

MEMORANDUM

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TOPIC Briefing Document
Biologic License Application STN BL 125036/0 for alefacept for
treatment of chronic plaque psoriasis

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I. INTRODUCTION

Filing of License Application

On August 6, 2001 Biogen submitted to the Center for Biologics Evaluation and Research a Biologics License Application STN BL 125036/0 for alefacept for the treatment of psoriasis.

Drug Product

Alefacept (LFA3TIP) is a recombinant glycosylated fusion protein consisting of the first domain of human LFA3 fused to the hinge and constant regions (C_H2 and C_H3) of a human IgG1 heavy chain. The protein is expressed by Chinese hamster ovary cells and is secreted as a 115 kD, disulfide-linked dimer.

The drug product is a sterile lyophilized powder containing LFA3/IgG1 10 mg/ml per vial and various excipients. The product is stored frozen (-70 °C) and is reconstituted with water. In the clinical trials placebo consisted of 0.9% Na Cl.

Rationale and Hypothesis

LFA-3 is a CD2 receptor ligand and enhances adhesiveness of T lymphocytes to antigen-presenting cells. CD2/LFA-3 interactions transduce signals not only to T lymphocytes but also to interacting monocytes resulting in secretion of cytokines involved in T lymphocyte responses. The immune response starts with interaction of T lymphocytes with antigen presenting cells. The binding of co-stimulatory molecules with their ligands (e.g. CD2/LFA-3, LFA-1/ICAM-1, CD28/B7, CD4/class II, and CD8/class I) is required for optimal T lymphocyte activation. Inhibiting the co-stimulatory interactions may reduce T lymphocyte responses. CD2 is expressed on all subsets of T lymphocytes and natural killer cells. CD2 increases T lymphocyte responses initiated through the T cell receptor (TCR/CD3). CD2 binding to LFA-3, co-stimulates T lymphocyte proliferation and cytotoxic T lymphocyte and NK effector functions.

Activated T lymphocytes may play a role in autoimmune diseases including plaque-type psoriasis and interference with T lymphocyte activation may be therapeutic. Blocking or reducing T-lymphocyte activation may improve the clinical manifestations of psoriasis.

Proposed Indication: Plaque Psoriasis

Psoriasis is a chronic skin disorder characterized by erythematous, scaly papules and plaques with a predisposition for the scalp, extensors of the limbs, lumbosacral area and genitalia. The condition affects between 1 and 3% of the general population. However, it is relatively infrequent among African-Americans, in Japanese populations and in the Native American population. Men and women are equally affected.

Psoriasis has a bimodal peak of onset, one in adolescents and young adults (at 16 to 22 years of age) and the second in older persons (at age 57-60). Onset is before the age of 15 in 27% of cases. Early onset disease is strongly linked to HLA Cw6 and DR7, while late onset disease is linked to HLA-Cw2. The cause of psoriasis is not fully known.

Psoriasis is a disorder of excessive proliferation of keratinocytes with secondary inflammation. Defects in cytokine expression, intracellular signaling, polyamine as well

as other abnormalities support this hypothesis. There is evidence that activated T cells are involved in the pathogenesis of psoriasis with excessive keratinocyte proliferation as a secondary phenomenon. The predisposition to psoriasis is thought to be polygenic with expression triggered by environmental factors such as streptococcal infection, stress, certain drugs, and HIV.

Plaque psoriasis is the most common form. The lesions are indurated/raised, erythematous and scaly. Approximately 1/3 of patients have moderate to severe disease. The disease waxes and wanes. Spontaneous remissions and relapses are the rule. Spontaneous durable remissions may occur.

Guttate (drop-like) psoriasis is sometimes triggered by streptococcal infection and is associated with development of chronic psoriasis. Pustular psoriasis varies in severity from localized to generalized forms with fever, malaise, and a relatively high mortality after prolonged courses. Erythroderma can be complicated by sepsis, temperature instability and high output cardiac failure. Psoriatic arthritis is a complication in approximately 10% of all psoriasis patients.

Patients with psoriasis report reduction in mental and physical functioning comparable to that seen in patients with cancer, or arthritis, The chief complaints of patients with psoriasis are scaling, itching, redness and tightness of the skin, bleeding and burning sensations. In a 1998 National Psoriasis Foundation Patient-Membership survey, patients reported depression, difficulties in the workplace and socialization caused by psoriasis.

