatment according to mean values (See Table 112).

Table 112 Change in Absolute Neutrophil Counts (K/cmm) from Baseline to Day 84 for Subjects Treated with Genentech Efalizumab

		Baseline				Change			
Treatment Group	N	Mean	Mdn	Min	Max	Mean	Mdn	Min	Max
Placebo	417	4.7	4.4	0.9	15.9	-0.16	-0.1	-11.0	8.0
Efalizumab 1.0 mg/kg/wk	816	4.6	4.5	1.1	18.0	0.26	0.2	-10.0	10.7
Efalizumab 2.0 mg/kg/wk	60	4.7	4.3	2.1	9.8	0.62	0.7	-4.8	4.0
Efalizumab (combined)	876	4.6	4.5	1.1	18.0	0.29	0.2	-10.0	10.7

Inlcudes Studies ACD2059g, ACD2390g and ACD2600g

Thus, while the mean absolute neutrophil counts increased, the percent neutrophils decreased because the increase in lymphocytes was relatively greater.

Shifts to low values of absolute neutrophils were also assessed. Overall, 0.5%, or 7/1387 patients who received 1.0 mg/kg/wk of efalizumab in the first exposure of the clinical trials, experienced a shift in absolute neutrophil counts to low from a normal baseline level. In addition, a listing of all patients with grade 3 or greater NCI toxicity criteria was evaluated for decreases in absolute neutrophil counts and failed to show decreases that were sustained or confirmed by repeat testing (data not shown).

Reviewer's comment: Most of the grade 3 or 4 abnormalities in absolute neutrophil counts in efalizumab-treated patients were not sustained and some of these events were also noted in placebo-treated patients. However, follow-up is not available on one patient with a grade 4 decrease in absolute neutrophil counts (45223) and one patient with a grade 3 decrease in neutrophil counts (45207). The clinical significance of the transient decreases in absolute neutrophils is not known.

7.6.2.4 Eosinophils

Mean values of eosinophils were increased in efalizumab-treated patients by 50% and there was an increase in high-value abnormalities. Approximately 10% of efalizumab-treated patients had treatment emergent elevations in eosinophil count compared to 3% of placebo-treated patients. Among patients who received 1 mg/kg/wk of efalizumab (GNE or XOMA) and had low or normal baseline eosinophil counts, 5.2% (35/675) experienced a shift to high eosinophil counts during the first 12 weeks of therapy compared to 1.4% (6/419) of placebo-treated patients. While the mean absolute eosinophils increased, the percent eosinophils decreased because the increase in lymphocytes was relatively greater.

7.6.2.5 Chemistry

Consistently observed in the chemistry panel, was an increase in mean alkaline phosphatase in efalizumab-treated patients compared with placebo-treated patients (See Table 89).

Table 113 Change in Alkaline Phosphatase (U/L) from Baseline to Day 84 of Each Period for Subjects Treated with Genentech Efalizumab

		Genentech Efalizumab, Mean			
Type of Study/Period	Placebo	2.0 mg/kg/qow	1.0 mg/kg/wk	2.0 mg/kg/wk	3.0–4.0 mg/kg/wk
FE/Controlled	−1.03	NA	5.29	9.57	NA
FE	NA	−1.3	5.5	11.1	23.2
EE-1	NA	9.27	7.48	33.40	0.87
EE-2	NA	NA	7.97	13.54	9.25
EE-3	NA	NA	6.92	11.98	12.00
EE-4	NA	NA	9.39	9.28	15.50
RE-1	NA	NA	14.43	8.63	NA
WO	NA	0.95	0.46	5.21	−1.42

The degree of elevation was higher in the 2.0 mg/kg/wk group than in the 1.0 mg/kg/wk group suggesting a dose effect. Both the liver and intestinal isoenzymes have demonstrated shifts to the upper limit of normal.

Liver function tests have been examined for concordant elevations in multiple tests for the first treatment period in the four phase 3 placebo-controlled studies: ACD2058g, ACD2059g, ACD2390g, and ACD2600g. See Table 114 below.

Table 114 Summary of High Shift in One or More Liver Function Tests during the First 12 Weeks in Studies ACD2058g, ACD2059g, ACD2390g, and ACD2600g

	Placebo	Efalizumab
No shift	562/604 (93.0%)	1203/1374 (87.6%)
Shift on one liver function test	31/604 (5.1%)	120/1374 (8.7%)
Shift on two liver function tests	9/604 (1.5%)	43/1374 (3.1%)
Shift on three liver function tests	2/604 (0.3%)	8/1374 (0.6%)
Shift on four liver function tests	0/604 (0.0%)	0/1374 (0.0%)
Shift on five liver function tests	0/604 (0.0%)	0/1374 (0.0%)

The summary represents the proportion of subjects with a shift from low or normal baseline values to values above the upper limit of normal at Day 84 on one or more liver function tests. The number of subjects with shifts on one or more liver function tests was higher in the efalizumab group than in the placebo group. No subjects had a shift above upper limit of normal on four or five liver function tests.

Transaminase elevations accounted for other shifts in liver function tests. Adverse events consisting of increases in SGPT occurred in 1.1% (n=29) of patients and SGOT occurred in 0.7% (n=19) patients. Bilirubinemia occurred as an adverse event in 0.1% of patients (n=3).

7.6.2.6 Inflammation-associated laboratory changes

Adverse events of thrombocythemia were observed in a small number of patients and appear to be reactive in etiology. In one patient (17512) thrombocythemia was associated with increases in peripheral white blood cell count, increases in serum CRP and peripheral edema. The clinical significance is unknown. Overall the frequency of high platelet counts was 4.0% (n=35) in efalizumab-treated patients vs. 2.7% (n=11) in placebo-treated patients.

Examination of changes in representative acute phase reactants and in complement activation products demonstrated some increases in efalizumab-treated subjects. In Study ACD2600g, mean levels of C-reactive protein and fibrinogen increased more in the efalizumab group (0.4 mg/dL and 46.8 mg/dL, respectively) than in the placebo group (0.1 mg/dL and 13.6 mg/dL, respectively) (See Table 115). The mean elevation in C-reactive protein was 66% and fibrinogen was 15%. Mean levels of both C3a and C5a decreased during the study. The decrease was greater in the placebo group for both analytes (data not shown). Shifts to elevated levels of CRP, fibrinogen, C3a, and C5a were all observed at rates approximately 10% higher in subjects receiving efalizumab compared with those receiving placebo. All of these markers show mean changes consistent with higher inflammation in the efalizumab-treatment group. The clinical significance of these changes in markers of inflammation is not known.

