Table 34. Efficacy Endpoints Based on Proportions Responding in the Second Course

	Placebo	7.5 mg
PATIENTS DOSED IN SECOND COURSE	142 (100)	154 (100)
Principal Endpoint: PASI ≥75% Reduction from Baseline	10 (7)	34 (22)[a]
Other Secondary Endpoints:		
-PGA 'almost clear' or 'clear'	7 (5)	30 (19)
-PASI ≥50% Reduction from Baseline	32 (23)	72 (47)

(a) Comparison of treatments adjusted for geographic region and stratum P<0.001

Another clinically meaningful estimate of response to treatment for course 2 is obtained by comparing PASI at end of course 2 (Visit 13 B) with PASI at the start of course 2 (Visit 1B). Comparison to visit 1B baseline yields a lower proportion of responders than comparison to visit 1A (**Table 35**). The absolute difference in the proportions achieving ≥ 75% improvement is six percent. Of note the proportion of responders in patients receiving their first exposure to alefacept in the second treatment course is an absolute eight percent.

Table 35. Response to Second Course (Visit 13 B) Using Visit 1B as Baseline

Outcome	LFA3TIP/LFA3TIP N=154	LFA3TIP/PLACEBO N= 142	PLACEBO/LFA3TIP N=153
PASI ≥ 75	11 (7)	1 (<1)	14 (9)
PASI ≥50	37 (24)	6 (4)	48 (31)

Relationship between Treatment Response and Body Weight Quartile

Study 711 evaluated fixed doses because weight did appear to be an important factor in the pharmacokinetic profile of alefacept. Patients who weighed < 50 kg received 30% less drug.

Table 36 summarizes response to treatment by body weight quartile. Response to treatment was lower in patients in the two higher body weight quartiles (4-5 % compared to 18%). Response was approximately four-fold lower in patients who weighed >85 kg compared to those who weighed ≤ 85 kg.

Table 36. Number of Treatment Responders [a] by Body Weight Quartile

Weight (kg)	Placebo	Alefacept	Change in Percent
< 75	1 (3) [b]	19 (21) [b]	18
75-<87.2	1 (2)	15 (20)	18
87.2-<102	3 (6)	10 (11)	5
102+	2 (4)	9 (8)	4
≤ 85	2 (3)	33 (22)	19
> 85	5 (4)	20 (9)	5

[a] 75% improvement in PASI from baseline at 2 weeks post treatment
[b] N (%)

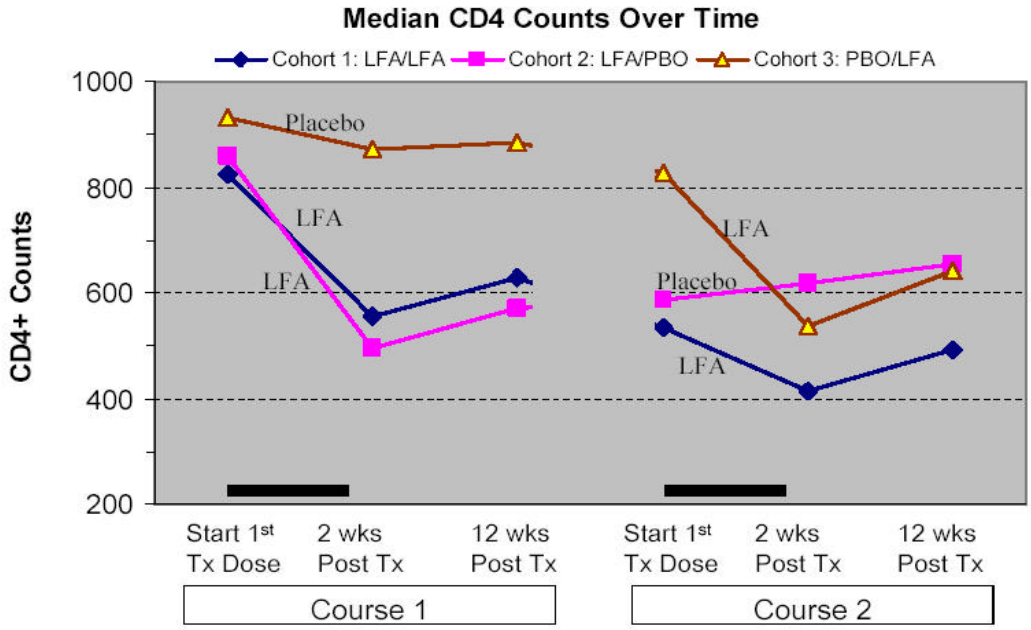
Correlation between PASI Scores and Lymphocyte Counts

The two figures below show the time course of median CD4 counts and PASI scores over two treatment courses. The plots are truncated because patients enetered the second treatment course at different times based on protocol safety and efficacy criteria.

In cohort 1 (alefacept/alefacept) at the end of the first course of alefacept, median PASI scores and median CD4 counts decline. The values do not return to baseline by the end of the follow up period. Upon retreatment the absolute declines in PASI scores and CD4 counts are less pronounced and CD4 counts tend to return to the new baseline. However there is suggestion of cumulative effects which is reflected in the lower median CD4 count in the alefacept /alefacept group than in the placebo/alefacept group seen in the figure below.

In cohort 2 (alefacept/placebo) median PASI scores and CD4 counts decline after the first treatment course. In the second treatment (placebo) course there is no further decline in CD4 counts; PASI scores increase to a level similar to that reached by patients in cohort 3 after their first treatment (placebo) course. CD4 counts tend to rise but do not return to baseline for up to 9 months after the end of the first treatment course.

In cohort 3 (placebo/alefacept) there is a decrease in median PASI score at the end of course 1, which probably reflects regression toward the mean and placebo effect. At the end of course 2 there is a further decrease in PASI that is accompanied by a drop in CD4 counts, which is attributable to alefacept. Of note, the final median PASI score in cohort 3 (placebo/alefacept) was similar to that of cohort 1 who received two courses of alefacept.



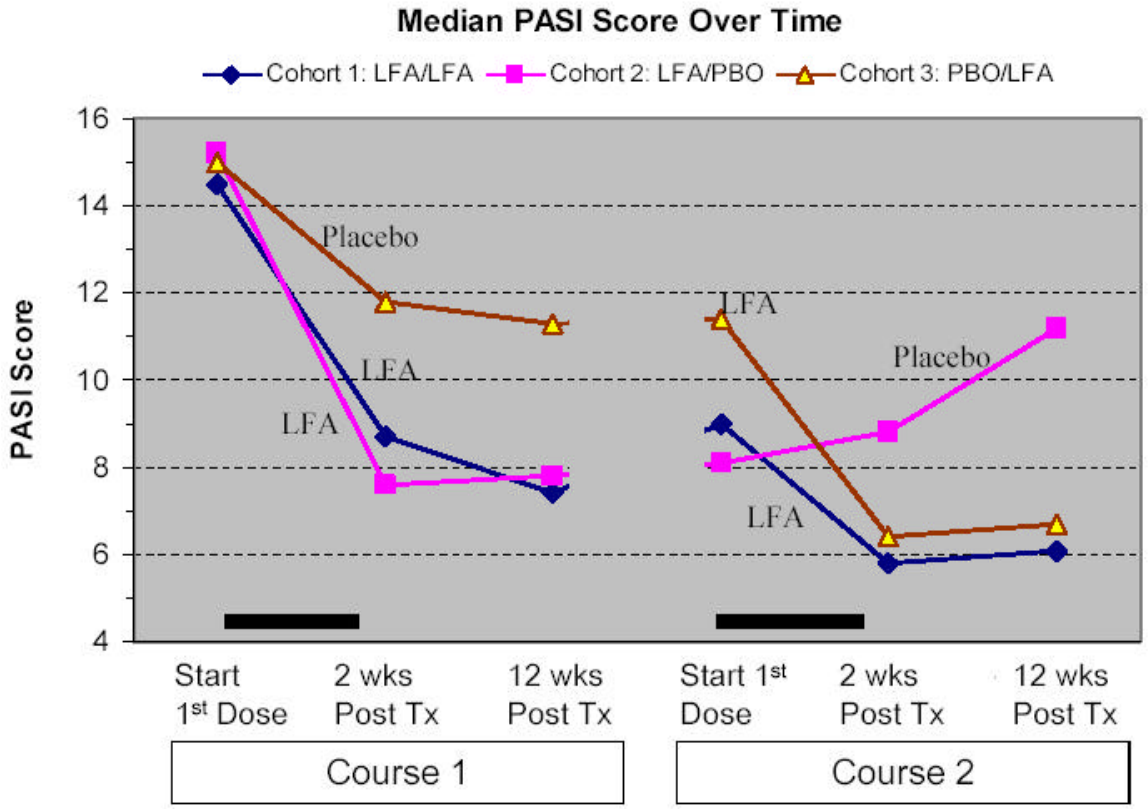


Table 37 shows the relationship between efficacy and CD4 counts. There is little relationship between lowest CD4 count at any time and maximum reduction in PASI with the value of the Spearman correlation being - 0.2.

Table 37. Relation Between Efficacy and CD4 Counts

Maximum Reduction in PASI at Any Time	Lowest CD4 at Any Time (cells/µL)		
	<300	300-400	400+
<50%	20 (11%)	40 (21%)	127 (68%)
50 to <75%	41 (26%)	29 (18%)	89 (56%)
75% +	68 (33%)	39 (19%)	100 (48%)

Spearman correlation r = -0.2

Onset of Response

The time to first reduction in PASI of 75% or more occurred relatively late into the treatment period. For the first treatment course the median time to response was 77 days in the placebo group and 92 days in the alefacept groups.

Duration of Response

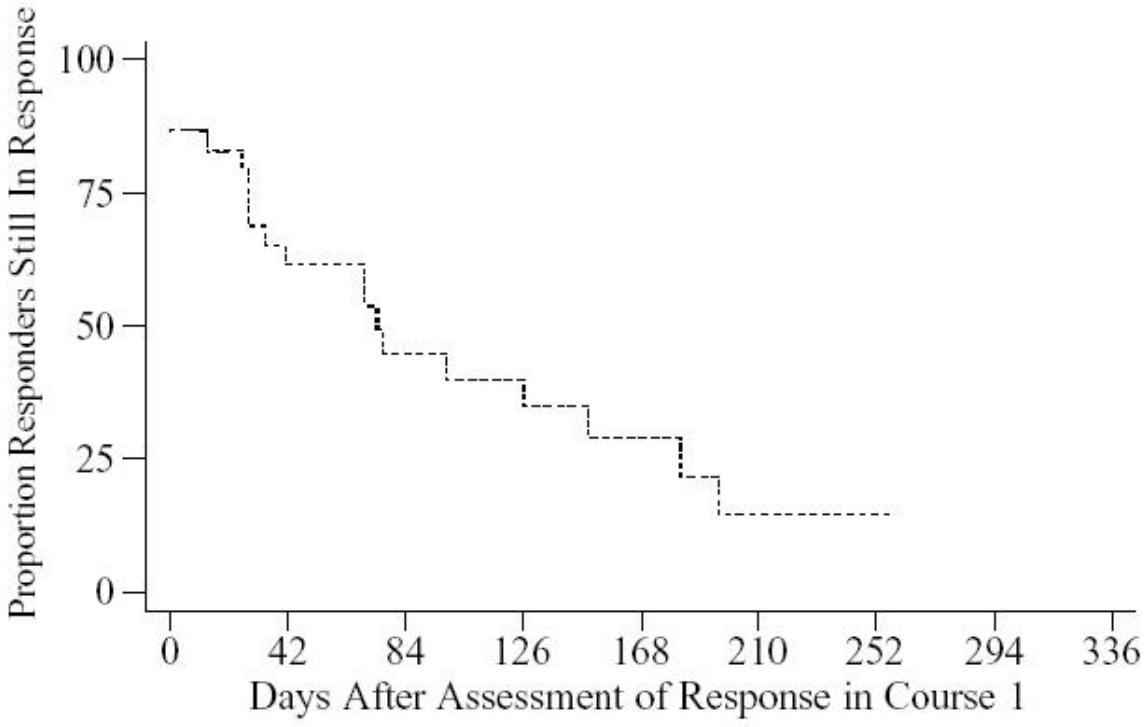
Duration of response was measured by a reduction in PASI of at least 75% from baseline in Courses 1 and 2 without the use of phototherapy or other systemic therapies. The start time is interpolated between the date of the visit in which there was less than a 75% reduction from baseline and the date of the visit in which a 75% or greater reduction was achieved. The stop time occurs at visit 17 A, at the time the patient withdraws, or at the

time phototherapy or another systemic therapy was initiated, or by interpolating between the visit when the patient still had a 75% or greater reduction and the visit when there was less than a 75% reduction from baseline PASI. For patients achieving a 75% decrease in PASI, the duration of 75% reduction was 52 days (median) with a range of 1 to 154 days. For patients who achieved a PGA of "clear" or "almost clear" the duration of response was 62 days (median) with a range of 14 to 128 days.

The duration of response for patients in cohorts 2 (alefacept, placebo) was estimated. The estimates excluded time on study drug and interpolation of observations at the end of the response intervals. The mean duration of response was 78 days and the median was 70 days. The Kaplan-Meier estimate of the median duration of response was 74 days. One third (10/30) patients of responders were still in response at the time of their last observation. Therefore, these data are underestimates of duration of effect.

Duration of response was not estimated in patients in cohorts 1 and 3 because these patients received alefacept in the second treatment course. Therefore, the estimate of duration of response would be truncated at the start of the second treatment course.

Duration of PASI 75 for Those Achieving Response at Visit 13: Excluding Time on Drug



Quality of Life

The sponsor states that the data indicate that treatment with alefacept confers a significant QOL benefit, and that patients experiencing reductions in disease severity, regardless of the definition of response, tended to show much greater improvement in quality of life than non-responders.

Table 38 shows the range in scores for the SF-36, DLQI, DQOLS, and Treatment Convenience scales and the direction of scoring that denotes improvement.

Table 38. Scale Score Ranges and Direction of the QOL Surveys

QOL Survey	Scale Names	Scale Score	Direction of Scoring
SF-36	Physical Function	0-100	Higher: better QOL
	Role Physical	0-100	
	Bodily Pain	0-100	
	General Health Perceptions	0-100	
	Vitality	0-100	
	Social Function	0-100	
	Role Emotional	0-100	
	Mental Health	0-100	
	Physical Component Summary	Norm	
	Mental Component Summary	Norm	
DLQI	Overall	0-30	Higher: worse QOL
DQOLS	Psychosocial	0-100	Higher: worse QOL
	Activities	0-100	
	Symptoms	0-100	
Treatment Convenience	Treatment Convenience	0-100	Higher: better QOL

Table 39 shows that after the first treatment course the absolute differences in quality of life changes from baseline are very minor between groups. For the DLQI and the DQOLS the differences in mean change favor alefacept and are approximately 3 points for DLQI and range from 3 to 10 points for DQOLS. For the SF-36 there is no discernible trend at all.

Table 39. Observed Mean Change in QOL Scores

	Cohort 1		Cohort 2		Cohort 3	
QOL Scale	**Mean Change**	**SD**	**Mean Change**	**SD**	**Mean Change**	**SD**
DLQI Overall Scale[†]	-4.6	6	-4.2	6.9	-1.7	6
DQOLS Scales[†]						
Psychosocial	-9.2	20	-11.3	21	-5.9	16
Activities	-10.7	20	-9	18	-4.4	16
Symptoms	-17.8	21	-19	22	-9	21
SF-36 Scales[2]						
Physical Function	-0.2	17	1.5	22	0.5	19
Role Physical	-2	32	3.0	37	-4.8	35
Bodily Pain	-0.4	23	5.4	24	-2.6	24
General Health	-0.4	15	2.4	16	-2.4	15
Vitality	-0.4	16	0.3	17	-3.6	17
Social Function	-0.1	24	1.9	22	-2.7	23
Role Emotional	0.4	29	5.0	35	-0.2	35
Mental Health	1.9	16	1.1	15	-1.8	15
Phys Comp Summary	-0.7	7	1.1	9	-0.8	7
Ment Comp Summary	0.6	9	0.7	9	-0.7	9
Treatm Conv Scale[2]	11.4	21	12	22	2.6	22

Reviewers' comment:
The original analysis involved replacing missing post-baseline data regarding DLQI with the baseline data. The FDA also requested that the data be analyzed using the most conservative approach of replacing missing data with the highest (worst) possible score. The results of this analysis were consistent with the sponsor's previous analysis.

Table 40 shows that when comparing the end of second treatment to first treatment baseline there is no difference in the improvement experienced by placebo and alefacept group or there is worsening in both groups.

Reviewers' comment
The QOL data lend little support to the primary efficacy outcome of the trial.

Table 40. Adjusted Mean Change in QOL From Visit 1A to Visit 13B.
Treatment Course 2: Cohort 1 *versus* Cohort 2

QOL Scale	Placebo Mean Change (SE)	7.5 mg Mean Change (SE)
DLQI Overall Scale	-5.50 (0.55)	-5.96 (0.54)
DQOLS Scales		
Psychosocial	-17.42 (1.88)	-17.99 (1.84)
Activities	-15.68 (1.69)	-16.98 (1.66)
Symptoms	-26.76 (2.22)	-27.58 (2.19)
SF-36 Scales		
Physical Function	-26.64 (3.75)	-18.09 (3.69)
Role Physical	-27.27 (4.10)	-16.06 (4.03)
Bodily Pain	-18.25 (3.44)	-11.80 (3.37)
General Health	-23.40 (3.25)	-16.96 (3.19)
Vitality	-17.57 (2.91)	-12.91 (2.86)
Social Function	-22.83 (3.82)	-15.63 (3.75)
Role Emotional	-23.56 (4.26)	-14.35 (4.19)
Mental Health	-23.13 (3.30)	-14.03 (3.24)
Physical Component Summary	-16.58 (2.13)	-11.31 (2.10)
Mental Component Summary	-17.13 (2.25)	-10.78 (2.21)
Treatment Convenience Scale	-14.08 (3.69)	-5.03 (3.66)

SAFETY ASSESSMENTS

Adverse Events by Body System, Severe Adverse Events

The incidence of adverse events (**Table 41**) in the first treatment course in the combined alefacept group was numerically somewhat higher compared to placebo overall (84 vs. 77%) and in the following body systems: body as a whole (62 vs. 56%), skin (26 vs. 18%), musculoskeletal (16 vs. 7%), and nervous (14vs. 9%).

Table 41. Incidence of Adverse Events at First Exposure by Body System

	First Course		Second course
	Cohort 3: Placebo	Cohorts 1 and 2: LFA3TIP	Cohort 3: LFA3TIP
No. of patients dosed	186 (100)	367 (100)	153 (100)
No. with an event	143 (77)	310 (84)	121 (79)
Body as a whole	104 (56)	228 (62)	79 (52)
Respiratory	58 (31)	112 (31)	36 (24)
Skin & appendages	34 (18)	94 (26)	27 (18)
Digestive	43 (23)	69 (19)	31 (20)
Musculoskeletal	13 (7)	59 (16)	16 (10)
Nervous	17 (9)	53 (14)	13 (8)
Cardiovascular	15 (8)	31 (8)	6 (4)
Special senses	10 (5)	25 (7)	10 (7)
Urogenital	8 (4)	23 (6)	5 (3)
Metabolic & nutritional	9 (5)	16 (4)	2 (1)
Endocrine	3 (2)	4 (1)	0
Hemic & lymphatic	4 (2)	4 (1)	0

Chills was the only adverse event that was higher (≥5%) in incidence in those in the combined alefacept group. Chills were reported by 37 patients (10%) in the alefacept group compared to two patients (1%) in the placebo group. Neither of the two patients in the placebo group and three of the 37 patients in the combined alefacept group experienced severe chills. The incidence of adverse events (**Table 41**) and of severe adverse events (**Table 42**) upon first exposure to alefacept in the placebo/alefacept group was lower compared to the incidence in the combined alefacept group. This may be due to lack of comparability of the two groups due to patient discontinuations.

Table 42. Incidence of Severe Adverse Events in the First Exposure

	First Course		Second Course
	Cohort 3 Placebo N=186	Cohort 1 and 2 LFA3TIP N=367	Cohort 3 LFA3TIP N=153
No. with severe AE	17 (9)	38 (10)	9 (6)
Pruritus	3 (2)	6 (2)	1 (<1)
Accidental injury	0	5 (1)	2 (1)
Chills	0	3 (<1)	0
Arthritis	1 (<1)	3 (<1)	0
Back pain	2 (1)	2 (<1)	0
Infection	1 (<1)	2 (<1)	1 (<1)
Syncope	0	2 (<1)	0
Carcinoma	0	1 (<1)	0
Cyst	0	1 (<1)	0
Flu syndrome	0	1 (<1)	1 (<1)
Infection fungal	0	1 (<1)	0
Suicide attempt	0	1 (<1)	0
Viral infection	0	1 (<1)	1 (<1)
Angina pectoris	1 (<1)	1 (<1)	0
Congestive heart failure	0	1 (<1)	0
Coronary artery disorder	0	1 (<1)	0
Myocardial infarct	0	1 (<1)	0
Nausea and vomiting	0	1 (<1)	0
Hyperglycemia	0	1 (<1)	0
Bursitis	0	1 (<1)	0
Epistaxis	0	1 (<1)	0
Pharyngitis	1 (<1)	1 (<1)	0
Pleural disorder	0	1 (<1)	0
Psoriasis	2 (1)	1 (<1)	0
Skin melanoma	0	1 (<1)	0
Blepharitis	0	1 (<1)	0
Corneal lesion	0	1 (<1)	0
Kidney calculus	2 (1)	1 (<1)	0
Prostatic carcinoma	0	1 (<1)	0
Chest pain	1 (<1)	0	0
Headache	1 (<1)	0	1 (<1)
Hernia	1 (<1)	0	0
Pain	2 (1)	0	1 (<1)
Photosensitivity reaction	1 (<1)	0	0
Migraine	2 (1)	0	1 (<1)
Diarrhea	0	0	1 (<1)
Tooth disorder	1 (<1)	0	0
Depression	0	0	1 (<1)
Rash	0	0	1 (<1)
Iritis	1 (<1)	0	0

As can be seen in **Table 42** above, the severe adverse events observed in the study are not clustered in specific body systems and do not suggest a common pathophysiologic mechanism.