The goal of treatment of psoriasis is to decrease the severity and extent of psoriasis to the point that it no longer interferes with the patient's occupation, personal or social life, or well-being.

Licensed Therapies for Psoriasis

Topical Therapy:

The initial treatment of stable plaque psoriasis affecting 10-20% of body surface area is topical. Topical therapies include emollients, corticosteroids, anthralin, tar, retinoids, calcipotriene, and salicylic acid. The mainstay of treatment is topical corticosteroids. Topical corticosteroids induce skin atrophy striae, purpura and may be absorbed, systemically leading to suppression of the hypothalamic-pituitary-adrenal axis. Another possible limiting factor to their use is tachyphylaxis. Other commonly used topical agents include calcipotriene (a vitamin D analogue), tazarotene (a retinoid prodrug) and anthralin. Salicylic acid is used as a keratolytic agent. Skin irritation is the most common adverse effect of these topical agents.

Phototherapy:

Phototherapy for psoriasis includes UVB, narrow band UVB, and psoralen, a photosensitizer, plus UVA (PUVA). PUVA induces responses in a high proportion of patients and can induce long-term remissions. PUVA causes premature aging of skin and increases the risk of cutaneous malignancy in a dose-related fashion. The relative increase in risk of a person with sun-sensitive skin (e.g. Fitzpatrick Type I or II skin;

always burn; tan never/sometime) developing squamous cell carcinoma is at least 5 times greater than that of control.

Systemic Therapy:

These products in general induce moderate improvement ($\geq 75\%$ clearing) in the majority of treated patients. These products are recommended for severe and/or recalcitrant psoriasis because they induce serious toxicities. Methotrexate, an antimetabolite folate analogue, appears to be more active in the treatment of psoriatic arthritis and pustular psoriasis than plaque psoriasis. Methotrexate may cause leukopenia, dose-dependent development of cirrhosis of the liver and severe pneumonitis. Methotrexate is also fetotoxic and an abortifacient. Cyclosporine an immunosuppressant calcineurin inhibitor induces hypertension, kidney disease, increased risk of malignancy (especially B cell lymphoma) and infection. Retinoids are the treatment of choice for pustular psoriasis and have also been used in the treatment of erythrodermic psoriasis. Of major consideration in women of childbearing potential is teratogenicity of retinoids. Other serious adverse events are hepatotoxicity, pancreatitis, depression, visual impairment, and hypertriglyceridemia.

Immunosuppressive Agents and Anti-metabolites: Risk/benefit in Psoriasis

Psoriasis is a serious chronic disease associated with significant morbidity and impairment. The disease is usually not life threatening and does not induce irreversible injury to skin or other organs. A number of serious toxicities are associated with the use of immunosuppressants and antimetabolites. These include serious infections, and neoplasms. In the case of neoplasms there may be a lag in the time to clinical detection and long-term follow-up of treated patients may be required to assess the excess risk. Therapies associated with significant risk of serious irreversible toxicity or mortality should be reserved for patients with severe, recalcitrant psoriasis. Long-term continuous treatment is usually not recommended. The goal of therapy is to bring disease under control and switch to the least toxic therapy.

II. SUMMARY OF CLINICAL STUDIES

PHASE 1 BA, PK STUDIES IN HEALTHY SUBJECTS.

Table 1 lists three single-center non-IND phase 1 studies conducted to assess the pharmacokinetics of alefacept in subjects not affected by psoriasis.

Table 1. Non-IND Phase 1 Studies in Healthy Subjects

Study #	Design (N)	Dosing
C95-701	Placebo- controlled single-dose, dose-escalation. N= 42	0.0, 0.005, 0.01,0.02,0.04,0.1,0.15, 0.025 mg/kg IV
C96-704	Open-label randomized, parallel group, single-dose. N=16	0.04 mg/kg IM or IV
C97-706	Double-blinded, placebo-controlled, randomized, single-dose study. N=54. -Part 1: Dose-escalation of BG9712. -Part 2:Parallel-group comparison of BG9712 and BG9273.	BG9712: IV infusion of 0.04 mg/kg, IV bolus of 0.04 mg/kg, IV bolus of 0.15 mg/kg, IM injection of 0.15 mg/kg, SC injection of 0.15 mg/kg, BG9273: IV bolus 0.15 mg/kg

PROTOCOL C95-701

Study Design

A phase 1, intravenous single-dose, controlled, blinded, dose escalation study was carried out in healthy volunteers in the UK. Seven cohorts of six subjects each were enrolled. Four subjects in each cohort received BG9273 and two subjects received placebo. The doses were 0.005, 0.01, 0.02, 0.04, 0.1, 0.15, and 0.225 mg/kg. A return to normal range of absolute lymphocyte counts was required in all subjects within a dose group before dose escalation. The study evaluated tolerability, pharmacokinetics and biologic activity (lymphocyte counts, delayed hypersensitivity testing).

