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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

STN/BLA 125075/0

**Clinical Pharmacology and Biopharmaceutics
Review**



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and
Research
1401 Rockville Pike
Rockville, MD 20852

CLINICAL PHARMACOLOGY REVIEW

Date: October 23, 2003

From: Anil K. Rajpal, M.D., Clinical Pharmacology Reviewer

Through: *MS 10/29/03*
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Subject: Clinical Pharmacology Review of Biologic License Application STN 125075 for
Genentech Inc. RAPTIVA™ (Efalizumab)

To: Center / Division / Office – CDER / ODE VI / DTBIMP
Primary Reviewer – Elektra Papadopoulos, M.D.

Please see the attached review.

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EXECUTIVE SUMMARY

Efalizumab is a recombinant humanized IgG1 kappa isotype monoclonal antibody that binds to human CD11a and has an approximate molecular weight of 150 kD. Efalizumab contains human framework regions with the complementarity-determining regions of a humanized murine antibody that binds to CD11a. Efalizumab is produced in a Chinese Hamster Ovary mammalian cell expression system. Efalizumab has a binding affinity for CD11a of approximately —

Efalizumab is intended for the treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. CD11a is the α subunit of leukocyte function antigen-1 (LFA-1) and is expressed on all leukocytes. Efalizumab inhibits the binding of LFA-1 to intercellular adhesion molecule-1 (ICAM-1), the expression of CD11a, and the adhesion of leukocytes to other cell types. The interaction of LFA-1 and ICAM-1 contributes to the initiation and maintenance of multiple functions, including activation of T lymphocytes, adhesion of T lymphocytes to endothelial cells, and migration of T lymphocytes to sites of inflammation. Lymphocyte activation and trafficking to skin plays a role in the pathophysiology of chronic plaque psoriasis. In psoriatic skin, ICAM-1 is upregulated on endothelium and keratinocytes.

The proposed dosing regimen is a single 0.7 mg/kg SC conditioning dose followed by weekly SC doses of 1 mg/kg.

The pharmacokinetics of efalizumab was evaluated in thirteen clinical studies. XOMA Ltd. conducted six of the studies, and Genentech, Inc. conducted seven of the studies. Study ACD2389g was a pharmacokinetic comparability study in healthy volunteers comparing XOMA-manufactured and Genentech-manufactured Efalizumab.

Efalizumab has a concentration-dependent clearance, suggesting receptor-mediated elimination which is saturable at efalizumab plasma levels above 1 $\mu\text{g/mL}$. In study ACD2142g, using an initial dose of 0.7 mg/kg followed by 11 weekly doses of 1.0 mg/kg/wk, efalizumab serum concentrations reached a steady-state at 4 weeks with a mean trough concentration of approximately 9 $\mu\text{g/mL}$ (n=26). After the last dose, the mean peak concentration was 12 $\mu\text{g/mL}$ (n=25). Mean steady-state clearance was 24 mL/kg/day (range — mL/kg/day, n = 25). Mean time to eliminate efalizumab after the last steady-state dose was 25 days (range 13 to 35 days, n=17).

A population PK analysis was done using a one-compartment linear PK model determined based on Study ACD2142g results. Pooled data was used from four studies (ACD2058g, ACD2059g, ACD2243g, and ACD2142g) that included 1088 patients in the psoriatic population. After a dose of 0.7 mg/kg, patients received 1 or 2 mg/kg subcutaneous (SC) weekly doses of efalizumab for 77 days, with 483 patients (44%) treated with Genentech material. Weight was found to be the most significant covariate affecting efalizumab clearance, supporting the validity of weight-based dosing. Dose level was also a significant covariate for efalizumab SC clearance, which is consistent with the drug's nonlinear PK. The other covariates of baseline PASI, baseline lymphocyte count, body mass index (BMI), and

age had less significant effects on clearance. Gender and race had no significant effect on efalizumab clearance.

Summary of Studies

A listing of the pharmacokinetic and pharmacodynamic studies are below:

Study	Product code	Route	Dose (mg/kg)	No of weekly doses	Total efalizumab subjects	Intensive sampling	Population PK Analysis
HU9602	102515 ^a	IV	0.03-10.0	1	31	X	
HUPS249	102515 ^a	IV	0.1-10.0	4 ^c , 7	39	X	
HUPS252	102515 ^a	IV	0.1, 0.3	8	97		
HUPS254	102646 ^a	SC	0.5-2.0	8	52	X	
HUPS256	102515 ^a , 102646 ^a	IV	0.3-1.0	12	68	X	
HUKT257	102646 ^a	SC	0.5, 2.0	12	38	X	
ACD2058g	102646 ^a	SC	1.0, 2.0	12	462		X
ACD2059g	102646 ^a , G176H ^b	SC	1.0, 2.0	12	579		X
ACD2243g	G176H ^b	SC	2.0 ^d , 1.0-4.0 ^e	12	339		X
ACD2390g	G176CR ^b	SC	1.0	12	368		
ACD2142g	G176H ^b	SC	1.0, 2.0	12	70	X	X
ACD2389g	102646 ^a , G176CR ^b	SC	1.0	1	184	X	
ACD2017g	102646 ^a	SC	2.0	8	36	X	

^a XOMA manufactured product

^b Genentech manufactured product

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SYNOPSIS**Study HU9602**

A Single Dose, Dose Escalation Study to Evaluate the Safety, Pharmacokinetics, and Biological Activity of hu1124 (Efalizumab) in Subjects with Moderate to Severe Plaque Psoriasis

Methods:

This was a Phase I open-label, single-dose, dose-escalation, multicenter study of efalizumab in subjects with a history of moderate to severe plaque psoriasis. Up to 41 subjects were to receive efalizumab, administered as a single intravenous infusion over 1 to 3 hours, and were to be followed for a minimum of 72 days after dosing.

There were eight dose groups which were to receive, respectively, 0.03, 0.1, 0.3, 0.6, 1.0, 2.0, 3.0 or 10.0 mg/kg. Of the 31 subjects, 4 subjects each were enrolled in the 0.03 and 0.1 mg/kg group, 8 were enrolled in the 1.0 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.

Blood samples were typically collected at pre-dose, 1, 2, 4, 8 hours, then 1, 3, 7, 14, 21, 28, 35, 42, 49, 56, and 70 days after start of infusion. Plasma samples were assayed for efalizumab by — The lower limit of quantification was — ng/mL.

Pharmacokinetic endpoints included C_{max}, clearance, AUC, and t_{end} (time after last dose when efalizumab level below — μg/mL).

Pharmacodynamic endpoints included CD11a down-modulation on T cells assessed by flow cytometry.

Results:

Pharmacokinetic results:

Noncompartmental PK Parameters of a Single IV Dose of Efalizumab in Psoriasis Subjects, Mean (± SD)					
Dose [mg/kg]	n	C _{max} [μg/mL]	AUC [day*μg/mL]	CL [mL/kg/day]	t _{end} [days]
0.03 ^a	2	0.5, 0.6	0.06, 0.1	245, 516	0.7, 1.4
0.1	3	0.8 (±0.1)	0.5 (±0.4)	308 (±278)	2.7 (±1.9)
0.3	7	4.4 (±1.3)	8.9 (±4.9)	48.4 (±38.1)	9.1 (±3.2)
0.6 ^a	2	5.0, 14.5	24.1, 56.3	10.1, 24.9	18.8, 19.0
1.0	7	18.7 (±5.9)	71.7 (±28.9)	15.5 (±5.0)	21.8 (±7.1)
2.0 ^a	1	39.9	183	10.9	27.0
3.0	4	54.6 (±18.1)	291(±57)	10.7 (±2.7)	36.5 (±6.4)
10.0 ^a	1	205	1513	6.6	65.8

t_{end} = time after last dose when efalizumab level below — μg/mL (lower level of quantification of XOMA assay)

^a There were fewer than 3 subjects in this group; data were insufficient to obtain an accurate estimate of the SD.

Efalizumab was cleared from the plasma in a concentration-dependent manner, with a clearance of 308 mL/kg/day at 0.1 mg/kg to 10.7 mL/kg/day at 3.0 mg/kg. The concentration-dependent clearance indicates non-linear kinetics.

Pharmacodynamic results:

Efalizumab reduced the CD11a expression measured on circulating CD3+ T lymphocytes. (see Appendix 1) At efalizumab levels below 1 µg/mL, the study drug was rapidly cleared from circulation and expression of CD11a started to return to baseline. The data suggests a receptor-mediated elimination which is saturable at plasma efalizumab concentrations above 1 µg/mL.

No depletion of T cells or CD8+ or CD4+ T-cell subtypes was observed.

Conclusions:

- Efalizumab was cleared from the plasma in a concentration-dependent manner, with a clearance of 308 mL/kg/day at 0.1 mg/kg to 10.7 mL/kg/day at 3.0 mg/kg. The concentration-dependent clearance indicates non-linear kinetics.
- Efalizumab reduced the CD11a expression measured on circulating CD3+ T lymphocytes. At efalizumab levels below 1 µg/mL, the study drug was rapidly cleared from circulation and expression of CD11a started to return to baseline. The data suggests a receptor-mediated elimination which is saturable at plasma efalizumab concentrations above 1 µg/mL.

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Study HUPS249

A Multiple-Dose, Escalating Dose Study to Evaluate the Safety, Pharmacokinetics, and Biological Activity of hu1124 (Efalizumab) in Subjects with Moderate to Severe Plaque Psoriasis

Methods:

This was a Phase I, open-label, multiple-dose, dose-escalation, multicenter study of the effects of efalizumab in subjects with moderate to severe plaque psoriasis. Subjects were to receive intravenous infusions of efalizumab administered either every two weeks or once weekly for seven weeks.

Dosing regimens in Groups A, B, C, D, and E were as shown in the table below. IV infusions were over 90 minutes.

Group	n	Dosing regimen
A	3	0.1 mg/kg qow IV x 4
B	5	0.1 mg/kg/wk IV x 7
C	16	0.3 mg/kg/wk IV x 7
D	6	Wk 1: 0.3 mg/kg IV; Wk 2: 0.4 mg/kg IV; Wk 3: 0.6 mg/kg/wk IV x 5
E	5	Wk 1: 0.3 mg/kg IV; Wk 2: 0.4 mg/kg IV; Wk 3: 0.6 mg/kg IV; Wk 4: 1 mg/kg/wk IV x 4

Blood samples were collected before dosing, and at 0.06, 0.15, 0.23, 7, 7.06, 7.15, 14, 14.06, 14.15, 21, 21.06, 21.15, 28, 28.06, 28.15, 35, 35.06, 35.15, 42, 42.06, 42.15, 56, 70, and 98 days after the start of the first dose.

Pharmacokinetic endpoints included C_{max} , C_{trough} , AUC_{SS} , CL_{SS} , and t_{end} . Plasma samples were assayed for efalizumab by — . The lower limit of quantification was \sim ng/mL.

Pharmacodynamic endpoints included CD11a down-modulation on T lymphocytes assessed by flow cytometry.

Results:**Pharmacokinetic Results:**

Summary of Peak and Trough Efalizumab Levels ($\mu\text{g/mL}$), Mean \pm SD						
Group	n	Peak (Day 0)	Trough (7 or 14 days)	Peak (7 or 14 days)	Trough (42 days)	Peak (42 days)
A: 0.1 mg/kg qow	3	0.911 \pm 0.423	BD	0.587 \pm 0.261	BD	0.699 \pm 0.166
B: 0.1 mg/kg/wk	5	0.561 \pm 0.140	BD	0.613 \pm 0.311	BD	0.871 \pm 0.184
C: 0.3 mg/kg/wk	16	5.78 \pm 1.35	0.273 \pm 0.255	6.41 \pm 1.03	1.37 \pm 1.12	8.06 \pm 3.25
D: 0.3-0.6 mg/kg/wk	6	4.44 \pm 0.88	0.192 \pm 0.146	9.17 \pm 1.61	5.49 \pm 1.76	13.4 \pm 6.1
E: 0.6-1.0 mg/kg/wk	5	15 \pm 23	0.108	9.55 \pm 2.54	9.55 \pm 7.34	41.5 \pm 20.2

BD=below assay detection levels

The mean peak and trough plasma levels of efalizumab appeared to be dose dependent and increased as the dose level of study medication increased. No accumulation of efalizumab was observed in the lower dose groups A, B, and C.

Accumulation was seen in the higher dose groups D and E. In subjects receiving weekly escalating doses of efalizumab at 0.3, 0.4, to 0.6 mg/kg (Group D), average peak efalizumab levels increased from 4.44 $\mu\text{g/mL}$ after the first dose to 13.8 $\mu\text{g/mL}$ by the third weekly dose (0.6 mg/kg), with no sign of accumulation thereafter. In subjects receiving weekly escalating doses of efalizumab at 0.3, 0.4, 0.6, to 1 mg/kg (group E), average peak efalizumab levels increased from 15.0 $\mu\text{g/mL}$ after the first dose to 26.5 $\mu\text{g/mL}$ by the fourth weekly dose (1 mg/kg), with additional increase to 41.5 $\mu\text{g/mL}$ by the last dose.

Noncompartmental Pharmacokinetic Parameters of Plasma Efalizumab after Last Dose in Subjects Receiving Weekly Intravenous Doses of Efalizumab (Mean \pm SD) (Study HUPS249)						
Group	T _{max} (Days)	C _{max} ($\mu\text{g/mL}$)	C _{trough} ($\mu\text{g/mL}$)	Time-end (Days)	AUC _{ss} ($\mu\text{g/mL}\cdot\text{Days}$)	CL _{ss} (mL/Day/kg)
A (n=3) 0.1 mg/kg qow x 4	0.067 \pm 0.002	0.699 \pm 0.166	BD	6.0 \pm 1.0	0.734 \pm 0.387	159 \pm 64
B (n=5) 0.1 mg/kg/wk x 7	0.064 \pm 0.001	0.871 \pm 0.184	BD	5.4 \pm 0.5	1.10 \pm 0.30	95.7 \pm 27.6
C (n=16) 0.3 mg/kg/wk x 7	0.110 \pm 0.043	8.16 \pm 3.57	1.37 \pm 1.12	13.3 \pm 9.3	20.1 \pm 13.0	25.3 \pm 21.1
D (n=6) Wk 1: 0.3 mg/kg Wk 2: 0.4 mg/kg Wk 3: 0.6 mg/kg/wk x 5	0.132 \pm 0.033	13.6 \pm 6.3	5.49 \pm 1.76	25.3 \pm 0.5	61.6 \pm 19.6	10.9 \pm 4.5
E (n=5) Wk 1: 0.3 mg/kg Wk 2: 0.4 mg/kg Wk 3: 0.6 mg/kg Wk 4: 1 mg/kg/wk x 4	0.114 \pm 0.045	42.2 \pm 20.1	9.55 \pm 7.34	35.2 \pm 14.5	126 \pm 72	11.2 \pm 8.5

BD=below assay detection levels

Time-end = Time after last dose when efalizumab level fell below $\mu\text{g/mL}$ (detection level)

The clearance (CL_{ss}) evaluated during the week of the last dose tended to decrease with weekly dose from 95.7 \pm 27.6 mL/day/kg (mean \pm SD, n = 5) at 0.1 mg/kg/wk to 11.2 \pm 8.5 mL/day/kg (n = 5) at 1 mg/kg/wk. A similar decrease in clearance with increasing dose was observed in patients receiving single intravenous doses of efalizumab. Consistent with these observations, the time after the last dose at which the efalizumab first fell below detection tended to increase with weekly dose, from 5.4 \pm 0.5 days at 0.1 mg/kg/wk to 35.2 \pm 14.5 days at 1 mg/kg/wk.

Pharmacodynamic Results:

Summary of CD11a Expression (Percentage of Predose) (Mean \pm SD)						
Group	n	Peak (Day 0)	Trough (7 or 14 days)	Peak (7 or 14 days)	Trough (42 days)	Peak (42 days)
A: 0.1 mg/kg qow IV	3	71.3 \pm 6.2	104 \pm 14	77.7 \pm 26.8	92.3 \pm 2.2	72.6 \pm 19.6
B: 0.1 mg/kg/wk IV	5	58.1 \pm 6.2	74.3 \pm 18.7	62.7 \pm 11.8	64.9 \pm 15.4	54.2 \pm 14.2
C: 0.3 mg/kg/wk IV	16	46.4 \pm 11.7	22.6 \pm 6.4	21.9 \pm 5.5	32.6 \pm 18.3	27.6 \pm 8.3
D: 0.3-0.6 mg/kg/wk IV	6	60.7 \pm 16.8	29.8 \pm 5.1	31.7 \pm 7.9	28 \pm 6	30 \pm 7
E: 0.6-1.0 mg/kg/wk IV	5	52.1 \pm 14.4	30.5 \pm 7.9	29.7 \pm 8.3	28.7 \pm 8.0	28.2 \pm 8.3

A decrease in CD11a expression was observed after study medication administration in all dose groups, with nearly full recovery noted before the next dose in the lower dose group A.