Deaths, Other SAEs, Other Clinically Significant Adverse Events

There was one death from suicide in cohort 2 at 9 weeks after withdrawing from study. The patient had a family history of suicide. He received 11 doses of alefacept and his PASI score improved from 29 to 11. The patient withdrew during the follow up period. At his last visit his PASI was 20. The investigator judged the event unrelated to study drug.

Table 43. Serious and Other Clinically Significant Adverse Events

	Cohort 1		Cohort 2		Cohort 3	
	Course 1 alefacept	Course 2 alefacept	Course 1 alefacept	Course 2 placebo	Course 1 placebo	Course2 alefacept
Patients with ≥1 Adverse Event	152 (83)	117 (76)	158 (86)	105 (74)	143 (77)	121 (79)
Patients with infectious AE	70 (38)	74 (48)	88 (48)	61 (43)	79 (42)	61 (40)
Patients with serious infectious AE	2 (1)	4 (3)	5 (3)	1 (<1)	2 (1)	4 (3)
Patients with malignancy	2 (1)	1 (<1)	4 (2)	1 (<1)	1 (<1)	1 (<1)
Serious Adverse Events	9 (5)	7 (5)	9 (5)	1 (<1)	5 (3)	2 (1)
AE leading to discontinuation	1 (<1)	0	6 (3)	1 (<1)	2 (1)	1 (<1)

Table 43 shows a numerically higher incidence of serious events including serious infectious events and malignancies in the alefacept-treated groups (malignancies in placebo *vs.* combined alefacept group: 0 *vs.* 4 (1%) patients; infection: 0 *vs.* 2 (<1%) These events in the alefacept groups include:

- Neoplasms: renal cell carcinoma, prostatic carcinoma, SCC, malignant melanoma
- Infections: pre-septal ocular cellulitis; infection of burn wound; pneumonia; abscess/breakdown of surgical shoulder repair
- Inflammatory: bursitis; scleritis-episcleritis bilateral
- GI: pancreatitis; gastroenteritis
- CV: MI, CAD, CHF, angina,
- Psychiatric: accomplished suicide; attempted suicide.

Six patients developed skin cancer (2 BC, 3 SCC, 1 melanoma). The duration of CD4 depression (<400 cells/mm3) was compared between the patients who did and patients who did not develop skin cancer. No differences were seen between the two subgroups.

Infections:

There was no difference between groups in the number of signs and symptoms compatible with possible infection.

Table 44 Symptoms and Signs of Infections in the First Alefacept Exposure

	First course		Second course
	Cohort 3: Placebo	Cohorts 1 and 2: Alefacept	Cohort 3: Alefacept
Dosed	186 (100)	367 (100)	153 (100)
Symptoms/signs of infection	79 (42)	158 (43)	61 (40)
Event			
Pharyngitis	18 (10)	34 (9)	13 (8)
Infection	19 (10)	32 (9)	16 (10)
Viral infection	12 (6)	29 (8)	8 (5)
Flu syndrome	5 (3)	28 (8)	15 (10)
Sinusitis	9 (5)	17 (5)	2 (1)
Herpes simplex	5 (3)	10 (3)	2 (1)
Bronchitis	5 (3)	5 (1)	4 (3)
Vaginal moniliasis	1 (<1)	5 (1)	2 (1)
Infection bacterial	3 (2)	4 (1)	4 (3)
Infection fungal	2 (1)	4 (1)	1 (<1)
Gastroenteritis	4 (2)	4 (1)	2 (1)
Fungal dermatitis	0	4 (1)	1 (<1)
Otitis media	1 (<1)	4 (1)	2 (1)
Urinary tract infection	2 (1)	4 (1)	0
Periodontal abscess	2 (1)	3 (<1)	0
Conjunctivitis	1 (<1)	3 (<1)	0
Cellulitis	0	2 (<1)	0
Chills	0	2 (<1)	0
Pleural disorder	0	2 (<1)	0
Pneumonia	2 (1)	2 (<1)	0
Rhinitis	2 (1)	2 (<1)	1 (<1)
Otitis externa	0	2 (<1)	1 (<1)
Headache	0	1 (<1)	0
Colitis	0	1 (<1)	0
Diarrhea	2 (1)	1 (<1)	0
Gingivitis	0	1 (<1)	1 (<1)
Nausea and vomiting	0	1 (<1)	0
Vomiting	0	1 (<1)	0
Dizziness	0	1 (<1)	0
Cough increased	1 (<1)	1 (<1)	0
Furunculosis	2 (1)	1 (<1)	0
Herpes zoster	0	1 (<1)	0
Pustular rash	0	1 (<1)	1 (<1)
Ear pain	0	1 (<1)	0
Cystitis	0	1 (<1)	1 (<1)
Abscess	1 (<1)	0	0
Nausea	1 (<1)	0	0
Tooth disorder	0	0	1 (<1)
Lymphadenopathy	1 (<1)	0	0
Lung disorder	1 (<1)	0	0
Rash	0	0	1 (<1)
Skin ulcer	1 (<1)	0	0
Blepharitis	0	0	1 (<1)
Vaginitis	0	0	1 (<1)

The number of infections was analyzed by lean body mass (<50, 50-59, 60-69, >70 kg). There was no imbalance between placebo and active treatment across these weight subgroups. The number of all adverse events was also analyzed in these weight subsets. No differences were identified.

Psoriasis flares, hypersensitivity:
There was evidence of occasional flaring of psoriasis and development of psoriasis variants during and after end of treatment with alefacept (see **Table 28)**. One episode of hypersensitivity reaction (urticaria) was reported.

Discontinuation of Study Treatment for Adverse Events
The events leading to discontinuation of treatment were slightly higher in the alefacept groups (see **Table 43)**. There were very few discontinuations due to adverse events $\leq$ 1 % in placebo and between 0-3% in the alefacept groups. In the placebo group one patient each discontinued for asthenia, worsening depression, and psoriasis. In the alefacept groups one patient each discontinued for pancreatitis, asthenia, flu syndrome, headache, pleural effusion, urticaria, prostatic carcinoma, and scleritis.

Laboratory data: Lymphocyte depletion
The tables below (**45-48**) show that there is persistent lowering of CD4+ and CD8+ lymphocyte counts in patients treated with alefacept compared to placebo.

Table 45. Depletion of CD4+ T Cells by Alefacept by Cohort and Course

	Cohort 1		Cohort 2		Cohort 3	
	LFA3TIP	LFA3TIP	LFA3TIP	Placebo	Placebo	LFA3TIP
Baseline: No. of Patients Evaluable (a)	154 (100)	154 (100)	142 (100)	139 (100)	153 (100)	151 (100)
Mean +/- s.d.	925 +/- 387	689 +/- 230	925 +/- 345	634 +/- 260	931 +/- 341	932 +/- 340
Emax (b): No. of Patients Evaluable (c)	154 (100)	154 (100)	142 (100)	139 (100)	153 (100)	153 (100)
Time to Emax (days) median (min max)	65 (8,99)	58 (8, 99)	70 (8,96)	36 (7,94)	43 (7,95)	65 (7,99)
Count at Tmax (cells/uL) Mean +/- s.d.	479 +/- 185	467 +/- 184	457 +/- 202	530 +/- 204	718 +/- 253	507 +/- 209
% Change from Baseline (d) Mean +/- s.d.	-46 +/-17	-47 +/-18	-49 +/-16	-41 +/-16	-21 +/-17	-44 +/-17
N (%). < LLN	63 (41)	64 (42)	66 (46)	42 (30)	11 (7)	48 (31)
N (%) Below: 400 (cells/uL)	66 (43)	66(43)	67 (47)	47 (33)	12 (8)	49 (32)
300	20 (13)	31(20)	35 (25)	9 (6)	1(1)	27 (18)
200	0	4 (3)	4 (3)	1 (1)	0	3(2)
100	0	0	0	0	0	0
EAUC (e): No. of Patients Evaluable (c)	154	154	142	139	153	153
Mean +/- s.d.	2536 +/-1367	2849 +/-1552	2774 +/-1388	2243 +/-1370	659 +/- 754	2428 +/-1442

(a) Any patient who had a baseline assessment and at least one post-baseline assessment in both courses.
(b) Maximum reduction in count during dosing period.
(c) Any patient with an assessment during the dosing period for the course.
(d) Baseline refers to the baseline from Course 1.
(e) Area under the effect curve during the dosing period based on percentage change from Course 1 baseline.
(f) Any patient with a post-baseline assessment in both courses.
(g) Any patient with a twelve-week post-dosing assessment completed between 10 and 14 weeks after the final dose in the course.
(h) Any patient with at least 2 samples during the follow-up period in the course.

Table 46. Recovery of CD4+ Count after Alefacept Treatment by Cohort and Course

	Cohort 1		Cohort 2		Cohort 3	
	LFA3TIP	LFA3TIP	LFA3TIP	Placebo	Placebo	LFA3TIP
LAST STUDY VISIT						
No. of Patients Evaluable (f)	154 (100)	154 (100)	142 (100)	142 (100)	153 (100)	153 (100)
Count (cells/uL)Mean +/- s.d.	686 +/- 220	677 +/- 276	648 +/- 253	697 +/- 259	933 +/- 335	687 +/- 279
% Change from Baseline (d)Mean +/- s.d.	-21 +/-24	-24 +/-25	-27 +/-21	-22 +/-21	3 +/-24	-24 +/-23
No. < LLN	1 (1)	24 (16)	3 (2)	12 (8)	0	22 (14)
12 WEEKS POST TREATMENT						
No. of Patients Evaluable (g)	151 (100)	137 (100)	140 (100)	118 (100)	152 (100)	138 (100)
Count (cells/uL)Mean +/- s.d.	677 +/- 253	673 +/- 272	636 +/- 264	691 +/- 262	929 +/- 332	690 +/- 274
%Change from Baseline Mean +/- s.d.	-23 +/-25	-23 +/-26	-29 +/-22	-23 +/-21	3 +/-24	-24 +/-23
No. < LLN	19 (13)	23 (17)	16 (11)	9 (8)	0	18 (13)

(a-h) see table 43 for explanation of variables

Table 47. Depletion of CD8+ T Cells by Alefacept by Cohort and Course

	Cohort 1 LFA3TIP	LFA3TIP	Cohort 2 LFA3TIP	Placebo	Cohort 3 Placebo	LFA3TIP
Baseline: No. of Patients Evaluable (a)	154 (100)	154 (100)	142 (100)	139 (100)	153 (100)	151 (100)
Mean +/- s.d.	511 +/- 272	376 +/- 227	488 +/- 271	315 +/- 239	462 +/- 222	469 +/- 265
Emax (b): No. of Patients Evaluable (c)	154 (100)	154 (100)	142 (100)	139 (100)	153 (100)	153 (100)
Time to Emax (days) Median Min., Max.	64 (8,9 9)	64 (8,99)	65 (8,99)	36 (7, 94)	43 (6, 93)	67 (7,99)
Count at Tmax (cells/uL)Mean +/- s.d.	250 +/- 171	234 +/- 157	212 +/- 154	251 +/- 161	348 +/- 164	223 +/- 136
%Change from Baseline (d)Mean +/- s.d.	-51 +/-20	-54 +/-22	-56 +/-16	-47 +/-17	-22 +/-19	-51 +/-19
No. < LLN	77 (50)	83 (54)	96 (68)	69 (50)	33 (22)	87 (57)
No. of Patients Below: 200 (cells/uL)	68 (44)	75 (49)	88 (62)	64 (45)	29 (19)	83 (54)
150	46 (30)	58 (38)	55 (39)	37 (26)	11 (7)	52 (34)
100	24 (6)	33 (21)	22 (15)	10 (7)	5 (3)	26 (17)
50	5 (3)	5 (3)	5 (4)	1 (1)	0	3 (2)
EAUC (e): No. of Patients Evaluable (c)	154	154	142	139	153	153
Mean +/- s.d.	2983 +/-1624	3511 +/-1914	3277 +/-1438	2728 +/-1450	706 +/- 832	3005 +/-1683

(a-h) see table 43 for explanation of variables

Table 48. Recovery of CD8+ Count after Alefacept Treatment by Cohort and Course

	Cohort 1 LFA3TIP	LFA3TIP	Cohort 2 LFA3TIP	Placebo	Cohort 3 Placebo	LFA3TIP
LAST STUDY VISIT						
No. of Patients Evaluable (f)	154 (100)	154 (100)	142 (100)	142 (100)	153 (100)	153 (100)
Count (cells/uL)Mean +/- s.d.	377 +/- 222	348 +/- 237	325 +/- 249	338 +/- 196	459 +/- 223	320 +/- 191
% Change from Baseline (d) Mean +/- s.d.	-23 +/-34	-31 +/-29	-33 +/-22	-29 +/-23	2 +/-28	-31 +/-25
No. < LLN	41 (27)	53 (34)	48 (34)	46 (32)	13 (8)	56 (37)
12 WEEKS POST TREATMENT						
No. of Patients Evaluable (g)	151 (100)	137 (100)	140 (100)	118 (100)	152 (100)	138 (100)
Count (cells/uL) Mean +/- s.d.	371 +/- 229	341 +/- 220	316 +/- 251	337 +/- 181	457 +/- 222	323 +/- 189
% Change from Baseline Mean +/- s.d.	-24 +/-34	-31 +/-29	-35 +/-22	-29 +/-24	2 +/-28	-30 +/-25
No. < LLN	45 (30)	48 (35)	50 (36)	40 (34)	13 (9)	49 (36)

(a-h) see table 43 for explanation of variables

Comparison of first and second treatment in cohort 1 (**Tables 45-48**) suggests that by criteria of cell counts and proportion of patients with counts lower than normal, there may be some cumulative affects of alefacept exposure. This interpretation is supported by the fact that in cohort 1 there is an "enrichment" effect in patients less susceptible to alefacept at the time of the second treatment. Comparison of placebo arm in cohort 2 and placebo arm in cohort 3 indicates the presence of significant carry-over effects of alefacept treatment on lymphocyte counts.

T memory cells were affected more than "naive" T cells. B cell counts did not appear to be affected; this finding is unexpected because there is some expression of CD2 in these cells. NK cell numbers also declined and showed tendency to recover.

Laboratory Data: Hematology, Clinical Chemistry, Urinalysis

There are no clinically meaningful trends observed when comparing shifts from baseline values to low or high values for hematology (excluding lymphocyte counts and lymphocyte subsets, see **Tables 45-48**) and clinical chemistry during the first course of treatment in study 711.

During the second course of treatment, of patients who had been treated with alefacept in the first course and who had normal baseline ALT values, 7.8% (9/114) and 17% (21/122) of placebo and alefacept patients, respectively, shifted to ALT level of 1-3 times greater that the ULN (upper limit of normal) or more. On the last study visit ALT values remained abnormal in 4/9 placebo and 13/21 alefacept-treated patients whose baseline values were normal. There was no excess of patients with shifts above the ULN for AST, when comparing the alefacept group to the placebo group.

Reviewers' comment: Patients who were positive for hepatitis B or C were eligible for enrollment as long as the baseline transaminase values were less than 3 times the upper limit of normal. We have requested from the sponsor an analysis of the patients who experienced elevations in transaminases and whether infection with hepatitis B or C could be identified as a risk factor. The results of the analysis failed to show that alefacept treatment was associated with an increased risk of liver inflammation as measured by transaminases in hepatitis B or C positive patients.

Urinalysis:

There was a suggestion of higher detection of occult blood when comparing alefacept treated group in the first or second course to placebo (respectively 10%, 9% and 5%). However there was no difference between groups in the detection of RBC by microscopic analysis. There was a trend towards higher detection of protein in the placebo group. It was concluded that alefacept did not induce clinically meaningful changes in urinalysis.

Classification of Adverse Events

The following are examples where the classification of severity and/or attribution of adverse events are questionable.

- Patient 127206; cohort3: Placebo/LFA3TIP; Dose 12; Day 304; Event: Overdose Med and Alcohol/ Attempted Suicide; Preferred Term: Suicide Attempt; Severity: Mild; Relationship: Unlikely

- Patient 135203; Course 2; Cohort 1: LFA3TIP; Dose 5; Day 203; R Shoulder Incision Infection; Preferred Term: Infection; Severity: Moderate; Causality: Unlikely [See appendix for full narrative.]

- Patient 135203; dose 8; day 272; Persistent R Shoulder Incision Drainage; Preferred Term: Skin Disorder; Severity Mild; Causality: Not Related

- Patient 209202; dose 12; day320; Pneumonia; preferred term pneumonia; Severity: Moderate; Relationship: Not Related

COMPARISON OF EFFICACY OF DRUG PRODUCT MANUFACTURED BY ---------- AND BIOGEN

Alefacept administered in Course 1 was derived from the material manufactured by ---------- and labeled ------- BG9273. In Course 2, alefacept from both ---------- BG9273 and from BIO BG9273, manufactured by Biogen, was administered. Patients received alefacept from either source but not from both within a given course. ------ BG9273 from lot ---------- was used. BIO BG9273 from lots 99-001, 00-001, 00-003, and 00-007 was used.

Pharmacodynamic criteria

By the pharmacodynamic criteria of lymphocyte depletion and recovery the BIO and --------- products appeared to be comparable. The tables below show numerically similar values for CD4 and in particular CD8 counts in the two study groups.

Table 49. CD4+ T Cell Count: Alefacept Naive Patients Who Received -------- or BIO BG9273

	------ BG9273	BIO BG9273
Baseline: No. of Patients Evaluable (a)	407 (100)	110 (100)
Mean +/- s.d.	905 +/- 358	931 +/- 350
Emax (b): No. of Patients Evaluable (c)	407 (100)	112 (100)
Time to Emax (days) Median Min., Max.	65 (7, 99)	65 (8,99)
Count at Tmax (cells/uL)Mean +/- s.d.	460 +/- 199	519 +/- 216
%Change from Baseline (d)Mean +/- s.d.	-47 +/-17	-42 +/-16
No. < LLN	182 (45)	33 (29)
No. of Patients Below:400 (cells/uL)	188 (46)	33 (29)
300	96 (24)	17 (15)
200	12 (3)	2 (2)
100	0	0
EAUC (e): No. of Patients Evaluable (c)	407	112
Mean +/- s.d.	2633 +/-1432	2289 +/-1432
LAST STUDY VISIT		
No. of Patients Evaluable (f)	407 (100)	112 (100)
Count (cells/uL) Mean +/- s.d.	649 +/- 249	706 +/- 287
% Change from Baseline (d) Mean +/- s.d.	-25 +/-23	-22 +/-23
No. < LLN	41 (10)	13 (12)

(a) Any patient who had a baseline assessment and at least one post-baseline assessment in the Course.
(b) Maximum reduction in count during dosing period.
(c) Any patient with a post-baseline assessment during the dosing period for the Course.

(d) Baseline refers to the baseline from Course 1.
(e) Area under the effect curve during the dosing period based on percentage change from baseline.
(f) Any patient with a post-baseline assessment in the Course.
(g) Any patient with a 12-week post-dosing assessment between 10 and 14 weeks after the final dose in the Course.
(h) Any patient with at least 2 samples during the follow-up period in the Course.

Table 50. CD8+ T Cell Count: Alefacept Naive Patients Who Received ------- or BIO BG9273

	------- BG9273	BIO BG9273
Baseline: No. of Patients Evaluable (a)	407 (100)	110 (100)
Mean +/- s.d.	494 +/- 271	463 +/- 248
Emax (b): No. of Patients Evaluable (c)	407 (100)	112 (100)
Time to Emax (days) Median Min., Max.	64 (7,99)	66 (8,99)
Count at Tmax (cells/uL)Mean +/- s.d.	230 +/- 163	222 +/- 127
% Change from Baseline (d) Mean +/- s.d.	-53 +/-19	-51 +/-19
No. < LLN	235 (58)	63 (56)
No. of Patients Below:200 (cells/uL)	215 (53)	59 (53)
150 (cells/uL)	149 (37)	34 (30)
100 (cells/uL)	72 (18)	17 (15)
50 (cells/uL)	16(4)	3(3)
EAUC (e): No. of Patients Evaluable (d)	407	112
Mean +/- s.d.	3096 +/-1597	2898 +/-1684
LAST STUDY VISIT		
No. of Patients Evaluable (f)	407 (100)	112 (100)
Count (cells/uL)Mean +/- s.d.	342 +/- 232	324 +/- 182
% Change from Baseline(d)Mean +/- s.d.	-30 +/-28	-29 +/-25
No. < LLN	135 (33)	38 (34)

(a-f) See previous table 49 for explanation of variables

Clinical Criteria

PASI scores showed qualitatively similar changes in the two groups receiving ------- and BIO manufactured product.