Table 115 C- Reactive Protein (mg/dL) Mean Changes from Baseline

Treatment Group	Baseline (min-max)	Day 84 (min-max)	Change (max)
Placebo (N=216)	0.6 (0.4-8.9)	0.7 (0.4-7.0)	0.09 (6.6)
Efalizumab (1.0mg/kg/wk) (N=425)	0.6 (0.4-5.4)	1.0 (0.4-22)	0.40 (22)

7.6.2.7 Urinalysis

During the first 12-week treatment period of the controlled clinical trials, hematuria was noted as an adverse event in 0.5% (6/1213) of patients who received 1 mg/kg of efalizumab and 0.7% (3/407) of patients who received 2 mg/kg/wk. None of the 715 placebo-treated patients had an adverse event of hematuria. Of the 9 patients, 5 had a report of microscopic hematuria and the other 4 had hematuria that was not specified (microscopic vs. gross). Each of the events was either mild or moderate in severity. Only one event resulted in holding of study drug; the remainder did not result in any action taken with respect to dosing. The clinical significance of this finding is not known.

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8 SUMMARY OF SAFETY

- Serious adverse events occurred at a comparable incidence in the two treatment groups, 2.2% in efalizumab-treated patients vs. 1.7% in placebo-treated patients.
- Serious infections
  - There has been a safety signal for serious infections in the controlled portion of clinical trials with efalizumab. The incidence of serious infection in the first exposure of the controlled studies was 0.4% for efalizumab (sepsis, pneumonia, cellulitis, gastroenteritis) and 0.1% for placebo (gastroenteritis).
  - Some of these infections have had atypical and life-threatening courses (vertebral Staphyloccal osteomyelitis with sepsis) and have required prolonged courses of antimicrobial therapy.
  - One opportunistic infection, *Legionella* pneumonia, has been reported in an efalizumab-treated patient.
- Malignancies
  - There is no clear evidence of increased risk of malignancy, but the numbers are small. Based upon the immunosuppressive action of efalizumab, further study is needed.
  - There have been two cases of lymphoproliferative malignancies in clinical trials of efalizumab.
  - The incidence of non-melanoma skin cancer was similar in efalizumab-treated patients vs. placebo (1.12% and 1.08% per 100 subject years, respectively). The incidence of non-melanoma skin cancer was higher in efalizumab-treated subjects than in the external reference cohort. The difference may represent ascertainment bias.
  - The point estimates for malignant melanomas and solid tumors in efalizumab-treated subjects are within the range expected based on external cohorts.
- Psoriasis-related adverse events
  - An increased incidence of psoriasis-related adverse events in placebo-controlled portions of clinical trials was seen in efalizumab-treated patients.
  - Serious and life-threatening psoriasis-related adverse events including psoriasis variants have occurred with a frequency that is greater than placebo.
  - Such adverse events have occurred during treatment as well as following discontinuation of efalizumab.
  - Further study is needed to assess how to identify patients at risk of psoriatic flare and manage these patients appropriately.
- Thrombocytopenia
  - There have been eight cases of clinically significant thrombocytopenia, (serious and/or with platelet counts of less than 50,000 cells per ul) among efalizumab-treated patients.
  - Thrombocytopenia associated with efalizumab appears to be immune-mediated. Treatment with systemic corticosteroids results in improvement in platelet counts. In some cases, where systemic corticosteroids were withdrawn, the thrombocytopenia recurred. Where performed, bone marrow biopsies have

shown normal maturation indicating a peripheral consumption or sequestration of platelets.

- Arthritis-related adverse events
  - Arthritis-related adverse events have occurred during treatment with efalizumab and have occasionally been serious.

- Inflammatory/ Autoimmune-related adverse events
  - Other rare, unexpected cases of potentially autoimmune adverse events- e.g. transverse myelitis, pneumonitis, and arthritis-have occurred in association with efalizumab-treatment.
  - One case of a serum sickness-like illness has occurred in an efalizumab-treated patient.
- Severe adverse events occurred at a rate of 10% in efalizumab-treated patients, nearly twice that seen in the placebo-treated group.

- Dose-related acute adverse events (e.g. fever, headache, nausea, vomiting, meningismus) occur after the first administration of therapeutic doses of efalizumab. The incidence of these events is lessened by the use of a subtherapeutic "conditioning dose" (0.7 mg/kg) as first dose. In some cases patients have had serious adverse events, e.g. aseptic meningitis, that have shown a temporal relationship to initiation of dosing despite the use of a conditioning dose.

- Laboratory abnormalities
  - Inflammation-associated laboratory analytes were higher in efalizumab-treated patients as compared to placebo. These included C reactive protein, fibrinogen and C3a and C5a.
  - Hematologic changes included increases in mean total white blood cell counts, approximate doubling of mean lymphocyte counts and smaller degrees of elevations in absolute eosinophil and neutrophil counts.
  - Elevations in alkaline phosphatase levels which are mostly unassociated with elevations in other hepatic tests. Both the intestinal and hepatic fractions are shown to be elevated. Other liver function tests (e.g.transaminases) have been also elevated in efalizumab-treated patients compared to placebo.
  - Efalizumab has been associated with anti-efalizumab antibody (HAHA) in 6.3% of patients. Injection site reactions may be associated with HAHA in some patients. The clinical association of HAHA with other adverse events is under investigation.

9 USE OF EFALIZUMAB IN SPECIAL POPULATIONS

See Appendix 2 for the use of efalizumab in special populations.

10 CONCLUSIONS: EFFICACY AND SAFETY OF EFALIZUMAB FOR THE TREATMENT OF PATIENTS WITH MODERATE TO SEVERE PSORIASIS

Patient population and efficacy outcomes:

Efalizumab has been studied in four efficacy trials in patients with moderate-to-severe stable, plaque psoriasis. Patients studied have had long-standing psoriasis (median 19 years), and 66% of patients have had a history of systemic therapy for psoriasis. The median PASI score was 19 and median body surface area involvement was 30%.

The treatment effect (proportion of PASI 75% responders) for efalizumab (1mg/kg/wk for 12 weeks SC) ranges from 18% to 37% depending on the study. Responses according to physician's static global assessment (16%-29%) and PASI 50 criteria (36%-46%) support the primary efficacy endpoint.

Efalizumab remains active during an extended treatment period. In patients who responded to 12 weeks of therapy with efalizumab, 77% maintain full clinical response during an additional 12-week treatment period.

When used to retreat responders who relapse off-treatment (loss of 50% of efalizumab treatment effect) efalizumab has shown limited ability to recapture response. Only about one third of patients respond upon retreatment.

With continuous treatment for an additional contiguous 12-week treatment period, an additional proportion of responders were captured (up to 11% with the 4 mg/kg/wk dose) who were non-responders to the first treatment period.