A reversible increase in the average number of lymphocytes was observed in the higher dose groups after Day 7 with a return to the pretreatment numbers after dosing was completed. No effects on the distribution of T and B subtypes or T-cell subclasses were observed with any dose.

Conclusions:

- The mean peak and trough plasma levels of efalizumab appeared to be dose dependent and increased as the dose level of study medication increased.
- The clearance (CL_{ss}) evaluated during the week of the last dose tended to decrease with weekly dose from 95.7 \pm 27.6 mL/day/kg at 0.1 mg/kg/wk IV to 11.2 \pm 8.5 L/day/kg at 1 mg/kg/wk IV.
- The time after the last dose at which the efalizumab first fell below detection tended to increase with weekly dose, from 5.4 \pm 0.5 days at 0.1 mg/kg/wk IV to 35.2 \pm 14.5 days at 1 mg/kg/wk IV.

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Study HUPS252

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

Methods:

This was a Phase II, 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).

Efalizumab assay: The limit of detection of the assay for efalizumab was typically — $\mu\text{g/mL}$.

CD11a expression: CD11a expression on T-Cells was assayed by flow cytometric methods

Results:

Summary of Peak and Trough Efalizumab Levels (Mean \pm SD)							
Group	Trough Day 0	Peak Day 0	Trough Day 28	Peak Day 28	Trough Day 56	Level Day 70	Level Day 140
0.1 mg/kg	BD	0.888 \pm 0.808	BD	1.06 \pm 0.69	BD	BD	BD
0.3 mg/kg	BD	5.89 \pm 0.32	1.05 \pm 0.92	6.98 \pm 2.22	1.73 \pm 1.75	0.878	BD

BD = Below assay detection levels.

Mean peak levels were 0.888 \pm 0.808 $\mu\text{g/mL}$ in the efalizumab 0.1 mg/kg group and 5.89 \pm 0.32 $\mu\text{g/mL}$ in the efalizumab 0.3 mg/kg group. By Day 56 (1 week after the last dose), the levels of efalizumab were below detection in the efalizumab 0.1 mg/kg group and ranged from below detection to — $\mu\text{g/mL}$ in the efalizumab — mg/kg group.

The average CD11a expression on circulating T lymphocytes was reduced by about 70% during treatment in the efalizumab 0.3 mg/kg group, although remaining efalizumab binding sites were only partially saturated prior to the next infusion. In addition, the average lymphocyte count increased almost two-fold during treatment. There were no major changes in the proportion of lymphocyte populations.

In the efalizumab 0.1 mg/kg group, lymphocyte counts were not increased and expression of CD11a was reduced by only 30-40%.

Lymphocyte numbers, CD11a expression, and available efalizumab binding sites returned to pretreatment levels by study Day 140 in all groups.

Study HUPS254

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

Methods:

This was a Phase I, open-label, single- and multiple-dose, escalating-dose, multi-center study of the effects of subcutaneously administered efalizumab in subjects with moderate to severe plaque psoriasis. 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 were as follows:

- Group A: 0.3 mg/kg administered as a single SC dose
- Group B: 0.5 mg/kg administered weekly for 8 weeks
- Group C and C.1: 0.5 mg/kg escalated to 1.0 mg/kg
- Group D: 0.7 mg/kg escalated to 1.5 mg/kg
- Group E and E.1: 1.0 mg/kg escalated to 2.0 mg/kg

See table below.

Treatment Schedule by Treatment Group								
Treatment Group	Day 0 (mg/kg)	Day 7 (mg/kg)	Day 14 (mg/kg)	Day 21 (mg/kg)	Day 28 (mg/kg)	Day 35 (mg/kg)	Day 42 (mg/kg)	Day 49 (mg/kg)
Group A (n = 2)	0.3	—	—	—	—	—	—	—
Group B (n = 4)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Group C (n = 6)	0.5	0.7	1.0	1.0	1.0	1.0	1.0	1.0
Group C.1 (n = 15)	0.5	0.7	1.0	1.0	1.0	1.0	1.0	1.0
Group D (n = 6)	0.7	1.0	1.5	1.5	1.5	1.5	1.5	1.5
Group E (n = 8)	1.0	1.5	2.0	2.0	2.0	2.0	2.0	2.0
Group E.1 (n = 15)	1.0	1.5	2.0	2.0	2.0	2.0	2.0	2.0

Blood samples were collected before (trough) and after (peak) study drug administration at specific times beginning 36 hours after the end of injection through Day 28 for the single dose group and through Day 91 for the multiple-dose groups.

Pharmacokinetic endpoints included C_{max} , C_{trough} , AUC_{SS} , CL_{SS} , t_{end} , and Bioavailability. Plasma samples were assayed for efalizumab by — The lower limit of quantification was — ng/mL.

Results:**Pharmacokinetic Results:**

For Group A, 0.3 mg/kg SC X 1 (n=2), PK parameters were not calculated as there were too many concentrations that were below limit of quantification.

Noncompartmental Pharmacokinetic Parameters of Plasma Efalizumab in Subjects Receiving Weekly SC Doses of Efalizumab (Mean ± SD) (HUPS254)							
Group	T _{max} Days	C _{max} g/mL	C _{trough} µg/mL	Time-end Days ^a	CL/F _{ss} mL/Day/kg	CL _{ss} IV mL/Day/kg	BIO%
B (n = 2) 0.5 mg/kg/wk X 8	2.0, 2.0	1.5, 8.0	0.5, 6.4	12.0, 26.0	10.2, 78.9	10.3 From: Group D 0.6 mg/kg/wk, Study HUPS249	13.1, 101
C (n = 16) 0.5 mg/kg 0.7 mg/kg 1.0 mg/kg/wk X 6	1.44 ±0.49	7.43 ±4.23	5.28 ±3.55	25 ±7	33.2 ±21.1	9.23 From: Group E 1 mg/kg/wk, Study HUPS249	39.0 ±24.6
D (n = 4) 0.7 mg/kg 1 mg/kg 1.5 mg/kg/wk X 6	1.66 ± 0.54	20.3 ±7.7	14.9 ±8.4	38 ±15	14.2 ±6.3	9.23 From: Group E 1 mg/kg/wk, Study HUPS249	76.0 ±36.0
E (n = 19) 1 mg/kg 1.5 mg/kg 2 mg/kg/wk X 6	1.68 ±1.44	22.1 ±13.6	13.3 ±9.3	33 ±14	27.5 ±25.7	9.23 From: Group E 1 mg/kg/wk, Study HUPS249	54.5 ±33.1

T_{max} = time to peak concentration of efalizumab after last dose;

C_{max} = peak concentration of efalizumab after last dose;

C_{trough} = concentration of efalizumab 1 week after the last dose (Day 56);

CL/F_{ss} = clearance of efalizumab during the week after the last SC dose;

CL_{ss} IV = clearance of efalizumab during the week after the last IV dose in Study HUPS249; Bio=bioavailability of SC administered efalizumab relative to IV administration.

^a Time-end = time after last dose when efalizumab level fell below — g/mL (detection level)

In the multiple-dose groups, the average peak levels after the last dose were 4.70 µg/mL for the 0.5 mg/kg group, 7.43 µg/mL for the 0.5-1.0 mg/kg group, 20.3 µg/mL for the 0.7-1.5 mg/kg group, and 22.1 µg/mL for the 1.0-2.0 mg/kg group. Average bioavailability (compared to IV administration from Study HUPS249) varied between 39.0% and 76.0% among the multiple-dose groups, with an overall average bioavailability of 50.7% ± 32.2% (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.

Conclusions:

- Average bioavailability (compared to IV administration) varied between 39.0% and 76.0% among the multiple-dose groups, with an overall average bioavailability of 50.7% ± 32.2%.

APPEARS THIS WAY
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Study HUPS256

An Open-label, Extended-duration, Multiple-dose Study to Evaluate the Safety, Pharmacokinetics, and Biological Activity of Intravenously and Subcutaneously Administered hu1124 (Efalizumab) in Subjects with Moderate to Severe Plaque Psoriasis

Methods:**Intravenous Phase**

This was a Phase I, open-label, extended-duration, multiple-dose, multicenter study of the effects of efalizumab administered by intravenous infusion to subjects with moderate to severe plaque psoriasis. A total of 16 subjects with a minimum PASI score of 12 and a minimum BSA coverage of at least 15% 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.

Subcutaneous Phase

This was a Phase I, open-label, extended-duration, multiple-dose, multicenter study of the effects of efalizumab administered by subcutaneous injection to subjects with moderate to severe plaque psoriasis. A total of 61 subjects with a minimum PASI score of 12 and a minimum BSA coverage of at least 15% were assigned to a dose group. The dose groups evaluated in this phase of the study were 0.7–1.0 mg/kg, 0.7–2.0 mg/kg, and 0.7–4.0 mg/kg administered weekly for 12 weeks.

Group	Dose	Dose Schedule
A (n=6)	0.3 mg/kg IV	Weeks 1-12
B (n=10)	0.3 mg/kg/wk IV	Week 1
	0.6 mg/kg/wk IV	Week 2
	1.0 mg/kg/wk IV	Weeks 3-12
C (n=20)	0.7 mg/kg/wk SC	Week 1
D (n=20)	0.7 mg/kg/wk SC	Week 1
	2 mg/kg/wk SC	Weeks 2-12
E (n=20)	0.7 mg/kg/wk SC	Week 1
	4 mg/kg/wk SC	Weeks 2-12

Pharmacokinetic endpoints included C_{max} , C_{trough} , AUC_{SS} , CL_{SS} , t_{end} , and Bioavailability. Plasma samples were assayed for efalizumab by — . The lower limit of quantification was — ng/mL.

Pharmacodynamic endpoints included distribution of circulating lymphocytes among T cells and T-lymphocyte subsets (CD3/CD4/CD8), natural killer (NK) cells, and B lymphocytes (flow cytometry).

Results:

Pharmacokinetic Results:

Summary of Noncompartmental Pharmacokinetic Parameters of Plasma Efalizumab for Subjects Receiving Weekly Intravenous or Subcutaneous Doses of Efalizumab (Mean ± SD)								
Group	Tmax (Days)	Cmax (µg/mL)	Ctrough (µg/mL)	Time-end (Days)	AUCss (µg/mL/Day)	CLss (mL/Day/kg)	CL _{ssIV} (mL/Day/kg)	BIO%
A (n = 5) IV 0.3 mg/kg/wk X 12	0.0664 ±0.0057	6.82 ±2.43	1.51 ±0.90	13 ±8	18.7 ±14.0	29.9 ±26.1	N/A	N/A
B (n = 7) IV 0.3 mg/kg 0.6 mg/kg 1 mg/kg/wk X 10	0.0658 ±0.0051	35.8 ±33.1	6.74 ±3.57	32 ±10	122 ±86	11.0 ±6.0	N/A	N/A
C (n = 20) SC 0.7 mg/kg 1 mg/kg/wk X 11	2.83 ±0.81	6.95 ±3.21	6.22 ±4.75	26 ±11	46.5 ±31.8	44.2 ±57.8	9.23 From: Group E 1 mg/kg/wk, Study HUPS249	42.9 ±29.7
D (n = 15) SC 0.7 mg/kg 2 mg/kg/wk X 11	1.63 ±0.60	16.6 ±8.8	13.8 ±11.4	37 ±13	110. ±72	29.5 ±27.4	9.23 From: Group E 1 mg/kg/wk, Study HUPS249	50.9 ±33.1
E (n = 18) SC 0.7 mg/kg 4 mg/kg/wk X 11	Not evaluated	Not evaluated	37.5 ±20.1	57 ±16	253 ±128	20.0 ±10.8	9.23 From: Group E 1 mg/kg/wk, Study HUPS249	58.5 ±29.6

Tmax = Time to peak concentration of efalizumab after last dose;

Cmax = Peak concentration of efalizumab after last dose;

Ctrough = Concentration of efalizumab on day 77 or 84;

Time-End = Time after last dose when efalizumab level fell below — µg/mL (detection level);

AUCss=AUC during last week of dosing;

CLss = clearance efalizumab during last week;

CL_{ss IV} = from Group E 1 mg/kg/wk Study HUPS249;

Bio% = bioavailability of SC efalizumab relative to IV administration

Intravenous Phase

The pharmacokinetic results in the two dose groups in this study were very similar to the results for the comparable dose groups in the HUPS249 study. In the 0.3 mg/kg group, the average peak concentration after the last dose was 6.82 ± 2.43 $\mu\text{g/mL}$; the average steady state trough concentration was 1.51 ± 0.90 $\mu\text{g/mL}$; and the steady state AUC was $18.7 \pm 14.0\%$ of that in the HUPS249 study. In the 0.3-1.0 mg/kg group, the average peak concentration after the last dose was 35.8 ± 33.1 $\mu\text{g/mL}$; the average trough concentration was 6.74 ± 3.57 $\mu\text{g/mL}$; and the steady state AUC was $122 \pm 86\%$ of that in the HUPS249 study.

Subcutaneous Phase

The pharmacokinetic results in this study were very similar to the results for the comparable dose groups in the HUPS254 study. Pharmacokinetic values increased with increasing dosages. In the 0.7-1.0 mg/kg group, the peak levels were 6.95 ± 3.21 $\mu\text{g/mL}$, steady state trough concentration was 6.22 ± 4.75 $\mu\text{g/mL}$, and the average bioavailability was $42.9 \pm 29.7\%$. In the 0.7-2.0 mg/kg group, peak levels were 16.6 ± 8.8 $\mu\text{g/mL}$, steady state trough concentration was 13.8 ± 11.4 $\mu\text{g/mL}$, and the average bioavailability was $50.9 \pm 33.1\%$. Peak levels were not measured in the 0.7-4.0 mg/kg group as per the protocol, but the steady state trough concentration was 37.5 ± 20.1 $\mu\text{g/mL}$, and average bioavailability was $58.5 \pm 29.6\%$.

The average bioavailability in groups C to E increased consistently with dose, from $42.9 \pm 29.7\%$, to $50.9 \pm 33.1\%$, to $58.5 \pm 29.6\%$, respectively. These bioavailability values are similar to those observed in study HUPS254 ($39.0 \pm 24.6\%$ at 1 mg/kg/wk and $54.5 \pm 33.1\%$ at 2 mg/kg/wk). The average bioavailability over groups C through E was $50.5 \pm 30.8\%$ similar to the average bioavailability of $50.7 \pm 32.2\%$ obtained in study HUPS254.

Pharmacodynamic Results:

Intravenous Phase:

An approximately two-fold increase in circulating lymphocytes was observed resulting in a small increase in WBCs during treatment (e.g., 22-30% on Day 77). The proportion of B and T lymphocytes remained consistent throughout the study, but a decrease in the mean CD4/CD8 ratio due to increased CD8 T cells and a decrease in the mean percentage of NK cells was observed. (see [Appendix 2](#))

CD11a expression on circulating T cells was decreased 70-85% in both dose groups. CD11a saturation was $\leq 95\%$ in the 0.3 mg/kg group, and $\geq 97\%$ in the 0.3-1.0 mg/kg group. With the exception of the difference noted in binding site saturation, no clear dose response was observed between the two dose groups.

Subcutaneous Phase:

An approximately two-fold increase in circulating lymphocytes was observed, resulting in a small increase in WBCs during treatment (22-49% on Day 77). The proportion of B and T lymphocytes remained consistent throughout the study, but decreases in the mean CD4/CD8 ratio were due to increased CD8 T cells. A decrease in the mean percentage of NK cells was also observed. (see Appendix 2)

CD11a expression on circulating T cells was decreased 70-85% in all dose groups. Saturation was >97% in all three dose groups. No clear dose response was observed between the three dose groups.

Conclusions:

- The average bioavailability in groups C to E increased consistently with dose, from $42.9 \pm 29.7 \%$, to $50.9 \pm 33.1 \%$, to $58.5 \pm 29.6 \%$, respectively. The bioavailability values are similar to those observed in study HUPS254 ($39.0 \pm 24.6 \%$ at 1 mg/kg/wk and $54.5 \pm 33.1 \%$ at 2 mg/kg/wk).
- With IV and SC dosing, an approximately two-fold increase in circulating lymphocytes was observed. With IV and SC dosing, the proportion of B and T lymphocytes remained consistent throughout the study, but a decrease in the mean CD4/CD8 ratio was seen due to increased CD8 T cells. With IV and SC dosing, a decrease in the mean percentage of NK cells was also observed.

**APPEARS THIS WAY
ON ORIGINAL**

Study HUKT257

A Phase I/II, Open-Label, Multicenter, Multiple-Dose Study to Evaluate the Safety, Pharmacokinetics/Pharmacodynamics, and Biological Activity of Subcutaneously Administered Efalizumab (anti-CD11a) in Subjects Receiving a Primary Renal Transplant

Methods:

Efalizumab was to be administered by SC injection for 12 weeks and subjects were then to be followed for an additional 13 weeks (follow-up later extended to 25 weeks). Two efalizumab dose levels (Group I [low] and Group II [high]) were separately paired with two sets of adjunctive immunosuppressive drugs (Arm A and Arm B) resulting in a total of four dose groups, as shown below.