Results and Discussion

Pharmacokinetics:

No data are available from the 0.225 mg/kg dose group. The disposition of BG9273 appears linear with peak serum concentrations ranging from 0.3 µg/ml to 2.74 µg/ml. The serum clearance was 0.3 ml/h/kg. The terminal serum half-life was approximately 200 hrs and the distribution volume ranged from 70-90 ml/kg.

Adverse Events:

No serious adverse events have been reported. The investigator brochure cites episodes of myalgias with headaches (two), chills (one), arthralgias (one) and morbilliform rash considered likely related to BG9273. No severe adverse events were reported. There were no differences in the reported adverse events between the BG9273-treated groups and the control group (except for decreased lymphocyte counts, see below).

Clinically Significant Laboratory Abnormalities. Lymphopenia:

No subject who received 0.005 mg/kg had a reduction in peripheral lymphocyte count. In the 0.01 mg/kg cohort two subjects developed lymphopenia (attributed to viral illness) that resolved within seven days. In the 0.1 and 0.15 mg/kg cohorts all BG9273 treated subjects had decreases in lymphocyte counts beginning at 4 hrs after infusion of drug with return to baseline by 48 hours. The decreased count was due to decreases in CD2+ cells, namely CD4+ and CD8+ lymphocytes. In the 0.225 mg/kg cohort all four BG9273 treated subjects had decreased lymphocyte counts that returned to normal by four days in three of the four subjects. One subject had persistently lower than normal counts (5-15%)

until day 35. The degree of reduction in lymphocyte counts correlated directly with the dose of BG9273. No changes in B lymphocytes (CD19+) were observed. The mechanism of these changes is thought to be cytolysis of lymphocytes

Reviewers' comments

Lymphocyte counts appear to be lowered at all dose levels and range from about 85% to 45% of baseline at 4 hrs after the infusion. CD4+ counts are lowered by the same amount as total lymphocyte counts; the magnitude of CD8+ decreases appears to be greater than that of CD4+ (range 70% to 30% of baseline). The lymphopenia and the neutrophilia (see below) are likely to be extensions of the mechanism of action of the drug.

Decreases in Staining Intensity of CD2+ Lymphocytes:

The sponsor states that at doses greater than 0.02 mg/kg, decreased CD2+ staining intensity was observed in all subjects. The decrease is called transient. The degree and duration of reduction of staining correlated with dose of BG9273. There was no change in CD4+ or CD8+ staining. The decrease in CD2+ staining could be due to interference by BG9273 with the anti-CD2+ antibody used in the assay, removal from circulation of cells expressing high density of CD2+, or down-modulation of CD2+ from cell surface of lymphocytes.

Reviewers' comments

A decrease in mean CD2+ staining intensity of CD4+ lymphocytes is seen at all dose levels. For the 0.225 mg/kg dose level the decrease in staining intensity is persistent (percent intensity is about 70% of baseline at the final sampling time). Findings for CD8+ lymphocytes are similar. At levels > 0.1mg/kg complete recovery of CD2+ staining intensity may not have been reached. The clinical significance of a decrease in the mean CD2+ staining intensity of CDD4+ lymphocytes is not known.

Neutrophil Elevations:

The absolute number of neutrophils increased up to five-fold in all subjects who received BG9273. The rise occurred within four hours of dosing, returned to normal by 24 hrs and the magnitude or duration did not appear to be related to dose. There were no clinical findings associated with the elevations in neutrophil counts.

PROTOCOL C96-704

Study Title

“Tolerability, pharmacokinetics, and biologic activity of BG9273 (LFA-3/IgG, fusion protein) when given as an intravenous infusion or as an intramuscular injection: an open-label, randomized, parallel group study in healthy male volunteers”

Study Objectives

To compare the pharmacokinetics and tolerability of a single 0.04 mg/kg BG9273 dose when administered as an IM injection or as a 30 minute IV infusion. To determine the

pharmacokinetics of a single 0.04 mg/kg BG9273 dose when administered as an IM injection or as a 30-minute IV infusion.