Safety Assessments:

- No deaths in psoriasis trials have been linked causally to the use of efalizumab.
- Malignancies in the first exposure, placebo controlled portion of trials were few (n=4) and were not higher in in efalizumab-treated patients relative to control or to external cohorts. However, the numbers of cases are too small to make any definitive conclusions with regard to cancer risk.
- There is no apparent increase in the incidence of NMSC in efalizumab-treated patients compared to placebo. However, the numbers are too small to assess the potential for increased risk due to efalizumab. Also, the data are limited by the duration follow-up among the efalizumab-treated patients (a median of 8 months).
- Serious infections have been reported in the first exposure of controlled clinical trials in a higher proportion of efalizumab-treated patients than placebo (0.4% vs. 0.1%). One opportunistic infection was observed, *Legionella* pneumonia. Other serious infections have consisted of severe local infections complicated by sepsis and seeding of distal sites.

- The potential for interaction between efalizumab and other immunosuppressive/antimetabolic agents that may be given as rescue or additional therapy
- The potential for interference of efalizumab with the efficacy of vaccines such as influenza or pneumococcal vaccines

Although, studies in the pediatric population are not recommended at this time, the sponsor should submit a plan for when it would be appropriate to reassess the issue of pediatric studies based upon further safety data from studies in adult patients.

RECOMMENDED REGULATORY ACTION

Efalizumab has been shown to be safe and effective for the treatment of moderate to severe chronic plaque-type psoriasis in adult patients. Therefore, the reviewers recommend approval of this marketing application provided that agreements are reached with the sponsor on the package insert and design of and timelines for completing postmarketing studies.

12 APPENDIX 1: AUDIOLOGIC ASSESSMENTS

12.1 Audiology

Audiologic testing was performed in three studies (HUPS254, HUPS256, ACD2058g) after 1 subject in the Phase 2 study (HUPS252) experienced a serious adverse event of transient unilateral hearing loss. All audiologic testing was performed in studies using XOMA efalizumab.

The criteria for meaningful threshold change in one ear relative to a pretreatment, baseline assessment were the same in all studies as follows:

- ≥ 20-dB Change at any one frequency
- ≥15-dB Change at any two frequencies
- ≥ 10-dB Change at any three frequencies

These criteria were used in the 1997 Anti-Infectives Drugs Advisory Committee Meeting review of tobramycin. An increase in decibels (dB) indicated worsening, and a decrease in decibels indicated improvement in hearing threshold.

Audiologic testing by air and bone conduction was performed by a certified audiologist prior to study drug administration and at the end of the FT, RT, and ET periods. Frequencies from 500 Hz to 8000 Hz were routinely assessed. If the audiologist had equipment and training for performance of high-frequency testing up to 16,000 Hz, this assessment was also conducted. The baseline audiogram was obtained up to 14 days prior to FT Day 0 and prior to study drug administration. A second audiogram was obtained within ±7 days of FT Day 84. Subjects who were responders at FT Day 84 entered the OB period, and when relapse occurred, began the RT period. These subjects were scheduled to have a third audiogram obtained ±7 days of RT Day 84. Subjects who were partial responders or non-responders at FT Day 84 were followed during the ET period when a third audiogram was obtained within ±7 days of ET Day 84. Retests were to be conducted after 2 weeks for any subject with a significant threshold shift, as defined in the Audiology Manual for Study ACD2058g. Determination of a significant threshold shift was made at the FT Day 84, the ET Day 84, and the RT Day 84 visits.

At screening, subjects were asked about their hearing history. Questions included whether they had experienced a hearing loss in the previous year, had experienced tinnitus, had been diagnosed with hearing problems, had previous surgery or trauma to the ear, had frequent exposure to loud noises, and whether their employer required periodic hearing tests. If hearing problems were diagnosed, six conditions were ascertained, including noise exposure.

A decrease in threshold (dB) at a frequency in either ear represented a potential improvement in hearing at that frequency; an increase in threshold (dB) at a frequency in either ear represented a potential worsening in hearing. For any of the criteria listed above, a worsening in one ear took precedence over an improvement in the same or in the other ear. Changes in values by bone conduction were not considered part of the "significant threshold shift" determination.

Based on the criteria above, a subject was classified as:

- "Worsened" if the subject's hearing was worse by any one individual criterion

• "Improved" if the subject's hearing was improved by any one individual criterion and had not been classified as "worsened"
• "Unchanged" otherwise

The tables below summarize the changes measured by audiologic tests.

Table 116 Study HUPS254:Treatment-Emergent Changes in Audiogram Testing

	Hearing Test Result	
Dose Group	Improved	Worsened
Group C (n=15) 1.0 mg/kg/wk SC	1 (6.7%)	1 (6.7%)
Group E [a] (n=15) 2.0 mg/kg/wk SC	5 (33.3%)	4 (26.7%)
Total (n=30)	6 (20.0%)	5 (16.7%)

[a] One of the 16 subjects enrolled did not have audiograms performed.

Table 117 Treatment-Emergent Changes in Audiogram Testing: Study HUPS256

	Hearing Test Result	
XOMA Efalizumab Dose Group	Improved	Worsened
0.3 mg/kg/wk IV (n=5)	1 (20.0%)	0 (0)
1.0 mg/kg/wk IV (n=10)	4 (40.0%)	1 (10.0%)
All IV subjects (n=15)	5 (33.3%)	1 (6.7%)
1.0 mg/kg/wk SC (n=20)	3 (15.5)	7 (35.0%)
2.0 mg/kg/wk SC (n=19)	6 (31.6%)	6 (31.6%)
4.0 mg/kg/wk SC (n=21)	6 (28.6%)	6 (28.6%)
All SC efalizumab (n=60)	15 (25.0%)	19 (31.7%)
Total (n=75)	20 (26.7%)	20 (26.7%)

Note: The numbers of subjects who improved or worsened differs slightly between the SCS and final report because of differences in analysis.

Table 118 Treatment-Emergent Changes in Audiogram Testing: Study ACD2058g

	Hearing Test Result	
Dose Group	Improved	Worsened
Placebo (n=156)	8 (5.1%)	6 (3.8%)
XOMA efalizumab 1.0 mg/kg/wk (n=148)	14 (9.5%)	11 (7.4%)
XOMA efalizumab 2.0 mg/kg/wk (n=152)	13 (8.6%)	16 (10.5%)
Total All XOMA efalizumab (n=300)	27 (9.0%)	27 (9.0%)

The audiology testing in studies HUPS254, HUPS256 and ACD2058g showed no evidence of efalizumab-induced hearing loss. Audiology testing was not performed in the clinical studies that followed. Please also refer to the audiology consultative review by Dr. James Kane.

13 APPENDIX 2 Use of Efalizumab in Special Populations

13.1 Pediatric Studies

Genentech, Inc. asked for and received a deferral of its obligation to carry out pediatric studies in the phase 3 program.

13.2 Pregnancy

Pregnant/ lactating women were excluded from the clinical trials. Female patients were monitored monthly with pregnancy testing and were instucted to use contraception during and 3 months after the study. Nine subjects became pregnant during clinical trial program. Study dosing was immediately discontinued in these patients. Patients were followed during pregnancy and for 6 months following birth.