Dose Groups		
Adjunctive Therapy	Efalizumab	
	Group I (0.5 mg/kg)	Group II (2.0 mg/kg)
Arm A: Half-dose cyclosporine/sirolimus/prednisone	Group IA	Group IIA
Arm B: Full-dose cyclosporine/MMF/prednisone	Group IB	Group IIB

Each subject was to receive an initial "conditioning" dose of efalizumab 0.5 mg/kg (Group I) or 0.7 mg/kg (Group II) on Day 0 up to 36 hours pre-transplant but no later than 1 hour pre-reperfusion. Thereafter, each subject was to receive a maintenance dose of efalizumab 0.5 mg/kg or 2.0 mg/kg, depending upon the dose group, at each weekly visit for 11 weeks.

Pharmacokinetic endpoints included C_{trough} and t_{end} . Plasma samples were assayed for efalizumab by —. The lower limit of quantification was —, ng/mL.

Results:

Pharmacokinetics Results:

Mean ± SD PK Parameters in Subjects Receiving Weekly SC Efalizumab				
Group	Dose	n	Mean ± SD	
			C_{trough}^a [µg/mL]	t_{end}^b [Days]
IA	0.5 mg/kg/wk X 12 SC	6	7.35 ± 3.41	52 ± 20
IB	0.5 mg/kg/wk X 12 SC	7	7.92 ± 4.81	51 ± 13
IIA	0.7 mg/kg SC 2.0 mg/kg/wk X 11 SC	6	35.2 ± 14.9	69 ± 12
IIB	0.7 mg/kg SC 2.0 mg/kg/wk X 11 SC	8 ^c	33.5 ± 16.1	67 ± 18

^a C_{trough} = Concentration of efalizumab on day 77 or 84

^b t_{end} = time after last dose when efalizumab level fell below — µg/mL (detection level)

^c n=7 for determination of t_{end} and effective $t_{1/2}$ for Group IIB subjects

Median (Range) PK Parameters in Subjects Receiving Weekly SC Efalizumab					
Group	Dose	n	Median (Range)		
			C_{trough}^a [$\mu\text{g/mL}$]	t_{end}^b [Days]	
IA	0.5 mg/kg/wk X 12 SC	6	8.95	—	55 (24-84)
IB	0.5 mg/kg/wk X 12 SC	7	9.62	—	57 (32-61)
IIA	0.7 mg/kg SC 2.0 mg/kg/wk X 11 SC	6	39.9	—	65 (57-86)
IIB	0.7 mg/kg SC 2.0 mg/kg/wk X 11 SC	8 ^c	31.3	—	60 (39-89)

^a C_{trough} = Concentration of efalizumab on day 77 or 84

^b t_{end} = time after last dose when efalizumab level fell below — ($\mu\text{g/mL}$ (detection level))

^c n=7 for determination of t_{end} and effective $t_{1/2}$ for Group IIB subjects

Both 0.5 mg/kg and 2.0 mg/kg doses produced higher levels than predicted or found in psoriasis subjects who were given equivalent doses. The trough levels with 0.5 mg/kg efalizumab measured in both background immunosuppression regimens were comparable to levels achieved at a 1.0 mg/kg dose level in psoriasis subjects. At the 2.0 mg/kg efalizumab dose, trough levels were approximately twice those seen in psoriasis subjects given an equivalent dose.

The clearance levels of cyclosporine, sirolimus and MPA were in the range reported in the literature for all subjects, suggesting that the presence of efalizumab did not alter the clearance of these immunosuppressive medications.

Pharmacodynamics Results:

Consistent with previous studies, efalizumab administration reduced CD11a expression within two days. The increased neutrophil counts and decreased lymphocyte counts that were observed on Day 2 were probably associated with the transplant procedure and/or the adjunctive medications. By Day 28, neutrophil counts had returned to pretreatment levels and lymphocyte counts were elevated, a pattern more typical of previous efalizumab studies. Lymphocyte counts and CD11a expression returned to baseline levels after drug clearance. A similar response was seen at both efalizumab dose levels.

APPEARS THIS WAY
ON ORIGINAL

Study ACD2058g

A Phase III, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multicenter, Multidose Study to Evaluate the Efficacy and Safety of Subcutaneously Administered Anti-CD11a in Adults with Moderate to Severe Plaque Psoriasis

Methods:

During the FT period of this study, approximately 450 subjects were to be randomly assigned to low-dose efalizumab (1.0 mg/kg), high-dose efalizumab (2.0 mg/kg), low-dose placebo, or high-dose placebo in a 2:2:1:1 ratio. During the FT period, subjects received a conditioning dose of 0.7 mg/kg followed by 11 weekly SC injections of 1.0 or 2.0 mg/kg study drug (efalizumab or equivalent placebo).

Pharmacokinetic samples on Day 84 were analyzed
assay

Results:

Pharmacokinetic Results:

Steady-State (Day 84) Trough Serum Efalizumab Concentration in PK-Evaluable Subjects Product 102646 (XOMA)		
Dosing Regimen	n	Serum Efalizumab Concentration [$\mu\text{g/mL}$] (Mean \pm SD)
0.7 mg/kg SC X 1 dose 1.0 mg/kg/wk SC X 11 doses	139	9.30 \pm 6.54
0.7 mg/kg SC X 1 dose 2.0 mg/kg/wk SC X 11 doses	135	24.05 \pm 14.50

APPEARS THIS WAY
ON ORIGINAL

Study ACD2059g

A Phase III, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multicenter, Multidose Study to Evaluate the Efficacy and Safety of Subcutaneously Administered Anti-CD11a in Adults with Moderate to Severe Plaque Psoriasis Who Are Candidates for Systemic Therapy

Methods:

During the FT period of this study, approximately 500 subjects were to be randomized in a 4:4:1:1 ratio to high-dose (2.0 mg/kg) efalizumab, low-dose (1.0 mg/kg) efalizumab, high-dose placebo, or low-dose placebo. Subjects received a conditioning dose of 0.7 mg/kg followed by 11 weekly SC injections of 1.0 or 2.0 mg/kg study drug (efalizumab or equivalent volume of placebo).

Pharmacokinetic samples on Day 84 were analyzed by assay

Results:

Pharmacokinetic Results:

Steady-State (Day 84) Trough Serum Efalizumab Concentration in PK-Evaluable Subjects			
Product	Dosing Regimen	n	Serum Efalizumab Concentration [µg/mL] (Mean ± SD)
102646 (XOMA)	0.7 mg/kg SC X 1 dose 1.0 mg/kg/wk SC X 11 doses	157	6.52 ± 4.87
G176H (Genentech)	0.7 mg/kg SC X 1 dose 1.0 mg/kg/wk SC X 11 doses	38	8.02 ± 5.50
102646 (XOMA)	0.7 mg/kg SC X 1 dose 2.0 mg/kg/wk SC X 11 doses	147	18.64 ± 11.55
G176H (Genentech)	0.7 mg/kg SC X 1 dose 2.0 mg/kg/wk SC X 11 doses	52	21.33 ± 13.54

Study ACD2243g

An Open-Label, Randomized, Multicenter Study to Evaluate the Safety, Tolerability, and Efficacy of Subcutaneously Administered Efalizumab Used in Combination with Topical Psoriasis Therapies for Prolonged Maintenance Treatment

Methods:

This is a study of up to 60 weeks of treatment with efalizumab. Trough levels were measured at two timepoints during the 12-week first-treatment (FT) period (n = 264) and at one timepoint during each of the four consecutive 12-week maintenance-treatment (MT) periods (n = 205, 209, 198, and 104 for Weeks 24, 36, 48, and 60, respectively) to assess long-term steady-state efalizumab levels.

Pharmacokinetic samples were analyzed

Results:

Pharmacokinetic Results:

Efalizumab Serum Trough Levels ($\mu\text{g/mL}$; mean \pm SD) in Study ACD2243g following Administration of Genentech Efalizumab					
Study Period / Duration	Study Day	Dose (mg/kg/wk)			
		1.0	2.0	3.0	4.0
FT/12 weeks	42	--	22.6 \pm 12.1 (n=261)	--	--
FT/12 weeks	84	--	27.3 \pm 15.4 (n=264)	--	--
MT1/12 weeks	84	14.5 \pm 9.2 (n=200)	29.7 \pm 23.7 (n=3)	--	24.8, 54.5 (n=2)
MT2/12 weeks	84	15.0 \pm 10.2 (n=175)	31.6 \pm 19.3 (n=26)	35.0 \pm 21.7 (n=4)	37.6 \pm 10.4 (n=4)
MT3/12 weeks	84	14.6 \pm 9.8 (n=158)	30.7 \pm 14.6 (n=35)	46.6 \pm 22.9 (n=4)	38.3 (n=1)
MT4/12 weeks	84	15.6 \pm 9.3 (n=68)	31.3 \pm 16.9 (n=35)	61.5 (n=1)	--

FT=first treatment(period); MT=maintenance treatment (period); n=number of subjects.

Consistent trough levels measured during five consecutive 12-week treatment periods in the 1-year extension study indicate that there was no unexpected accumulation during long-term treatment.

Study ACD2142g

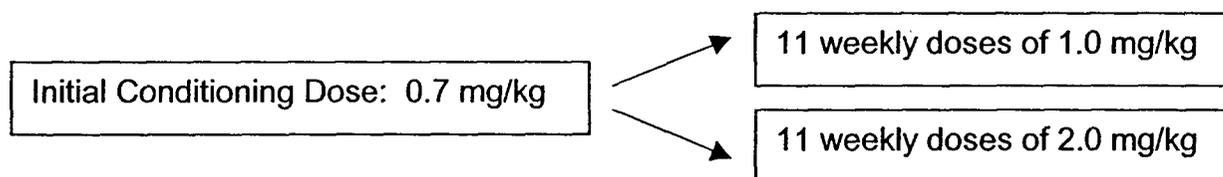
A Phase I, Open-Label, Multicenter Study to Characterize the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Anti-CD11a Administered Subcutaneously for 12 Weeks to Adults with Moderate to Severe Plaque Psoriasis.

Methods:

The study was divided into two parts: a screening and treatment period extending from Day -28 to Day 84 (Week 12) and a posttreatment follow-up period extending from Day 85 to Day 168 (Week 24).

Day -28 to Day 0	Day 0 to Day 84	Day 85 to Day 168
Screening period	Treatment period	Post-treatment Follow-up Period

During the treatment period, subjects received an initial conditioning dose of 0.7 mg/kg efalizumab, followed by 11 weekly doses of 1.0 or 2.0 mg/kg efalizumab.



Pharmacokinetics:

Pharmacokinetic endpoints included the following:

- Observed maximum concentration following administration of the last dose.
- Time to observed maximum concentration following administration of the last dose
- Steady-state clearance unadjusted for bioavailability (CL/F_{ss}).
- Area under the concentration–time curve during one dosing interval at steady-state.
- Time from the last dose to the time when serum efalizumab concentration fell below the limit of quantification of $\text{— } \mu\text{g/mL}$ (t_{end}).
- $t_{1/2}$ for the portion of the curve where concentration is above $1 \mu\text{g/mL}$.

The pharmacokinetic profile of efalizumab was characterized using sera collected at the following timepoints: predose on Days 0, 7, 28, 56, and 77, and on Days 78, 79, 80, 84, 91, 98, 112, and 133. Efalizumab steady-state parameters were determined after the 12th (final) dose of efalizumab on Day 77.

Serum efalizumab concentrations were determined by —

quantification (LOQ) for the assay was $\text{— } \mu\text{g/mL}$.

The limit of

Results:**Pharmacokinetic Results:**

Trough Efalizumab Concentrations [$\mu\text{g/mL}$]		
	Mean ($\pm\text{SD}$)	
	Efalizumab 1.0 mg/kg/wk (n=26)	Efalizumab 2.0 mg/kg/wk (n=29 ^a)
Day 7	1.8 (± 1.2)	1.3 (± 1.1)
Day 28	9.3 (± 5.2)	19 (± 8.5)
Day 56	9.6 (± 6.8)	21.6 (± 10.6)
Day 77	6.7 (± 5.3)	21.0 (± 10.4)
Day 84	9.1 (± 6.7)	23.5 (± 12.2)

^a n=28 for Day 7 and day 84 trough levels; n=27 for day 28 trough level

Trough Efalizumab Concentrations [$\mu\text{g/mL}$]		
	Median (Range)	
	Efalizumab 1.0 mg/kg/wk (n=26)	Efalizumab 2.0 mg/kg/wk (n=29 ^a)
Day 7	1.5 —	1.2 —
Day 28	8.9 —	20.6 —
Day 56	9.0 —	23.2 —
Day 77	5.7 —	21.3 —
Day 84	8.7 —	24.5 —

^a n=28 for Day 7 and day 84 trough levels; n=27 for day 28 trough level

LTR is replaced by — $\mu\text{g/mL}$ (one half of detection level)

Efalizumab serum trough levels of 9.1 ± 6.7 and 23.5 ± 12.2 $\mu\text{g/mL}$ were achieved after 12 weeks of SC efalizumab treatment at 1.0 mg/kg/wk or 2.0 mg/kg/wk, respectively. Steady-state serum efalizumab levels were achieved following four weekly doses in the 1.0 mg/kg/wk group and following eight weekly doses in the 2.0 mg/kg/wk group.

Noncompartmental Pharmacokinetic Parameters after Last SC Weekly Dose (Day 77)		
	Mean ($\pm\text{SD}$)	
	Efalizumab 1.0 mg/kg/wk (n=25 ^b)	Efalizumab 2.0 mg/kg/wk (n=28 ^c)
T_{max} (day)	3.1 (± 2.9)	2.3 (± 1.1)
C_{max} ($\mu\text{g/mL}$)	12.4 (± 7.5)	31.0 (± 13.8)
C_{trough} ($\mu\text{g/mL}$)	9.1 (± 6.7)	23.5 (± 12.2)
AUC_{SS} (day $\cdot\mu\text{g/mL}$)	67.7 (± 45.0)	177 (± 83.2)
CL/F_{SS} (mL/kg/day)	24.3 (± 18.5)	15.7 (± 12.6)
t_{end} (day)	25.4 (± 8.1)	44.3 (± 10.0)
$t_{1/2}$ ^a (day)	6.2 (± 3.1)	7.4 (± 2.5)

^a Half-life for the portion above 1 $\mu\text{g/mL}$

^b n=26 for C_{trough} ; n=17 for t_{end}

^c n=26 for t_{end}

Noncompartmental Pharmacokinetic Parameters after Last SC Weekly Dose (Day 77)		
	Median (Range)	
	Efalizumab 1.0 mg/kg/wk (n=25 ^b)	Efalizumab 2.0 mg/kg/wk (n=28 ^c)
T _{max} (day)	2.0 —	2.0 —
C _{max} (ug/mL)	12.3 (±3.2-30.8)	32.2 —
C _{trough} (ug/mL)	8.7 —	21.3 —
AUC _{SS} (day*µg/mL)	64.3 —	180.4 —
CL/F _{SS} (mL/kg/day)	15.8 —	11.3 —
t _{end} (day)	29.4 —	48.0 —
t _{1/2} ^a (day)	6.1 —	7.4 —

^a Half-life for the portion above 1 µg/mL

^b n=26 for C_{trough}; n=17 for t_{end}

^c n=26 for t_{end}

LTR is replaced by — 5 µg/mL (one half of detection level)

Consistent with nonlinear pharmacokinetics, CL/F_{SS} was dose dependent at 24.3 ±18.5 and 15.7 ±12.6 mL/kg/day for the 1.0 mg/kg/wk and 2.0 mg/kg/wk groups, respectively. Serum efalizumab levels fell below the measurable level by 25 ± 8 and 44 ±10 days following the 12th dose in the 1.0 mg/kg/wk and 2.0 mg/kg/wk groups, respectively. This was also consistent with the nonlinear nature of efalizumab pharmacokinetics. The t_{1/2} for the portion of the concentration–time curve where concentration was above 1 µg/mL was 6.2 ±3.1 and 7.4 ±2.5 days, for the 1.0 mg/kg/wk and 2.0 mg/kg/wk groups, respectively.