Study Design

Phase 1, open-label, randomized, parallel group study in healthy men. 8 subjects received 0.04 mg/kg BG9273 by 30-minute IV infusion, 8 subjects received 0.04 mg/kg BG9273 by IM injection.

Clinical and Laboratory Assessments

Adverse event reporting, physical examination, vital signs, ECG monitoring, hematology, peripheral lymphocyte subsets, immunoglobulins, serum C3 and C4 complement, blood chemistry, urinalysis, assessment of the injection site, subject assessment of injection site pain. Blood drawn for determination of antibody formation to BG9273.

Results and Discussion

16 Caucasian men ages 23 to 38 years were enrolled; 15 completed, 1 lost to follow-up; 16 analyzed. Peak serum BG9273 concentrations following IM injection were approximately 30% of the peak concentrations achieved following IV infusion. Serum BG9273 concentrations became observable approximately 6 hours following IM injection and peaked approximately 3 days following injection. Absorption phase was complete between 4 to 6 days.

The relative bioavailability of IM injection to IV infusion based on AUC was about 50%. This apparent incomplete absorption may be due to limited assay sensitivity (0.075 µg/ml) or pre-systemic clearance by the lymphatic system. Following absorption, BG9273 appeared to be eliminated from serum at a rate consistent with the IV half-life. The elimination half-life following IM injection was nearly 10-fold longer than the absorption half-life. Mean serum pharmacokinetic parameters are shown in **Table 2**.

Table 2. Pharmacokinetic parameters

	IV Infusion	IM Injection
C _{max} (µg/ml)	0.96	0.29
T _{max} (h)	2.8	78
AUC (µg.h/ml)	197	105
T _{1/2} Absorption (h)	-----	26
T _{1/2} Elimination (h)	254	165

The most common adverse events were headache (19%), pharyngitis (19%), rash (19%), and myalgia (13%). No serious events were reported. At the injection site following IM injection, 4 subjects (50%) had mild erythema and induration, 2 (25%) had tenderness and mild pain, and 2 subjects (25%) developed palpable, but non-tender, lymph nodes. Erythema and induration was 3 mm or less. No clinically significant

abnormalities were noted during physical examinations, vital signs, or ECGs. No antibodies to BG9273 were detected.

There were transient increases in neutrophil count following IV infusion and IM injection. Total lymphocyte count, CD2, CD3, CD4, CD8, and CD19 counts decreased in more subjects within 24 hours of IV infusion than after IM injection. No subjects' lymphocyte count was below the lower limit of normal. The following abnormal laboratory values were observed: Elevated CK (3X upper limit of normal 13 weeks after dosing) with CK-MB just above upper limit of normal; positive urobilinogen (one subject), proteinuria (4 subjects), hematuria (two subjects).

Reviewers' comments

The administration of drug IM induced localized reactions that were tolerable. Systemic absorption of drug by IM route is substantially lower and has a different PK profile. This may reflect increased exposure and clearance of alefacept by the lymphatic system. A number of clinically significant abnormal laboratory values were observed (clinical chemistry, urinalysis). The etiology of these is unclear. No significant changes in T cells were seen at the doses tested.

PROTOCOL C97-706

Study Title

A Randomized, Placebo-Controlled, Single-Dose Study in Healthy Male Volunteers of BG9712 and BG9273¹.

Enrollment Criteria

Inclusion criteria: Healthy men, ages 18-45, who were within 15% of body mass index. Exclusion criteria: evidence of viral or bacterial infection, history of severe allergic or anaphylactic reactions; history of significant cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, renal and/or other major disease; prior treatment with an immunosuppressant or an antibody.