Table 119 Pregnancies that Occurred during the Efalizumab Psoriasis Program

Subject ID/ Study	Treatment Group	Outcome and Comments
15065/ ACD2058g	1.0 mg/kg/wk XOMA efalizumab	Vaginal delivery of healthy infant. Eleven doses of efalizumab were administered before discovery of pregnancy, 5 weeks from last dose.
16004/ ACD2058g	2.0 mg/kg/wk XOMA efalizumab	Delivery of healthy infant. Twelve doses of efalizumab were administered before discovery of pregnancy, 10 weeks from last dose.
81216/ ACD2059g	2.0 mg/kg/wk XOMA efalizumab	Vaginal delivery of healthy infant. Twelve doses of efalizumab were administered before discovery of pregnancy, 5 days from last dose.
19505/ ACD2062g	1.0 mg/kg/wk Genentech efalizumab	Partner of male subject became pregnant. Pregnancy ended in spontaneous miscarriage. Thirty-one doses of efalizumab were administered before discovery of pregnancy, 9 weeks from last dose
21406/ ACD2062g	1.0 mg/kg/wk XOMA efalizumab	Vaginal delivery of healthy infant. Twelve doses were administered in Study ACD2062g before discovery of pregnancy, 3 months from last dose
27106/ ACD2243g	2.0 mg/kg/wk Genentech efalizumab followed by 1.0 mg/kg/wk efalizumab	Estimated date of delivery was 28 January 2002. Fourteen doses of efalizumab were administered before discovery of pregnancy, 7 days from last dose. Subject was lost to follow-up.
27130/ ACD2243g	2.0 mg/kg/wk Genentech efalizumab followed by 1.0 mg/kg/wk efalizumab	Estimated date of delivery was 8 August 2002. Thirty-eight doses of efalizumab were administered before discovery of pregnancy, 1 day from last dose.
27706/ ACD2243g	2.0 mg/kg/wk Genentech efalizumab followed by 1.0 mg/kg/wk efalizumab	Subject voluntarily terminated pregnancy.
29208/ ACD2243g	2.0 mg/kg/wk Genentech efalizumab followed by 1.0 mg/kg/wk efalizumab	Partner of male subject became pregnant and voluntarily terminated pregnancy.
547/ ACD2389g	1.0 mg/kg/wk XOMA efalizumab	Estimated date of delivery as 28 September 2002. One dose of efalizumab was administered before the discovery of pregnancy, 4 weeks from last dose. Subject was lost to follow-up.
2564130607/ HUPS256	4.0 mg/kg/wk XOMA	Subject delivered healthy infant.

The data of use during pregnancy are limited. Thus far, there is no evidence for fetal harm. Prospective studies are needed to further evaluate the risks of use during pregnancy if the product is licensed.

13.3 Safety and Efficacy in the Geriatric Population

Of the 1620 patients who received efalizumab in controlled trials, 128 were ≥ 65 years of age and 2 were ≥ 75 years of age. Although, the numbers of patients age 65 or older were relatively small, efficacy did not appear to be different among patients over the age of 65.

With regard to adverse events, of the two cases of hypothyroidism, both were in patients older than 65. Skin related adverse events that were more commonly seen in patients older than age 65

were psoriasis, pruritus and rash. For example, 4.8% of patients over 65 had psoriasis-related adverse events vs. 2.9% of patients 41-64 and 1.9% of patients 18-40. No clear safety signals were identified in patients over the age of 65.

The table below shows the incidence rate for infections that required hospitalization for patients by age group.

Table 120 Incidence Rate for Infections that Required Hospitalization by Age Group Total Exposure All Subjects Treated with Efalizumab in Psoriasis Studies

COSTART Preferred Term	Age Group	Number of Events	Subject-Years	95% CI for Observed Number of Events	Incidence Rate Per 100 Subject-Years	95% CI for Incidence Rate Per 100 Subject-Years
- TOTAL -	18 - 40 yr	7	634.60	[2.81, 14.42]	1.10%	[0.44, 2.27]
	41 - 64 yr	18	942.06	[10.67, 28.45]	1.91%	[1.13, 3.02]
	>= 65 yr	2	104.02	[0.24, 7.22]	1.92%	[0.23, 6.95]

Although the numbers are small, there is not an indication of an increased incidence of hospitalization for infections among patients over the age of 65.

Overall, no clear safety concerns arose with the use of efalizumab in the geriatric population.

14 APPENDIX 3: Phase 1 study protocols

14.1 Selected Phase 1 Studies of Efalizumab in Patients with Psoriasis

The Phase 1 clinical studies were conducted in patients with psoriasis. These studies are reviewed primarily from the perspective of clinical safety and activity of efalizumab.

14.1.1 Protocol HU9602

Xoma completed the first Phase 1 study of efalizumab, HU9602, in 1998. This study investigated single intravenous (IV) doses (0.03, 0.1, 0.3, 0.6, 1.0, 2.0, 3.0 or 10.0 mg/kg) of efalizumab administered in a dose-escalation manner to 31 subjects moderate to severe plaque psoriasis. The subjects were enrolled at seven study centers. Of the 31 subjects, 4 subjects each were enrolled in the 0.03 and 0.1 mg/kg groups, 8 were enrolled in the 0.3 mg/kg group, 1 was enrolled in the 0.6 mg/kg group, 8 were enrolled in the1.0 mg/kg group, 1 was enrolled in the 2.0 mg/kg group, 4 were enrolled in the 3.0 mg/kg group and 1 was enrolled in the 10.0 mg/kg group.

The subjects were to be followed for a minimum of 72 days after dosing.

Table 121 Summary of Most Frequently[a] Reported Adverse Events Subjects Evaluable for Safety

Body System and Preferred term	≤ 0.3 mg/kg N	≥ 0.6 mg/kg N	Combined N (%)
Total Number of Subjects	16	15	31
Body as a Whole	12	14	26 (84)
Headache	4	8	12 (39)
Chills	2	8	10 (32)
Infection[b]	4	4	8 (26)
Fever	1	6	7 (23)
Pain	4	1	5 (16)
Skin and Appendages	6	9	15 (48)
Psoriasis[c]	5	6	11 (36)
Pruritus	4	1	5 (16)
Digestive System	6	6	12 (39)
Nausea	0	5	5 (16)

[a] Defined as any adverse event reported by ≥ 5 subjects.

[b] Infections included cold symptoms (four subjects), infection at biopsy site (three subjects), and infection at left buttock suture site (one subject).

[c] Indicated worsening of psoriasis post treatment.