Pharmacodynamic Results:

CD11a Expression and Available CD11a Binding Sites on T Lymphocytes:

CD11a Expression and Available CD11a Binding Sites (ABS) on T Lymphocytes								
Timepoint	% Baseline: Mean (± SD)							
	CD11a Expression				Available CD11a Binding Sites			
	n	Efalizumab 1.0 mg/kg/wk	n	Efalizumab 2.0 mg/kg/wk	n	Efalizumab 1.0 mg/kg/wk	n	Efalizumab 2.0 mg/kg/wk
Day 0	26	100 (NA)	27	100 (NA)	26	100 (NA)	27	100 (NA)
Day 7	26	14.1 (±5.30)	27	14.6 (±4.76)	26	2.62 (±2.93)	27	3.48 (±2.33)
Day 28	25	15.8 (±4.50)	27	18.1 (±5.94)	25	1.26 (±0.53)	27	1.83 (±0.97)
Day 56	25	19.2 (±7.44)	27	24.5 (±7.32)	25	2.59 (±5.95)	27	2.03 (±1.05)
Day 84	24	21.1 (±20.0)	27	21.6 (±7.04)	24	3.79 (±13.1)	27	1.8 (±0.867)
Day 91	23	19.2 (±6.51)	24	20.9 (±7.11)	23	3.46 (±5.58)	24	2.32 (±1.19)
Day 112	22	74.3 (±42.7)	26	63.8 (±55.5)	22	59.5 (±41.6)	26	49.1 (±59.2)
Day 133	23	91.3 (±17.6)	24	136 (±45.1)	23	85.9 (±16.1)	24	135 (±43.7)
Day 168	23	71.5 (±15.0)	25	174 (±98.1)	23	82.0 (±12.1)	25	149 (±38.1)

Both doses produced maximum down-modulation of CD11a to approximately 15%–25% of baseline and saturated greater than 95% of CD11a binding sites on T lymphocytes, even

though higher serum efalizumab levels were achieved after the 2.0 mg/kg/wk dose. As serum efalizumab concentrations diminished, both CD11a expression and available binding sites showed a similar temporal pattern of return toward baseline, which occurred between 35 and 56 days after the last dose for both dose groups.

At the end of the follow-up period, CD11a expression and available binding sites had increased above baseline levels in the 2.0 mg/kg/wk group but not in the 1.0 mg/kg/wk group. (see [Appendix 3](#)) Nineteen of 25 subjects in the 2.0 mg/kg/wk group had CD11a expression levels > 125% of baseline at the end of follow-up (Day 168). Although 1 of those 19 subjects had a PASI level that exceeded baseline by 50% (<-50% improvement), 11 of the 19 remained partial responders or responders (> 50% improvement). Results for subjects with available binding sites >125% of baseline were similar. The increase in CD11a expression and available binding sites beyond baseline levels at the end of the follow-up period was not predictive of a corresponding increase in PASI levels above baseline.

CD11a expression on circulating CD4+ lymphocytes, CD8+ lymphocytes, B lymphocytes, NK cells, monocytes, and neutrophils was down-modulated to approximately 10%–15%, 15%–25%, 20%–30%, 40%–50%, 55%–65%, and 45%–55% of baseline, respectively. In both dose groups, CD11a binding sites were >95% saturated on CD4+ lymphocytes, CD8+ lymphocytes, and NK cells and >90% saturated on B lymphocytes, monocytes, and neutrophils.

Total Leukocytes and Leukocyte Subsets:

Absolute Counts of Leukocytes (cells/mm ³ /1000) following Weekly Efalizumab Administration				
Timepoint	Efalizumab 1.0 mg/kg/wk		Efalizumab 2.0 mg/kg/wk	
	n	Mean (±SD)	n	Mean (±SD)
Day 0	26	7.51 (±1.97)	27	6.81 (±1.66)
Day 7	26	9.32 (±2.59)	27	9.14 (±2.18)
Day 28	25	9.26 (±2.57)	25	9.28 (±2.41)
Day 56	25	10.45 (±3.53)	26	9.93 (±1.95)
Day 84	24	10.53 (±3.08)	27	10.18 (±2.01)
Day 91	23	9.99 (±2.93)	22	10.03 (±2.18)
Day 112	21	8.24 (±2.49)	26	9.01 (±2.12)
Day 133	24	7.54 (±1.74)	23	7.42 (±1.67)
Day 168	6	7.32 (±1.34)	13	7.24 (±1.68)

Lymphocytes (% Total Leukocytes) following Weekly Efalizumab Administration				
	Efalizumab 1.0 mg/kg/wk		Efalizumab 2.0 mg/kg/wk	
Timepoint	n	Mean (\pm SD)	n	Mean (\pm SD)
Day 0	26	27.9 (\pm 7.34)	27	28.4 (\pm 8.77)
Day 7	25	42.5 (\pm 7.46)	27	41.0 (\pm 10.6)
Day 28	25	41.4 (\pm 8.99)	25	42.6 (\pm 9.36)
Day 56	25	43.5 (\pm 9.77)	26	44.6 (\pm 11.6)
Day 84	24	42.8 (\pm 9.08)	27	41.5 (\pm 11.3)
Day 91	23	41.5 (\pm 7.29)	22	45.0 (\pm 9.61)
Day 112	21	32.6 (\pm 9.7)	26	37.4 (\pm 12.2)
Day 133	24	27.5 (\pm 7.84)	23	31.2 (\pm 6.36)
Day 168	6	27.0 (\pm 12.9)	13	29.7 (\pm 10.1)

Absolute Lymphocyte Count (% of Baseline) following Weekly Efalizumab Administration				
	Efalizumab 1.0 mg/kg/wk		Efalizumab 2.0 mg/kg/wk	
Timepoint	n	Mean (\pm SD)	n	Mean (\pm SD)
Day 0	26	100.0	27	100.0
Day 7	26	197.5 (\pm 37.0)	27	216.50 (\pm 123.2)
Day 28	25	188.8 (\pm 50.0)	25	227.4 (\pm 160.0)
Day 56	25	226.1 (\pm 55.0)	26	265.2 (\pm 155.9)
Day 84	24	223.6 (\pm 60.9)	27	242.9 (\pm 108.4)
Day 91	23	206.0 (\pm 46.1)	22	256.7 (\pm 151.3)
Day 112	21	137.0 (\pm 58.7)	26	183.0 (\pm 64.5)
Day 133	24	103.0 (\pm 25.8)	23	115.5 (\pm 29.0)
Day 168	6	104.9 (\pm 44.0)	13	127.1 (\pm 53.0)

Increases in the absolute counts of circulating leukocytes were observed after treatment with efalizumab. Absolute WBC count increased by 2.5–3.5 X 10³ cells/ μ L following 1.0 and 2.0 mg/kg/wk efalizumab to approximately 10 X 10³ cells/ μ L. The largest change occurred in the absolute count of circulating lymphocytes. With weekly efalizumab dosing, proportions of circulating lymphocytes increased by nearly 60% and absolute counts approximately doubled compared with predose levels, and remained elevated with continued dosing. Lymphocyte levels returned to baseline between 5 and 8 weeks after the 12th dose for both the 1.0 mg/kg/wk and 2.0 mg/kg/wk groups.

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Proportions of Lymphocytes:

Cell Type	Mean (\pm SD) [n] of Circulating Absolute Counts (cells/ μ L)					
	1.0 mg/kg/wk			2.0 mg/kg/wk		
	Pre-dose Counts (n=26)	Maximum Counts ^d (n=25 ^e)	Day 133 Counts (n=24)	Pre-dose Counts (n=27)	Maximum Counts ^d (n=26)	Day 133 Counts (n=23)
Monocytes ^a	430 (\pm 130) [n=26]	510 (\pm 370) [n=25]	470 (\pm 180) [n=24]	370 (\pm 170) [n=27]	450 (\pm 200) [n=26]	410 (\pm 130) [n=23]
Neutrophils ^a	4830 (\pm 1620) [n=26]	5170 (\pm 1550) [n=25]	4820 (\pm 1450) [n=24]	4250 (\pm 1300) [n=27]	5150 (\pm 1500) [n=27]	4460 (\pm 1330) [n=23]
B lymphocytes ^b	359 (\pm 191) [n=26]	720 (\pm 327) [n=24]	379 (\pm 200) [n=24]	349 (\pm 181) [n=27]	760 (\pm 358) [n=22]	412 (\pm 222) [n=24]
NK cells ^c	178 (\pm 92.6) [n=26]	283 (\pm 143) [n=26]	153 (\pm 73.1) [n=24]	173 (\pm 81.1) [n=27]	260 (\pm 169) [n=26]	155 (\pm 74.1) [n=23]

^a Data obtained from CBC.

^b Mean B lymphocytes returned to baseline in the 2.0 mg/kg/wk group by Day 133, but increased on Day 168. Absolute counts are derived from flow cytometry data.

^c Mean NK-cell absolute counts continued a slight downward trend after returning to baseline but remained within the normal range. Absolute counts are derived from flow cytometry data.

^d Highest observed mean \pm SD for the group.

T-lymphocyte and B lymphocyte counts approximately doubled, whereas natural killer (NK) cell count increased by approximately 50%. Mean absolute counts of circulating monocytes and neutrophils remained fairly stable.

Conclusions:

- Consistent with nonlinear pharmacokinetics, CL/F_{ss} was dose dependent at 24.3 ± 18.5 and 15.7 ± 12.6 mL/kg/day for the 1.0 mg/kg/wk and 2.0 mg/kg/wk groups, respectively.
- Serum efalizumab levels fell below the measurable level by 25 ± 8 and 44 ± 10 days following the 12th dose in the 1.0 mg/kg/wk and 2.0 mg/kg/wk groups, respectively. This was also consistent with the nonlinear nature of efalizumab pharmacokinetics.
- The average $t_{1/2}$ ($t_{1/2}$ of the linear portion of the log concentration–time curve) was 6.2 ± 3.1 and 7.4 ± 2.5 days, for the 1.0 mg/kg/wk and 2.0 mg/kg/wk groups, respectively.
- Both doses produced maximum down-modulation of CD11a to approximately 15%–25% of baseline and saturated greater than 95% of CD11a binding sites on T lymphocytes; even though higher serum efalizumab levels were achieved after the 2.0 mg/kg/wk dose.
- As serum efalizumab concentrations diminished, both CD11a expression and available binding sites showed a similar temporal pattern of return toward baseline, which occurred between 35 and 56 days after the last dose for both dose groups. At the end of the follow-up period, CD11a expression and available binding sites had increased above baseline levels in the 2.0 mg/kg/wk group but not in the 1.0 mg/kg/wk group.
- The increase in CD11a expression and available binding sites beyond baseline levels at the end of the follow-up period was not predictive of a corresponding increase in PASI levels above baseline.

- CD11a expression on B lymphocytes was down-modulated to an extent similar to that on T lymphocytes, but down-modulation was less for NK cells, monocytes, and neutrophils.
- Saturation of CD11a binding sites was >95% on CD4+ lymphocytes, CD8+ lymphocytes, and NK cells and >90% on B lymphocytes, monocytes, and neutrophils.
- Increases in the absolute counts of circulating leukocytes were observed after treatment with efalizumab. The largest change occurred in the absolute count of circulating lymphocytes. Absolute counts approximately doubled compared with predose levels. Lymphocyte levels returned to baseline between 5 and 8 weeks after the 12th dose for both the 1.0 mg/kg/wk and 2.0 mg/kg/wk groups. T-lymphocyte and B lymphocyte counts approximately doubled, whereas natural killer (NK) cell count increased by approximately 50%.

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Pharmacodynamics:

The pharmacodynamics of efalizumab were determined from flow cytometry of whole-blood samples collected at screening, on Day -1, predose on Day 0, and on Days 1, 2, 7, 14, 21, 28, and 35 of Periods 1 and 2.

Flow cytometry analysis was used to measure CD11a expression and available CD11a binding sites (ABS) on T lymphocytes (CD4+ and CD8+ subsets), monocytes, NK cells, and neutrophils so that a comparison of the PD effects of XOMA efalizumab and Genentech efalizumab could be made. All data for CD11a expression and ABS were expressed as a percentage of baseline for each period.

Results:

Pharmacokinetic Results:

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. (see [Appendix 4](#)) The point estimate and confidence intervals were outside the prespecified 80%–125% interval and therefore did not meet the criterion for comparability. (see table below) However, this difference in exposure did not translate into differences in extent or duration of PD activity, suggesting that the higher exposure with Genentech efalizumab may not be clinically meaningful. (see [Appendix 4](#))

Mean ± SD Efalizumab Pharmacokinetic Parameters		
Parameter	XOMA Efalizumab (n=79)	Genentech Efalizumab (n=79)
C _{max} (µg/mL)	4.1 ± 2.0	4.9 ± 2.0
T _{max} (day) ^a	3.5 —	3.5 —
AUC _t (µg-day/mL)	32.6 ± 18.9	43.6 ± 24.5
Initial t _{1/2} (day)	5.0 ± 2.1	5.6 ± 2.4
Final t _{1/2} (day)	1.7 ± 1.6	1.7 ± 1.7

^a Data are expressed as median and range.

[Appendix 4](#) shows logarithmic (top panel) and linear (bottom panel) plots of mean (±SD) serum efalizumab concentration versus time for XOMA and Genentech efalizumab following single 1.0 mg/kg SC doses. Serum levels of Genentech efalizumab were higher than XOMA efalizumab as early as the first timepoint on Day 1, and this trend continued for the duration of the study, suggesting that the increased exposure was likely due to an early process (i.e., absorption or bioavailability). The large SDs at concentrations above 1.0 µg/mL (range, — — µg/mL) demonstrated that the variability in exposure between subjects receiving the same material (XOMA or Genentech efalizumab) was greater than the difference between the two manufacturers in mean exposure at a timepoint (range, 0.35–0.82 µg/mL). The median T_{max} of 3.5 days was identical between XOMA and Genentech efalizumab.

The ANOVA included terms for dosing group (see table below), sequence of treatment, subject within group and sequence, period, and treatment (i.e., manufacturer). The ratio of geometric means for AUC_{inf} of Genentech to XOMA material was 1.32, with a 90% confidence interval of 1.19–1.47 (see table below). The protocol-specified secondary outcome variables, AUC_t and C_{max}, were also significantly higher after administration of the Genentech efalizumab dose.

Primary Analysis of Pharmacokinetic Comparability by ANOVA in Pharmacokinetic Evaluable Subjects						
	N	Geometric LS Mean		Ratio Estimate (Genentech: XOMA)	90% Two-Sided Confidence Interval	
		XOMA	Genentech		Lower Limits	Upper Limits
AUC _{inf} (µg-day/mL)	79	27.8	36.9	1.32	1.19	1.47
AUC _t (µg-day/mL)	79	26.9	35.6	1.32	1.19	1.48
C _{max} (µg/mL)	79	3.6	4.2	1.17	1.07	1.29

The difference in exposure between the two materials appeared greater during Period 1 than during Period 2 (data not shown). However, as assessed by the test for the sequence term in ANOVA, there was no statistically significant period by treatment interaction for AUC_{inf} (p=0.104). The dosing group and period main effect covariates were also not statistically significant in the model (p=0.156 and p=0.373, respectively). The washout period between the two doses was 42 days. Efalizumab levels were below the level of detection for approximately 14 days prior to the second dose; however, CD11a expression failed to return completely to baseline by Day 0 of Period 2: mean percent of baseline was 84% for those administered XOMA efalizumab and 79% for those administered Genentech efalizumab in Period 1 (see [Appendix 4](#)).

Pharmacodynamic Results:

CD11a Expression and Available CD11a Binding Sites (ABS) on T Lymphocytes after Efalizumab 1.0 mg/kg SC: Pooled data from periods 1 and 2								
Timepoint	% Baseline: Mean (±SD)							
	CD11a Expression				Available CD11a Binding Sites			
	n	Genentech (G176CR)	n	XOMA (102646)	n	Genentech (G176CR)	n	XOMA (102646)
Day 0	79	100 (NA)	78	100 (NA)	79	100 (NA)	78	100 (NA)
Day 1	78	22.8 (±10.5)	78	21.5 (±7.0)	78	2.4 (±1.8)	78	2.5 (±1.6)
Day 2	78	14.9 (±4.1)	77	14.2 (±4.6)	78	1.1 (±0.9)	77	1.2 (±0.9)
Day 7	79	13.5 (±3.5)	77	13.2 (±4.5)	79	1.2 (±0.8)	77	1.3 (±0.8)
Day 14	77	14.0 (±5.6)	77	14.4 (±5.4)	77	3.7 (±7.9)	77	4.5 (±5.7)
Day 21	77	32.0 (±21.2)	77	39.8 (±22.3)	77	27.9 (±26.7)	77	36.0 (±25.5)
Day 28	79	65.9 (±27.5)	75	71.9 (±23.0)	79	74.6 (±34.0)	75	82.5 (±34.6)
Day 35	77	84.6 (±22.5)	77	89.8 (±21.4)	77	96.1 (±29.1)	77	101.0 (±31.7)

Although the exposure obtained with the two different materials was significantly different, the PD effects on all cell types were comparable (see Appendix 4). For both XOMA and Genentech efalizumab, there was a sharp decrease in CD11a expression and ABS as early as Day 1; this effect was maintained until Day 14, when efalizumab serum levels decreased to $<1 \mu\text{g/mL}$ (the level previously identified as the saturation concentration for CD11a on T lymphocytes). CD11a down-modulation and saturation reflected the serum levels of efalizumab and were consistent with data from previous efalizumab clinical trials. CD11a expression and ABS returned toward baseline over the next 3 weeks. These PD effects were similar for all cell types measured for both XOMA and Genentech efalizumab, including T lymphocytes, CD4+ cells, CD8+ cells, NK cells, monocytes, and neutrophils. Although Genentech efalizumab produced higher serum concentrations, the extent and duration of effects on CD11a down-modulation and binding site saturation were similar for both materials.