Clinical and Laboratory Assessments

History and physical examination, VS, chemistry, hematology, lymphocyte subsets, urinalysis, ECG, immunoglobulins, complement, adverse events, anti-alefacept antibodies, alefacept concentrations,

Results

Pharmacokinetics: For the 0.04 mg/kg BG9712 dose the C_{max} was comparable by IV infusion or as a bolus, AUC was somewhat reduced in subjects receiving the bolus. Bioavailability followed the pattern: IV>IM>>SC. For the 0.15 mg/kg BG9712 dose, the SC route yielded, mean C_{max} and AUC values 20% and 35% of those values obtained by IV bolus. The IM route yielded mean C_{max} and AUC values 30% and 75% of those values obtained by IV bolus. Elimination half-life appeared unaffected by the route of

¹ BG9712 is an alefacept drug product that was dropped from development due to lower pharmacodynamic and clinical activity when compared to BG9273, the alefacept drug product used in the efficacy trials.

administration. BG9712 yielded somewhat lower concentration of alefacept (83%) compared to BG9273.

Safety: No serious adverse events were reported. No suggestion of cytokine release or capillary leak syndrome. A greater number of subjects had greater decreases in lymphocyte subsets after dosing with BG9273 than after BG9712. No significant reductions in serum C3 and C4 and immunoglobulin. No antibodies to alefacept. When compared with the control group, subjects receiving 0.15 mg/kg alefacept IV experienced transient lymphocytopenia, the effect appeared more marked for BG9273. Minor depression of lymphocyte and subsets was observed for the IM dose of 0.15 mg/kg consistent with reduced concentrations of alefacept by this route. Two thirds of subjects had transient elevations in neutrophil counts

III. SUMMARY OF CLINICAL STUDIES

PHASE 1 STUDIES OF ALEFACEPT IN PATIENTS WITH PSORIASIS.

Table 3 lists the Phase 1 clinical studies conducted in patients with psoriasis. These studies are reviewed primarily from the perspective of clinical safety and activity of

Table 3. Phase 1 Safety, Activity, and PK/PD Studies Reported in the Original Submission

Study Title	Design (N)	Dosing	Objectives
C96-703: Randomized, double-blind, dose-escalation study to evaluate tolerability, pharmacokinetics, activity, and efficacy of alefacept given once weekly for eight doses in subjects with chronic psoriasis.	Blinded, randomized, dose-escalation. N=33	BG9273 0.005-0.075 mg/kg IV weekly; 0.05 mg/kg IM weekly x 8 weeks	Safety, PK, activity, DTH of alefacept
C96-705: Randomized, double-blind, dose-escalation study to evaluate the tolerability, pharmacokinetics, activity, and efficacy of alefacept given once every 4 weeks for two doses in subjects with chronic psoriasis.	Blinded, randomized, dose-escalation. N=19	BG9273 0.05, 0.10, 0.15 mg/kg monthly IV x 2 months	Safety, PK, activity, DTH of alefacept
C98-709: Randomized, multiple-dose, dose-escalation study of tolerability and plasma concentration of alefacept in subjects with moderate to severe plaque psoriasis	Blinded (to dose), randomized, dose escalation. N=123	BG9712 0.15-0.75 mg/kg weekly IV, IM, SC x 12 weeks	Safety, activity, PK/PD
C98-710: Blinded, multiple-dose, study to determine tolerability of repeated courses of Alefacept in subjects with moderate, moderate to severe and severe plaque psoriasis	Open label (after C97-708 data lock) retreatment. N=141	BG9712 0.0125-0.15mg/kg weekly IV x 12 weeks	Safety of repeat courses of alefacept
C99-716: Single center, multiple-dose, open-label study of the effect of alefacept on psoriatic lesional T cells in situ in subjects with chronic plaque psoriasis	Open label. N=9	BG 9273 7.5 mg weekly IV x 12 weeks	PD, effect of alefacept on lesional T cells in situ
C99-718: Randomized, open-label, controlled study of the effect of intravenous alefacept on T cell dependent humoral responses to recall and neoantigens in patients with chronic plaque psoriasis	Open label, randomized. N=46	BG9273 7.5 mg weekly IV x 12 weeks	PD: T cell humoral response to neoantigen and recall antigen

alefacept. Included in this listing are two studies of BG9712 an alefacept drug product that was not developed further because of lower PD and clinical activity compared to BG9273.

PROTOCOL C96-703

Study Title

“A randomized double-blind, repeat-dose, dose escalation study to evaluate the tolerability, pharmacokinetics, biologic activity and efficacy of BG9273 (LFA-3/IgG1 fusion protein) in patients with chronic psoriasis.”

Study Objectives

Evaluate the safety, pharmacokinetics, effect on delayed-type hypersensitivity, and activity of eight once weekly doses of BG9273.