Conclusions

Efficacy

Study 711 confirms the activity of alefacept in plaque psoriasis shown in study 708. The treatment effect in study 711 appears to be lower than the treatment effect in study 708.

- There was a modest increase (11% absolute) in the proportion of responders (>75% improvement in PASI) in patients treated with alefacept compared to placebo. There are no baseline variables identified that affect treatment outcome.
- Various secondary outcomes (e.g. PGA) reflecting similar assessments of disease supported the primary efficacy outcome.
- The patient population studied (eligibility criteria included PGA, %BSA involvement, treatment history, and response to prior treatment) is representative of patients with moderate to severe psoriasis.
- Response to a second course of treatment appeared to be somewhat lower compared to response to the first treatment course. The assessment of response may have been confounded by carry-over effects of the first treatment period in alefacept and placebo groups.
- There is no convincing evidence of cumulative treatment effect of alefacept across two treatment courses.

- There was substantial use of non-allowed antipsoriatic medications. This raised concerns about confounding of efficacy outcome; however, the use of concomitant treatment appeared to be similar across study arms.
- It is not clear if differences in duration of response or in quality of life between treatment groups are clinically meaningful.
- By pharmacodynamic and clinical criteria alefacept manufactured by Creative Biomolecules appears to be comparable to alefacept manufactured by Biogen.

Safety

Alefacept depletes total lymphocyte counts. CD4+ and CD8+ lymphocyte subsets as well as CD16/CD56 (NK cells) are the cell populations primarily affected. B cells also express CD2 on the cell surface; however, B cell depletion was not seen. at the dose levels studied.

- Only lymphocytes in the blood pool were assessed; the effects of alefacept on lymphoid tissues were not examined. There is little or no information about lymphocytes in other tissues.
- The IV route of administration may underestimate the toxicity of alefacept if other routes of administration such as IM result in greater exposure of lymphoid tissue to alefacept
- CD2 expression by various lymphocyte subsets differs and there is a correlation between level of expression and depletion. However, the clinical implications for alefacept's efficacy and its long-term toxicity are not known.
- The study may underestimate the effect on lymphocytes and infections because the protocol required that CD counts be >250 cells/microL in order to dose. If marketed, this has implications for how patients should be monitored and how alefacept should be dosed.
- Study 711 confirms that lymphocyte counts decrease and do not recover to baseline in a substantial proportion of patients after a prolonged observation period.
- Comparison of lymphocyte counts and of proportion of patients with lower than normal counts after the first and second treatment suggests that the lymphocyte depletion is cumulative.
- In this study no clinically significant changes in hematology (except for lymphocytes), clinical chemistry and urinalyses were observed.
- There was a somewhat higher number of serious adverse events including infections and malignancy in the alefacept treated groups. However given the small number of events the significance of this observation is not clear.
- There was a suggestion of alefacept-induced hypersensitivity reaction (one case of urticaria) and of possible deleterious effect on healing (serious complications of burn wound and surgical wound infection).
- There was no evidence that depressions in lymphocyte counts were associated with serious adverse events, particularly infections.
- Long-term studies in larger patient populations are needed to assess the risk of infection and malignancy and the recovery of lymphocyte counts to baseline/normal.

- The incidence of reported adverse events in certain patients seemed low given the duration of observation (1 year) and concomitant diseases and the variability in number of reports per patient was high. The possibility that this may have been due to ascertainment procedures was considered.

PROTOCOL C99-712

Study Title

"A randomized, double-blind placebo-controlled, dose-comparison study to evaluate the efficacy and safety of intramuscular administration of LFA3TIP in subjects with chronic plaque psoriasis "

Study Objectives

Demonstrate in subjects with chronic plaque psoriasis the efficacy and safety of LFA3TIP administered as a weekly intramuscular injection of either 10 or 15 mg for 12 weeks. Efficacy will be evaluated by measuring the proportion of subjects who by visit 13 experience a ≥75% reduction in PASI score from baseline.

Demonstrate the safety and efficacy of a second course of treatment with LFA3TIP (See protocol C99-717)

Study Rationale

The proposed label for LFA3TIP includes the administration of drug by the IM and IV route. In selecting the dose(s) administered IM in the present study, the sponsor assumed an IV: IM equivalence ratio of about 1.5. The sponsor evaluated two doses of drug because there are insufficient safety, PK and activity data using the product by the IM route.

Study Design

Phase 3, multicenter (approximately 50 sites), randomized, double blind, stratified, parallel-group, placebo-controlled (saline), study of LFA3TIP administered IM (10 or 15 mg weekly for 12 weeks) in 500 subjects with chronic plaque psoriasis. Subjects would be followed for 12 weeks after the end of treatment. Subjects who prematurely withdraw from the study were not be replaced.

Randomization:

Subjects were randomized (centrally) in a 1:1:1 ratio to 0 (placebo), 10 or 15 mg LFA3TIP.

Stratified randomization was used with 4 strata namely 1) patients with PASI > 20 and no history of systemic therapy or phototherapy, 2) PASI > 20 and previously received systemic therapy or phototherapy, 3) PASI ≤ 20 and never received systemic therapy or phototherapy, 4) PASI ≤ 20 and previously received systemic therapy or phototherapy. A central randomization service was used in this study.

Blinding:

Laboratory data from the central laboratory was sent directly to an independent (blinded) investigator at each site (the "laboratory assessing physician"). The

laboratory-assessing physician was able to change or withhold dosing with study drug (substitution with placebo). He could not communicate any information to the other investigators, study coordinators, or the sponsor. The only person at each site who was unblinded was the pharmacist or designee who prepared study drug.

Retreatment protocol:

All subjects who completed this study were eligible to receive a second course of IM study treatment (see protocol 99-717). Patients who received placebo during the first treatment would receive 10 mg per dose. Patients who received active drug 10 or 15 mg/dose would receive the same dose in the second treatment.

Screening Log

All screened candidates would be entered into a log and reason(s) for exclusion of subjects would be documented.

Dose Modification Rules

Administration of each dose of study drug was to be separated by 7 (±2 days). Treatment was to be withheld for any evidence of significant viral, bacterial, or fungal infection.

Withholding dose:

Dosing was to be withheld for 2 weeks for body temperature >38^{o}C or clinically significant infection.

Switching from study drug to placebo:

The study drug was to be substituted with placebo if the absolute $CD4^{+}$ lymphocyte count from the previous week was below 250 cells/mm^{3}.

Discontinuation of study drug:

The study drug was to be permanently substituted with placebo if any subject experienced a reduction in number of absolute $CD4^{+}$ lymphocytes below 250 cells/mm^{3} for 4 or more consecutive visits. Subjects who prematurely discontinued study drug were to remain in the study and continue the protocol-specified follow-up evaluations. All subjects were to be followed until their absolute $CD4^{+}$ lymphocyte counts returned to within normal limits.

Other reasons for discontinuation of study drug:

Absolute: pregnancy, subject's choice, and medical emergency
Discretionary: investigator's choice (e.g. medical reasons, non-compliance)

Concomitant treatments

Moderate potency topical corticosteroids, keratolytics, coal tar or vitamin D were allowed on groin, scalp, palms and soles only. Low potency topical corticosteroids were allowed everywhere but on target lesions. Subjects could not apply topical treatments to skin within 12 hrs of a scheduled study visit. If a subject discontinued study drug, systemic medications for psoriasis could be initiated only after a 4-week washout.

Inclusion Criteria

Subjects 18 years of age or older with chronic plaque-type psoriasis for more than 12 months with a body surface involvement of ≥10% and $CD4^+$ lymphocyte counts above the lower limit of normal were eligible.

Exclusion Criteria

The following were grounds for exclusion.

- Any clinically significant abnormal hematology, chemistry, or urinalysis data. Erythrodermic, guttate, or generalized pustular psoriasis within 28 days.
- Serious local infection (e.g., cellulitis, abscess) or systemic infection (e.g., pneumonia, septicemia) within 3 months.
- Positive hepatitis C antibody or positive hepatitis B surface antigen with an ALT or AST greater than three times upper limit of normal. Positive HIV antibody.
- History of malignancy. Subjects with a history of basal cell carcinomas or fewer than 3 squamous cell carcinomas were eligible.
- Other skin disease that might interfere with psoriasis status assessments.
- Previous participation in any LFA3TIP study. Treatment with another investigational drug within 4 weeks.
- Treatment with phototherapy, systemic retinoids, systemic steroids, methotrexate, cyclosporine, azathioprine, or thioguanine within 4 weeks.
- Treatment with high potency topical corticosteroids (Class I and II) within 4 weeks or with moderate potency topical corticosteroids (Class III and IV) (other than on the scalp, palms, groin, and/or soles) within 2 weeks.
- Treatment with vitamin D analogues, topical retinoids, keratolytics or coal tar (other than on the scalp, palms, groin, and/or soles) within the 2 weeks.
- Women who were postmenopausal for at least 1 year, surgically sterile, or willing to practice effective contraception during the study.
- Nursing mothers, pregnant women and women planning to become pregnant while on study.

Primary Efficacy Endpoint

The proportion of patients with ≥75% improvement in PASI score at the end of the treatment period (visit 13 on day 92) was the primary efficacy endpoint. A standard Psoriasis Area and Severity Index was used.

Principal Secondary Efficacy Endpoint

The proportion of patients with a score of clear to almost clear by Physician Global Assessment was the principal secondary endpoint. The following 7-point scale was used: Severe, Moderate to Severe, Moderate, Mild to Moderate, Mild, Almost Clear, and Clear.

Other Secondary Efficacy Endpoints

Quality of Life (Dermatology Life Quality Index). Target Skin Lesion Assessment. 50% Improvement in PASI. Percentage Change in PASI. Quality of Life (SF-36, DQOLS scale, and Treatment Convenience scores). Summation of Response during Treatment, and Follow-up. Duration of Response Onset of Clinical Response.

Clinical and Laboratory Assessments

Assessment of Efficacy and PK

The following were measured: PASI, Physician Global Assessment, target lesion assessment, body surface photography, and quality of life assessment. LFA3TIP serum concentrations were measured.

Assessment of Safety

The following were performed: physical examinations including assessment of injection site; monitoring for adverse events; monitoring for infections; blood chemistry, hematology, lymphocyte subset analyses; urinalysis; antibodies to LFA3TIP. Peripheral lymphocyte subset quantification using flow cytometric analysis ($CD3^+$, $CD4^+$, $CD8^+$, and $CD19^+$). Antibodies to LFA3TIP.

Monitoring Responsibilities

Screening:

The examining physician (a dermatologist) collected and evaluated all clinical data.

Treatment and Follow Period:

The examining physician performed the following: physical examination including measurement of vital signs; photography; Physician Global Assessment of efficacy; PASI; Assessment of target skin lesion; Assessment of any new or ongoing viral, bacterial, or fungal infections. The Laboratory Assessing Physician evaluated all lab data and in particular hematology and analysis of peripheral lymphocyte subsets.

Safety Analyses

Any subject who received one dose of study drug and had post baseline data was considered evaluable for tolerability/safety analyses.

Statistical Analysis Plan

Sample size considerations:

The sponsor assumed that at endpoint the proportion of responders ($\geq$75% improvement in PASI after the first treatment) would be 25% in the active groups and 10% in the placebo group. A sample size of 402 subjects would have 80% power and a overall type I error rate of 5% (2.5 % for comparison between 10 mg

vs. placebo; and 2.5 % for the comparison 15 mg vs. placebo) to show efficacy. The sponsor increased the sample size to 504 to allow for a 25% dropout rate.

Baseline Data:
Data were summarized for each treatment group. Study centers were pooled by geographic regions. Subjects were stratified by screening PASI and prior systemic therapy into four strata.

Efficacy Analyses:

No interim analyses were planned All tests were two-sided and were considered significant at the 0.05 % level. The comparison was between the 10 mg per dose and placebo and 15 mg per dose and placebo. Confirmatory analyses were based on an intent-to-treat population comprising those who were randomized, received at least one dose of study drug, and had at least one post-treatment efficacy assessment. Exploratory analyses on subjects compliant with the dosing regimen were conducted.

The method of last observation carried forward was used for missing response endpoints except for analyses of duration of response, summation of response, and time to response.

Subjects who discontinued study medication and/or used non-allowed therapies were evaluated using the last endpoint measured. The duration of response endpoint was to be truncated 12 weeks after the last retreatment injection of study drug. Subjects in response at the end of the study had 14 days added for the duration of response.

Binary outcomes were modeled by logistic regression, continuous responses by analysis of variance or covariance, and time to event responses by a Cox proportional hazards model. The model included terms for geographic region, strata, and treatment. The interactions of treatment group and geographic region, plus treatment group and strata, were tested and included in the model if significant at the 5% level. Additional covariates including baseline PASI, gender, race, age, body surface area, and baseline weight were tested.

Primary Efficacy Analysis:
The proportion of subjects with a reduction in PASI $\geq$ 75% from baseline without the use of other systemic therapies was evaluated at Visit 13A (Day 92) using logistic regression with the general model described above.

Additional Secondary ("Tertiary") Efficacy Analyses:
Target Skin Lesion:
The proportion of subjects with induration of 0 in the target lesion at Visits 13A was be compared between active (cohorts 1 and 2) versus placebo (cohort 3) treatment arms using logistic regression and the general analysis model.

50% Improvement in PASI:
The proportion of subjects with a reduction in PASI of at least 50% from baseline at 2 weeks after the last retreatment dose (Visit 13B) was evaluated with logistic regression using the general analysis model.

Percentage Change in PASI:
PASI scores and percentage change from baseline in PASI scores were analyzed at each psoriasis assessment visit with ANOVA or ANCOVA. Repeated measures ANOVA were used to evaluate PASI scores over time using the general analysis model.

Quality of Life:
SF-36, DQOLS scale, and Treatment Convenience scores were analyzed by ANCOVA using the general analysis model and including baseline QoL score. The interaction between treatment and baseline QoL score were tested and included in the model if significant at the 5% level.

Summation of Response:
Summation of response for each of the response definitions (PASI 75% below baseline, PGA of 'almost clear' or 'clear', and PASI 50% below baseline) was evaluated with ANOVA using the general analysis model. Only subjects who responded to treatment were included in the analysis. The summation of response was calculated as days between the first visit at which response was achieved and the next visit they were assessed as either a non-responder, the subject withdrew, or the subject reached the end of the study, whichever came first. The summation of response endpoint was truncated at the end of the study. Subjects who were in response at study end had 14 days added for the summation of response

Duration of Response:
Duration of response for each of three definitions was evaluated with summary statistics. Only subjects who responded to treatment were included in the analysis. The duration of response would be calculated after the last dose as days between the first visit at which response was achieved and the next visit they were assessed as either a non-responder, the subject withdrew, or the subject reached the end of the study, whichever came first. The duration of response endpoint was truncated at the end of the study. Subjects who were in response at study end would have 14 days added for the duration of response.

Onset of Clinical Response:
Time of onset (time from baseline to first occurrence of response) based on the endpoint of PASI 75% below baseline and PGA of 'clear' or 'almost clear' would be analyzed using Cox Proportional Hazards using the general analysis model. Time-to-event curves would be plotted using the Kaplan-Meier method. Subjects who withdrew or did not respond by their last visit or the end of the study would be censored.

Protocol Amendments

Study 712 has many similarities with the protocol for the companion efficacy study 711. The firm and the agency agreed on a number of relatively minor modifications to the protocol at a teleconference on November 24, 1999. The firm sent to the IND the final version of study 712 (version 2, dated January 22, 2000).

Study Results

Disposition, Demographics and Baseline Disease Characteristics

Enrollment occurred between March 23, 2000 and October 12, 2000. The last patient follow-up visit took place on January 5, 2001. Thirty investigators in Europe and 34 in the United States and Canada enrolled a total of 526 patients into this study. Study site 156, which enrolled 16 subjects, was disqualified because of poor compliance with good clinical practices. An additional three patients at other centers were inappropriately randomized and were not dosed. Therefore, 507 subjects remained and were included in the analysis**.**

Table 51. Patient Disposition

	Placebo	**10 mg**	**15 mg**
RANDOMIZED	169	173	168
DOSED	168 (100)	173 (100)	166 (100)
DID NOT COMPLETE TREATMENT	26 (15)	21 (12)	15 (9)
Lost to Follow-up	0	0	2 (1)
Adverse Event	4 (2)	4 (2)	2 (1)
Laboratory Abnormality	0	1 (<1)	0
Worsening of Disease	6 (4)	5 (3)	2 (1)
Voluntary Withdrawal	11(7)	8 (5)	6 (4)
Other	5 (3)	3 (2)	3 (2)
WITHDRAWN FROM TREATMENT	7 (4)	2 (1)	9 (5)
Lost to Follow-up	0	0	3 (2)
Adverse Event	2 (1)	0	0
Worsening of Disease	0	0	1 (<1)
Voluntary Withdrawal	3 (2)	1 (<1)	3 (2)
Other	2 (1)	1 (<1)	2 (1)
COMPLETED FOLLOW-UP	152 (90)	167 (97)	152 (92)

Throughout the study, the percentage of subjects withdrawn was slightly higher in the placebo group compared to the active treatment groups (**Table 51**). Overall, 36 patients, or 7% of the total enrolled withdrew from the study with half withdrawing during the treatment period and the other half during the follow-up period. The most common reason was voluntary withdrawal. The most common reasons for discontinuing treatment were patient decision and worsening of psoriasis.

Demographics: Populations Enrolled and Analyzed

Demographic characteristics were balanced among the treatment groups (**Table 52**).

Table 52. Demographics

		Placebo	**10 mg**	**15 mg**
DOSED(N)		168	173	166
AGE(yrs):	mean(min-max)	46 (20-80)	44 (18-72)	45 (19-78)

BODY WEIGHT (kg): median(min-max)		86 (45-144)	84 (40-170)	83 (43-142)
GENDER:	men	110 (65%)	120 (69%)	103 (62%)
	women	58 (35%)	53 (31%)	63 (38%)
ETHNIC GROUP:	Caucasian	147 (88%)	160 (92%)	150 (90%)
	Black	6 (4%)	2 (1%)	3 (2%)
	Asian	2 (1%)	3 (2%)	3 (2%)
	Hispanic	7 (4%)	6 (3%)	6 (4%)
	Other	6 (4%)	2 (1%)	4 (2%)

The disease severity (PASI >20 or ≤ 20) and the history of previous systemic therapy or phototherapy (yes/no) were stratification variables and these factors were well balanced across groups. Overall the proportion of patients enrolling in each stratum was as follows (**Table 53**).

Table 53. Enrollment by Stratum in the Three Study Groups

PASI >20 No prior therapy	**PASI > 20 Prior therapy**	**PASI ≤ 20 No prior therapy**	**PASI ≤ 20 Prior therapy**	**TOTAL**
24 (5%)	108 (21%)	115 (23%)	260 (51%)	507

More detailed characteristics of psoriasis at baseline are shown in **Table 54**. The median duration of disease was 19 years (range 2-70 years). The median PASI score was 14. The baseline BSA, PGA and PASI scores were roughly balanced across the groups.

Table 54. Baseline Disease Characteristics

	Placebo(N=168)	10mg(N=173)	15mg(N=166)
% Surface Area Involved[a]	24 (7-90)	22 (9-95)	20 (6-85)
Physician Global Assessment			
Mild	2 (1)	4 (2)	3 (2)
Mild to Moderate	22 (13)	18 (10)	25 (15)
Moderate	62 (37)	70 (40)	65 (39)
Moderate to Severe	66 (39)	64 (37)	53 (32)
Severe	16 (10)	17 (10)	20 (12)
PASI			
< 5.0	0	2 (1)	5 (3)
5.0-9.9	32 (19)	31 (18)	32 (19)
10.0-19.9	94 (56)	85 (49)	84 (51)
20.0-29.9	26 (15)	35 (20)	27 (16)
30.0-39.9	13 (8)	16 (9)	12 (7)
40.0-49.9	3 (2)	2 (1)	4 (2)
50.0-59.9	0	2 (1)	2 (1)

[a]medians (min-max)

A total of 332 patients (65%) received twelve injections. One patient in the 10 mg group received 13 injections due to site error.

Study Conduct

Study site 156, which enrolled 16 subjects, was disqualified because of poor compliance with good clinical practices. According to the sponsor, the most commonly reported protocol deviations relate to

• study drug administration, such as selection and rotation of injection sites
• visits missed or out of the scheduled window
• rectal and genital exams not performed as part of physical examinations,
• commencement of disallowed therapies,
•discovery of the use of prior systemic medications after randomization

Protocol deviations to the eligibility criteria were 1 percent or less in all categories (not shown). **Table 55** shows that a substantial proportion of patients (1/3) in each of the study arms the study received non-allowed major anti-psoriatic treatment.

Reviewers' comment
The use of concomitant major therapies was interpreted as an unfavorable indication of quality of the study conduct and of the perceived activity of study treatment. Caution is called for in the interpretation of at least some of the efficacy outcomes given the potential confounding effects of these concomitant treatments.