Conclusions:

- 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 point estimate and confidence intervals were outside the prespecified 80%–125% interval and therefore did not meet the criterion for comparability.
- The pharmacodynamics appear to be comparable, suggesting that the higher exposure with Genentech efalizumab may not be clinically meaningful.
- For both XOMA and Genentech efalizumab, there was a sharp decrease in CD11a expression and ABS as early as Day 1; this effect was maintained until Day 14.

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Study ACD2017g

A Phase II, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of hu1124 in Adults with Allergic Asthma Undergoing Aeroallergen-Provoked Bronchoconstriction

Methods:

This was a Phase II, multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of eight weekly SC injections of up to 2.0 mg/kg efalizumab in adults with mild to moderate allergic asthma.

Twenty-five subjects were randomized to receive efalizumab, and 12 subjects were randomized to receive placebo.

Initial dose of 0.7 mg/kg, and 2.0 mg/kg for all subsequent administrations.

Serum concentrations of efalizumab were listed for all randomized subjects, and summarized by visit for all efalizumab-treated subjects.

Results:Pharmacokinetic Results:

Mean (\pm SD) Serum Efalizumab Concentration vs. Time		
Visit	Efalizumab Concentration (ng/mL)	n
Day 7	1243 (\pm 839)	23
Day 14	7480 (\pm 3120)	24
Day 21	13837 (\pm 3955)	24
Day 42	20613 (\pm 8911)	23
Day 49	21830 (\pm 9548)	24
Day 78	6206 (\pm 4524)	22

Before dosing, serum efalizumab concentrations were below the limit of detection for all but 1 subject (95305 in the efalizumab group). The mean serum trough efalizumab concentration was 1,243 ng/mL on Day 7, 7,480 ng/mL \pm 3,120 ng/mL on Day 14, and peaked at 21,830 ng/mL \pm 9,548 ng/mL on Day 49. Thirty days following the last dose of efalizumab, the mean serum concentration of efalizumab was 6,206 ng/mL \pm 4,524 ng/mL. Because only trough concentrations were obtained in this study, there were insufficient data for a more thorough pharmacokinetic analysis.

Study ACD2390g

A Phase IIIb, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of 1.0 mg/kg Subcutaneously Administered Efalizumab in Adults with Moderate to Severe Plaque Psoriasis

Methods:

This is a Phase IIIb, randomized, double-blind, parallel-group, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of efalizumab administered at weekly SC doses of 1.0 mg/kg in subjects with moderate to severe plaque psoriasis who are candidates for systemic therapy:

The study consists of a screening and a treatment period. All subjects begin in the screening phase extending from Day -28 to Day -1. Eligible subjects continue to the treatment phase from Day 0 through Day 84. On Day 0, subjects will be randomized in a 2:1 ratio to receive either 12 weeks of 1.0 mg/kg/wk SC efalizumab or placebo.

Dosing Schedule												
	Day											
	0	7	14	21	28	35	42	49	56	63	70	77
Dose (mg/kg)	0.7	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Efalizumab: Serum pharmacokinetic samples were obtained from all subjects; The pharmacokinetic samples were collected at predose (trough) on Days 56 and 84. Serum efalizumab concentrations were determined by _____

_____ as the reporter. The limit of quantification (LOQ) for the assay was _____ µg/mL.

Pharmacodynamic analysis: Whole blood samples were obtained for the pharmacodynamic analysis by _____ predose on Days 0 and 84 in approximately half of the subjects at selected sites. Total leukocytes and leukocyte subsets were determined by routine hematologic analysis (CBC). Flow cytometry (_____) analysis was used for the determination of lymphocyte subset proportions as well as the determination of CD11a expression and available CD11a binding sites on the following subsets: total T lymphocytes, T lymphocyte subsets (CD4+ and CD8+), B lymphocytes, natural killer (NK) cells (CD56+), monocytes, and neutrophils. Lymphocyte subsets were reported as a percentage of the total lymphocyte population. CD11a expression and available CD11a binding site results were expressed as antibody binding capacity (ABC) for each lymphocyte subset and were reported as a percentage of the baseline ABC value (at Day 0). ABC is a measure of the mean number of binding sites on a per-cell basis.

After completion of this trial through Day 84, all subjects could transfer to the open-label study, ACD2391g. Subjects who discontinued early from this study were to transfer to Study ACD2391g for follow-up.

Results:

Pharmacokinetic Results:

Steady-State Trough Serum Efalizumab Concentration in PK-Evaluable Subjects		
	Serum Efalizumab Concentration ^a [$\mu\text{g/mL}$] (Mean \pm SD)	
	Day 56	Day 84
n	269	275
Mean \pm SD	10.33 \pm 7.10	11.06 \pm 7.85
Median (Range)	9.59 (—)	10.10 (—)

Note: Values less than reportable were replaced by — $\mu\text{g/mL}$, which is half of lower limit of quantification.

^a 7 days following the 12th weekly SC dose of efalizumab.

Efalizumab administered subcutaneously at a dose of 1.0 mg/kg/wk over 12 weeks produced serum trough levels of 11.1 \pm 7.9 $\mu\text{g/mL}$ on Day 84. (see [Appendix 5](#))

Pharmacodynamic Results:

Cell Type	Percent of Baseline CD11a Expression at Steady State		Percent of Baseline Available CD11a Binding Sites at Steady State	
	(Mean \pm SD)		(Mean \pm SD)	
	Placebo (n = 34)	1.0 mg/kg/wk (n = 56)	Placebo (n = 34)	1.0 mg/kg/wk (n = 56)
T lymphocyte (CD3 +)	96.8 \pm 17.5	19.0 \pm 5.6	97.2 \pm 19.6	0.8 \pm 0.9
CD4 + phenotype	98.9 \pm 15.7	14.7 \pm 3.3	101 \pm 17.9	0.5 \pm 0.7
CD8 + phenotype	95.5 \pm 20.0	21.9 \pm 7.2	93.7 \pm 21.5	1.1 \pm 1.1
B lymphocytes	101 \pm 21.7	32.5 \pm 14.4	102 \pm 20.5	1.9 \pm 3.2
NK cells	96.2 \pm 14.9	42.6 \pm 7.8	92.8 \pm 13.2	1.1 \pm 0.9
Monocytes	96.4 \pm 18.8	60.1 \pm 9.4	93.3 \pm 18.7	6.5 \pm 2.6
Neutrophils	98.1 \pm 17.8	45.5 \pm 7.9	97.6 \pm 19.7	3.6 \pm 3.5

n = number of subjects with PD data.

On Day 84, CD11a expression on peripheral blood T lymphocytes was down-modulated to 19.0% \pm 5.6% of baseline expression, and CD11a was saturated as indicated by a decrease in available CD11a binding sites to <5% of that at baseline.

Conclusions:

- Efalizumab administered subcutaneously at a dose of 1.0 mg/kg/wk over 12 weeks produced serum trough levels of 11.1 \pm 7.9 $\mu\text{g/mL}$ on Day 84.

- On Day 84, CD11a expression on peripheral blood T lymphocytes was down-modulated to $19.0\% \pm 5.6\%$ of baseline expression, and CD11a was saturated as indicated by a decrease in available CD11a binding sites to $<5\%$ of that at baseline.

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Report 02-132-1046

Population Pharmacokinetics of Efalizumab following Weekly Dosing: Structural Model Identification, Mean Population Pharmacokinetic Parameter Estimation, and Covariate Analysis.

Methods:

The effect of demographic and pathophysiological covariates on the PK of efalizumab was assessed using population PK (population PK) analysis.

The population PK analyses for efalizumab were based on the pooled dataset from four clinical studies in the psoriatic population: Phase I Study ACD2142g (Genentech material only), Phase III Studies ACD2058g (XOMA material only) and ACD2059g (Genentech and XOMA materials), and Phase IIIb Study ACD2243g (Genentech material only). The analyses encompassed a total of 1869 efalizumab concentrations from 1088 subjects who received weekly SC doses of efalizumab at 1.0 or 2.0 mg/kg/wk for 77 days, with 484 subjects (44%) treated with Genentech material and 604 subjects (56%) treated with XOMA material.

Serum efalizumab concentration versus time data were modeled using a population analysis approach to estimate efalizumab population PK parameters (mean and interindividual variability), as well as relationships between the PK parameters and various covariates. The population PK base model, a one-compartment linear PK model in NONMEM (program Version V), was determined based on results from Phase I Study ACD2142g.

A pooled dataset including all available concentrations was used in the covariate analyses. Predose trough samples were obtained on Day 84 if one sample was taken (Studies ACD2058g and ACD2059g) and on Days 42 and 84 if two samples were taken (Study ACD2243g).

The pathophysiologic factors at baseline, including body weight (WT), body mass index (BMI), Psoriasis Area and Severity Index (PASI) score, lymphocyte counts (LYM), age (AGE), height (HT), obesity factor (OBS; BMI \geq 30 kg/m² was considered obese), race, and sex (SEX), were evaluated for their effects on apparent SC clearance (CL/F) based on $p < 0.005$ for the likelihood ratio test. ($p < 0.005$ corresponds to a change in objective function of $\delta = 7.88$ for 1 degree of freedom.)

Following inclusion of significant demographic and pathophysiologic covariates in the model, the effects of Genentech versus XOMA material (MATE) and of 1.0 mg/kg/wk versus 2.0 mg/kg/wk efalizumab dosing (DGRP) on CL/F were evaluated to yield the Final Model.

These analyses were performed using the original NONMEM dataset (dated 19 March 2002) to yield the Final Model (Report 02-132-1046). The Final Model was then applied to the updated NONMEM database (dated 15 August 2002). No notable differences were observed in parameter estimates between the original and updated datasets (Amendment 1 to Report 02-132-1046).

Results:

Population parameter estimates are summarized in the table below.

Population Parameter Estimates for the Final Model Using the Updated Database (Amendment 1 to Report 02-132-1046)	
Parameter	Value
Evaluable subjects (n)	1088
Evaluable data points	1869
Objective function	9203.725
θ_1 , Typical V/F (L)	9.13 (19.6)
θ_2 , Typical k_a (day ⁻¹)	0.191 (35.2)
θ_3 , Typical CL/F (L/day)	1.29 (4.1)
Covariate Exponent or Multiplier for CL/F	
θ_4 (for WT)	0.754 (14.7)
θ_5 (for OBS)	0.0997 (50.8)
θ_6 (for PASI)	0.220 (20.0)
θ_7 (for LYM)	0.165 (32.2)
θ_{10} (for AGE)	0.218 (28.3)
θ_{12} (for DGRP)	- 0.240 (12.9)
ω_V (%)	28.6 (46.4)
ω_{k_a} (%)	0 (Fixed)
ω_{CL} (%)	48.2 (6.3)
σ_{Prop} (%)	26.3 (13.0)
σ_{Add} (g/mL)	1.58 (36.8)

Note: The coefficient of variation of the estimate is given in parentheses.

θ = model parameter/covariates; k_a = absorption rate constant; ω = inter-subject variability; σ = residual variability.

The following covariates were included in the Final Model: BW, OBS, PASI, LYM, AGE, and DGRP. The equation for the efalizumab CL/F value for a typical subject is as follows (Amendment 1 to Report 02-132-1046):

$$CL/F = \theta_3[(WT/91)^{\theta_4}(1 + \theta_5 \text{OBS})(PASI/17.1)^{\theta_6}(LYM/1.82)^{\theta_7}(AGE/44)^{\theta_{10}}(1 + \theta_{12}(\text{DGRP} - 1))]$$

Covariates in the Final Model explained approximately 27% of the inter-individual variance in CL/F ($\omega_{CLF} = 56.4\%$ versus 48.2% in the Base and Final Models, respectively). The results for the bootstrap analysis (randomly sampling $n = 500$ with replacements) showed that the Final Model was stable and its parameters were reasonably estimated.

When the effects of Genentech versus XOMA material (MATE) and of 1.0 mg/kg/wk versus 2.0 mg/kg/wk efalizumab dosing (DGRP) on CL/F were evaluated to yield the Final Model, the change in objective function for DGRP was 6.773 (corresponding to $p < .005$) and the change in objective function of MATE was 6.420 (corresponding to $p = 0.0112$). As the p value was $< .05$ but not $< .005$ for MATE, the population PK analyses did not provide

conclusive evidence as to whether the CL/F after administration of Genentech material would differ from the CL/F after administration of XOMA material. There was not conclusive evidence as to whether the

The effects of each of the covariates in explaining inter-individual variability in CL/F is summarized below.

Predicted Efalizumab Clearance for Theoretical Subjects According to the Final Model (Amendment 1 to Report 02-132-1046)				
	Covariate Value or Category	CL/F (L/day)	% CL/F Change from Typical	Corresponding Pred. Trough Conc. at Steady-State ^b (µg/mL)
Typical Psoriasis Patient	Typical patient with: WT=91.0 kg, PASI =17.1, LYM =1.8 K/cm ³ , AGE =44 yr, BMI <30, DGRP =1 mg/kg/wk	1.29	0	9.04
Covariate or Category				
Baseline Body Weight (kg)	57.2 – 139 (2.5 th -97.5 th percentile)	0.91 to 1.78	-29.5 to +37.6	8.32 to 9.60 ^c
Baseline PASI Score	12.0 - 41.6 (2.5 th -97.5 th percentile)	1.19 to 1.57	-7.5 to +21.6	9.88 to 7.25
Baseline lymphocyte Count (K/ccm)	0.91 - 3.43 (2.5 th -97.5 th percentile)	1.15 to 1.43	-10.8 to +11.0	10.3 to 8.06
Baseline Age (year)	22 - 69 (2.5 th -97.5 th percentile)	1.11 to 1.42	-14.0 to +10.3	10.7 to 8.12
Obesity	Body Mass Index ≥ 30	1.42	+10.0	NA
Dose Group	Dose Group = 2 mg/kg	0.98	-24.0	NA

NA = Not applicable.

^a Theoretical effect (% change with respect to typical value) of the covariate considered alone, the other covariates being set to their median values (covariates as continuous variables), or the reference category (covariates as categorical variables).

^b Corresponding efalizumab trough concentrations at the steady-state based on model prediction. These values were based on the predictions by NONMEM program using the population mean for V/F and k_a values, the 2.5th/97.5th theoretical CL/F values reported in this table, typical covariate values, and the corresponding total dose[WT • DGRP].

^c Since weight-based dosing was used, the trough levels in such a wide range of patient weight was still very similar.

The most important covariate in explaining inter-individual variability in CL/F was baseline WT. Weight affects predicted trough concentration less because the dose is weight based. The changes from the population mean CL/F value for patients whose weight was in the 2.5th percentile (57.2 kg) and 97.5th percentile (139 kg) were 29.5% and 37.6%, respectively. These findings support the current dosing strategy, in which efalizumab is administered based on a body weight-adjusted dose (mg/kg).

Baseline PASI score showed less effect than WT; the changes from the population mean CL/F value for typical patients with PASI scores in the 2.5th percentile (2.0) and 97.5th percentile (40.6) subjects were -7.5% and 21.6%. The other pathophysiological covariates in

the Final Model, OBS, LYM, and AGE, had only modest effects. Patients in the 2 mg/kg dose group had a 24.0% decrease in CL/F from the population mean CL/F value. This is consistent with the nonlinear PK profile of efalizumab shown in other studies.

The individual parameter and steady-state exposure estimates are shown in the table below.

Individual Parameter and Steady-State Exposure Estimates for Studies ACD2142g, ACD2058g, ACD2059g, and ACD2243g (n=1088)				
Parameter	Parameter Estimate Medians (2.5 th -97.5 th percentiles)			
	Study ACD2142g		Studies ACD2058g, ACD2059g, and ACD2243g	
	Dose = 1.0 mg/kg/wk (n=31)	Dose = 2.0 mg/kg/wk (n=35)	Dose = 1.0 mg/kg/wk (n=336)	Dose = 2.0 mg/kg/wk (n=686)
V/F (L)	9.18 (5.98-10.6)	8.77 (5.01-12.3)	9.10 (8.74-9.29)	9.09 (8.33-9.99)
K _a (day ⁻¹)	0.191 (Fixed) ^a	0.191 (Fixed) ^a	0.191 (Fixed) ^a	0.191 (Fixed) ^a
CL/F (L/day)	1.52 (0.440-3.72)	1.09 (0.410-2.45)	1.50 (0.525-3.04)	1.05 (0.416-2.48)
C _{trough,Last} (µg/mL) ^b	6.23 (2.23-25.3)	21.2 (2.85-36.8)	7.48 (3.80-22.6)	22.0 (8.68-51.6)
AUC _{ss} (µg*day/mL) ^c	52.2 (27.3-173)	158 (69.6-274)	60.5 (32.8-168)	174 (82.7-387)
t _{1/2,pred} (day) ^d	4.32 (1.85-9.42)	5.63 (2.53-10.7)	4.26 (2.01-12.0)	6.05 (2.45-15.1)

^a Interindividual variability for k_a was fixed as 0 in the analysis.