Study Design

This was an uncontrolled, multicenter, multiple-dose, dose-escalation study of BG9273 administered intravenously once weekly for eight weeks in 18 subjects with moderate to severe chronic psoriasis. In the original protocol three doses 0.025, 0.05, and 0.075 mg/kg were planned. In the first cohort four subjects would receive 0.025 mg/kg open-label. In the subsequent second and third cohorts treatment assignment was randomized and double-blinded. In the second cohort, two subjects would receive 0.025 mg/kg and four subjects would receive 0.05 mg/kg. In the third cohort, two subjects would receive 0.05 mg/kg and six subjects would receive 0.075 mg/kg.

Reviewers' Comments

The protocol was modified to add a dose cohort of 0.005 mg/kg. This starting dose was expected to produce measurable blood levels of drug and some pharmacodynamic effects; in addition the dose would expand the range of the maximal drug concentrations achieved at steady state thus increasing the pharmacokinetic exposure from a three-fold to a ten-fold range. An IM dose cohort (0.05 mg/kg) was also added. The investigators were given the option of administering the IV dose as a bolus or as an infusion.

Standard Treatment

The use of mild to moderately potent topical corticosteroids was allowed.

Multiple Dosing Rules

Each dose was separated by an interval of at least seven days. The absolute lymphocyte count was to be $\geq 75\%$ of the lower limit of normal within 24 hrs before dosing. From the pre-dosing sample from the previous dose, the absolute number of any of the lymphocyte subsets CD4+, CD8+, or CD19+ must be $\geq 75\%$ of the lower limit of normal.

Dose Escalation Rules

Progression to next dose group would occur after the last subject in the previous dose group received the fourth dose of study drug and safety data including hematology, chemistry, urinalysis, and adverse events were reviewed. Progression to the next dose would not occur if a subject experienced a reduction in absolute number of lymphocytes or lymphocyte subsets (CD4+, CD8+, or CD19+) that met all the following criteria:

related to study treatment, <50% of lower limit of normal, \geq 50% reduction from baseline, sustained > 28 days post-dosing in any two consecutive determinations made after the 28th day.

Withdrawal Rules

Permanent discontinuation is required for: pregnancy, subject's wishes, investigator or sponsor's discretion. Patients who have withdrawn for non-safety reasons may be replaced.

Inclusion Criteria

Men or women between the ages of 21 and 70 years with: moderate-to-severe chronic plaque-type psoriasis with body surface area involvement \geq 10%; body weight within 50% of ideal; normal ECG; lack of clinically meaningful abnormalities in CBC and differential count, serum creatinine, LFTs; stable dose (at least 14 days) of maintenance medication.

The sponsor was asked to specify what baseline level of total lymphocyte count and CD4+, CD8+ counts are acceptable and to require a history of systemic treatment or phototherapy as an entry criterion; subjects controlled with topical therapy alone would not be studied.

Exclusion Criteria

Erythrodermic, guttate, or palmar pustular psoriasis. Unwillingness to practice adequate contraception. History of severe allergic or anaphylactic reactions. History of clinically significant disease. Serious local or systemic infection within previous three months. Fever or symptomatic viral or bacterial infection within one week of the first dose of study drug. HCV, HBV, HIV infection. Treatment with systemic retinoids or systemic immunosuppressant (e.g. high dose steroids, >25 mg prednisone/day) within four weeks. UV therapy within two weeks.

Outcome Measures

The primary endpoint was the number of subjects with at least a 50% decrease in the target lesion score or in the PASI score. The secondary endpoints were the minimum PASI score, total erythema score, total induration score total desquamation score, severity of itching, global assessment of activity.

The sponsor was asked to specify PASI score and physician global assessment score as main outcome criteria. PASI score of selected skin lesions would be a secondary outcome measure.

Clinical and Laboratory Assessments

Enrollment (\leq 28 days): history and physical; ECG; urinalysis; chemistry; hematology; PT; leukocyte subsets; pregnancy test; HCV, HBV, HIV testing; skin testing for delayed hypersensitivity; serum IgG, IgA, and IgM; serum isohemagglutinin; serum C3 and C4. In a subset of subjects skin biopsy and lymphocyte proliferation assays would be done.

Before each dose: physical exam; leukocyte subset analysis; hematology; chemistry; urinalysis; pregnancy testing; PASI, target skin lesions and itching assessment.