Table 122 Summary of Serious Adverse Events

Dose group(mg/kg)	Subject	Gender	Age	Adverse Event	Onset (Day)	Severity	Relation: Study Drug

0.6	031	F	35	Meningismus	0	Severe	Probable
1.0	028	F	59	Carcinoma skin	36	Mild	Possible
1.0	029[a]	M	55	Ataxia	11	Moderate	Possible
				Vertigo	11	Severe	Possible
				Nausea	11	Moderate	Possible
				Vomiting	11	Severe	Possible
				Nystagmus	12	Mild	Possible
1.0	007	M	51	Aseptic meningitis	0	Moderate	Probable
3.0	010	M	56	Chills	0	Moderate	Probable
				Hypertension	0	Moderate	Probable
				Fever	0	Moderate	Probable
10.0	013	M	28	Vomiting	0	Severe	Probable

There were no deaths in the study. Fever was commonly reported within 24 hours after completion of infusion. A dose-related incidence and severity of headache, chills, fever and nausea was observed.

Infusion reactions had not been observed in a safety study conducted in chimpanzees, a species that shares a similar binding affinity for efalizumab as humans, after administration of up to 40 mg/kg efalizumab. However, adverse side effects, including fever, headache and nausea, were seen in the several hours after the first intravenous infusion of efalizumab in psoriasis patients. Body temperature began to increase within 2 hours after the infusion, and returned to the normal range within 24 hrs. In addition, white blood cell counts were elevated within 8 hours of infusion and increased expression of the activation marker CD69 was observed on a subpopulation of circulating T cells. The circulating CD69-positive T cells do not seem to express CD25, suggesting that they are not fully activated. Plasma samples collected after efalizumab administration indicated elevated levels of TNF-α, IL-6 and the acute phase proteins CRP and LBP within the first 48 hours of dosing. Plasma TNF-α was detected in some patients 2 hours after infusion, but showed no correlation with dose level or severity of adverse events. Adverse symptoms and the associated neutrophil counts and CD69 expression usually subsided after the first 48 hours, even when plasma levels of efalizumab remained relatively high. In subsequent studies where efalizumab was administered multiple times on a weekly basis, adverse events were most common after the first dose hence the phenomenon was called a "first-dose" effect. The first dose response may be initiated by activation of cells of the monocytic/macrophage lineage. Activation of macrophages in vitro could be induced by immobilized efalizumab..

Reviewer's comments
It was concluded that efalizumab was poorly tolerated at doses needed to achieve target serum levels of drug. The repeat-dosing studies would be designed to achieve these safety objectives: to find an initial tolerable dose of efalizumab and determine if upon repeated dosing the infusion reactions continued or worsened. The starting dose level for the study would be conservative to take into account the potential for additive toxicity of repeated dosing. The hypothesis would also be tested that the initial infusion reaction would induce tolerization and would permit ratcheting up to the optimal paharmacologic dose. This lead to the dev of an initial low "tolerization dose." Treatment with acetaminophen or nonsteroidal anti-inflammatory medications was allowed in the clinical trials for management of these acute adverse events.

14.1.2 Protocol HUPS249
Another Phase 1 study (HUPS249) investigated multiple IV doses (0.1-1.0 mg/kg/wk), which were also administered in a dose-escalation manner.

This study was to examine the safety, immunogenicity, and tolerability of multiple doses of efalizumab in subjects with moderate to severe plaque psoriasis; to determine the pharmacokinetics and pharmacodynamics of efalizumab; and to determine the in vitro and in vivoimmunosuppression correlates to drug dose levels.

Reviewer's comment:
Following the Phase 2 study (HUPS252), a transition was made to subcutaneous (SC) dosing.

14.1.3 Protocol HUPS254
14.1.3.1 Study Title
"A Single-dose and Multiple-dose, Escalating-dose Study to Evaluate the Safety, Pharmacokinetics, and Biological Activity of Subcutaneously Administered hu1124 (Efalizumab) in Subjects with Moderate to Severe Plaque Psoriasis"

14.1.3.2 Study Objectives
The objectives of this study were as follows:
To evaluate the safety, immunogenicity, and tolerability of a single dose and multiple doses of efalizumab administered by subcutaneous injection to subjects with moderate to severe plaque psoriasis
To determine the pharmacokinetics and pharmacodynamics of efalizumab.

14.1.3.3 Study Design
A Phase I study (HUPS254) evaluated the safety, PK, and PD of multiple SC doses (0.5–2.0 mg/kg/wk) administered for 8 weeks in a dose-escalation manner. For groups C-E, the study employed both an inter-patient dose escalation (escalation between dose groups and an intra-patient dose escalation (higher maintenance doses after an intial "tolerization" dose.

At least 56 subjects were to receive subcutaneous injections of efalizumab administered as a single dose of 0.3 mg/kg or as escalating multiple doses of 0.5-2.0 mg/kg.

The dose groups evaluated in this study were:
0.3 mg/kg administered as a single dose (Group A),
0.5 mg/kg administered weekly for 8 weeks (Group B),
0.5 mg/kg escalated to 1.0 mg/kg (Group C and C.1),
0.7 mg/kg escalated to 1.5 mg/kg (Group D),
1.0 mg/kg escalated to 2.0 mg/kg (Group E and E.1) administered weekly for 8 weeks.

Subjects in the single-dose group were followed for a minimum of 28 days and subjects in the multiple-dose groups were followed for a minimum of 91 days.

Subjects in Groups C.1 and E.1 had extra target lesion and hearing assessments.

Reviewer's comment:
In the phase 1 studies, the adverse events included facial, vestibular and auditory nerve impairment and meningeal irritation. In addition to careful neurologic assessments, auditory testing was added to assess the potential for development of subclinical ototoxicity.

14.1.3.4 Results and Discussion
Safety:
The total proportion of patients experiencing a drug-related adverse event was 58%. The most frequently reported adverse events were headache (19/57 [33%]), pain (14/57 [25%]), rhinitis (11/57 [19%]), leukocytosis (10/57 [18%]), pharyngitis (10/57 [18%]), increased cough (9/57 [16%]), nausea (7/57 [12%]), chills (6/57 [11%]), and myalgia (6/57 [11%]). There was only one adverse event (peripheral edema) in the single-dose group. Acute adverse events of fever, headache, nausea, chills, and myalgia within 48 hours after study drug administration were reported by 21/57 (37%) of the subjects.

One (2%) subject in the study (Subject 22 in the 1.0-2.0 mg/kg group) experienced a serious adverse event. The serious adverse event of kidney calculus was severe in nature and considered to be unrelated to the study drug.

Audiology tests were performed for the 31 subjects in Groups C.1 (0.5-1.0 mg/kg) and E.1 (1.0-2.0 mg/kg). The hearing abnormalities observed during this study were not consistent with a pattern of ototoxicity because improvements in hearing were observed in some subjects at the same time as deteriorations in hearing, and because deteriorations in hearing were not consistently evident in the higher sound frequencies. One (2%) subject experienced a hearing-related adverse event (decreased hearing secondary to impacted cerumen), which was considered to be unrelated to the study drug.