^b From the individual predictions (IPRED) on Day 7 after the last dose administered.

^c AUC_{ss} = Total Dose/(CL/F). Total Dose is the nominal total dose based on baseline body weight (WT) and Dose Group (DGRP). Individual CL/F values were obtained from POSTHOC predictions using the first order (FO) estimation method.

^d t_{1/2,pred} = 0.693/[(CL/F)/(V/F)]. This is the predicted half-life based on a one-compartment PK model. This parameter does not represent the terminal half-life during the washout. Individual CL/F and V/F values were obtained from POSTHOC predictions using the FO estimation method.

Conclusions:

- Body weight was found to be the most significant covariate affecting efalizumab clearance, consistent with weight-based dosing. Baseline PASI, baseline lymphocyte count, or age had less significant effects on clearance. The clearance of efalizumab was not significantly affected by gender or race. The observed intersubject variabilities in clearance were explained by body weight as follows: CL/F(L/day)=1.29 x [Weight(kg)/91]**0.754

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ADDITIONAL ANALYSES

Bioavailability

Because the pharmacokinetics of Genentech efalizumab has not been studied following IV doses, an "estimate" of bioavailability for Genentech SC efalizumab was calculated as follows: (1) XOMA SC bioavailability at 1 mg/kg/wk SC was calculated. (2) Genentech SC bioavailability was estimated using either (a) the AUC difference between Genentech efalizumab and XOMA efalizumab as calculated from study ACD2389g after a single 1 mg/kg SC dose, or (b) the steady-state trough comparison of Genentech efalizumab and XOMA efalizumab in study ACD2058g.

XOMA SC Bioavailability

A comparison across studies of the PK of XOMA efalizumab in multiple-dose IV Study HUPS249 (Product Code 102515) and SC Studies HUPS254 and HUPS256 (Product Code 102646) was performed in order to calculate the relative bioavailability of the SC formulation (Product Code 102646) after multiple doses at steady state.

Bioavailability was calculated using the SC dose-normalized $AUC_{\tau,ss}$ and the IV dose-normalized $AUC_{\tau,ss}$ at the dose closest to the SC dose.

Mean Percent Bioavailability with SC Administration of XOMA Efalizumab		
Dose (mg/kg/wk)	Study	
	HUPS254	HUPS256
0.5	13.1, 101 (n=2)	ND
1.0	39.0 (n=16)	42.9 (n=20)
1.5	76.0 (n=4)	ND
2.0	54.5 (n=19)	51.9 (n=14)
4.0	ND	57.2 (n=16)

ND= not determined.

Following SC doses at 1.0 mg/kg/wk, the SC bioavailability for XOMA Product Code 102646 was approximately 41% (average from two studies).

Estimate of Genentech SC bioavailability

Bioavailability of Genentech efalizumab was estimated by two methods; each method relies on the assumption that IV CL_{ss} of Genentech efalizumab and XOMA efalizumab are similar.

First, based on the approximately 23% higher steady-state trough levels for Genentech efalizumab (Product Code G176H) compared with XOMA efalizumab (Product Code 102646) in Study ACD2059g, the bioavailability of Genentech efalizumab Product

Code G176H can be estimated to be 50% (23% higher than the bioavailability of XOMA efalizumab).

Second, it is assumed that AUC differences between XOMA efalizumab and Genentech efalizumab after single doses are similar to those seen after multiple doses (a likely overestimation of AUC because multiple dose CL/F_{ss} is smaller than single dose CL/F). Since the single-dose crossover Study ACD2389g (XOMA Product Code 102646 vs. Genentech Product Code G176CR) showed 32% higher AUC with Genentech Product Code G176CR with a 90% CI of 1.19–1.47, the bioavailability of Genentech Product Code G176CR was estimated to be 54%.

Together, these two estimates suggest that the bioavailability of Genentech efalizumab at 1.0 mg/kg/wk SC doses was approximately 50%.

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Steady-State Trough Levels in the Phase III Studies

Efalizumab trough levels on Day 84 following SC administration in the Phase III studies (ACD2058g, ACD2059g, ACD2243g, and ACD2390g) are summarized in the table below.

In the Phase III studies, steady-state efalizumab levels were measured at one or two timepoints after the 6th, 8th, or 12th doses on Days 42, 56, and 84, respectively.

Steady-State Efalizumab Trough Levels ($\mu\text{g/mL}$) at Day 84 in the Phase III Studies			
Product	Study	Trough Level (Mean \pm SD)	
		1.0 mg/kg/wk SC	2.0 mg/kg/wk SC
XOMA (10246)	ACD2058g, ACD2059g	7.8 \pm 5.9 (n=296)	21.2 \pm 13.3 (n=282)
Genentech (G176H)	ACD2059g	8.0 \pm 5.5 (n=38)	21.3 \pm 13.5 (n=52)
	ACD2243g	--	27.3 \pm 15.4 (n=264)
Genentech (G176CR)	ACD2390g	11.1 \pm 7.9 (n=275)	ND

At both doses, regardless of study, steady-state levels were within the saturating range for efalizumab on T-lymphocyte CD11a.

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Immunogenicity

Samples were obtained periodically from subjects in all Genentech-sponsored studies and assayed for antibodies to efalizumab. A summary of accumulated data from subjects with samples is presented in the table below.

Since the presence of circulating efalizumab can interfere with the assay, data are also presented in a subset of subjects who participated in studies with follow-up assessments.

	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.

Efalizumab steady-state serum trough concentrations from SC studies in psoriasis subjects are shown below.

Study	Product	HAHA Sampling Schedule (Days)	Dose Group (mg/kg/wk)	Study Duration (weeks)	Day	Mean ± SD (n) Steady-state Efalizumab Trough Concentration (µg/mL)	
						HAHA – patients	HAHA + patients
ACD2142g	G176H	0, 28, 56, 84, 133, 168	1	12	84	9.1 ± 6.7 (26)	7.56, —
			2	12	84	23.5 ± 12.0 (29)	0.63, —
HUPS254 ²	102646	0, 28 ^a , 56, 91	2	8	56	13.3 ± 9.3 (19)	47.3 ^{3,4}
HUPS256 ²	102515, 102646	0, 105, 133	2	12	77	15.4 ± 11.8 (14)	—
			4	12	77	35.2 ± 18.7 (16)	57.7, —
ACD2390g	G176CR	0, 56, 84	1	12	84	11.06 ± 7.85 (275)	1.83 ± 2.39 (8)
ACD2058g	102646	FT: 0, 84 ^b	1	12	84	9.3 ± 6.5 (139)	9.6 ± 8.1 (7)
			2	12	84	24.1 ± 14.5 (135)	5.7 ± 6.6 (6)
ACD2059g	102646, G176CR	FT: 0, 84 ^c	1	12	84	6.8 ± 5.0 (195)	4.5 ± 5.4 (14)
			2	12	84	19.3 ± 12.1 (199)	10.9 ± 10.4 (8)

^a 0.3 mg/kg dose group

^b HAHA sampling (ACD2058g) was FT: Days 0, 84; OB: Days 28, 84, 168; RT: Days 0,84; ET: Day 84; FU: Days 28, 84

^c HAHA sampling (ACD2059g) was FT: Days 0,84; ET: Days 56, 84; FU: Days 28, 84

¹ n=2, individual data presented

² Plasma efalizumab was measured in this study

³ n=1, individual data presented

⁴ Last available trough value following 4 doses

In study ACD2390g, the mean trough serum efalizumab concentrations in HAHA-positive subjects were reduced compared with subjects who were not HAHA positive. Mean trough serum efalizumab concentrations in HAHA-positive subjects were also reduced compared with subjects who were not HAHA-positive for the 2 mg/kg/wk dose groups of studies ACD2058g and ACD2059g.

In study ACD2142g, pharmacokinetic and pharmacodynamic parameters in HAHA-positive subjects were determined and compared to HAHA-negative subjects.

Pharmacokinetic and Pharmacodynamic Parameters in HAHA-Positive Subjects						
Group/Subject ID	HAHA Positive (Day)	HAHA Titer (RU/mL)	Serum Efalizumab Cmax. ($\mu\text{g/mL}$)	t_{end} (days)	Max. Change, CD11a Expression	Max. Change, Available Binding Sites
1.0 mg/kg/wk group						
Subject 419	168	6.35				
Subject 428	168	14.3				
Group average \pm SD ^a	NA	NA	12.4 \pm 7.34	25.3 \pm 7.82	12.9 \pm 3.93	0.76 \pm 0.43
Group range ^a	NA	NA				
2.0 mg/kg/wk group						
Subject 110	28	30.8				
	56	207				
	84	12.3				
	133	711				
	168	353				
Subject 116	133	322				
	168	379				
Group Average \pm SD ^a	NA	NA	30.9 \pm 13.8	44.3 \pm 10	13 \pm 4.78	1.06 \pm 0.592
Group Range ^a	NA	NA				

NA=not applicable.

Note: The HAHA LOQ was --- RU/mL.

^a Dose group summary values do not include data from HAHA-positive subjects.

This study also suggests that serum concentrations may be lowered in the HAHA+ subjects.

Efalizumab was shown to interfere with the detection of HAHA in both the XOMA and Genentech assays. XOMA reported that the detection of --- ng/mL goat anti-human IgG was reduced to --- ng/mL in the presence of efalizumab at --- ng/mL. Genentech found that the detection of --- RU/mL cynomolgus monkey anti-humanized antibody was reduced to --- RU/mL in the presence of efalizumab at --- ng/mL (--- ng/mL efalizumab in serum). These data indicate that while an antibody response may be detectable at a reduced level in the presence of some circulating drug, the level of drug interference in the assay depends on the concentration, affinity, and avidity of the antibody response.

Anti-efalizumab antibodies interfere with the efalizumab assay. The presence of anti-efalizumab antibody can interfere with the efalizumab pharmacokinetic assay. This is demonstrated by preincubating efalizumab for one hour at ambient temperature with an affinity-purified cynomolgus monkey anti-efalizumab antibody added to healthy human serum. A decrease of measured

concentration of efalizumab was observed, depending on the level of anti-efalizumab antibodies present in the serum. The table below summarizes this data.

Anti-Efalizumab Antibody Interference in the Efalizumab Pharmacokinetic Assay			
Anti-Efalizumab (RU/mL)	Measured Concentration of Efalizumab [ng/mL]		
0	289	3007	29756
30	265 (92%)	ND	ND
300	188 (65%)	2756 (92%)	ND
3000	0	1661 (55%)	26907 (90%)
30000	ND	0	16657 (56%)
300000	ND	ND	0

Because efalizumab may interfere with the assay used to measure HAHA, and because HAHA may interfere with the assay used to measure efalizumab, a conclusion cannot be drawn with regard to the effect of HAHA(+) on plasma levels of efalizumab.

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CONCLUSIONS

- In Study HU9602, efalizumab was cleared from the plasma in a concentration-dependent manner, with a clearance of 308 mL/kg/day after a single 0.1 mg/kg dose to 10.7 mL/kg/day after a 3.0 mg/kg dose. The concentration-dependent clearance indicates non-linear kinetics.
- In Study HU9602, efalizumab reduced the CD11a expression measured on circulating CD3+ T lymphocytes. At efalizumab levels below 1 µg/mL, the study drug was rapidly cleared from circulation and expression of CD11a started to return to baseline. The data suggests a receptor-mediated elimination which is saturable at plasma efalizumab concentrations above 1 µg/mL.
- In Study HUPS254, average bioavailability (compared to IV administration) varied between 39.0% and 76.0% among the multiple-dose groups, with an overall average bioavailability of 50.7% ± 32.2%.
- From Study ACD2142g, the following conclusions were made:
 - Consistent with nonlinear pharmacokinetics, CL/F_{ss} was dose dependent at 24.3 ± 18.5 and 15.7 ± 12.6 mL/kg/day for the 1.0 mg/kg/wk and 2.0 mg/kg/wk groups, respectively.
 - Serum efalizumab levels fell below the measurable level by 25 ± 8 and 44 ± 10 days following the 12th dose in the 1.0 mg/kg/wk and 2.0 mg/kg/wk groups, respectively.
 - The $t_{1/2}$ for the portion of the concentration–time curve where concentration was above 1 µg/mL was 6.2 ± 3.1 and 7.4 ± 2.5 days, for the 1.0 mg/kg/wk and 2.0 mg/kg/wk groups, respectively.
 - Both doses produced maximum down-modulation of CD11a to approximately 15%–25% of baseline and saturated greater than 95% of CD11a binding sites on T lymphocytes, even though higher serum efalizumab levels were achieved after the 2.0 mg/kg/wk dose.
 - As serum efalizumab concentrations diminished, both CD11a expression and available binding sites showed a similar temporal pattern of return toward baseline, which occurred between 35 and 56 days after the last dose for both dose groups. At the end of the follow-up period, CD11a expression and available binding sites had increased above baseline levels in the 2.0 mg/kg/wk group but not in the 1.0 mg/kg/wk group.
 - The increase in CD11a expression and available binding sites beyond baseline levels at the end of the follow-up period was not predictive of a corresponding increase in PASI levels above baseline.
 - CD11a expression on B lymphocytes was down-modulated to an extent similar to that on T lymphocytes, but down-modulation was less for NK cells, monocytes, and neutrophils.
 - Saturation of CD11a binding sites was >95% on CD4+ lymphocytes, CD8+ lymphocytes, and NK cells and >90% on B lymphocytes, monocytes, and neutrophils.
 - Increases in the absolute counts of circulating leukocytes were observed after treatment with efalizumab. The largest change occurred in the absolute count

of circulating lymphocytes. Absolute counts approximately doubled compared with predose levels. Lymphocyte levels returned to baseline between 5 and 8 weeks after the 12th dose for both the 1.0 mg/kg/wk and 2.0 mg/kg/wk groups. T-lymphocyte and B lymphocyte counts approximately doubled, whereas natural killer (NK) cell count increased by approximately 50%.

- Conclusions from Study ACD2389g were as follows:
 - 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 point estimate and confidence intervals were outside the prespecified 80%–125% interval and therefore did not meet the criterion for comparability.
 - The pharmacodynamics appear to be comparable, suggesting that the higher exposure with Genentech efalizumab may not be clinically meaningful.
 - For both XOMA and Genentech efalizumab, there was a sharp decrease in CD11a expression and ABS as early as Day 1 and a maximal decrease in CD11a expression and ABS by Day 2.
- Conclusions from a population PK analysis of 1088 patients:
 - Body weight was found to be the most significant covariate affecting efalizumab clearance, consistent with weight-based dosing. Baseline PASI, baseline lymphocyte count, or age had less significant effects on clearance. The clearance of efalizumab was not significantly affected by gender or race. The observed intersubject variabilities in clearance were explained by body weight as follows: $CL/F(L/day) = 1.29 \times [Weight(kg)/91]^{0.754}$

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APPENDICES

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Study HU9602

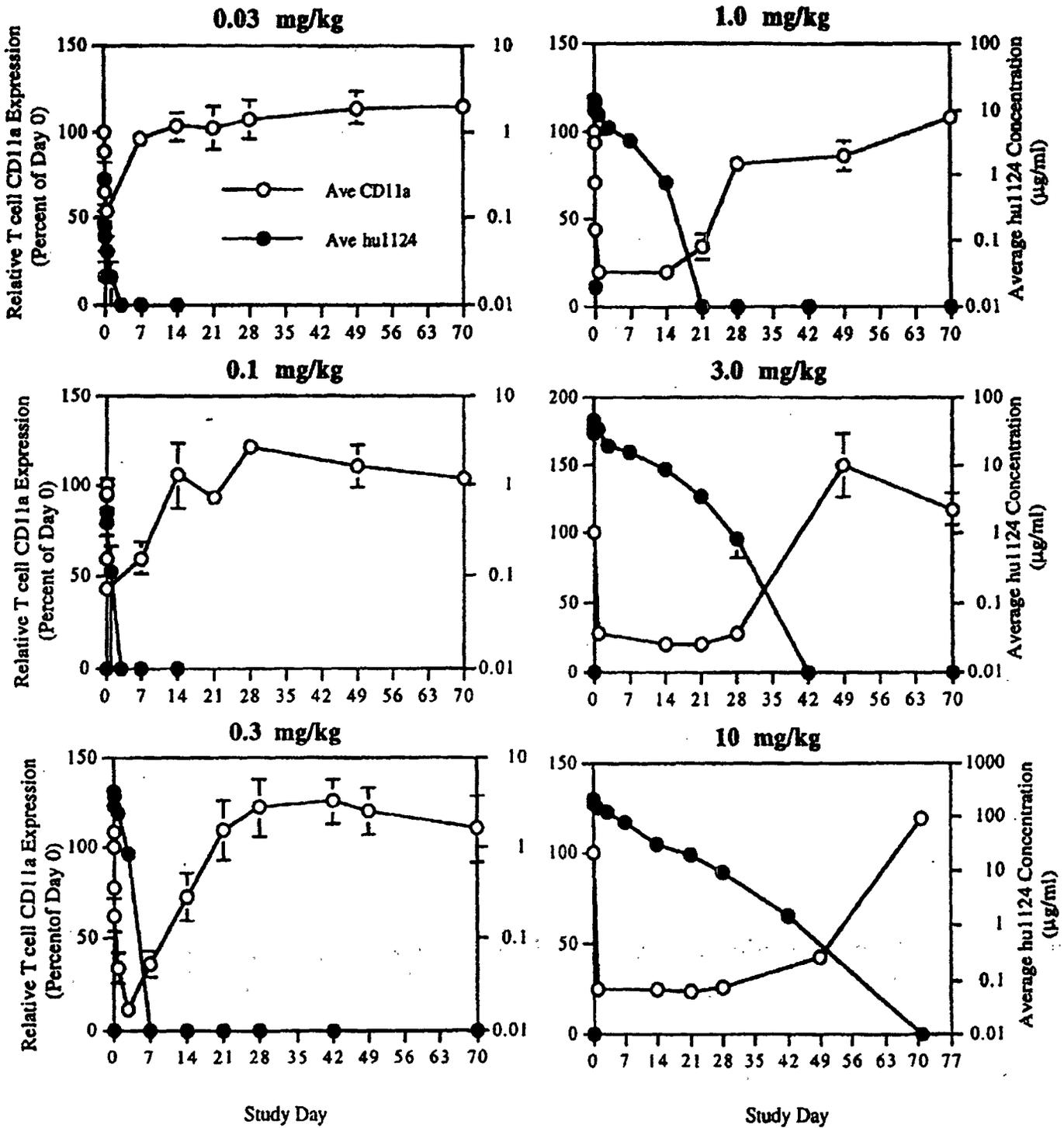


Figure 1. Plasma hu1124 concentration versus CD11a levels on circulating CD3-positive cells. Values shown are the average for all data available at each time point +/- SEM.