Table 55. Concomitant Anti-psoriatic Treatments

	IM Injection			
	Placebo	10 mg	15 mg	Total
Number of Patients Dosed	168 (100)	173 (100)	166 (100)	507 (100)
Number Taking Concomitant Meds	50 (30)	50 (29)	39 (23)	139 (27)
Topical Steroids: Mild	2 (1)	1 (<1)	2 (1)	5 (<1)
CORTATE	0	0	2 (1)	2 (<1)
CORTISONE	1 (<1)	1 (<1)	0	2 (<1)
CORTICOSTEROID NOS	1 (<1)	0	0	1 (<1)
Topical Steroids: Moderate	2 (1)	2 (1)	3 (2)	7 (1)
DERMA-SMOOTHE-FS	2 (1)	2 (1)	3 (2)	7 (1)
Topical Steroids: Potent	14 (8)	7 (4)	4 (2)	25 (5)
CLOBETASOL	3 (2)	2 (1)	1 (<1)	6 (1)
DERMOVATE	1 (<1)	2 (1)	0	3 (<1)
PSORCON	2 (1)	0	1 (<1)	3 (<1)
TEMOVATE	1 (<1)	2 (1)	0	3 (<1)
TOPICORT	1 (<1)	2 (1)	0	3 (<1)
CLOBETASOL PROPIONATE	1 (<1)	0	1 (<1)	2 (<1)
CYCLOCORT	1 (<1)	1 (<1)	0	2 (<1)
LIDEX	1 (<1)	0	1 (<1)	2 (<1)
DERMOVAL	1 (<1)	0	0	1 (<1)
DIFLORASONE	1 (<1)	0	0	1 (<1)
DIPROGENTA	1 (<1)	0	0	1 (<1)
HALOG	1 (<1)	0	0	1 (<1)
Topical Steroids: SuperPotent	21 (13)	21 (12)	22 (13)	64 (13)
DIPROSALIC	3 (2)	4 (2)	7 (4)	14 (3)
DIPROLENE CREAM	2 (1)	4 (2)	4 (2)	10 (2)
DIPROSONE	2 (1)	4 (2)	4 (2)	10 (2)
BETNOVATE	5 (3)	1 (<1)	2 (1)	8 (2)
BETAMETHASONE	1 (<1)	1 (<1)	4 (2)	6 (1)
BETNOVAT	2 (1)	3 (2)	1 (<1)	6 (1)

BETNELAN	1 (<1)	3 (2)	1 (<1)	5 (<1)
CELESTODERM	2 (1)	1 (<1)	1 (<1)	4 (<1)
BETAMETHASONE VALERATE	1 (<1)	2 (1)	0	3 (<1)
BETNEVAL	0	0	3 (2)	3 (<1)
CELESTAN	2 (1)	0	0	2 (<1)
VALISONE	0	1 (<1)	1 (<1)	2 (<1)
BETAMETHASONE BENZOATE	0	0	1 (<1)	1 (<1)
BETAMETHASONE DIPROPIONATE	0	1 (<1)	0	1 (<1)
CELESTENE	0	0	1 (<1)	1 (<1)
CELESTONE	1 (<1)	0	0	1 (<1)
DIPRODERM	0	1 (<1)	0	1 (<1)
DIPROLEN	0	1 (<1)	0	1 (<1)
DIPROSEPT	0	1 (<1)	0	1 (<1)
ECTOSONE	0	0	1 (<1)	1 (<1)
ULTRAVATE	0	1 (<1)	0	1 (<1)
Systemic Treatment & Phototherapy	25 (15)	21 (12)	15 (9)	61 (12)
UVB	7 (4)	4 (2)	8 (5)	19 (4)
METHOTREXATE	4 (2)	3 (2)	0	7 (1)
PREDNISONE	1 (<1)	5 (3)	1 (<1)	7 (1)
HYDREA	4 (2)	1 (<1)	1 (<1)	6 (1)
CICLOSPORIN	4 (2)	0	0	4 (<1)
ACITRETIN	1 (<1)	0	1 (<1)	2 (<1)
FUMADERM "VIFOR"	1 (<1)	1 (<1)	0	2 (<1)
PUVA	0	2 (1)	0	2 (<1)
ZORAC	0	1 (<1)	1 (<1)	2 (<1)
ARAVA	0	0	1 (<1)	1 (<1)
ARISTOSPAN	1 (<1)	0	0	1 (<1)
CORTANCYL	0	0	1 (<1)	1 (<1)
DEPO-MEDROL	0	1 (<1)	0	1 (<1)
DIFFERIN	0	0	1 (<1)	1 (<1)
ENBREL	0	0	1 (<1)	1 (<1)
HYDROXYUREA	1 (<1)	0	0	1 (<1)
IMMUNOGLOBULINS	1 (<1)	0	0	1 (<1)
INFLIXIMAB	1 (<1)	0	0	1 (<1)
MEDROL	0	1 (<1)	0	1 (<1)
METHOTREXAT	0	1 (<1)	0	1 (<1)
MTX	0	1 (<1)	0	1 (<1)
NEORAL	0	0	1 (<1)	1 (<1)
NEOTIGASON	0	1 (<1)	0	1 (<1)
PREDNISOLONE ACETATE	1 (<1)	0	0	1 (<1)
PREDNISOLONE SODIUM SUCCINATE	0	1 (<1)	0	1 (<1)
SORIATANE	0	1 (<1)	0	1 (<1)
ULTRACORTENOL	0	1 (<1)	0	1 (<1)

Primary Efficacy Outcome

Table 56 shows the primary efficacy outcome based on the comparison of the proportions of responders between the two alefacept dose groups and placebo. The percentages of patients achieving the primary endpoint (≥75% reduction from baseline PASI at Visit 13) were 5, 12, and 21% respectively for placebo, 10 and 15 mg groups.

The 15 mg dose group was statistically different from placebo with adjustment for geographic region and stratum (absolute difference 16%, $p<0.001$). The 10 mg dose

group was not different from placebo (p>0.025). The following secondary outcome measures supported the primary outcome: PGA of “almost clear” to “clear”, target induration of zero and 50% reduction in PASI from baseline.

Table 56. Efficacy Outcomes: Proportions Responding

	Placebo (n=168)	10 mg (n=173)	15 mg (n=166)
Primary: ≥75% Reduction from Baseline PASI	9 (5)	21 (12)	35 (21)
Secondary: PGA 'almost clear' or 'clear'	8 (5)	18 (10)	23(14)
≥50% Reduction from Baseline PASI	30 (18)	62 (36)	68 (41)
Target lesion induration of zero	12 (7)	24 (14)	28 (17)

Treatment Response in Patient Subgroups

Treatment responses were examined in various patient subgroups based on geographic region, study center, and demographic factors (**Table 57**).

Table 57. Percentage Responding to Treatment[1] by Geographic Region

	Placebo	10 mg	15 mg
Geographic Region A	3/ 21 (14)	5/ 23 (22)	7/ 25 (28)
Geographic Region B	1/ 22 (4)	2/ 29 (7)	9/ 28 (32)
Geographic Region C	0/ 28	6/ 25 (24)	1/ 19 (5)
Geographic Region D	2/ 29 (7)	2/ 29 (7)	4/ 35 (11)
Geographic Region E	1/ 32 (3)	5/ 39 (13)	10/ 29 (34)
Geographic Region F	2/ 36 (6)	1/ 28 (4)	4/ 30 (13)

[1] ≥75% reduction in baseline PASI

The proportion of responders was numerically higher in the 15 mg group compared to placebo across all geographic regions examined. Of note, similar to study 711, study 712 showed a lower proportion of responders at visit 13 in the Southernmost United States (Region D in study 712, Region E in study 711). This finding was not due to difference in the baseline characteristics in the Southern United States populations vs. the remainder of the geographic regions. Also, with the exception of Martinez, GA and Dallas, TX, the centers did not overlap between study 711 and 712.

No differences in response by age or gender were observed (**Table 58**). Caucasians had numerically higher proportions of response than non-Caucasians. However, the number of non-Caucasians in the study was small.

Table 58. Percentage Responding to Treatment[1] By Age, Gender, and Race

	Placebo	10 mg	15 mg

AGE			
<30	2/ 15 (13)	5/ 26 (19)	6/21 (29)
30-39	3/ 42 (7)	6/ 35 (17)	11/ 42 (26)
40-49	1/ 42 (2)	5/ 49 (10)	6/ 38 (16)
50-59	1/ 40 (2)	2/ 46 (4)	3/ 35 (9)
>59	2/ 29 (7)	3/ 17 (18)	8/ 30 (27)
GENDER			
Women	3/ 58 (5)	7/ 53 (13)	14/ 63 (22)
Men	6/110 (6)	14/120 (12)	20/103 (20)
RACE			
Non-Caucasians	0/ 21	1/13 (8)	0/16
Caucasians	9/147 (6)	20/160 (12)	34/150 (23)

[1] >75% reduction in baseline PASI

Table 59. Percentage Responding to Treatment[1] by Body Weight

	Placebo	10 mg	15 mg
WEIGHT (kg)			
<50 kg	0/ 3	1/ 1 (100)	1/ 1 (100)
50-69 kg	1/ 23 (4.3)	7/ 31 (22.6)	7/ 36 (19.4)
70-84 kg	2/ 56 (3.6)	7/ 56 (12.5)	13/ 54 (24.1)
85-99 kg	5/ 43 (11.6)	4/ 42 (9.5)	8/ 45 (17.8)
100-114 kg	0/ 32	2/ 23 (8.7)	3/ 22 (13.6)
115+ kg	1/ 11 (9.1)	0/ 20	2/ 8 (25.0)

[1] ≥75% reduction in baseline PASI

The number of subjects who weighed below 50 kg and more than 115 kg was relatively small. However, excluding these extremes, the percentage responding in the subgroups weighing less than 85 kg was numerically higher than those weighing at least 85 kg (**Table 59**).

Patients whose body weight at screening was 50 kg or more were to receive placebo, 10 mg, or 15 mg of alefacept. Patients whose body weight at screening was less than 50 kg were to receive placebo or an adjustment to the dose to which they had been randomized: patients randomized to a 10 mg dose were to receive 6.7 mg alefacept and patients randomized to a 15 mg dose were to receive 10 mg alefacept .

Review of efficacy outcome by study site (63 sites) that were included in the analysis, showed that any one site did not unduly influence the overall efficacy results.
In the 15 mg and placebo groups the response to treatment was numerically similar across the US, North America and Europe. In the 10 mg dose group response to treatment was numerically higher in Europe compared to US and North America (**Table 60**).

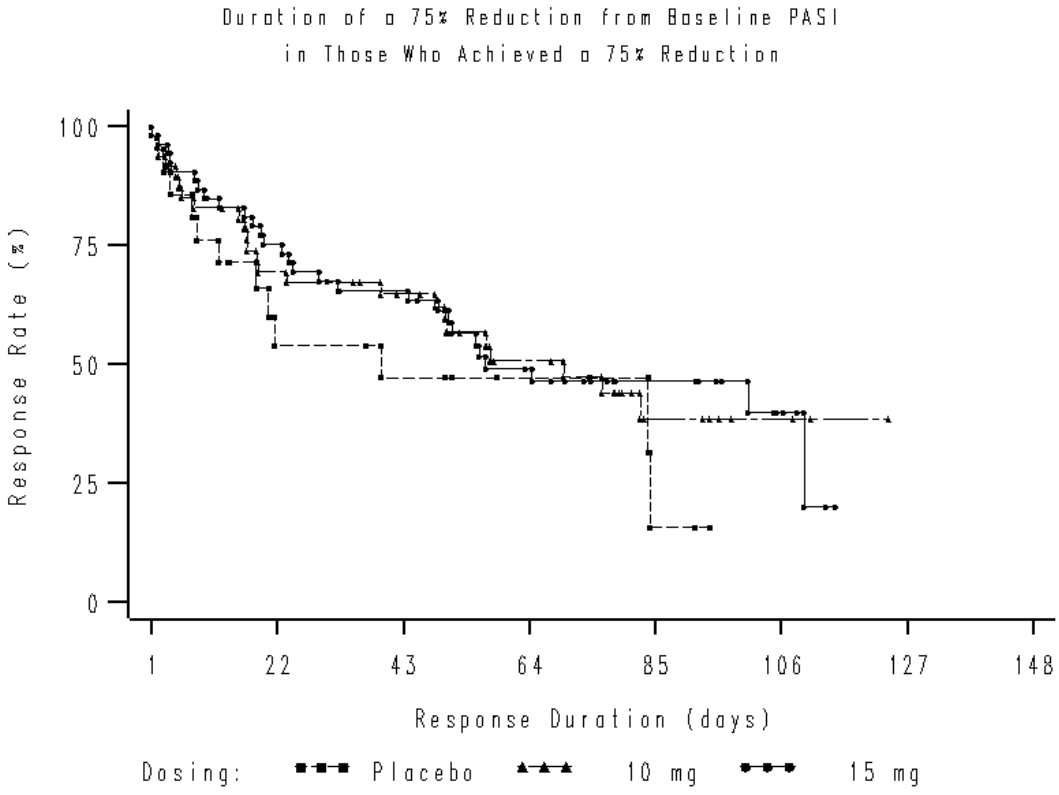
Table 60. Treatment Response by Geographic Region

	Group					
	10 mg		15 mg		Placebo	
	% Change in PASI		% Change in PASI		% Change in PASI	
	<75% Reduction	75%+ Reduction	<75% Reduction	75%+ Reduction	<75% Reduction	75%+ Reduction
	N	%	N	%	N	%	N	%	N	%	N	%
Region												
Europe	64	83.1	13	16.9	55	76.4	17	23.6	67	94.4	4	5.6
N America	88	91.7	8	8.3	76	80.9	18	19.1	92	94.8	5	5.2
US	72	91.1	7	8.9	61	80.3	15	19.7	66	93.0	5	7.0

Secondary Efficacy Outcome

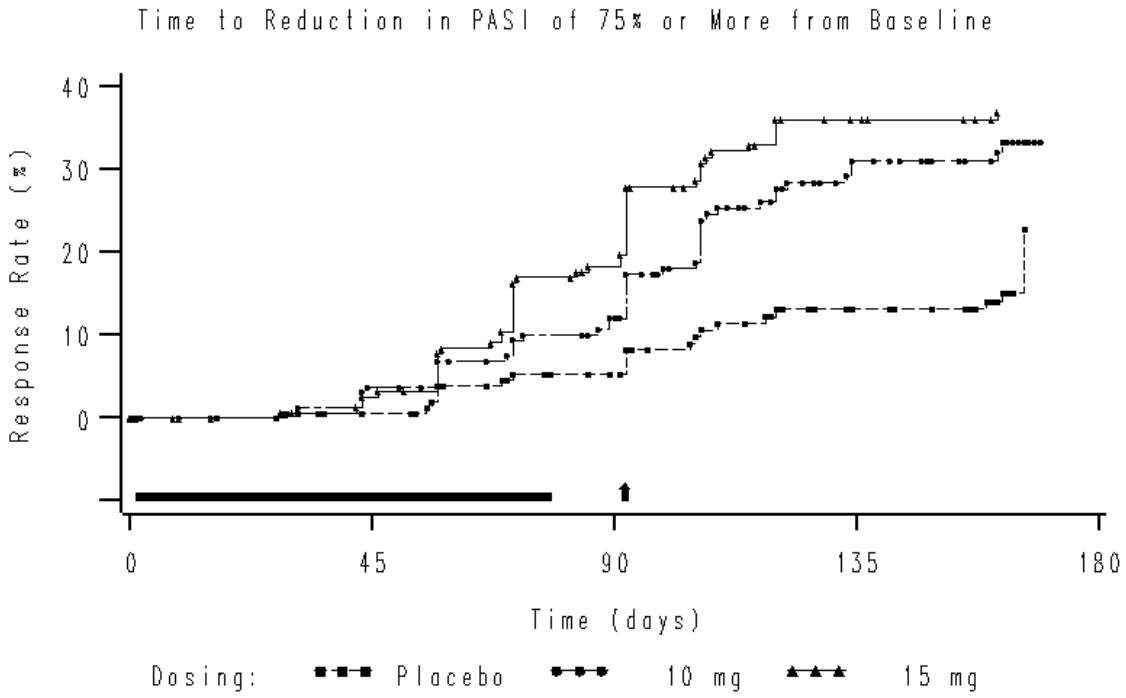
Duration of Response

Median duration of response in those patients achieving a 75% reduction in PASI was not statistically different between the placebo and alefacept groups. Mean durations were21, 49, and 50 days for placebo, 10 and 15 mg groups respectively (See **Figure below**).



Time to response

Mean time to response was 94, 92, and 82 days in the 0, 10, and 15 mg dose groups. Visual inspection indicates that the plots begin to separate only by the very end of the treatment period. The sponsor reports that both alefacept arms are significantly different from placebo.



Solid bar indicates dosing interval.
Arrow indicates time of primary endpoint.

Quality of life measures

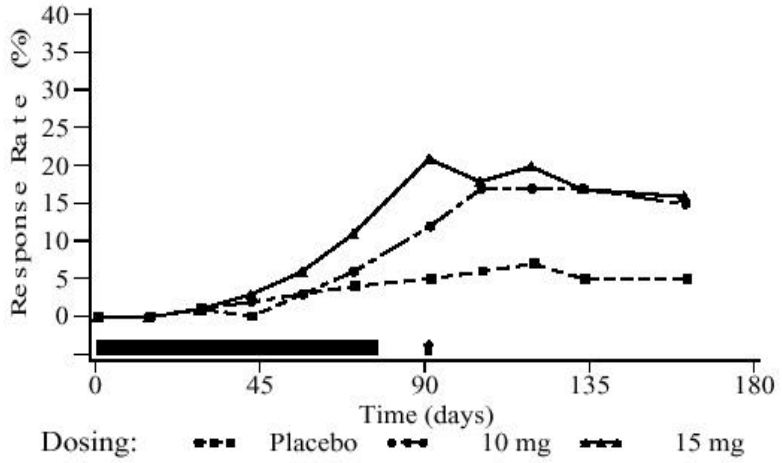
The DLQI overall scale was the principal QOL outcome. The mean change was 2.7, 3.8 and 4.9 in the 0, 10 and 15 mg groups respectively. The difference between placebo and 15 mg groups was significant; this represents a 2.3-point (improvement in the score. Examination of the DQOLS and SF-37 scales shows that for some of the components of the scales statistical differences existed between the placebo and the 15 mg dose groups. However, these differences, also, were small and for the DQOLS scales ranged from a 5 to 9-point improvement for the psychosocial component and the symptoms component, respectively.

Reviewers' comment

The quality of life results measured by DLQI do not provide strong support for treatment response.

Response rates of the two active dose groups cross at day 135.This suggests the hypothesis that the superior performance of the 15 mg arm may be due to shorter time to response (See **Figure 3.3-6**).

Figure 3.3-6 Proportion of patients with a reduction of 75% or more from baseline PASI without the use of phototherapy or systemic therapies in Study 712



Solid bar indicates dosing interval.
Arrow indicates time of primary endpoint.

Safety

All Adverse Events

Few events had higher incidence in the alefacept groups compared to placebo as shown by **Table 61**. For injection site reactions (pain, inflammation) pruritus (not established whether generalized and/ or at injection site) and infection there is a suggestion of dose-dependent incidence. The proportion of patients with an adverse event leading to discontinuation of treatment was 1-2% in the three study arms.

Table 61. Adverse Events ≥5% Incidence in Any Alefacept Group Compared to Placebo

	Placebo	10 mg	15 mg	Total LFA3TIP
Number of patients dosed	168 (100)	173 (100)	166 (100)	339 (100)
Headache	26 (15)	34 (20)	30 (18)	64 (19)
Pruritus	16 (10)	24 (14)	30 (18)	54 (16)
Infection	19 (11)	25 (14)	26 (16)	51 (15)
Rhinitis	11 (7)	24 (14)	9 (5)	33 (10)
Injection site pain	4 (2)	8 (5)	15 (9)	23 (7)
Injection site inflammation	0	5 (3)	8 (5)	13 (4)

Deaths and Serious Adverse Events

One death occurred from myocardial infarction in a patient screened but not yet randomized. The number of patients with at least one serious adverse event during the course of the study was 10 (6%), 8 (5%) and 7 (4%) in the placebo, and 10 and 15 mg alefacept groups, respectively.

Severe adverse events

The overall numbers of patients with a severe event were19 (11%) 18 (10%) and 26 (16%) for 0, 10, and 15 mg groups respectively. Differences in severe adverse event rates

of at least 5% were observed between any alefacept group and placebo in body- as- a -whole only 4, 7, and 9% for 0, 10 and 15 mg groups respectively.

Infections

There is a suggestion of increased number of infections in the alefacept-treated groups.