The proportion of subjects who experienced an infection-related adverse event was 75% in the 0.5 mg/kg group, 24% in the 0.5-1.0 mg/kg group, 17% in the 0.7-1.5 mg/kg group, and 58% in the 1.0-2.0 mg/kg group. The most frequently reported infection-related adverse events were rhinitis, pharyngitis, and increased cough. Additionally, two subjects (4%) in the 0.5-1.0 mg/kg group experienced *Herpes simplex* infections.

The incidence of CMV disease and evidence of CMV reactivation was evaluated in this study because CMV disease is known to increase in subjects who receive immunosuppressive medications. One subject developed a new positive CMV IgM response at Day 91, having had a negative CMV IgM response at screening. This subject had a positive IgG titer at baseline and did not experience any clinical signs or symptoms of CMV disease.

Reviewer's comment:
The report does not state whether the patient had a symptomatic illness.

Lymphocyte counts approximately doubled within 2–7 days after the first dose of study drug in the multiple-dose groups. No increase was observed in the single-dose group. The mean proportion of B and T lymphocytes remained consistent throughout the study; however, a significant decrease in the proportion of NK cells was noted from a pretreatment level of 10% to

approximately 6% after Day 14. The average CD11a expression on circulating T lymphocytes decreased by 70-80% within 2-3 days after treatment in all dose groups, and a small increase in CD69 expression was observed. Efalizumab binding sites were not saturated in the single-dose group, but were generally more than 95% saturated in the multiple-dose groups during treatment. Lymphocyte counts, CD11a and CD69 expression, and available binding sites returned to pretreatment levels by Day 91 in all treatment groups; however, the mean percentage of NK cells had not returned to pretreatment levels.

Antibody response to the study drug was assessed in 53/57 patients in the study. A positive response (4.7 ng/mL equivalents/mL) was detected in 1/53 of the subjects (1.0–2.0 mg/kg dose group). Competition studies indicated the response was anti-idiotypic in nature. The positive response was not associated with any adverse events
that would be expected during immune complex formation and deposition.

PK results:
In the multiple-dose groups, the average peak levels after the last dose were 4.7 µg/mL for the 0.5 mg/kg group, 7.4 µg/mL for the 0.5-1.0 mg/kg group, 20 µg/mL for
the 0.7-1.5 mg/kg group, and 22 µg/mL for the 1.0-2.0 mg/kg group. Average bioavailability (compared to IV administration) varied between 39.0% and 76.0% among the multiple-dose groups, with an overall average bioavailability of 51% ± 32% (mean ± sd, n = 41). In the single-dose group, the peak level was below the level of detection and bioavailability was not applicable for a single dose.

14.1.4 Protocol HUPS256
Study Title
An Open-Label, Extended-Duration, Multiple-Dose Study to Evaluate the Safety, Pharmacokinetics, and Biological Activity of Intravenously and Subcutaneously Administered hu1124 in Subjects with Moderate to Severe Plaque Psoriasis

14.1.4.1 Study Objectives
This Phase 1 study evaluated the safety, efficacy, PK, and PD of multiple IV or SC doses (0.3–1.0 mg/kg/wk IV and 1.0–4.0 mg/kg/wk SC) administered for 12 weeks.

In addition, it evaluated the safety, pharmacokinetics, immunogenicity, and tolerability of 12 multiple doses of efalizumab administered weekly by subcutaneous injection.

14.1.4.2 Protocol
Eligible patients were required to have a minimum PASI score of 12 and a minimum BSA of 15%.

For the intravenous phase, 16 patients were assigned to a dose group. The dose groups evaluated in this phase of the study were 0.3 mg/kg or 0.3–1.0 mg/kg administered weekly for 12 weeks.

For the subcutaneous phase, a total of 61 subjects were assigned to a dose group. The doses evaluated were: 0.7-1.0 mg/kg, 0.7-2.0 mg/kg, and 0.7-4.0 mg/kg weekly for 12 weeks.

All subjects were to be followed for up to Day 180.

14.1.4.3 Outcome Measures

- PGA and PASI scores at Day 84 were compared with baseline.
- Additionally, arthritis symptoms and psoriatic itching evaluations were performed.

14.1.4.4 Clinical and Laboratory Assessments

- Safety assessments included: adverse events, hearing assessments, clinical laboratory assessments, physical and neurological examinations, and pre- and post-treatment vital signs.
- Immunologic activity was assessed by analyzing lymphocyte subpopulations by flow cytometry and testing for human anti-humanized antibody (HAHA) response. Immunologic recovery assessments for the reconstitution of CD11a on T lymphocytes compared with baseline measurement were performed; patients were to be monitored every 20 to 30 days up to 90 days after the final visit until recovery of ≥ 75% expression of CD11a.
- The pharmacodynamic assessments were also performed.

14.1.4.5 Results and Discussion

14.1.4.6 Intravenous Phase

A total of 16 subjects with moderate to severe plaque psoriasis were enrolled at six study centers. Of these 16 subjects, 6/16 received 12 weekly doses of 0.3 mg/kg and 10/16 received 12 weekly doses of 0.3-1.0 mg/kg. The majority of subjects were male 9/16 and Caucasian 14/16. Subjects ranged in age from 21 to 70 years of age and from 63 to 119 kg in weight. Median baseline BSA affected by psoriasis ranged were 27.1 and 37.5, and the median baseline PASI scores were 16.8 and 20.6. Five of 16 patients had previous exposure to efalizumab. All subjects were evaluated for safety and efficacy.

14.1.4.7 Subcutaneous Phase

A total of 61 subjects with moderate to severe plaque psoriasis were enrolled at 11 study centers. Of these subjects, 20/61 received a single conditioning dose of 0.7 mg/kg followed by 11 weekly doses of 1.0 mg/kg, received 12 weekly doses of 0.7–2.0 mg/kg, 20/61 (33%) received a single conditioning dose of 0.7 mg/kg followed by 11 weekly doses of 2.0 mg/kg, and 21/61 (34%) received a single conditioning dose of 0.7 mg/kg followed by 11 weekly doses of 4.0 mg/kg. The majority of subjects were male 41/61 and Caucasian 51/61. Subjects ranged in age from 21 to 71 years of age and from 65 to 123 kg in weight. Median BSA affected by psoriasis ranged from 25.3 to 28.5, and the median baseline PASI scores ranged from 17.6 to 20.6.

The most frequently reported adverse events (reported by at least 10% of subjects) are tabulated below.