Appendix 2

HUPS256: CD4⁺ and CD8⁺ T cell Counts
(Cells/mm³, Mean (SEM))

	CD4			CD8		
	Day 0	EOS*	p-value**	Day 0	EOS	p-value
<u>Intravenous</u>						
Group A (n = 4)	837 (116)	760 (151)	0.575	438 (55)	553 (148)	0.579
Group B (n = 7)	838 (105)	876 (135)	0.557	527 (89)	720 (123)	0.028
<u>Subcutaneous</u>						
Group C (n = 20)	871 (65)	860 (76)	0.831	594 (72)	737 (72)	0.068
Group D (n = 16)	755 (64)	749 (51)	0.880	477 (64)	800 (103)	0.004
Group E (n = 18)	916 (80)	881 (67)	0.474	478 (40)	571 (51)	0.142

*EOS = End of Study = Day 133 for Groups A, B, C and D
= Day 180 for Group E

** p-value derived from a two-tailed paired T-test of CD4 and CD8 counts from Day 0 and EOS.

HUPS256: NK Cells
(Mean Percent of Lymphocytes +/- SEM)

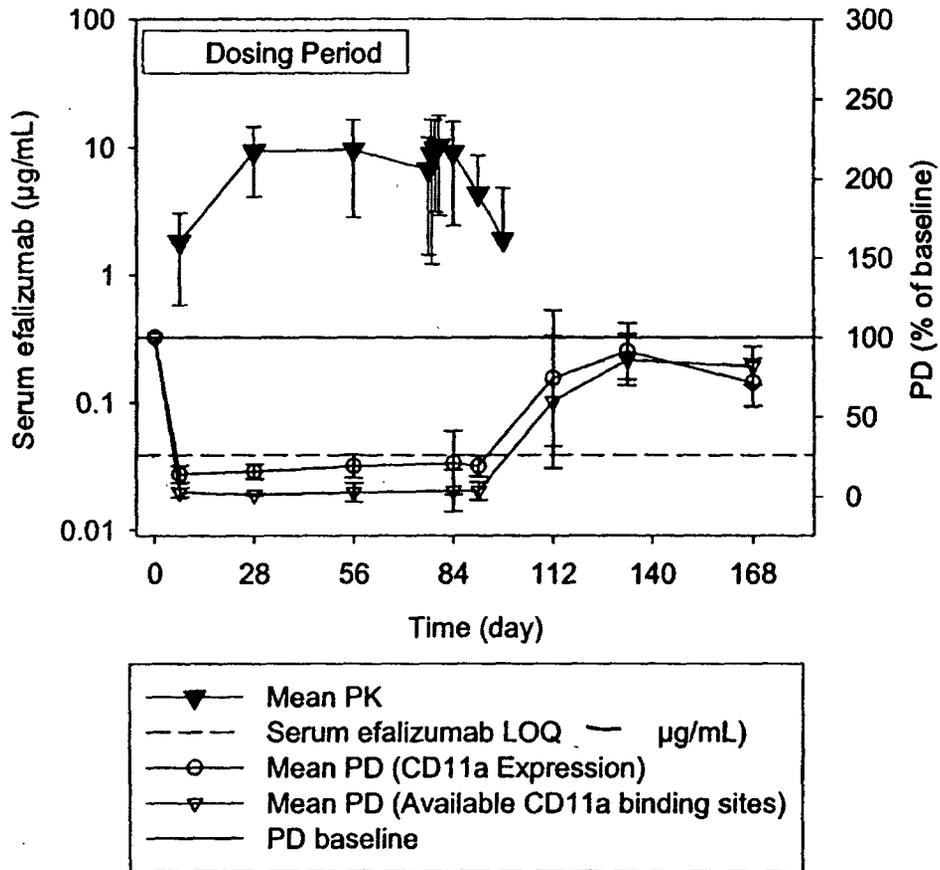
	Pretreatment (Day 0)	End of Study*	p-value**
<u>Intravenous</u>			
Group A (n = 4)	8.00 +/- 1.08	7.00 +/- 0.82	0.4228
Group B (n = 7)	8.57 +/- 1.29	4.14 +/- 0.74	0.0394
<u>Subcutaneous</u>			
Group C (n = 20)	9.45 +/- 0.83	7.35 +/- 0.93	0.0317
Group D (n = 17)	7.65 +/- 0.874	5.88 +/- 0.87	0.0668
Group E (n = 18)	9.00 +/- 0.97	6.22 +/- 0.95	0.0207

*End of Study = Day 133 for Groups A, B, C and D
= Day 180 for Group E

**p-value derived from a two-tailed paired T-test of percent NK cell values from Day 0 and End of Study.

Appendix 3

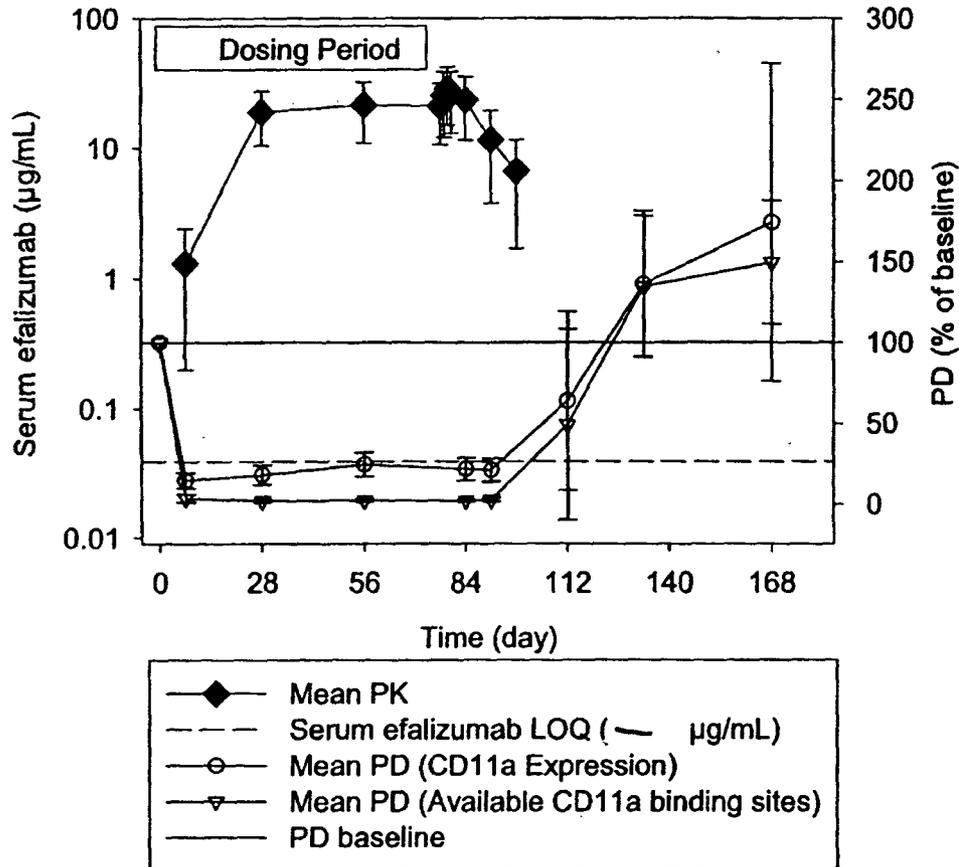
Mean (\pm SD) Serum Efalizumab Concentration (PK), CD11a Expression, and Available CD11a Binding Sites on T Lymphocytes (PD) following Administration of Efalizumab at 1.0 mg/kg/wk for 12 Weeks (n=26) in Study ACD2142g



Note: Less than reportable (LTR) serum efalizumab concentration values were treated as half the limit of quantification (LOQ) (0.05 µg/mL) for summary calculations. On Day 112, more than one third of subjects had efalizumab levels below the LOQ and therefore summary is not presented here.

Appendix 3 (cont'd)

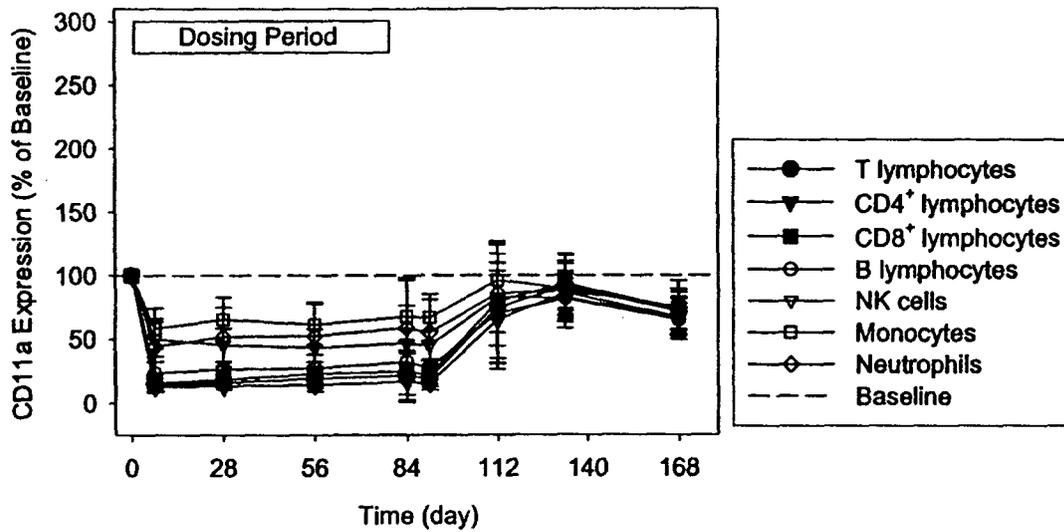
Mean (\pm SD) Serum Efalizumab Concentration (PK), CD11a Expression, and Available CD11a Binding Sites on T Lymphocytes (PD) following Administration of Efalizumab at 2.0 mg/kg/wk for 12 Weeks (n=29) in Study ACD2142g



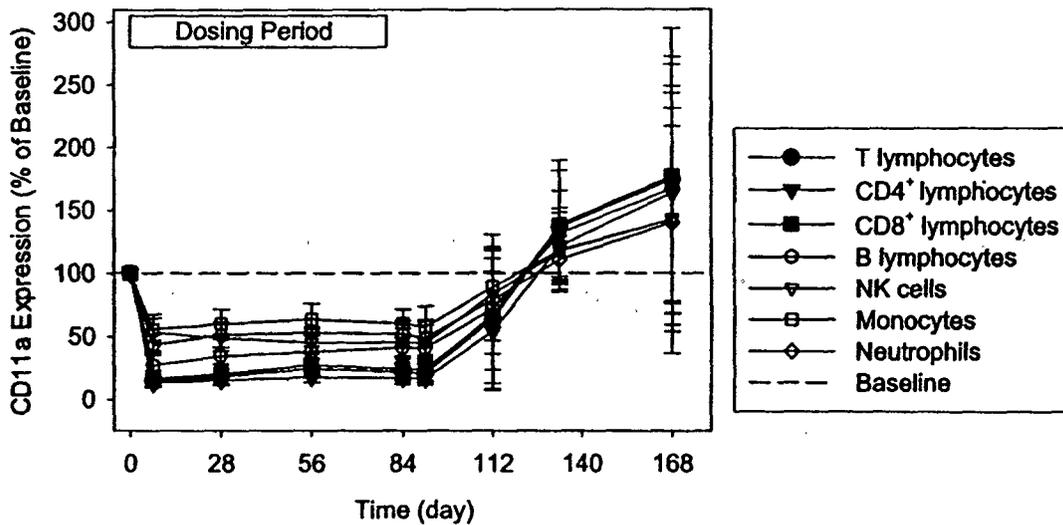
Note: Less than reportable (LTR) serum efalizumab concentration values were treated as half the limit of quantification (LOQ) $\mu\text{g/mL}$ for summary calculations. On Day 112 more than one third of subjects had efalizumab levels below the LOQ and therefore summary is not presented here.

Appendix 3 (cont'd)

Mean (\pm SD) CD11a Expression on Leukocyte and Lymphocyte Subsets during 12 Weeks of Dosing with 1.0 mg/kg/wk Efalizumab and 12 Weeks of Follow-Up

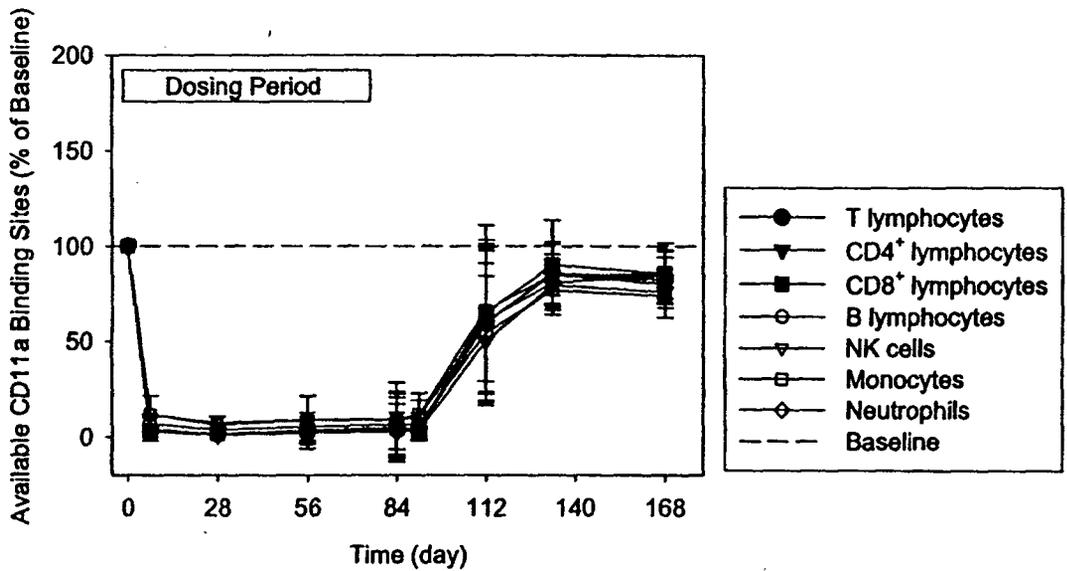


Mean (\pm SD) CD11a Expression on Leukocyte and Lymphocyte Subsets during 12 Weeks of Dosing with 2.0 mg/kg/wk Efalizumab and 12 Weeks of Follow-Up