Table 62. Incidence of Infections

	Placebo	10 mg	15 mg	Total LFA3TIP
Number of patients dosed 168 (100)		173 (100)	166 (100)	339 (100)
No. With an infection event	64 (38)	79 (46)	78 (47)	157 (46)
Infection	19 (11)	25 (14)	26 (16)	51 (15)
Viral infection	15 (9)	13 (8)	10 (6)	23 (7)
Flu syndrome	13 (8)	10 (6)	12 (7)	22 (6)
Pharyngitis	8 (5)	11 (6)	8 (5)	19 (6)
Bronchitis	2 (1)	4 (2)	5 (3)	9 (3)
Herpes simplex	2 (1)	3 (2)	6 (4)	9 (3)
Infection bacterial	5 (3)	7 (4)	2 (1)	9 (3)
Sinusitis	5 (3)	6 (3)	3 (2)	9 (3)
Infection fungal	2 (1)	6 (3)	2 (1)	8 (2)
Conjunctivitis	3 (2)	4 (2)	3 (2)	7 (2)
Gastroenteritis	2 (1)	6 (3)	1 (<1)	7 (2)
Periodontal abscess	2 (1)	3 (2)	4 (2)	7 (2)
Otitis media	1 (<1)	4 (2)	2 (1)	6 (2)
Rhinitis	1 (<1)	3 (2)	3 (2)	6 (2)
Abscess	2 (1)	1 (<1)	3 (2)	4 (1)
Cellulitis	0	2 (1)	2 (1)	4 (1)
Lymphadenopathy	2 (1)	3 (2)	1 (<1)	4 (1)
Blepharitis	1 (<1)	3 (2)	0	3 (<1)
Vaginal moniliasis	1 (<1)	0	3 (2)	3 (<1)
Cough increased	0	2 (1)	0	2 (<1)
Cystitis	0	0	2 (1)	2 (<1)
Fever	2 (1)	0	2 (1)	2 (<1)
Furunculosis	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Otitis externa	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Urinary tract infection	3 (2)	1 (<1)	1 (<1)	2 (<1)
Acne	1 (<1)	0	1 (<1)	1 (<1)
Colitis	0	0	1 (<1)	1 (<1)
Cutaneous moniliasis	0	0	1 (<1)	1 (<1)
Ear disorder	0	1 (<1)	0	1 (<1)
Fungal dermatitis	0	1 (<1)	0	1 (<1)
Gingivitis	0	1 (<1)	0	1 (<1)
Herpes zoster	0	0	1 (<1)	1 (<1)
Hypertonia	0	1 (<1)	0	1 (<1)
Lung disorder	0	1 (<1)	0	1 (<1)
Skin benign neoplasm	1 (<1)	0	1 (<1)	1 (<1)
Vaginitis	0	1 (<1)	0	1 (<1)
Cheilitis	1 (<1)	0	0	0
Chills and fever	1 (<1)	0	0	0
Diarrhea	2 (1)	0	0	0
Keratitis	1 (<1)	0	0	0
Pancreatitis	1 (<1)	0	0	0

With regard to severity of the infections, there is a suggestion that severity tended to be greater in the alefacept groups compared to placebo (See **Table 63**).

Table 63. Severity of Infectious Events						
Dose	**N**	**Total N with event**	**Mild**	**Moderate**	**Severe**	**Adverse event terms classified as severe**
0	168	64 (38)	33	30	1	Abscess, chills, fever
10	173	79 (46)	40	34	5	Abscess, flu, infection (2), gastroenteritis, bronchitis
15	166	78 (47)	40	34	4	Cellulitis(2), infection bacterial, pharyngitis

There was no relationship between infections and decreases in lymphocyte counts.

Neoplasms

Two patients in the 15 mg alefacept group had diagnoses of basal cell carcinoma of the skin. One patient in the placebo group had diagnosis of prostatic carcinoma.

Laboratory Data: Lymphocyte depletions

Tables 64-66 show dose-dependent decreases in total lymphocyte, CD4+ counts that persist in some patients up to the last study visit

Table 64. Total Lymphocyte Count

	Placebo N=167	10 mg N=173	15 mg N=166
Baseline Mean +/- s.d.	2162 +/- 689	2139 +/- 618	2159 +/- 637
Emax (b): No. of Patients Evaluable (c)	166 (100)	173 (100)	166 (100)
Time to Emax (days) Median (Min., Max.)	43 (7, 97)	50 (6, 99)	50 (7, 110)
Count at Tmax (cells/uL)Mean +/- s.d.	1758 +/- 553	1511 +/- 478	1384 +/- 439
% Change from Baseline Mean +/- s.d.	-17 +/-14	-28 +/-15	-35 +/-15
No. < LLN	6 (4)	12 (7)	15 (9)
No. of Patients Below: 900 (cells/uL)	8(5)	16(9)	16(10)
800	2(1)	12(7)	7(4)
700	0	7(4)	5(3)
600	0	3(2)	3(2)
500	0	0	1 (<1)
EAUC (d): No. of Patients Evaluable (a)	166	173	166
Mean +/- s.d.	498 +/- 634	1151 +/- 959	1597 +/-1107
LAST STUDY VISIT			
No. of Patients Evaluable (c)	167 (100)	173 (100)	166 (100)
Count (cells/uL)Mean +/- s.d.	2118 +/- 648	1914 +/- 668	1831 +/- 538
% Change from Baseline Mean +/- s.d.	1 +/- 24	-9 +/- 21	-13 +/- 23
No. < LLN	0	5 (3)	3 (2)
No. < 75% of Baseline	9 (5)	40 (23)	51 (31)

(a) Any patient with a baseline sample and at least one post-baseline sample.
(b) Maximum reduction in count during dosing period.
(c) Any patient with a post-baseline sample.
(d) Area under the effect curve during the dosing period based on % change from baseline.

(e) Any patient with a 12- week post dosing assessment completed 10-14 weeks after the final dose.
(f) Any patient with at least 2 samples during the follow-up period.

Table 65. CD4+ T Cell Count

	Placebo 167	10 mg 173	15 mg 166
Baseline Mean +/- s.d.	914 +/- 340	901 +/- 323	909 +/- 305
Emax (b): No. of Patients Evaluable (c)	166 (100)	173 (100)	166 (100)
Time to Emax (days) Median (Min., Max).	38(7, 108)	56(6, 99)	57(8, 94)
Count at Tmax (cells/uL)Mean +/- s.d.	729 +/- 255	583 +/- 223	542 +/- 217
% Change from Baseline (Mean +/- s.d.)	-18 +/-16	-34 +/-16	-39 +/-16
No. < LLN	13 (8)	39 (23)	52 (31)
No. of Patients Below: 400 (cells/uL)	13(8)	42(24)	47(28)
300	3(2)	13(8)	15(9)
200	0	3(2)	4(2)
100	0	0	0
EAUC (d): No. of Patients Evaluable (a)	166	173	166
Mean +/- s.d.	518 +/- 624	1508 +/-1219	1956 +/-1341
LAST STUDY VISIT			
No. of Patients Evaluable (c)	167 (100)	173 (100)	166 (100)
Count (cells/uL) Mean +/- s.d.	914 +/- 335	784 +/- 306	743 +/- 279
% Change from Baseline Mean +/- s.d.	3 +/-22	-12 +/-23	-16 +/-27
No. < LLN	1(<1)	14 (8)	13 (8)

See table 62 for definition of terms

Table 66. CD8+ T Cell Count

	Placebo N=167	10 mg N=173	15 mg N=166
Emax (b): No. of Patients Evaluable (c)	166 (100)	173 (100)	166 (100)
Time to Emax (days)Median (Min., Max.)	43(7,97)	57(6, 99)	56(8, 94)
Count at Tmax (cells/uL)Mean +/- s.d.	400 +/- 198	293 +/- 167	269 +/- 157
% Change from Baseline Mean +/- s.d.	-20 +/- 16	-40 +/- 16	-47 +/- 18
No. < LLN	27 (16)	59 (34)	77 (46)
No. of Patients Below: 200 (cells/uL)	26(16)	58(34)	64(39)
150	10(6)	38(22)	39(23)
100	1 (<1)	14(8)	12(7)
50	0	2(1)	3(2)
EAUC (d): No. of Patients Evaluable (a)	166	173	166
Mean +/- s.d.	551 +/- 647	1862 +/-1295	2450 +/-1605
LAST STUDY VISIT			
No. of Patients Evaluable (c)	167 (100)	173 (100)	166 (100)
Count (cells/uL)Mean +/- s.d.	493 +/- 248	411 +/- 251	394 +/- 224
% Change from Baseline Mean +/- s.d.	0 +/-24	-16 +/-26	-21 +/-32
No. < LLN	14 (8)	35 (20)	35 (21)

See table 62 for definition of terms

Most of the changes in total lymphocyte counts were accounted for by changes in CD4 and CD8 cells. There were no changes in B cells. There was a suggestion of decline and recovery to baseline of NK cells.

Chemistry data:

Shift to high in AST levels occurred in 9, 8 and 13% of patients in the placebo, 10mg and 15mg dose groups, respectively. In addition, there was a greater proportion of patients with shift of albumin to low and shift of bilirubin to high in the 10 and 15 mg dose groups than in the placebo group. See **Table 67** below.

Table 67. Summary of Shifts from Baseline for Blood Chemistry

	Placebo		10 mg		15 mg	
	Shift to Low	Shift to High	Shift to Low	Shift to High	Shift to Low	Shift to High
Albumin	1/163(< 1)	3/160(2)	2/172(1)	3/170(2)	3/159(2)	4/160(3)
ALT	0/164	21/145(14)	2/172(1)	12/135(9)	0/161	18/134(13)
AST	0/164	14/150(9)	0/172	11/145(8)	0/161	18/139(13)
Tot. Bilirubin	15/153(10)	1/163(<1)	12/159(8)	4/170(2)	8/146(5)	4/161(2)
Creatinine	0/163	4/161(2)	0/172	3/169(2)	0/160	1/158(<1)

Conclusions

Efficacy Outcomes

- The response to treatment in the 15 mg group is superior to the response in the placebo group. The absolute difference was 15%.
- The response to treatment in the 10 mg group is intermediate between the response in the 15 mg dose group and the placebo group.
- There was no meaningful difference in response by age, gender, ethnic group, geographic region, or study center.
- The proportion of responders in patients weighing less than 85 kg tended to be higher compared to patients weighing more than 85 kg.
- There was an insufficient number of patients weighing < 50 kg to base a recommendation for lower dose in this group.
- Median duration of response and time to response were not different among study arms
- DQOL outcomes showed very small degrees of improvement (4-9%) in the 15 mg group that did not provide strong support for efficacy of this dose.

Safety Outcomes

- The incidence and severity of infections appeared to be higher in the alefacept groups compared to placebo.
- There was a dose-dependent increase in injection site reactions (pain and inflammation) in the alefacept groups compared to placebo.
- The incidence of severe reactions was somewhat higher in the alefacept groups compared to placebo. The incidence of serious adverse events appeared to be numerically similar among groups.
- Alefacept induced dose-dependent decreases in total lymphocyte counts. The decreases were mainly due to CD4 and CD8 T cell counts. At the end of follow up period CD4 counts remained below normal in <1% of placebo patients and 8% of alefacept patients; CD8 T cell counts remained below normal in 8% of placebo

patients and 20% of alefacept patients. NK cells showed a tendency to decline and return to baseline. B cells appeared to be unaffected.

Review of Clinical Photography

Clinical photographs were systematically reviewed by study center for the two Phase 3 studies, 711 and 712. The purpose of the clinical photography review was to verify the methods of assessing the degree of involvement of psoriasis at visit 1A and 13A by comparison of the photographs and PASI database.

IV. INTEGRATED SAFETY ANALYSIS

This analysis includes comparisons between placebo and alefacept-exposed patients in the first course of the placebo-controlled experience present in the original alefacept BLA submission of August 2001. Additionally, based upon the integrated safety update submitted to the agency in March of 2002, safety data is available from patients who went on to receive one or more courses of alefacept in one the studies below.

For *first course exposure in placebo-controlled studies*, 413 patients received at least one dose of placebo and 876 patients received at least one dose of alefacept in the placebo-controlled studies (Studies 708, 711, and 712).

As of the data cut-off for the integrated safety update, 1357 patients had received at least one course, 756 at least two courses, and 199 at least three courses of alefacept (**Table 68**). Studies that are included in this safety update include dose-escalation studies (Studies 703, 705, and 709), placebo-controlled studies (Studies 708, 711, and 712), and studies offering further treatment (Studies 710, 714, 717, and 724).

Table 68. Patients Included in the Multiple Course Experience

	First Course	Second Course	Third Course	Fourth Course	Fifth Course
No. of Patients	1357	756	199	81	46

Serious Adverse Events and Malignancies

The safety population included all patients who were randomized and received at least one dose of study medication. Less common adverse events including serious adverse events and malignancies can be analyzed by comparing the safety profile of alefacept with that of placebo from the placebo-controlled, single course experience; 413 patients received placebo and 876 received alefacept in Studies 708, 711 and 712 combined. See **Table 69** for the summary of serious adverse events.

A serious adverse event is defined as:(1) Any death; (2) Any life-threatening event (one which places the subject at immediate risk of death); (3) Any event that requires or prolongs in-patient hospitalization; (4) Any event that results in significant or persistent disability/incapacity; (5) Any congenital anomaly/birth defect diagnosed in the child of a subject who participated in this study and received study drug; or (6) Other medically important event that, in the opinion of the investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

Table 69. Incidence of Serious Adverse Events in the First Course of Placebo-Controlled Studies

	Placebo	Alefacept
No Patients dosed	413 (100)	876 (100)
No with a Serious Event	19 (5)	42 (5)
Event		
Coronary artery disorder	0	4 (<1)
Cellutitis	0	3 (<1)
Myocardial infarction	0	3 (<1)
Accidental injury	0	2 (<1)
Carcinoma	0	2 (<1)
Chest pain	1 (<1)	2 (<1)
Diabetes mellitus	0	2 (<1)
Gastroenteritis	0	2 (<1)
Pancreatitis	1 (<1)	2 (<1)
Psoriasis	6 (1)	2 (<1)
Abscess	0	1 (<1)
Angioedema	0	1 (<1)
Arthritis	1 (<1)	1 (<1)
Asthma	0	1 (<1)
Atrial Fibrillation	0	1 (<1)
AV block complete	0	1 (<1)
Back pain	0	1 (<1)
Bursitis	0	1 (<1)
Cholelithiasis	2 (<1)	1 (<1)
Congestive heart failure	0	1 (<1)
Infection	1 (<1)	1 (<1)
Kidney calculus	1 (<1)	1 (<1)
Menorrhagia	0	1 (<1)
Pleural effusion	0	1 (<1)
Prostatic carcinoma	1 (<1)	1 (<1)
Skin carcinoma	0	1 (<1)
Skin melanoma	0	1 (<1)
Accomplished Suicide	0	1 (<1)
Angina pectoris	1 (<1)	0
Arthralgia	1 (<1)	0
Bronchitis	1 (<1)	0
Gastrointestinal disorder	1 (<1)	0
Gum hemorrhage	1 (<1)	0
Hernia	2 (<1)	0
Pain *	1 (<1)	0
Rectal hemorrhage	1 (<1)	0
Syncope	1 (<1)	0

*****The patient was hospitalized for pain in his shoulder. Chest x ray, ECG and blood studies were negative and the shoulder pain was not attributed to any specific cause or organ system.

The patient with syncope was a 49-year old male who experienced syncope of unknown cause. He underwent hospitalization and an extensive evaluation that did not reveal any positive findings.

Deaths

In the first course placebo-controlled experience, there were no deaths in patients who received placebo and one death by suicide in a patient (143-202) who received alefacept. Please see the narrative appended below.

Serious Infections

Table 70 shows the incidence of serious infections in the first course of the placebo-controlled studies. The proportion of patients diagnosed with a serious infection was higher in the alefacept arm than the control arm. Of the three patients in the alefacept arm who developed cellulitis, one was diagnosed with an otitis externa complicated by facial necrotizing cellulitis requiring debridement and another was diagnosed with orbital preseptal cellulitis. One patient in the alefacept arm developed a peritonsillar abscess requiring hospitalization. Two patients in the alefacept arm required hospitalization for gastroenteritis. One patient with preexisting asthma experienced an exacerbation of asthma that, for the first time, required hospitalization; the adverse event was thought to be triggered by a viral upper respiratory infection and was classified by the investigator and the sponsor as infectious.

Reviewers' comment: A case of pancreatitis (330-306) that occurred in the placebo arm was included in the sponsor's licensing application as a serious infection. However, the narrative does not support infection as an etiology. Based on laboratory values, clinical signs and symptoms, and previous history, this diagnosis of pancreatitis was most likely related to alcohol use.

Table 70. Incidence of Serious Infections in the First Course of Placebo-Controlled Studies

	Placebo	Alefacept
No. of patients dosed	413	876
No. with a serious infection		8 (0.91%)
Body as a whole	0	5
Cellulitis	0	3
Abscess	0	1
Wound Infection	0	1
Digestive system	0	2
Gastroenteritis	0	2
Respiratory system	1	1
Asthma	0	1
Bronchitis	1	0

Malignancies

Malignancies in the first course, placebo-controlled experience are shown in **Table 74**. The most common occurrence was cutaneous malignancy; seven cutaneous malignancies- four squamous cell carcinomas and three basal cell carcinomas-occurred in the alefacept group vs. one basal cell carcinoma in the placebo group. Additionally, patient 150-208 in the alefacept-treated group was diagnosed with a cutaneous malignant melanoma. Please see the appended narratives.

Some patients developed multiple skin cancers during alefacept treatment. Patient 114-204, assigned to receive two courses of alefacept, was reported to develop three skin cancers: a squamous cell carcinoma, and two additional skin lesions, for which no biopsy report is available.

Non-cutaneous malignancies diagnosed during the first course placebo-controlled experience included one diagnosis of each of the following malignancies: renal carcinoma, prostatic carcinoma and testicular carcinoma.

Table 74. Incidence of malignancies experienced in the first course of placebo-controlled studies

	Placebo	Alefacept
No. dosed	413	876
No. with malignancy	2 (0.48%)	11 (1.1%)
Skin carcinoma	1	7
Carcinoma		
Renal cell ca		1
Testicular ca		1
Prostatic ca	1	1
Skin Melanoma		1

Two cases of lymphoid malignancy in psoriasis patients have been reported: stage III non-Hodgkin's follicular cell lymphoma in a 68 year-old woman (169-306) and mixed cellularity Hodgkin's disease stage IV in a 62 year-old man (332-310). Both cases have occurred outside of the first course, placebo-controlled experience during subsequent cycles of alefacept treatment and were judged by the investigators to be related to alefacept treatment. Please see the appended narratives.

Cardiovascular events

In the first course of placebo-controlled studies, a higher incidence of cardiovascular events was noted in the alefacept-treated group compared to placebo. In particular, there were three episodes of myocardial infarction and four episodes of coronary artery disease in the alefacept group and none in the placebo group. Of the cases of cardiac ischemia, all occurred in patients with risk factors for cardiovascular disease and all were classified as having no relationship to study drug by the investigator. One case was of unexplained hypertension and chest pain in a 50 year-old man (145-211)

Psoriasis:

There were no reports of rebound of disease associated with withdrawal of therapy. Rebound was defined as clinically significant improvement on therapy followed by a marked worsening off-treatment resulting in hospitalization.

Hospitalization following treatment with alefacept occurred in two cases (See appendix). In neither case, did the patient respond to treatment with alefacept.

To determine whether use of alefacept may be associated with rapid worsening of psoriasis during or after treatment, control and alefacept-treated groups were compared using the following post-hoc definitions and timepoints.

- An increase of 50% from baseline during dosing,
- An increase of 20 PASI points from baseline during dosing,
- An increase of 50% from two weeks after the last dose, and
- An increase or 20 PASI points from two weeks after the last dose.

The results are shown in **Table 75** and **76**.

Table 75. Worsening of Psoriasis During Treatment

	IV, C99-711				IM, C99-712					
	Placebo		7.5 mg		Placebo		10mg		15mg	
	n	%	n	%	n	%	n	%	n	%
Visit	**186**		**367**		**168**		**173**		**166**	
3	2	1.1	3	5%	3	1.8	3	1.7	4	2.4
5	1	0.5	2	4%	2	1.2	0	0	2	1.2
7	0	0	4	3%	1	0.6	4	2.3	2	1.2
9	2	1.1	3	7%	1	0.6	0	0	1	0.6
11	0	0	1		4	2.4	0	0	0	0
Total	5	2.7	13	3.5	11	6.5	7	4.0	9	5.4

No patients in C99-711 experienced an increase of ≥ 20 PASI points during dosing in either treatment group. Three patients in C99-712 experienced an increase of ≥ 20 PASI points during dosing; one was in the placebo group (visit 5) and two were in the 10 mg group (visits 3 and 7). Therefore, the risk of substantial worsening of psoriasis during treatment is low and not different between the alefacept and placebo groups.

Table 76. Worsening of Psoriasis Following Treatment - 50% Increase in PASI from Visit 13 Following Dosing

	Placebo		7.5 mg		Placebo		10mg		15mg	
	n	%	n	%	n	%	n	%	n	%
Visit	**166**		**340**		**158**		**169**		**154**	
14	8	5%	16	5%	10	6%	11	7%	10	6%
15	6	4%	15	4%	6	4%	11	7%	10	6%
16	4	2%	11	3%	6	4%	9	5%	8	5%
17	7	4%	25	7%	13	8%	24	14%	16	10%
Interim	1	1%	4	1%	0	0%	0	0%	0	0%
Total	26	16%	71	21%	35	22%	55	33%	44	29%

All patients who were evaluated at two weeks after the last dose are included in these analyses.