Table 123 Summary of Most Frequently Reported Drug-related Adverse Events in IV Groups (HUPS256)

Body System	0.3 mg/kg (N = 6) n (%)	0.3-1.0 mg/kg (N = 10) n (%)	Total Combined (N = 16) n (%)
Subjects Reporting at Least One Drug –Related AE	6 (100)	10 (100)	16 (100)
Body as a Whole	5 (83)	5 (50)	10 (63)
Headache	2 (33)	3 (30)	5 (31)
Pain	2 (33)	1 (10)	3 (19)
Asthenia	2 (33)	0	2 (13)
Chills	0	2 (20)	2 (13)
Skin and Appendages	2 (33)	6 (60)	8 (50)
Psoriasis	1 (17)	2 (20)	3 (19)
Pruritus	1 (17)	1 (10)	2 (13)
Urticaria	0	2 (20)	2 (13)
Hemic and Lymphatic	0	3 (30)	3 (19)
Lymphadenopathy	0	2 (20)	2 (13)
Respiratory	2 (33)	1 (10)	3 (19)
Rhinitis	1 (17)	1 (10)	2 (13)
Digestive	1 (17)	1 (10)	2 (13)
Nausea	1 (17)	1 (10)	2 (13)

Acute events of headache, nausea, and chills within one day after study drug administration were reported for 7/16 (44%) of the subjects. Two of the sixteen subjects (13%) experienced at least one hearing-related adverse event. One of these subjects, with decreased hearing as a result of impacted cerumen, was considered to have hearing loss unrelated to the study drug. The other subject experienced two incidences of vertigo which were possibly related to the study drug, but resolved within 5 hours.

14.1.5 Protocol HUPS252

14.1.5.1 Study Title

A Double-blind, Placebo-controlled, Multi-center Phase 2 Study to Assess the Safety, Biological Activity, and Efficacy of hu1124 (Efalizumab) in Patients with Moderate to Severe Plaque Psoriasis

14.1.5.2 Study Objectives

The study objective were to evaluate

- the safety of multiple dosing with efalizumab when administered to subjects with moderate to severe plaque psoriasis
- the pharmacodynamic effects of 8 weekly intravenous treatments with efalizumab on the expression of CD11a and skin histology, as compared with placebo; and
- the efficacy of 8 weekly treatments with efalizumab on the severity of psoriasis as compared with placebo.

14.1.5.3 Study Design

This was a Phase 2, double-blind, multiple-dose, placebo-controlled, multi-center study to evaluate the effects of two different doses of efalizumab compared with placebo in subjects with moderate to severe plaque psoriasis. A total of 145 subjects with a minimum Psoriasis Area and Severity Index (PASI) of 12 and at least 10% of BSA coverage by psoriasis were randomized to receive 8 weekly intravenous infusions of efalizumab or placebo at a 2:1 ratio within each of the two dose groups. The first 31 subjects were randomized to receive either efalizumab 0.1mg/kg (n = 22) or placebo (n = 9). The remaining subjects were randomized to receive either efalizumab 0.3 mg/kg (n = 75) or placebo (n = 39). Subjects were to be followed for at least 91 days after the last treatment.

14.1.5.4 Results and Discussion

A total of 145 subjects were randomized to receive treatment at 10 study centers. One subject randomized to placebo in the 0.3 mg/kg treatment group did not receive treatment. Of the 144 subjects randomized and dosed, 22/144 (15%) of the subjects received efalizumab 0.1 mg/kg, 75/144 (52%) received efalizumab 0.3 mg/kg, and 47/144 (33%) received placebo.

The majority of treated subjects were Caucasian (93%) and men (66%). The subjects ranged from 21 to 72 years of age. Baseline BSA affected by psoriasis ranged from 10.5 to 73%, with the median BSA affected by psoriasis ranging from 18.2% to 26.5% across treatment groups. Baseline PASI ranged from 11.4 to 57.2, with the median PASI ranging from 14.5 to 17.7 across treatment groups.

A dose-dependent improvement in the severity of psoriasis was noted by primary outcome measures (PGA) and by secondary outcomes (PASI score).

Table 124 Reduction in PASI score at Endpoint (day 56)

	PASI score Mean ±SD		% Reduction ±SD
	Baseline	Endpoint	
Placebo (n=48)	16.2 ±4.4	13.9±27	16.5±27
Efalizumab 0.1 mg/kg (n=22)	18.2±6.7	14.2±8.9	24.2±28.9
0.3 mg/kg (n=75)	19.1±7.3	10.9±8.4	43.8±29.4

There were no deaths in the study. A total of 16 subjects discontinued study drug prematurely. Of these, six discontinued treatment because of adverse events. In the efalizumab 0.1 mg/kg group, 2/22 (9%) (headache, worsening psoriasis). In the efalizumab 0.3 mg/kg group, 2/75 (3%) (worsening psoriasis,hearing loss and tinnitus). In the placebo group, 2/47 (4%) (worsening psoriasis,dizziness).

Acute adverse events of headache, fever, chills, nausea, and vomiting within 24 hours after study drug administration were higher in the efalizumab 0.3 mg/kg group (42/75 [56%]) than the efalizumab 0.1 mg/kg (8/22 [36%]) or the placebo (11/47 [23%]) groups.

Antibody response to efalizumab was detected in 1/19 (5%) of the subjects in the efalizumab 0.1 mg/kg group, 10/70 (14%) of the subjects in the efalizumab 0.3 mg/kg group, and none of the

subjects in the placebo group. Competition experiments indicated that the response was anti-idiotypic in nature. These were low titer antibodies and were not associated with any adverse events suggestive of immune complex formation and deposition.

14.1.5.5 Safety

Table 125 Patients with Serious Adverse Events

Treatment Group	Patient	Sex	Age	Adverse Event [Preferred Term]	Onset Day	Severity	Relation to Study Drug[a]	Number of Doses Received
0.1 mg/kg	462	F	50	Fractured r hand [bone fractspontan]	36	Severe	Unrelated	8
0.3 mg/kg	422	M	55	Psoriatic Arthritis [arthritis]	61	Severe	Possible	8
				Carpaltunnel syndrome [tenosynovitis]	122	Severe	Possible	
0.3 mg/kg	582	M	49	Synovitis [synovitis]	20	Severe	Unrelated	8
0.3 mg/kg	642	M	54	Hearing loss – lear (sensorineural hearing loss) [deaf]	36	Severe	Possible	6[b]
0.3 mg/kg	703	M	68	Retrosternalpain [pain chest substern]	134	Moderate	Unrelated	8
Placebo	239	F	34	Gastroenteritis [gastroenteritis]	112	Severe	Unrelated	8
Placebo	419	M	29	Psoriatic arthritis (Hands and Feet) [arthritis]	100	Severe	Unrelated	8
Placebo	464	M	66	Fractured r ribs [bone fract spontan]	38	Moderate	Unrelated	8
Placebo	641	M	42	Chestpain (notyet diagnosed) [pain chest]	58	Severe	Possible	8

[a] As judged by the investigator.
[b] Patient 642 did not receive thefinal two doses of study drug due to this adverse event.