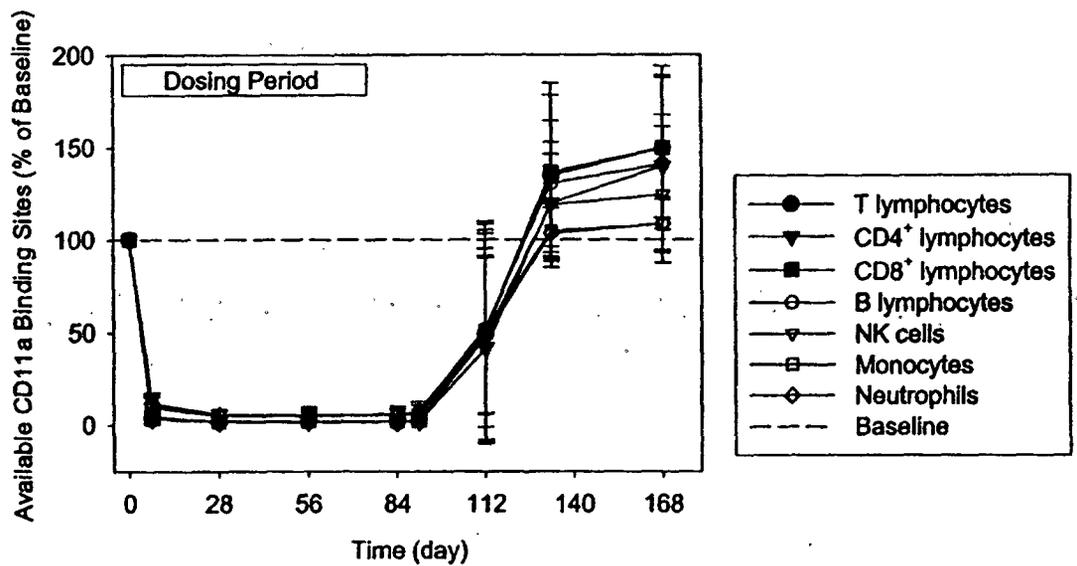


Appendix 3 (cont'd)

Mean (\pm SD) Available CD11a Binding Sites on Leukocyte and Lymphocyte Subsets during 12 Weeks of Dosing with 1.0 mg/kg/wk Efalizumab and 12 Weeks of Follow-Up



Mean (\pm SD) Available CD11a Binding Sites on Leukocyte and Lymphocyte Subsets during 12 Weeks of Dosing with 2.0 mg/kg/wk Efalizumab and 12 Weeks of Follow-Up

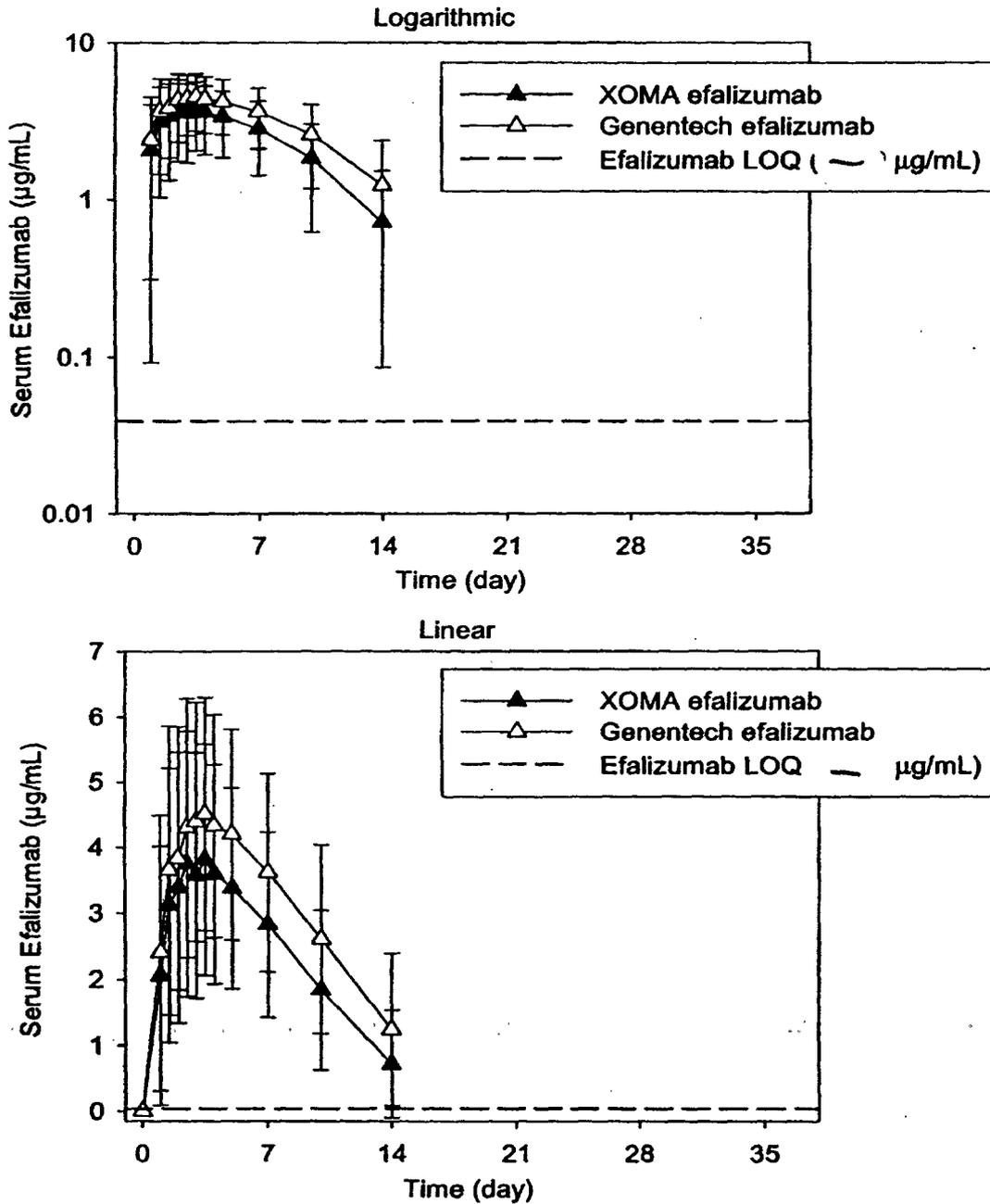


Study ACD2389g

Appendix 4 (cont'd)

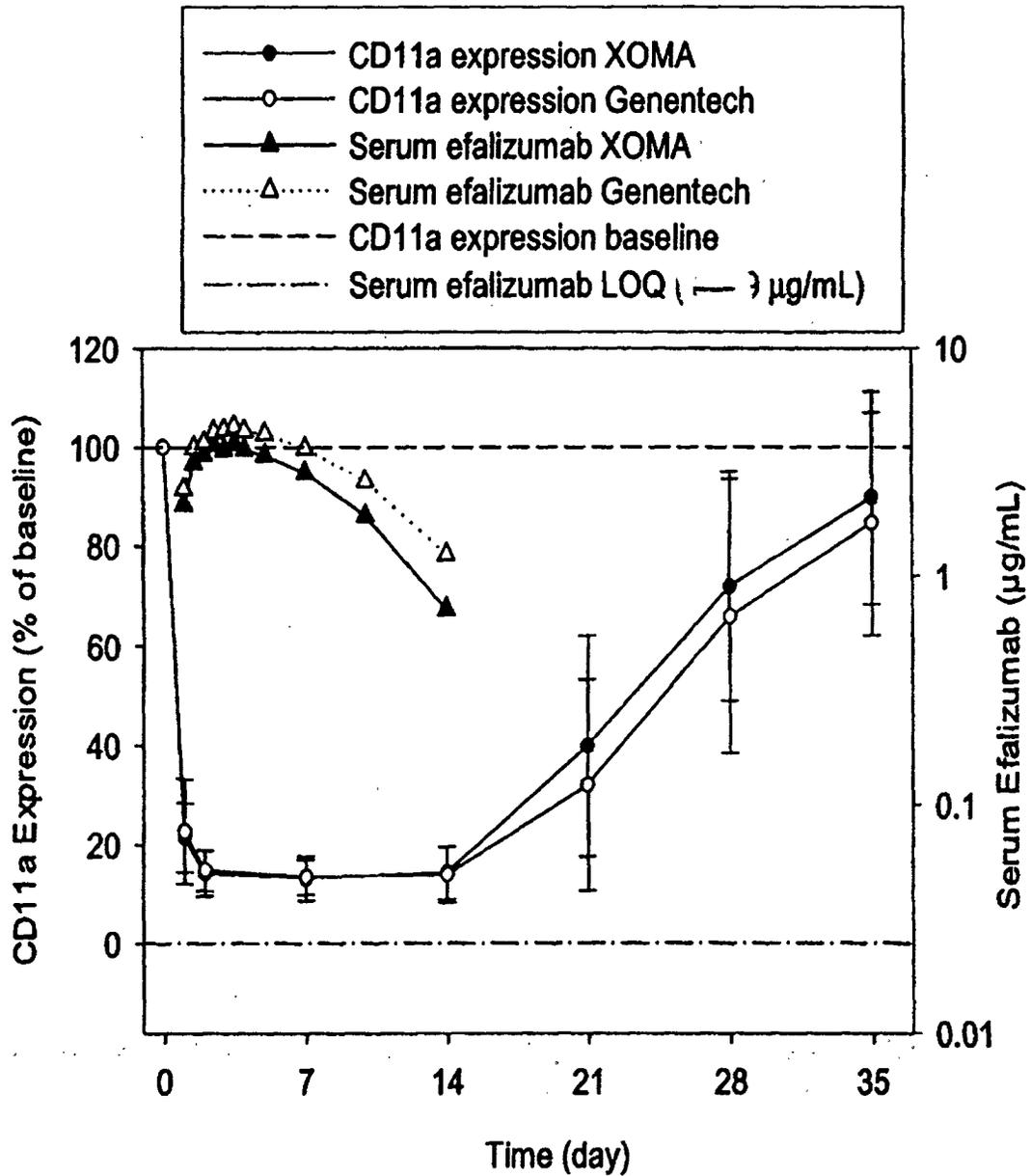
Study ACD2389g

Serum Efalizumab Concentration (Mean \pm SD) following a Single 1.0 mg/kg SC Dose of XOMA or Genentech Efalizumab



Note: Less than reportable (LTR) serum efalizumab concentration values were treated as half of limit of quantitation (LOQ) (— µg/mL) for summary calculations. On Days 21, 28, and 35, more than one-third of subjects had efalizumab levels below the LOQ (their data are not included).

Mean Serum Efalizumab Concentration and Mean \pm SD CD11a Expression on T Lymphocytes

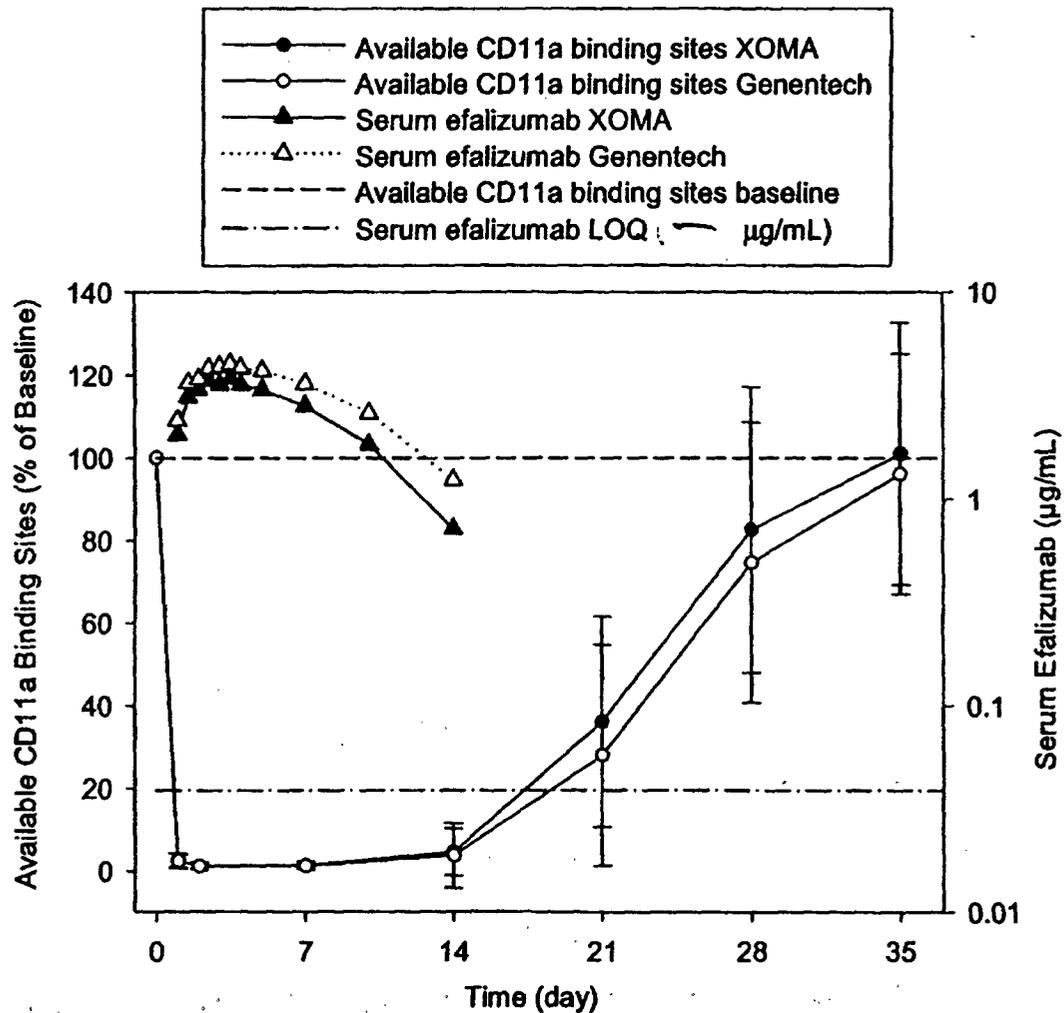


Note: LTR serum efalizumab concentration values were treated as half of LOQ (— µg/mL) for summary calculations. On Days 21, 28, and 35, more than one-third of subjects had efalizumab levels below the LOQ (their data are not included).

Appendix 4 (cont'd)

Study ACD2389g

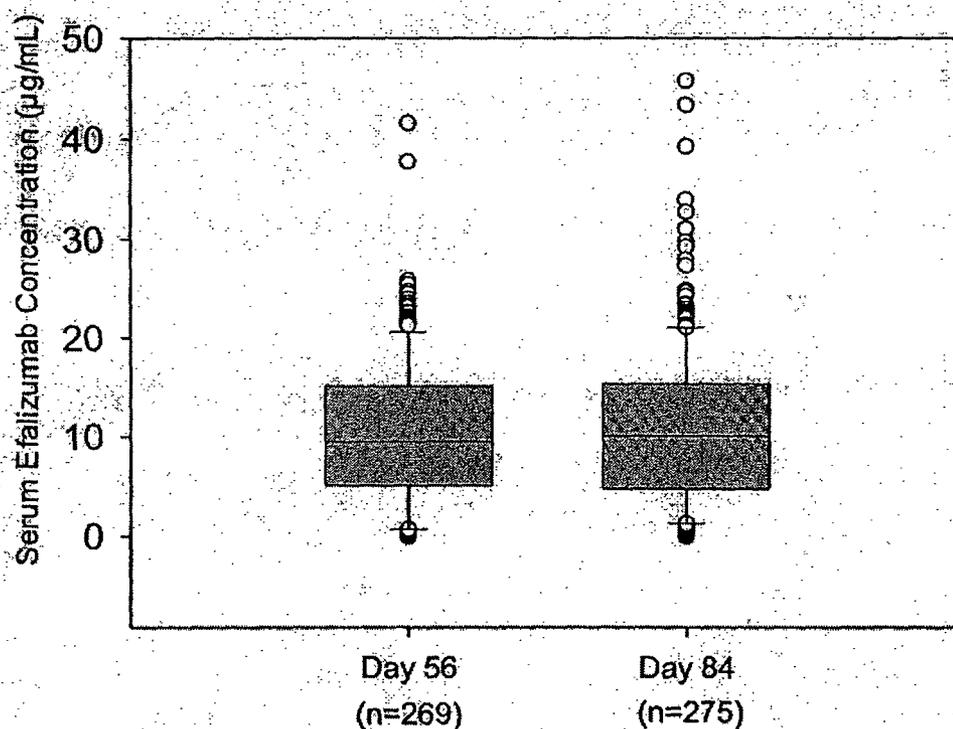
Mean Serum Efalizumab Concentrations and Mean \pm SD Available CD11a Binding Sites on T Lymphocytes



Note: LTR serum efalizumab concentration values were treated as half of LOQ (0.01 µg/mL) for summary calculations. On Days 21, 28, and 35, more than one-third of subjects had efalizumab levels below the LOQ (their data are not included).

Appendix 5

Box and Whiskers Plot of Steady-State Efalizumab Concentrations



The boundaries of the box indicate the 25th and 75th percentiles, the line within the box marks the median, and the whiskers indicate the 10th and 90th percentiles. The lower quantification limit of the assay was — µg/mL.