Table 77. Worsening of Psoriasis Following Treatment-20 Point Increase in PASI from Visit 13 Following Dosing

Study C99-711					
Patient ID	Treatment Group	Baseline PASI	Visit 13 PASI	PASI at Visit of Event	Visit*
113-204	7.5	40.8	16.0	42.4	16A
146-201	0	16.5	17.7	37.8	15A
210-204	7.5	44.0	16.2	44.0	17A
210-206	7.5	50.4	12.7	38.4	Interim 1
210-208	7.5	44.1	8.0	46.7	Interim 1
210-210	7.5	39.5	6.7	29.8	17A
Study C99-712					
210-304	10	42.9	10.8	34.6	17

321-310	15	20.6	10.8	31.9	17
324-302	10	33.7	17.9	39.6	17
330-310	10	36.7	19.4	41.4	17
*Visit at which the PASI was first noted to be 20 points worse than Visit 13.					

From the above patient listing, it is notable that almost all of the patients experiencing a 20-point worsening of their psoriasis received active drug. Only one patient of the ten received placebo. In addition, among the patients who received active drug, the 20-point worsening was seen in those patients who had significant improvement at visit 13 compared to baseline. Therefore, with the exception of patient 321-310, the PASI score worsening represented a return to baseline.

The sponsor notes that none of the above alefacept-treated patients qualify as rebound by the National Psoriasis Foundation's definition of a return to a disease level greater than 150% of baseline within 6 weeks of cessation of treatment.

Psoriatic Arthritis:

There were no safety signals noted in alefacept-treated patients with concomitant psoriatic arthritis. In the first course of placebo-controlled studies, the incidence of arthralgia was 6% (N=24) in the placebo group and 5% (N=42) in the alefacept group. The incidence of severe arthritis was small and was <1% (N=2) in the placebo group and <1% (N=5) in the alefacept group. No etiology was given in approximately half of the cases of arthritis and arthralgia. The etiology of the arthritis/arthralgia, where available, frequently cited psoriatic arthritis, possible study drug infusion, and osteoarthritis. However, there was no obvious imbalance in the numbers of psoriatic arthritis between alefacept and placebo.

Study 715 was an open-label study in patients with psoriatic arthritis in which approximately 20 patients were enrolled. The results of this study are currently under analysis by the sponsor and have not been submitted for FDA review.

Allergic Reactions:

Urticaria, asthma and rare cases of angioedema were among possible allergy-mediated adverse events observed during clinical development. During the first course of the placebo-controlled experience, urticaria occurred in six of 876 alefacept-treated patients and one of 413 placebo-treated patients, accounting for less than 1% of treated patients. Four of the six alefacept-treated patients experienced urticaria during the 12-week dosing period, and one patient in the alefacept group discontinued therapy secondary to urticaria.

Asthma was reported in 1.3% (11/876) of alefacept-treated patients vs. 0% (0/413) of placebo–treated patients. In the alefacept-treated group, eight of the 11 cases of asthma were observed during the 12-week dosing period. None of these cases resulted in discontinuation of treatment.

Two cases of angioedema attributed to alefacept were reported during clinical development, one of which required hospitalization. Both patients permanently discontinued therapy. Please see the appended narratives.

Coding of Infections

Adverse Events judged to be infectious were flagged by the investigator on the CRF and were coded by the sponsor in the CRT. Malignancies were not flagged; benign tumors were termed “neoplasm” while malignant tumors were given the COSTART term “carcinoma or melanoma.” A number of inconsistencies were noted in the coding of infectious adverse events. No inconsistencies were noted in the coding of malignancies and other neoplasms.

The following **tables 78 and 79** show examples of inconsistencies in the coding in the alefacept and placebo treated groups in the entire alefacept safety database.

Table 78 Inconsistencies in infectious coding in the alefacept adverse event database

AE CODE	PID	SYMPTOM	ETIOLOGY	SEVER	INF
Cellulitis	186301	Cellulitis		1	N
FLU SYND	127006	FLU SYMPTOMS	POSSIBLE VIRAL	2	N
FLU SYND	149301	INFLUENZA		1	N
FLU SYND	205203	FLU.	VIRAL	2	N
INFECT	143207	COLD	VIRAL SYNDROME	1	N
INFECT	149304	COLD		1	N
INFECT	161206	TONSILLITIS {INFECTION}	INJECTED TONSILS	2	N
INFECT	218309	COMMON COLD	POSSIBLE VIRAL ORIGIN	1	N
PHARYNGITIS	105205	COLD SYMPTOMS		1	N
PHARYNGITIS	114005	SORE THROAT	OTHER: SINUSITIS	2	
PHARYNGITIS	121008	SORE THROAT	POSSIBLE VIRAL INFECTION	1	
PHARYNGITIS	126209	COLD SYMPTOMS		2	N
PHARYNGITIS	127127	SORE THROAT	POSSIBLE VIRAL	1	N
PHARYNGITIS	127201	SORE THROAT	POSSIBLE VIRAL	1	N
PHARYNGITIS	127201	SORE THROAT	POSSIBLE VIRAL	1	N
PHARYNGITIS	136207	COLD SYMPTOMS		1	N
PHARYNGITIS	137203	COLD S/S		1	N
PHARYNGITIS	143212	POSSIBLE VIRAL SYNDROME		2	N
PHARYNGITIS	143304	SORE THROAT	POSSIBLE VIRAL SYNDROME	1	N
PHARYNGITIS	144210	COLD SYMPTOMS		1	N
PHARYNGITIS	150213	COLD SYMPTOMS		1	N
PHARYNGITIS	151205	POSSIBLE VIRAL URI	MILD COLD	1	N
PHARYNGITIS	160208	COLD SYMPTOMS		1	N
PHARYNGITIS	172312	COLD SYMPTOMS		1	N
PHARYNGITIS	207202	COLD SYMPTOMS		1	N
PHARYNGITIS	207203	COLD SYMPTOMS		1	N
PHARYNGITIS	207208	COMMON COLD SYMPTOMS		1	N
PHARYNGITIS	207208	COMMON COLD SYMPTOMS		1	N
PHARYNGITIS	209206	COLD-LIKE SYMPTOMS		1	N
PHARYNGITIS	209208	COLD-LIKE SYMPTOMS		1	N
PHARYNGITIS	209213	COLD-LIKE SYMPTOMS		2	N
PHARYNGITIS	209216	COLD-LIKE ILLNESS		2	N
PHARYNGITIS	209303	COLD-LIKE ILLNESS		1	N

PHARYNGITIS	209303	COLD-LIKE SYMPTOMS		1	N
PHARYNGITIS	209303	COLD-LIKE SYMPTOMS		1	N
PHARYNGITIS	210206	COLD SYMPTOMS		2	N
PHARYNGITIS	210206	COLD SYMPTOMS		1	N
PHARYNGITIS	210211	COLD SYMPTOMS		1	N
PHARYNGITIS	300304	PHLEGM PRODUCTION		1	N
RHINITIS	105011	NASAL CONGESTION	COMMON COLD	1	N
RHINITIS	116001	SINUS CONGESTION	POSSIBLE VIRAL INFECTION-FROM CHILD	2	
RHINITIS	121008	SINUS CONGESTION	POSSIBLE VIRAL INFECTION	1	
SINUSITIS	102001	SINUS INFECTION	COMMON COLD (URI)	2	
DERM FUNG	121104	JOCK ITCH		2	N
FURUNCULOSIS	300302	BOIL ON LOWER ABDOMEN		1	N
OTITIS EXTERNA	323302	PAIN, EXTERNAL OTITS	PSORIASIS IN THE EARS	1	N
OTITIS EXTERNA	350310	OTITIS EXTERNA	PSORIASIS	1	N
ABSCESS	142202	TOOTH ABSCESS	S/P SURGERY	2	N
INFESTION	106108	APPENDICITIS		3	N
INFECTION (bac)	127018	WORSENING OF DIARRHEA	BACTERIAL COLITIS	2	N
GASTROENTERITIS	114210	STOMACH VIRUS		2	N
GASTROENTERITIS	116208	VOMITING , STOMACH VIRUS		1	N
GASTROENTERITIS	143201	GASTROENTERITIS	VIRAL SYNDROME	2	N
HERPES SIMPLEX	114002	FEVER BLISTER	PRIMARY DISEASE	1	N
NEOPL SKIN	151206	MULTI-VERRUCAS ON HAND		1	N
NEOPL SKIN	186306	VERRUCA VULGARIS	PAPILLOMA VIRUS	1	N

Table 79. Inconsistencies in Infectious Coding in the Placebo Adverse Event Database

AE code	PID	Symptom	Etiology	Severity	Inf
Pharyngitis	209306	cold like symptoms	--	--	N
Conjunctivitis	361303	conjunctivitis	Foreign body		Y
Conjunctivitis	209302	left and right eyes	Injected Sclera	3	N
Pancreatitis	330306	pancreatitis	Alcohol consumption	2	Y

The total number of infectious adverse events in selected categories from the entire safety database is shown in **Table 80.** The distribution of adverse events is proportionally similar between the alefacept and placebo groups. The highest number was observed in the upper respiratory infection category.

Table 80. Infectious Adverse Events from the Entire Safety Database

	Alefacept AE	**Placebo AE**
Skin, viral	79	3
Skin, Pyoderma, cellulitis	163	20

Skin, fungal	47	3
URI (cold, flu)	1297	128
pneumonia	22	1
URI (OM, Strep throat)	43	4
Dental abscess	43	3
Genitourinary infection	92	5
Gastrointestinal infection	61	35
Constitutional (chills, fever)	143	8

Multiple Course IV Experience

Study 724 offered up to three additional courses of 7.5 mg alefacept IV to patients who had received at least 8 injections of alefacept, and had completed the final follow-up visit in study 711. To be eligible for dosing, patients had to have a CD4+ count at or above the LLN prior to their first dose, and should not have received phototherapy, systemic retinoids, systemic steroids, methotrexate, cyclosporine, azathioprine, thioguanine, or other systemic immunosuppressant agents within the 28 days prior to dosing. If the criteria for dosing were not met, patients continued to be followed at interim visits until they were eligible for dosing.

Two hundred fifty-five were enrolled into study 724. Eight patients withdrew from study 724 prior to being dosed and 33 patients remain in interim visits. Of the 214 patients dosed, 119 (56%) completed treatment and 91 (43%) remained in active treatment. Only one patient had completed follow-up hence completing one course. At the time of the submission of amendment 8, only one patient completed the full course, therefore, the time of observation was not a full course (24 weeks) for the remainder of the patients.

There was one serious infection in the third course of treatment. The narrative follows:

Bronchitis

Patient 130-209, a 49-year old man with a 30-year smoking history was hospitalized for bronchitis, 5 weeks after his last dose of alefacept in study 724. His chest x-ray and sputum cultures were normal. He was discharged on the fourth hospital day. The event was reported as resolved without sequelae 1 month after onset.

There were no malignancies in the third course of treatment.

Reviewers' comment: One must take care in interpreting the incidence of serious adverse events as the total number of patients dosed has diminished substantially over subsequent courses, especially, between courses 2 (N=449) and 3 (N=214). This would preclude direct comparisons across courses.

Two Course IM Experience

The safety database reveals that, overall, the risk of experiencing a serious adverse event does not increase with a second course of treatment. The safety data beyond two courses of therapy are very limited. **(Table 81)**

Table 81. Incidence of Serious Infections with Repeat IM dosing

	712 0 mg/717 10 mg		712 10 mg/717 10 mg		712 15 mg/717 15 mg	
	First Course	Second Course	First Course	Second Course	First Course	Second Course
NUMBER OF PATIENTS DOSED	168	115	173	129	166	131
NO. WITH A SERIOUS INFECTION	1 (<1)	0	3 (2)	0	2 (1)	1 (<1)
ABSCESS	0	0	1 (<1)	0	0	0
CELLULITIS	0	0	0	0	1 (<1)	0
INFECTION BACTERIAL	0	0	0	0	1 (<1)	0
GASTROENTERITIS	0	0	2 (1)	0	0	0
PANCREATITIS	0	0	0	0	0	0
HERPES SIMPLEX	0	0	0	0	0	1 (<1)

Injection site reactions occurred in up to 19% of treated patients in the first course of therapy and did not appear to increase with subsequent treatment.

Effect of Repeat IM Treatment on CD4 Counts

Table 82 depicts CD4+ lymphocyte counts with repeat courses of intramuscularly administered drug.

Table 82. CD4+ T Cell Counts: Studies 712 and 717

	712 Placebo/717 10 mg		712 10 mg/717 10 mg		712 15 mg/717 15 mg	
	Course 1	Course 2	Course 1	Course 2	Course 1	Course 2
Baseline:						
Number of Patients Evaluable (a)	167	114	173	129	166	130
Mean± s.d.	914±340	908±349	901±323	812±318	909±305	740±274
Emax (b):						
No.of Patients Evaluable (c)	166	114	173	129	166	130
Count at Time of Emax Mean± s.d.(cells/uL)	729±255	566±236	583±223	553±213	542±217	505±230
Percentage Change from Baseline (d) Mean ±s.d.	-18±16	-34±20	-34±16	-38±17	-39±16	-43±18
No. < LLN	13(8)	37(32)	39(23)	37(29)	52(31)	50(38)
Number of Patients Below:						
400 (cells/uL)	13(8)	38(33)	42(24)	38(29)	47(28)	51(39)
300 (cells/uL)	3 (2)	11(10)	14(8)	13(10)	16(10)	21(16)
200 (cells/uL)	0	0	4 (2)	4 (3)	4 (2)	4 (3)
100 (cells/uL)	0	0	0	0	0	0
12 Weeks Post Treatment: No. of Patients Evaluable (e)	149	101	161	109	147	108
Count cell/ul mean±sd	914±334	705±264	784±310	745±296	745±282	704±285
No.<LLN	2(1)	12(12)	14(9)	11(10)	11(7)	12(11)

NOTE: Numbers in parentheses are percentages.

(a) Any patient who had a baseline assessment and at least one post- baseline assessment

(b) Maximum reduction in count during dosing period.

(c) Any patient with an assessment during the dosing period for the study.

(d) Baseline refers to the baseline from study 712.

(e) Any patient with a twelve-week post-dosing assessment completed between 10 and 14 weeks after the final dose in the study.

CD4+ T cell counts showed a dose-dependent decline with the repeat course of therapy. The greatest drop from baseline was seen in the group of patients who received two courses of the higher dose, with the mean percentage change from baseline of –43% in this group. In addition, the proportion of patients dropping below certain thresholds (400 and 300 cells/µl) was greater in the cohort who had received two courses of 15 mg IM than those who had received two courses of 10 mg IM. At each dose level, the proportion of patients with CD4+ T cell counts below the lower limit of normal was higher in the second treatment course of alefacept compared to the first.

Immunogenecity

Anti-alefacept Antibodies

Patients were screened for the development of antibodies in the integrated database. However, patients in studies 703 and 705 are not included in the sponsor's anti-alefacept antibody analysis due to the use of a different assay in these two studies from the remainder of the studies.

Patients were tested at baseline and during each course. Titers were checked only if there was a positive screening to anti-alefacept antibodies. Titers <5 were considered negative. Of note, there were low-level titers detected in 5 placebo patients (<1%) including baseline and during the course of treatment with placebo.

Study 708: No anti-alefacept antibodies were reported.

Study 709: Two patients in the IM dose group developed low titer antibodies to BG9712 after start of dosing.

The incidence during treatment of anti-alefacept antibodies during the pivotal IV study, 711 was low. Six patients, less than 1% of those dosed, developed antibodies for the first time during treatment. The highest titer reached was 160 units in one patient.

Table 83 shows the incidence of anti-alefacept antibodies with IM dosing in studies 712 and 717. After the first course of therapy, in study 712, 4% of alefacept-treated patients developed antibodies to alefacept; incontrast, as stated above, <1% of patients in study 711 (IV dosing) developed anti-alefacept antibodies after the first course of therapy. Following the last dose of study 712, 0 (0%), 10 (6%) and 4 (2%) of patients in the placebo, 10 and 15 mg groups, respectively, tested positive for anti-alefacept antibodies.

The titers ranged from 5 to 320, and were not associated with identifiable safety or efficacy issues.

Table 83. Incidence of Anti-alefacept Antibodies With Repeat IM Dosing

	712 Placebo/717 10 mg		712 10 mg/717 10 mg		712 15 mg/717 15 mg	
	First Course	Second Course	First Course	Second Course	First Course	Second Course
NUMBER OF PATIENTS DOSED	168	115	173	129	166	131
Prior to First Dose	1/168 (<1)	0/115	0/172	1/129(<1)	0/166	3/131 (2)
At Any Time After the First Dose	0/164	5/113 (4)	10/171(6)	0/125	4/161 (2)	3/127 (2)

Pregnancy Outcomes

The sponsor has maintained a pregnancy registry during alefacept's clinical development. Pregnant patients were discontinued from study drug treatment upon the report of their pregnancies and, whenever possible, followed until the pregnancy outcome was known.

Table 84 summarizes the pregnancy outcomes during clinical development. Of the 384 women exposed to alefacept, six women reported pregnancies including one twin gestation. Of the six pregnancies, three resulted in live births, one was terminated electively, and two were lost to follow-up. There were no reported congenital anomalies or spontaneous abortions. No pregnancies were reported in placebo-treated patients.

In alefacept-treated patients, four patients were exposed in the first trimester and none in the subsequent trimesters. Estimated duration of exposure ranged from 5 days to 4 weeks. Of the three live births reported, one mother had completed 12 doses of alefacept, one month prior to her last menstrual period (LMP).

Reviewers' comment: The experience during the clinical trials is very limited and, the longest follow-up of the infants was 6 months. Because during early infancy the immune system is supplemented by maternal antibodies, it is not possible to exclude some defects in immunity that could be attributable to study drug exposure in utero.

Table 84. All Pregnancy Outcomes by Treatment Group

Patient No.	Study No., Dosage, No. doses before conception	Maternal Age At conception	Earliest Trimester Exposed	*Estimated Duration of In Utero Exposure	Pregnancy Outcome	Comments
104-002	Study 708 0.15 mg/kg IV (7 doses)	24 years	1st	2 weeks 4 days	Live Birth	Vaginal delivery of 7 lb. 3 oz. Normal female. Normal development at 2, 4, and 6 months of age.
113-107	Study 709 0.225 mg/kg IV (5 doses)	24 years	~ 1st	5 days	Unknown	Patient lost to follow-up.
123-214	Study 711 7.5 mg IV (12 doses)	32 years	No Exposure	No Exposure	Live Birth	Uncomplicated pregnancy. Vaginal delivery of 8 lb. 2 oz. Normal male. Normal development at 2 months old.
168-310	Study 712 15 mg IM (8 doses)	37 years	1st	8 days	Unknown	Twin gestation. Lost to follow-up.
172-306	Study 712 15 mg IM (7 doses)	28 years	1st	4 weeks 3 days	Live Birth	Uncomplicated pregnancy. Delivered 7 lb. male infant with low heart rate via Cesarean section. Infant was normal.
127-009	Study 714 7.5 mg IV (11 doses)	41 years	No Exposure	No Exposure	Elective Termination	History of smoking and alcohol use.

*Duration of exposure is time from 2 weeks after the date of last menstrual period to the date of discontinuation of study drug.

Safety in the Geriatric Population

In the phase 3 studies, there were 32 and 57 patients age 65 years and older in the placebo and alefacept groups, respectively. The total incidence of adverse events during course 1 was 72% and 84% in placebo and alefacept groups, respectively. The most common adverse events were headache, accidental injury, pruritus, and infection; see Table 83, below. The adverse events which differed by more than 5% between patients receiving placebo and alefacept, respectively, are as follows: pruritus (19% *vs.* 12 %), infection (3% *vs.* 11%), chills (3% *vs.* 9%), pain (3% *vs.* 9%), arthralgia (0 *vs.* 5%), viral infection (9% *vs.* 4%), diarrhea (9% *vs.* 2%) and peripheral edema (13% *vs.* 2%).

The incidence of serious adverse events in patients 65 and older in the first course of treatment are listed in **Table 85**. The proportion of serious adverse events totaled 9% in the alefacept arm and 6% in placebo.

Table 85. Incidence of Serious Adverse Events in the First Course of Phase 3 Studies for Patients 65 Years and Older

	Placebo	LFA3TIP
No Dosed	32 (100)	57 (100)
No with Serious Adverse Event	2 (6)	5 (9)
Event		
Coronary Artery Do.	0	2 (4)
Diabetes Mellitus	0	2 (4)
Prostatic Carcinoma	1	1(2)
Skin Melanoma	0	1(2)
Psoriasis	1(3)	0

Of the patients age 65 and older, there was a higher proportion of infectious adverse events reported in the alefacept-treated group (33%,19/57 patients) than in the placebo-treated (22%, 7/32 patients) group in the first course placebo-controlled experience. The majority of infectious adverse events involved the upper respiratory system. No atypical infectious adverse events were noted. Although, the numbers were too small for meaningful analysis, we cannot exclude that geriatric patients may be at increased risk of infection while taking alefacept.