14.1.6 Protocol ACD2389g

14.1.6.1 Study Title

A Randomized, Open-Label, Single-Center, Two-Period Crossover Study in Healthy, Adult Volunteers to Evaluate the Pharmacokinetic Comparability and Safety of Single 1.0 mg/kg Subcutaneous Doses of XOMA-Manufactured and Genentech-Manufactured Efalizumab (ACD2389g)

14.1.6.2 Study Objectives

The study's primary objective was to determine the pharmacokinetic (PK) comparability of single, subcutaneous (SC) doses of XOMA and Genentech efalizumab as measured by the area under the concentration–time curve from time 0 until infinity (AUCinf). The goal of the study was to obtain a 90% confidence interval on the relative bioavailability of Genentech to XOMA efalizumab and to determine whether the interval was completely within 80%–125%.

Study Design

Subjects were randomized in an equal ratio to one of two treatment sequences: Genentech efalizumab on Day 0 of Period 1 with crossover to XOMA efalizumab on Day 0 of Period 2 (GX Group) or XOMA efalizumab on Day 0 of Period 1 with crossover to Genentech efalizumab on Day 0 of Period 2 (XG Group). A single 1.0 mg/kg dose was administered subcutaneously at Day 0 of each period. Each dose was followed by a 5-week sample collection period, during which serial blood draws were taken for both PK and pharmacodynamic (PD) measurements. The total time from screening to study completion was approximately 13 weeks.

A population of healthy volunteers was chosen to avoid concomitant medications and co-existing disease state interactions. A 6-week washout period was selected based on the expected half-life of approximately 7 days and previous clinical data demonstrating that CD11a expression returns to baseline approximately 4 weeks after a single intravenous (IV) dose of efalizumab.

14.1.6.3 Results and Discussion

Ninety-nine subjects were randomized in this study. A total of 81 subjects completed the study.

Of the 20 subjects who were not PK evaluable, 10 were randomized to the XG group and 10 were randomized to the GX group, leaving 39 PK evaluable subjects from the XG group and 40 subjects from the GX group for a total of 79 PK evaluable subjects.

Overall, the treatment groups were comparable with regard to demographic and baseline characteristics.

Pharmacokinetics:

Table 126 Mean ±SD Efalizumab Pharmacokinetic Parameters

Parameter	XOMA Efalizumab (n=79)	Genentech Efalizumab (n=79)
Cmax (µg/mL)	4.1±2.0	4.9±2.0
Tmax (day) a	3.5 (1.0–7.0)	3.5 (1.4–8.0)
AUCt (µg day/mL)	32.6±18.9	43.6±24.5
AUCinf (µg day/mL)	33.4±19.1	44.9±24.8
Linear t1/2 (day)	5.0±2.1	5.6±2.4
Nonlinear t1/2 (day)	1.7±1.6	1.7±1.7

The results of the study demonstrated that single 1.0 mg/kg SC doses of Genentech efalizumab produced an approximately 30% higher exposure (AUC_{inf}) and an approximately 20% higher C_{max} in healthy volunteers compared with an identical dose of XOMA efalizumab. The protocol-

specified secondary outcome variables, AUC_t and C_{max}, were also significantly higher after administration of the Genentech efalizumab dose.

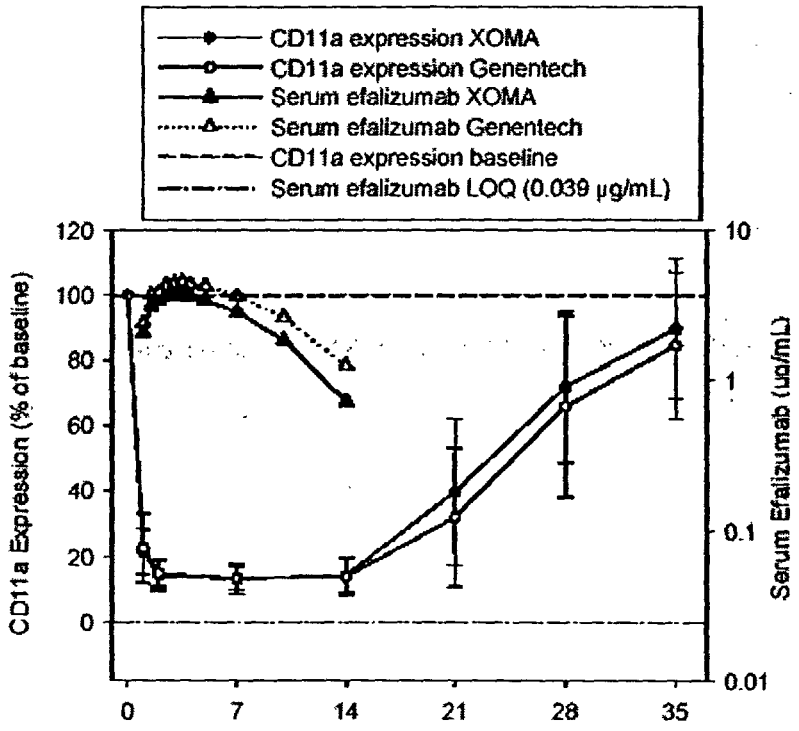
	n	Geometric LS mean Xoma	GNE	Ratio GNE/Xoma	90% CI	
AUC_{inf} (:g·day/ml	79	27.8	36.9	1.32	1.19	1.47

The point estimate and confidence intervals were outside the prespecified 80%–125% interval and therefore did not meet the criterion for comparability.

This difference in exposure did not translate into differences in extent or duration of PD activity (CD11a saturation and CD11a down-modulation on T lymphocytes). XOMA and Genentech efalizumab induced a rapid decrease in CD11a expression and available binding sites with maximal decrease by day 2. This effect was maintained until day 14, when efalizumab serum levels
decreased to <1 :g/mL . These PD effects appeared to be similar for all cell types measured for both XOMA and Genentech (T lymphocytes, NK cells, monocytes, and neutrophils).

Figure 10

Mean Serum Efalizumab Concentration and
Mean ±SD CD11a Expression on T Lymphocytes



No differences in safety including immunogenicity of the two products were detectable in this small study.

Reviewer's comments.
This study was conducted at the request of the Agency. The sponsor hypothesized that the cause of these observed differences in exposure was related to differences in systemic bioavailability of the two products. Differences in the formulation of the two products might account for these differences; in particular the higher concentration of surfactant (polysorbate 20) in the GNE formulation.

The 30% higher serum concentrations of GNE efalizumab did not raise safety concerns strictly on the grounds of exposure given the available clinical safety data that exceeded that exposure. The lack of appreciable difference in the magnitude and duration of CD11a receptor saturation and down-modulation induced by the Xoma and GNE products was also interpreted as suggesting that the GNE product would not manifest higher immunosuppressant clinical activity (including treatment response). The sponsor and the agency agreed that an adequate safety database would be required to demonstrate the safety of GNE efalizumab. Whether or not the clinical safety data using Xoma efalizumab could be supportive of the safety of GNE efalizumab would become a review issue.