In alefacept-treated patients, two cases of colitis were reported. One case of colitis took place in patient 144-212, a 68 year-old white female, who had an exacerbation of diverticulitis; the other occurred in patient 179306 in study 712, a 73 year-old white female, whose colitis was not described other than "worsening colitis." Neither of these cases constituted serious adverse events; furthermore, the first was classified as mild and the second as moderate in severity.

Patients 75 years of age and older were very few, numbering nine in all. Of these nine patients in the phase 3 studies, 4 received placebo and 5 received alefacept. Two serious adverse events during the first course placebo-controlled experience occurred in patients randomized to alefacept, skin melanoma (150-208) and coronary artery disease (135-202). Please see the patient narratives appended. No serious adverse events were noted in the placebo group.

V.SUMMARY: ALEFACEPT FOR THE TREATMENT OF MODERATE TO SEVERE CHRONIC PLAQUE PSORIASIS

Patient Population, Efficacy Outcomes

- The patient population studied (eligibility criteria included PASI, %BSA involvement, treatment history, and response to prior treatment) is representative of patients with moderate to severe psoriasis.
- The response to treatment ($\geq$ 75% improvement in PASI from baseline) in the 7.5 mg IV alefacept group is superior to the response in the placebo group. The absolute difference was 11%.
- The response to treatment in the 15 mg IM alefacept group is superior to the response in the placebo group. The absolute difference was 15%.
- There was no meaningful difference in response by age, gender, ethnic group, geographic region, and baseline severity of psoriasis or history of previous anti-psoriasis therapy.
- The proportion of responders in patients weighing less than 85 kg tended to be higher compared to patients weighing more than 85 kg.
- There was an insufficient number of patients weighing < 50 kg to base a recommendation for lower dose in this group.
- QOL outcomes showed very small degrees of improvement (3-9 points), and some lack of consistency and did not provide strong support for efficacy of alefacept.
- Response to second course of treatment appeared to be somewhat lower compared to response to the first treatment course. The assessment of response may have been confounded by carry-over effects of the first treatment period in alefacept and placebo groups.
- It is not clear if differences in duration of response between treatment groups are clinically meaningful.
- There was substantial use of non-allowed antipsoriatic medications. This raised concerns about confounding of efficacy outcomes; however, the use of concomitant treatment appeared to be similar across study arms.

Safety Assessments

- Alefacept decreases total lymphocyte counts. In individual phase 3 studies up to 22% (79) of patients had total lymphocyte counts below normal, during a first treatment course.
- The lymphocyte subsets, CD4+, CD8+, and CD16/CD56 (NK cells) are the cell populations primarily affected. In individual phase 3 studies up to 48% of patients (175) had CD4+ T cell counts below normal and up to 59% (217) had CD8+ T cell counts below normal in the first course of phase 3 studies B cells also express CD2 on the cell surface; however at least at the dose levels studied, B cell depletion was not seen.
- CD2 expression by various lymphocyte subsets differs and there is a crude correlation between level of expression and depletion. However the clinical implication for long-term toxicity of and for efficacy of alefacept are not known.
- The studies may underestimate the effect of alefacept on lymphocytes and infections because the protocol required that CD counts be >250 cells/microL in

order to dose. If marketed, this has implications for how patients should be monitored and how alefacept should be dosed.

- Studies consistently showed that lymphocyte counts decrease and do not recover to baseline in a substantial proportion of alefacept-treated patients after a prolonged observation period. The maximal effect on lymphocytes was observed within 6-8 weeks of initiation of treatment. Twelve weeks after a course of therapy (12 weekly doses), up to 4% (16), 19% (68), and 33%(121), respectively, of patients had total lymphocyte CD4+, and CD8+ T cell counts below normal..
- A second course of alefacept decreased CD4 and CD8 counts below normal and to a lower nadir in a slightly higher proportion of patients compared to a single course of therapy
- This observation suggests that the lymphocyte depletion is cumulative.
- There was a somewhat higher number of serious adverse events including infections, malignancy and cardiac ischemia in the alefacept treated groups.
- In the first course of placebo-controlled studies, serious infections (infections requiring hospitalization) were seen at a rate of 0.9 % (8/876) in alefacept and 0.2%(1/413) in the placebo group; some of these infections had a severe atypical course. In patients receiving repeated courses of therapy, the rates of serious infections were 1% and 2% in the second and third course of therapy respectively. Serious infections in alefacept-treated patients included necrotizing cellulitis, peritonsillar abscess, post-operative and burn wound infection , toxic shock, pneumonia ,appendicitis, pre-septal cellulitis, cholecystitis, gastroenteritis and herpes simplex
- In the first course of placebo-controlled studies the incidence of malignancies was 1.2% (11/876) for alefacept compared to 0.5% (2/413) in the placebo group. The malignancies which occurred in the placebo arm were one case of prostatic carcinoma and one case of basal cell carcinoma. The malignancies in the alefacept arms (n=13) were carcinoma of skin (5 squamous cell, 4 basal cell), and one case each of skin melanoma, renal cell, testicular, and prostatic carcinoma
- There was a suggestion of alefacept-induced hypersensitivity reaction (rare cases of urticaria and angioedema) and of possible deleterious effect on healing (serious complications of burn wound and surgical wound infection).
- There was no evidence that depressions in lymphocyte counts were associated with serious adverse events, particularly infections.
- Long-term studies in larger patient populations are needed to assess the risk of infection and malignancy and the recovery of lymphocyte counts to baseline/normal.
- There was no evidence of opportunistic infections or reactivation of latent/chronic infections. DTH data were inconclusive.
- Rarely patients developed low titer antibodies to alefacept.

VI. CONCLUSIONS

Alefacept is an immunosuppressive biologic that causes a prolonged decrease in number of circulating T lymphocytes in particular CD4 and CD8 memory T lymphocytes. At the end of a 12-week treatment course (IV or IM) after adjustment for placebo response, the following are the absolute percentages of responders. Ten to sixteen percent of patients

achieve ≥75% reduction from baseline PASI , 23-28% of patients achieve ≥50% reduction from baseline PASI and 7-9% of patients achieve an assessment of "almost clear" or "clear" by PGA.

The safety database show a higher number of serious infections and malignancies in alefacept- treated patients compared to placebo. In addition, insufficient data are available to assess the safety and efficacy of repeated cycles of therapy due to a large proportion of patients who withdrew from treatment with each subsequent course of therapy.

Additional studies are needed in the post-marketing phase to explore the following issues

- The effect of body weight on efficacy and safety
- Safety and efficacy of multiple courses of treatment, including effects on T cell subsets
- Risk of malignancy
- Risk of serious infections and infections with an atypical course or presentation
- Recovery of lymphocyte counts and important subsets
- Efficacy in the treatment of psoriasis variants and psoriatic arthritis
- Safety in special populations such as psoriasis patients with diabetes, those with concurrent HIV infection and, women who are pregnant
- The potential for interaction between alefacept and other immunosuppressive/antimetabolic agents that may be given as rescue or additional therapy
- The potential for interference of alefacept with the efficacy of vaccines such as influenza or pneumococcal vaccines

VII. RECOMMENDED REGULATORY ACTION

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

VIII. APPENDIX: PATIENT NARRATIVES

Deaths:

Suicide (143202)

A 34-year old man (143-202) had a 26-year history of psoriasis. The personal history was negative for psychiatric illness. The family history was notable for suicide in the patient's father. The patient received 11 doses of alefacept 7.5 mg in course 1 of study 711and withdrew from the study due to worsening of disease. Eleven weeks after his last dose of alefacept, the patient committed suicide.

Myocardial infarction (103-005)

A 47-year old man (103-005) with a past history of coronary artery disease, hypertension, obesity and smoking was enrolled into study 714 (7.5 mg alefacept IV) and died due to a myocardial infarction six weeks after his last dose.

Esophageal carcinoma (302-302)

See narrative of patient 302-302 below.

Lung carcinoma

See narrative of patient 137-211 below.

Seizure (168-302)

The patient is a 43-year old male (168-302) with a life-long history of seizures died in his sleep of a seizure 10 months after his last dose of alefacept. The subject had completed studies C99-712, in which he received placebo, and study 717, in which he received alefacept 7.5 mg IM weekly, without incident. The investigator stated that the relationship to study drug was none.

Placebo Group: Serious Infections in the First Course Placebo-Controlled Experience

Bronchitis (121-007)

A 52 year-old woman (121-007) with a history of chronic obstructive pulmonary disease due to heavy smoking was hospitalized with bronchitis attributed to "type A influenza". She was randomized to placebo in study c97-708. Her symptoms consisted of cough, unresponsive to antibiotics by mouth, a low-grade fever (99F) and dyspnea with mild hypoxemia (O2 saturation of 91% on room air). Her chest x-ray did not reveal any signs of pneumonia and she was discharged 4 days later.

Alefacept Group: Serious Infections in the First Course Placebo-Controlled Experience

Necrotizing facial cellulitis (119-006)

A 50 year-old Caucasian man (119-006) had been receiving study drug for 12 weeks in study 708. The patient developed an otitis externa complicated by right facial cellulitis requiring hospitalization and debridement. Cultures grew *S. aureus* and beta-hemolytic Streptococcus group A and B. The investigator graded the otitis externa and facial cellulitis as severe and stated that there was no relationship between the event and study drug.

Pre-septal Cellulitis (137-201)
A 44-year old Caucasian woman (137-201) enrolled in study 711 was diagnosed with blepharitis and pre-septal cellulitis12 weeks after her first dose of alefacept in course 1. There was no involvement of the globe. The event was attributed to the patient's manipulation of a sty. The patient's most recent total lymphocyte and CD4+ counts prior to onset of the event were normal. The patient was managed with a course of amoxicillin/clavulinic acid. The investigator graded the serious adverse event as moderate and classified the relationship to study drug as 'unlikely'.

Cellulitis (144-305)
A 52-year old Caucasian man (144-305) enrolled in study 712. The patient's past medical history included a myocardial infarction, hyperlipidemia, obesity, hypertension, asthma, and hypothyroidism. He was randomized to the 15 mg dose group and received 1 dose. One week after his first and only dose of alefacept, he reported flu-like symptoms 2 hours after his injection as well as "swelling of both legs." His physician in clinic who noted he was afebrile and hypertensive (168/110) with a normal pulse and respiratory rate saw him. His lower extremities showed "2+ pitting edema without signs of infection." That evening, however, the patient complained of chills, fever, nausea and chest pain and was admitted to hospital. On admission he was again afebrile, hypertensive (165/92), and had an O2 saturation of 93% on room air. His extremities revealed "3+ pitting edema and marked large confluent areas of psoriatic changes with possible surrounding cellulitis." Work-up showed an ECG with no acute changes, a stress echocardiogram with no acute ischemia, and a venous Doppler exam with no deep venous thrombosis. Blood cultures were also negative. The patient's lowest lymphocyte and CD4+ count were on the day of the event and were 990 cells/µL and 312 cells/µL, respectively. The patient was treated with ampicillin/sulbactam, dicloxacillin, nitrates, and diuretics. He was discharged to home three days later with a diagnosis of psoriasis with cellulitis, atypical chest pain, asthma and COPD. The patient had voluntarily withdrawn from the study with the onset of symptoms. The investigator graded the serious adverse event as severe and classified the relationship to study drug as 'likely.'

Reviewers' comment: ----------

Peritonsillar Abscess (332-303)
A 43-year old man (332-303) enrolled in study 712 (10 mg alefacept arm). The patient received 8 doses prior to onset of symptoms of a sore throat and was eventually hospitalized for a peritonsillar abscess. On admission his white blood cell count was 13.3 x 1000/uL and CRP 4.8. The patient's lowest lymphocyte and CD4+ count prior to onset was 1300 cells/µL and 457 cells/µL, respectively. The patient was treated with incision and drainage of the abscess twice and IV antibiotics. Participation in the study 712 was continued. The investigator graded the serious adverse event as severe and classified the relationship to study drug as 'likely.'

Wound Infection of a Burn (150-218)

A 55-year old man (150-218) with diabetes mellitus, hypertension, hypercholesterolemia, and obesity was enrolled into C99-711 and randomized to receive alefacept in Courses 1 and 2. During Course 1, one month after his first dose, he developed erythema and pain associated with a recent burn. Six days earlier he had sustained an 18 x 24 cm burn to the mid abdomen. The patient's most recent total lymphocyte and CD4+ count prior to onset of the event were 1890 cells/ul and 1014 cells/ul, respectively. He was hospitalized and treated successfully with IV antibiotics and local care. Participation in the C99-711 study was continued. The investigator graded the serious adverse event as severe and classified the relationship to study drug as 'unlikely'.

Gastroenteritis (183-309)

The patient, a 30-year old woman (183-309), was enrolled into study 712 and randomized to the 10 mg dose group. One week after her sixth dose of alefacept, she reported back pain, food intolerance, nausea, vomiting, and diarrhea. Her concomitant therapy at the time of onset was adapaline gel, clindamycin, butalbital/acetaminophen/caffeine, and acetaminophen. She was hospitalized and further evaluation revealed normal liver function studies, a negative test for C. difficile toxin, and a normal abdominal ultrasound with no evidence of renal or gallstones. No cultures were performed. The patient's lowest lymphocyte and CD4 count prior to onset of the event were 1290 cells/µL and 546 cells/µL. She was diagnosed with gastroenteritis and was managed successfully by IV fluids, metronidazole, and phenergan. Further participation in the C-712 study was continued. The investigator graded the serious adverse event as severe and classified the relationship to study drug as 'not related.'

Gastroenteritis (330-301)

A 44-year old woman (330-301) was enrolled into C-712 and was randomized to the 10 mg dose group. Five weeks after her first dose and 5 days after her fifth dose of alefacept, she reported diarrhea. She was hospitalized. On admission her blood pressure was 90/60, serum potassium was 3.3 mEq/L, CRP 20.6. No cultures were performed. The patient's lowest lymphocyte and CD4 count was 690 cells/µL and 374 cells/µL, 1 day after onset. She was diagnosed with gastroenteritis, which the patient believed to be food- related. She was treated successfully with IV fluids and loperamide. Participation in the C-712 study continued. The investigator graded the adverse event as moderate and classified the relationship to study drug as 'unlikely'. This case of gastroenteritis was believed to be food-related and occurred after the fifth dose of study drug.

Reviewers' comment: Both of the above patients with gastroenteritis continued study drug with no further adverse events.

Asthma (103-004)

This 42-year old woman (103-004) enrolled in study 708 was hospitalized for an exacerbation of asthma. She had a history of ten asthma exacerbations since she was diagnosed nine years earlier but never before required hospitalization. The subject developed wheezing and dyspnea after spending time outdoors. Having failed outpatient therapy with bronchodilators, she was admitted to hospital three days later for asthma. She was treated with albuterol, Atrovent and IV methylprednisolone followed by a

prednisone taper. A chest X-ray was reported to be within normal limits with no interval change in comparison to a prior chest X-ray several months earlier. Her CBC and chemistry profile were within normal limits. The investigator stated that the relationship of study drug to event was "none".

The patient was not withdrawn, so not likely to be a hypersensitivity. The case was classified by the investigator and sponsor as infectious and secondary to a viral upper respiratory infection.

Narratives of Selected Treatment-Emergent Serious Infections:
Outside the placebo-controlled first course experience, several serious infections of note occurred. These are summarized below.

Alefacept First Course-Post Dosing
Bacterial infection of surgical wound (113-002)

The patient, a 27-year old man (113-002) had had psoriasis for 14 years. He had participated in study 708 and received placebo. The patient enrolled in study 710 and received 11 doses t of 0.15 mg/kg alefacept. Six weeks after his last dose he fell and sustained multiple tibial fractures. He underwent pinning and casting and one week later had a fever of 102 ^{o} F, purulent drainage from the incision and at the site of pin insertion. His incisional infection was treated with antibiotics, analgesics and surgery (NOS). The patient's lowest lymphocyte and CD4+ count prior to onset of the event were 710 cells/µL and 278 cells/µL, respectively seven weeks before his injuty. The infection resolved without sequelae at follow up. This adverse event was graded as serious. The investigator stated that the relationship between the study drug and the event was "none".

Reviewers' comment: The abnormal total lymphocyte and CD4 counts indicates that the patient's infection might be related to the study drug.

Alefacept Retreatment/Course 3 (IV)
Bronchitis (130-209)
Patient 130-209, 49-year old with a past medical history of smoking for 30 years was hospitalized for bronchitis 5 weeks after his last dose of alefacept in study 724. He had no prior history of asthma, COPD or chronic bronchitis. He had received 24 doses in study 711 and 12 doses in study 724

Alefacept Retreatment/Course 2 (IM)
Periorbital herpes simplex infection (332-302)
Patient 332-302, a 50-year old man, was diagnosed with a periorbital herpes simplex infection 5 weeks after his last dose in study 717. He had received 12 doses (15 mg IM) in study 712 and 11 doses (15 mg IM) in study 717. No cytologic smears, biopsies or cultures were performed. His most recent lymphocyte counts were normal. He was admitted to the hospital for IV acyclovir and antibiotics and recovered without sequelae.

Alefacept First Course
Pneumonia (310-913)

The subject, a 32-year old man (310-913), received two 7.5 mg doses IV of alefacept, (one dose of BIO BG9273 followed by one dose of ------- BG9273 two months later). He had a 12-year smoking history. Three weeks after his last dose of alefacept he reported diaphoresis and dyspnea. A chest x-ray revealed pneumonia. He admitted to hospital and treated with antibiotics. The subject's most recent CD4+ T cell count, was 423 cells/µL, and his most recent lymphocyte count was 1269 cells/µL. The subject was discharged from hospital 4 days later and, the event resolved without sequelae. The investigator graded the serious adverse event as moderate in severity and classified the relationship to study drug as 'unlikely'.

Alefacept Retreatment/Course 2 (IM)
Peritonitis (336-307)
Patient 336-307, a 42-year old man with diabetes mellitus was hospitalized with a diagnosis of peritonitis after a sudden onset of abdominal pain. He had received 12 doses of alefacept 10 mg IM in study 712 and 5 doses IM in study 717. The event occurred on the day of his fifth dose in study 717. Abdominal ultrasound and chest X-ray were normal. The WBC count was $13.3x10^9$/L, bilirubin was e2.5 mg/dl and blood sugar 308 mg/dl. The patient was treated with berlocombin and trimethoprim/sulfamerazin. The final diagnosis was "pseudoperitonitis diabetica." The patient continued dosing in study 717 without sequelae.

Reviewers' comment:
Given the increase in white blood cell count accompanying the abdominal pain and the response to antibiotics, this adverse event should be considered as possibly infectious in etiology.

Alefacept Retreatment/Course 2(IM)
Post-operative wound infection with abscess and fistula formation (135-203)
Patient 135-203, a 58-year old man with psoriasis, non-insulin dependent diabetes, hypertension and obesity took part in study 711 and received alefacept in courses 1 and 2. A diagnosis of rotator cuff tear was made during course 1, 3 weeks after completing the first dosing period and he was treated surgically. Six weeks post-operatively, after receiving the first 5 doses in course 2 of alefacept, an abscess developed at the surgical site and was was incised and drained. The infection failed to resolve with antibiotics (cephalexin) and he underwent wound exploration and incision and drainage and treatment with IV cephalexin. Four months post-operatively, he underwent a second exploration of the incision site with drainage and irrigation. The patient had breakdown of the original repair and a large fistula tract extending to the humeral joint. Cultures grew *Serratia marcescens*. The wound was packed and left open. Five months post-operatively, he underwent a third wound exploration, extensive debridement and reconstruction of the right shoulder. The patient had residual loss of right arm function on follow-up.
The investigator graded both the accidental injury and infectious adverse events as moderate. The relationship to study drug for the accidental injury was classified as 'none' and for the infection as 'unlikely'.

Alefacept Post-dosing/Course1 (IV)
Septic Shock Secondary to Cellulitis
A 56 year old woman, patient 101-113, in study 709 with a history of arthritis, recurrent DVT and pulmonary emboli was hospitalized on with sepsis approximately 3 months after the last 0.750 mg/kg IV dose of BG9712. She presented with arthralgia, increased joint swelling, muscle aches and chills 9 weeks after the last dose of study drug. She was hospitalized 2 weeks later for diarrhea and rectal bleeding. Abdominal CAT scan was unremarkable. She was discharged within 24 hours with a diagnosis of a 'viral infection'.

About one day later, she was re-admitted with an edematous right lower leg, a temperature of 105°F, sepsis and acute renal failure. A right lower leg fasciotomy showed no evidence of necrotizing fasciitis. Her condition deteriorated despite IV antibiotics and she developed respiratory failure requiring mechanical ventilation. A pathogen was not isolated from joint, skin, fascia or lung. TSST-1 toxin antibody screen was positive. The patient ultimately survived. Of note, the patient's total lymphocyte and CD4 + counts were within normal limits throughout the study. The investigator diagnosed toxic shock syndrome secondary to right lower leg cellulitis, and the relationship to study drug was classified as "none".

Reviewers' comment:
Disagree with assessment of causality. Given high dose of alefacept, the relatively long half-life, and the atypical features of the case, the event should be classified as at least possibly related.

Basal cell carcinoma of the skin (166-306)
A 66-year old Caucasian man (166-306), had psoriasis for 38 years. No previous therapy for his skin disorder was recorded. The patient was enrolled into study 712. He was randomized to the 15 mg dose group and received 12 doses. Seven weeks after his last dose of alefacept, he underwent biopsy of a 1.4 X 1.3 cm left chest skin lesion. The histologic diagnosis was basal cell carcinoma. The residual lesion was completely excised. The patient's lowest lymphocyte and CD4+ count prior to onset of the event were 1970 cells/µL and 808 cells/µL, respectively, 7 weeks before onset. The investigator graded the adverse event as mild and classified the relationship to study drug as 'unlikely.'

Basal cell carcinoma of the skin (326-301)
A 36-year old Caucasian woman (326-301), had psoriasis for 15 years prior to study entry and had previous received phototherapy (PUVA, UVB). The patient was enrolled into study 712, randomized to the 15 mg group. Eighteen weeks after the first dose and 6 weeks after her last dose of alefacept, she underwent excision of a pigmented skin lesion of her right breast. The histologic diagnosis was pigmented basal cell carcinoma. The patient's lowest lymphocyte and CD4+ count prior to onset of the event were 1520 cells/µL and 618 cells/µL, respectively, 8 weeks before onset. The investigator graded

the serious adverse event as moderate and classified the relationship to study drug as 'likely.'

Squamous cell carcinoma of the skin (145-209)

The patient, a 64-year old Caucasian man (145-209), had had psoriasis for 32 years prior to study entry. He had previously received PUVA (for 2 months, last dose 1980) for his skin disorder, but had not received UVB or any oral medication. The patient was enrolled into study 711 and randomized to receive alefacept in Courses 1 and 2. He received 12 doses in Course 1 and no doses in Course 2. Seven and a half months after his first dose of alefacept, a 1cm left shoulder lesion was noted which was diagnosed by biopsy as a squamous carcinoma and eventually completely excised. The patient's most recent total lymphocyte and CD4+ counts prior to onset of the event were 1180 cells/ul and 336 cells/ul. Prior to Course 2, his CD4+ count was below the lower limit of normal, and therefore, he was not eligible for entry to Course 2. The investigator graded the serious adverse event as mild and classified the relationship to study drug as 'unlikely'.

Squamous cell carcinoma of the Skin (114-204)

The patient, a 66-year old Caucasian man (114-204), had had psoriasis for 20 years prior to study entry. He had previously received methotrexate (for 48 months, last dose January 2000) and UVB (for 3 months, last dose 1998) for his skin disorder, but had not received PUVA. The patient's past medical history included a squamous cell carcinoma of the skin in 1995. The patient was enrolled in study 711 and was randomized to receive alefacept in Courses 1 and 2. During Course 1 and 2, three skin cancers were reported from the following sites: left temple; forehead; and shoulder, 20 days, 24 weeks, and 31 weeks after his first dose, respectively. By report, the shoulder lesion was a "questionable basal cell carcinoma" and the patient was neither biopsied nor treated. The forehead and temple lesions were excised. A pathology report was available only for the left temple lesion, which revealed a 5 x 5 x 1.5 mm squamous cell carcinoma in situ. Each lesion was associated with total lymphocyte and CD4+ counts ranging from 1470 to 1870 cells/µl and 427 to 615 cells/µ l, respectively. The investigator graded both the forehead and left temple carcinomas as moderate and classified their relationship to study drug as 'none'. The untreated questionable basal cell carcinoma was graded as mild and its relationship to study drug as 'unlikely'.

Squamous cell carcinoma of the skin (139-209)

A 55-year old Caucasian woman (139-209) had psoriasis for 35 years prior to study entry. She had previously received methotrexate (for 369 months, last dose 1999), but no PUVA or UVB for her skin disorder. The patient was enrolled in study 711 and randomized to receive alefacept in Course 1 and placebo in Course 2. During Course 1, 3 months after her first dose of alefacept, a 0.8 cm right lateral knee skin lesion was reported. The histologic diagnosis was well-differentiated squamous cell carcinoma. The patient's total lymphocyte and CD4+ counts on the day of the event were 1650 cells/µl and 393 cells/µl, respectively. The investigator graded the serious adverse event as moderate and classified the relationship to study drug as 'likely'.

Squamous cell carcinoma of the skin (106-008)

The patient, a 50-year old Caucasian man (106-008) had had psoriasis for 28 years prior to study entry. He had previously received UVB (for 3 months), PUVA (for 6 months), methotrexate (for 6 months) and systemic retinoids (for 18 months) for his skin disorder. The patient had previously had a squamous cell carcinoma of the right arm and leg in 1996 and 1997, respectively. The patient was enrolled in study 708 and was allocated to the 0.025 mg/kg group and received 10 doses. Seven weeks after his first dose of BG9273, a lesion was detected on his left leg. He underwent curettage, measuring 1.2 x1.1 cm in dimension, which showed an invasive well-differentiated squamous carcinoma. The patient's lowest lymphocyte and CD4 counts on the day of detection of the lesion were 1110 cells/µl and 598 cells/µl, respectively. An excision, measuring 5.3 x 1.4 x 0.8 cm, was performed, but tumor was present at the deep and lateral margins. Ultimately, the patient underwent Moh's surgery for complete excision. The investigator graded the adverse event as moderate and classified the relationship to study drug as none.

Reviewers' comment:
This event was notable for the invasiveness of the tumor. It is unusual for a skin cancer on the leg to require re-excision with Moh's surgery.

Serious Adverse Event: Renal cell carcinoma (128-205)
The patient, a 37-year old man (128-205), had psoriasis for 2 years prior to study entry. The patient's past medical history included back pain and gross hematuria (dates of onset unknown), chronic hepatitis C, coronary artery disease, hypertension, and hyperlipidemia. The patient was enrolled in study 711 and received 12 doses of alefacept in Course 1. Three weeks after his first dose of alefacept, the patient underwent a CT scan, which identified a right renal mass. The mass had previously been detected on an X-ray for back pain (date unknown). The patient's most recent total lymphocyte and CD4+ count prior to onset of the event were 2370 cells/ul and 1017 cells/ul, respectively, 6 days before onset. He underwent a right radical nephrectomy. The surgical pathology report noted an 11.5 cm Grade 4 renal cell carcinoma with negative margins and no evidence of metastatic disease. His course was uncomplicated, a full recovery occurred. He received no adjuvant therapy. No sequelae were documented. The patient, however, decided to discontinue study participation, after completing Course 1, due to his diagnosis of cancer. The investigator graded the serious adverse event as severe and classified the relationship to study drug as 'none'.

Serious Adverse Event: Testicular Carcinoma (112-002)
A 24-year old male (112-002) was enrolled in study 708 and received alefacept 0.15 mg/kg. Approximately four months after his last dose, he was diagnosed with testicular teratocarcinoma with pulmonary metastases. He completed chemotherapy, orchiectomy and radiotherapy. The tumor was clinically undetectable after treatment.
The investigator graded this serious adverse event as severe and the relationship to study medication as unlikely.

Serious Adverse Event: Prostatic carcinoma (145-203)

A 67-year old male (145-203) was enrolled in study 711 and received 2 doses of alefacept in Course 1. Approximately one month prior to study drug administration, he was noted to have an elevated PSA. He underwent a prostate needle biopsy which showed focal prostatic adenocarcinoma (Gleason grade 3+3). Following his diagnosis, the patient prematurely withdrew consent for study 711. He was not seen during follow up visits, and it is unknown if he received further therapy. The investigator classified the relationship to study drug as 'none'.

Serious Adverse Event: Skin melanoma (150-208)

A 77-year old Caucasian man (150-208) had psoriasis and had received UVA/UVB/oxsoralen (for 51 months, last dose 1993), PUVA (for 9 months, last dose 1994), UVB (for 8 months, last dose 1995), and systemic retinoids (for 5 months, last dose 1998) for his skin disorder. The patient's past medical history included a right leg and a right arm squamous carcinoma (1997 and 1999). He had no family history of melanoma. The patient enrolled in study 711 and received 12 doses of alefacept in Course 1. During Course 1, 2.5 months after his first dose, a 1cm x 1 cm black papule, which had undergone a color change, was noted on his right lower back. The patient's most recent total lymphocyte and CD4+ counts prior to onset of the event were 840 cells/ul and 198 cells/ul, respectively. He underwent a biopsy which revealed malignant melanoma in situ with no evidence of invasion. He underwent a complete excision, which showed no residual tumor and, he had no evidence of metastatic disease. The patient decided to discontinue study participation, after completing Course 1, due to his diagnosis of melanoma. The investigator graded the serious adverse event as severe and classified the relationship to study drug as 'none'.

Reviewer's comment: Of note, the patient's most recent total lymphocyte counts and CD4 counts were below normal.

Narratives of Selected Treatment-Emergent Malignancies: Beyond the First Course of the Placebo-Controlled Experience

Discussed here are the narratives of treatment emergent malignancies diagnosed in patients enrolled in the open label trials and those diagnosed in patients who had completed the first course of the placebo-controlled trials.

Alefacept Retreatment: Course 3 (IM)

Serious Adverse Event: B cell Lymphoma (169-306)

A 68-year old female (169-306) enrolled in study 728, developed a right intraparotid lymph node enlargement. She had received a total of 20 doses (15 mg IM) of alefacept in previous studies. Her CD4 and CD8 counts were within the normal range at all measurements in each study in which she participated. Further evaluation including excision of the lymph node revealed a B-cell lymphoma by histology and immunophenotype. Flow cytometry showed a 'population of mature B cells expressing HLA-DR, CD45, CD19, intermediate density of CD20, CD21, and high density lambda light chains present in 53% of the lymphocytes'. Staging workup revealed no evidence of disseminated lymphoma. The patient was treated surgically and with chemotherapy. The investigator reported that the relationship between this event and the administration

of alefacept was "likely". The EBV studies of the resected specimen are negative. The sponsor considers it very unlikely that this case of non-Hodgkin's lymphoma is a result of immunosuppression.

Alefacept Retreatment: Course 2 (IM)
Serious Adverse Event: Hodgkin's Disease (332-310)
A 62-year old white male (332-310) developed fever and weight loss approximately 5 months after his last dose of alefacept in study 717. His cumulative alefacept dose at that time was 24 doses of 15 mg administered IM. Throughout both courses of alefacept, the patient's CD4 and CD8 counts remained within the normal range. His previous treatment for psoriasis included PUVA (2 months) and UVB(1 month); he had no history of methotrexate or cyclosporin use. The patient's pre-existing medical conditions included: alcohol use associated with elevated liver enzymes 2-3 years prior, non-insulin-dependent diabetes mellitus, and a 15 pack-year history of smoking. The patient's HIV status at diagnosis was negative and his family history is negative for Hodgkin's disease. The histology obtained showed, mixed cellularity Hodgkin's disease stage IV with enlarged cervical and celiac lymph nodes and liver lesions of unknown etiology. The patient received chemotherapy, four cycles of prednisone, procarbazin, cyclophosphamide, doxorubicin, and etoposide. The investigator classified the event as severe and likely related to study drug.

Alefacept Retreatment: Course 2 (IM)
Serious Adverse Event: Optic Nerve Melanoma (301-302)
Patient 301302, a 41-year old man was diagnosed with a right optic nerve melanoma. He was enrolled in study 712 and was randomized to the 10 mg dose group. He was diagnosed with an optic nerve nevus approximately 32 weeks after his first dose and 20 weeks after his last dose of alefacept on routine ophthalmologic exam. On follow-up exam approximately 8 weeks after his last dose in study717, the diagnosis was revised to optic nerve melanoma 1.7 mm in thickness based on photography and ultrasound. No biopsy was performed. There was no family history of melanoma or optic nevi. He was treated with 4 days of radioactive disc placement.

Alefacept Retreatment: Course 2 (IM)
Serious adverse event: Esophageal adenocarcinoma (302-302)
Patient 302-302, a 53-year old man with a history of diaphragmatic hernia and Barrett's esophagus, was diagnosed with esophageal adenocarcinoma. He had enrolled in study 712 followed by study 717 and received two courses of alefacept 15 mg IM. Thirty-six weeks after his first dose and 1 week after his last dose, he complained of dysphagia. He was diagnosed with a poorly differentiated esophageal adenocarcinoma associated with intestinal metaplasia. The investigator stated that the relationship between the study drug and the event was "none".

Reviewers' comment: Of note, the patient had had endoscopy and biopsy approximately 2 years earlier and no dysplasia was noted at that time.

Alefacept Retreatment: Course 3 (IV)
Carcinoma of the lung and intraductal pancreatic neoplasm (137-211)
Patient 137-211, a 46-old male was diagnosed with adenosquamous carcinoma of the lung, stage IIIB, and a pancreatic mucinous "intraductal papillary neoplasm." The pancreatic neoplasm and the lung carcinomas were believed to be two primaries. He was enrolled in study 711 (cohort 2) and received 12 doses of alefacept (7.5 mg IV) prior to event onset. The patient was diagnosed with carcinoma of the lung nearly 3 months after completing his last dose; however, he had had a 6-week history of hemoptysis prior to diagnosis. His risk factors included a 25-year history of smoking (1-3 packs per day).

The patient received palliative chemotherapy. He died of his malignancies after developing refractory metastatic disease. No autopsy was performed. The investigator classified the relationship between study drug and the lung carcinoma and pancreatic neoplasm as 'likely'.

Alefacept Retreatment: Course 3 (IV)
Serious adverse event: Carcinoma of the Lung (121-114)
A 65-year-old white male in study 714 (121-114) developed lung carcinoma after receiving 3 courses of alefacept. The investigator graded this serious adverse event as severe and its relationship to study drug as 'unlikely'.

Alefacept Retreatment: Course 3(IV)
Serious adverse event: Hemorrhage of colon
Adverse event/Malignancy: Carcinoma/GI Neoplasia (104-003)
The patient, a 65-year-old woman (104-003), was diagnosed with a sigmoid colon polyp with carcinoma in situ. She had psoriasis for 17 years prior to study entry. The patient's past medical history of relevance included a recent history of guaiac positive stools (exact date in relation to this study unknown) and a strong family history of colon cancer. The patient was enrolled into study 714 on 3 December 1999. She received 12 doses (7.5 mg IV) of alefacept in Course A, 12 doses in Course B, and 4 doses in Course C, as of 31 December 2000.

During Course B, on 26 September 2000, 41.6 weeks after her first dose in 714, she underwent a colonoscopy (for guaiac positive stools) and polypectomy. Later in the day, she experienced a lower gastrointestinal bleed accompanied by hypotension and requiring transfusion with 2 units of packed red blood cells and emergent colonoscopy with cauterization of bleeding sites. The surgical pathology report had revealed 4 colonic adenomas. One adenoma (0.8 cm) showed a focus of adenocarcinoma in situ and the other adenoma (1.3 cm) showed moderate to severe dysplasia. The other two adenomas showed mild to moderate dysplasia. The patient's most recent lymphocyte and CD4+ T cell counts were within normal limits. Further participation in study 714 was not terminated and the patient went onto receive 4 further doses of alefacept. The investigator graded the serious adverse event as 'severe' and classified the relationship to study drug as 'none.'

First Course of Alefacept

Non-serious adverse event: Cutaneous melanoma in-situ (121-116)
Patient 121-116, a 69-year old male was diagnosed with a cutaneous melanoma in-situ of the left post ear (8/99). He was enrolled in study 709. During his first course of alefacept three weeks post-dosing, he was diagnosed with melanoma in-situ.

Alefacept Retreatment: Course 2 (IV)
Squamous cell carcinoma of the skin (111-101)
Patient 111-101, a 58 year-old white male, was diagnosed with four cutaneous squamous cell carcinomas in the second course of treatment with alefacept. He received his first course of alefacept in study 907, followed by treatment with PUVA and finally received a second course of alefacept in study 714, 7.5 mg IV. Previously, he received PUVA (11 months, last dose 1998), methotrexate (1 month, last dose 1968) and coal tar (5 months, last dose 1998). He had no prior history of skin cancer.

During study 714, the patient developed four squamous cell carcinomas in the following locations: left knee, left inner thigh, left calf and left shin. The left knee lesion was detected prior to dosing and biopsied after dosing in the second treatment course. However, the remainder of the above lesions were both detected and biopised after dosing beginning approximately 7 weeks after the first dose in the second course. These were considered serious adverse events of moderate severity and were unlikely related to the study medication according to the investigator.

The patient's most recent lymphocyte and CD4 cell counts prior to the third treatment-emergent malignancy were 1210 and 301 cells/µl, respectively. Although, the patient completed study 714, he declined to participate in further studies due to the number of skin cancers that he developed.

Reviewers' comment: This patient is notable for the number of squamous cell carcinomas that developed in his second course of therapy. In addition, this points to a possible priming effect by the PUVA that the patient received. The study report did not summarize this case fully and described the patient has having squamous cell carcinoma of the skin diagnosed before dosing in Course A.

First Course Alefacept-Post Dosing
Squamous cell carcinoma in situ (111-104)
A 45 year-old woman (111-104) with no history of cutaneous malignancy was diagnosed with squamous cell carcinoma in situ of the left calf. She had previously received PUVA (for 10 years, last dose 1989); UVB (for 5 years, last dose in 1989); methotrexate (8 years, last dose 1987) and retinoids for (1 year, last dose 1988). The patient had completed study 709 when she first noted her lesion on the left calf. The investigator graded the serious adverse event as moderate and classified the relationship to study drug as "unlikely".

First Course Alefacept
Squamous cell carcinoma (keratoacanthoma type) (128-004)
A 37 year-old woman (128-004) developed a squamous cell carcinoma (keratoacanthoma-type) of the left back one month after initiating dosing with alefacept

(0.15 mg/kg). She participated in study 708 where she received placebo followed by study 710 where she received alefacept. The patient's lowest lymphocyte and CD4 count before the adverse event were 1130 and 401 cells/μL respectively. She went on to complete dosing with study drug. The relationship to study drug was classified as "none"

First Course Alefacept (Post-dosing)
Questionable basal cell carcinoma (114-209)
A 39 year old white male (114-209) had psoriasis for over two-decades and received PUVA (for 1 month, last dose 1985) and UVB (for 3 months, last dose 1999), but no oral medication for his skin disorder. His past medical history included epilepsy (since 1976). The patient was enrolled in study 711 and randomized to cohort 2. He received 12 doses of alefacept in Course 1 and placebo in course 2. During Course 2, 11 months after his first dose, a questionable left upper back basal cell carcinoma was detected. The lesion was neither biopsied nor treated. The patient's total lymphocyte and CD4+ counts on the day of onset were 1200 cells/ul and 564 cells/ul, respectively. Follow-up from the physician indicates he is observing the lesion. The investigator graded the adverse event as moderate and classified the relationship to study drug as 'none'.

Reviewers' comment: The diagnosis of basal cell carcinoma is not at all uncommon in a Caucasian person of this age group. In addition, this patient had a history of PUVA. Recommended that a biopsy be performed.

Hospitalization for psoriasis following treatment with alefacept:

Hospitalization for Severe Psoriasis (337-304)
A 36-year old man (337-304) with a 21-year history of psoriasis was hospitalized 4 weeks after his last dose of alefacept. He was enrolled in study 712 and randomized to receive the 10 mg dose. It was reported that he did not respond to the study drug. Although, the PASI score had reduced by 22%, his PGA remained 'moderate to severe'.

Pustular and Erythrodermic Psoriasis (325-306)
A 50-year old man (325-306) with a 21-year history of psoriasis previously treated with cyclosporin, methotrexate, systemic retinoids and PUVA was hospitalized with erythrodermic psoriasis and arthritic symptoms. In addition, pustular lesions were described on his extremities and were associated with a fever. He had been randomized to the 15 mg dose group and received 7 weeks of treatment at the time of hospitalization. He was treated with cyclosporin and withdrew from the study.

Hypersensitivity Reactions following Alefacept
Angioedema:
Life-threatening recurrent angioedema (105-004)

A 56 year-old man, 105004,was hospitalized after experiencing symptoms described as angioedema by the Principal Investigator.

The subject received alefacept (0.025mg/kg) in study 708. Approximately one week after his last dose, he developed a sensation of swelling in his throat followed by difficulty

swallowing and periods of gasping for breath, drooling, and an inability to speak. The subject was taken to the emergency room and was found to have a swollen tongue. He was treated with 100 mg IV hydrocortisone sodium succinate and 50 mg IM diphenhydramine hydrochloride. Alefacept was permanently withdrawn. The investigator stated that the relationship of study drug to the event was "likely".

Three days after completing his last dose of steroids, the subject experienced mild angioedema characterized by mild tongue swelling. The subject received cetirizine hydrochloride, ranitidine and prednisone. After discontinuing cetrizine, approximately one month later, the patient again experienced angioedema characterized by tongue swelling and difficulty swallowing. The subject was instructed to take prednisone and restart cetrizine. The investigator suspects the cause of the angioedema to be environmental allergies.

Angioedema (176-305)

Patient 176-305 a 20-year old woman with no significant past medical history received 11 doses of laefacept (15 mg IM) in study 712 with no adverse events. After her second dose of alefacept (15 mg IM) in study 717, she developed a moderate injection site reaction. After her third dose in study 717, it was reported that she had a moderate generalized allergic reaction with angioedema. The exact timing in relation to the third alefacept injection is unknown. She was receiving no concomitant systemic medications at event onset. The following day she was treated with diphenhydramine and loratadine with resolution. The event was classified as likely related to study drug and dosing was discontinued. She had no additional reported allergic reactions.

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