After each dose: at 1,4, 8, and (if available) 24 hrs: hematology and leukocyte subset analysis. Subjects would be followed for eight weeks after the last dose.

Photography of skin was done monthly. Pharmacokinetic sampling was done before and at 0.5, 8, 24 hrs after each infusion and at 7, 14, 28 and 56 days after the last infusion. Anti-BG9273 antibody testing was done.

The sponsor was asked to follow subjects until substantial (at least 75% of baseline) recovery of leukocyte subsets and CD2+ staining intensity was documented.

Case Report Form

The sponsor was asked to capture data on all infections using a check-off form in the CRF.

Results and Discussion

Thirty-three subjects entered the study. Three subjects in the second dose group withdrew, one for an adverse event, two for “other” (reason not otherwise specified). Patients were considered responders if they experienced $\geq 50\%$ reduction in PASI. By these criteria seven patients responded during the treatment period and seven during the follow-up period.

There were two serious adverse events judged to be unrelated to study treatment: cholecystitis followed by uncomplicated cholecystectomy (0.025 mg/kg) and chest pain ultimately diagnosed as GI in origin (0.5 mg/kg). There was a suggestion of dose-dependent increase in adverse events associated with infection. None of the infections was serious and none was associated with lymphopenia or neutropenia.

Except for the subjects in the lowest IV dose and in the IM dose group, all other subjects experienced transient reduction in CD3, CD4 and CD8 T lymphocytes that returned to normal. PMN counts increased in three subjects and platelet counts decreased in two subjects. One subject (0.05 mg/kg) had low-titer anti-alefacept antibodies at baseline and during study.

Skin hypersensitivity testing (**Table 4**) showed the following shifts from baseline to post- treatment.

- Positive to negative: tetanus (N=8), diphtheria (N=2), candida (N=3), tricophyton (N=1) and proteus (N=3).
- Negative to positive tuberculin (2).
- No shifts: streptococcus and glycerin (all were negative at baseline and remained negative post-treatment).

Table 4. Shift table. Skin testing of Delayed-type Hypersensitivity

		0.005 mg/kg IV		0.025 mg/kg IV		0.05 mg/kg IV		0.075 mg/kg IV		0.05 mg/kg IM	
		Post-treatment		Post-treatment		Post-treatment		Post-treatment		Post-treatment	
		+	-	+	-	+	-	+	-	+	-
Tuberculin	Baseline +	0	0	0	0	0	0	0	0	0	0
	-	1	4	0	5	0	8	1	5	0	6
Candida	Baseline +	0	0	0	2	0	0	0	0	0	1
	-	0	5	0	3	0	8	0	6	0	5
Tricophyton	Baseline +	0	0	0	1	0	0	0	0	0	0
	-	0	5	0	4	0	8	0	6	0	6
Proteus	Baseline +	2	0	1	1	1	1	0	0	0	1
	-	0	3	0	3	0	6	0	6	0	5
Tetanus	Baseline +	3	0	2	3	2	4	2	0	0	1
	-	0	2	0	0	0	2	0	4	0	5
Diphtheria	Baseline +	0	0	0	1	1	0	0	1	0	0
	-	0	5	0	4	0	7	0	5	0	6
Streptococcus	Baseline +	0	0	0	0	0	0	0	0	0	0
	-	0	5	0	5	0	8	0	6	0	6
Glycerin control	Baseline +	0	0	0	0	0	0	0	0	0	0
	-	0	5	0	5	0	8	0	6	0	6

Reviewers' Comments:

The investigators used the MULTITEST CMI for skin testing. The protocol contained detailed instructions for application of the antigens to non-lesional skin and for reading the results. Induration greater than 2 mm in diameter was considered positive. The data listings show dichotomous readings of "positive" or "negative" for individual patients.

The significance of the antigen testing results is not clear. The shifts from positive to negative reaction are not dose dependent. However the shifts do not appear to be random because they were not associated with corresponding shifts from negative to positive reaction. The only shifts from negative to positive were the two tuberculin shifts, one isolated, the other associated with a positive to negative reaction shift for another antigen. The maximum number of antigen shifts in one patient (04204) was three. Three patients (05-303, 304 and 306) who shifted from positive to negative for tetanus antigen were retested; one patient retested positive and two patients retested negative.

PROTOCOL C96-705

Title of Study

A randomized, double-blind, dose-escalation study to evaluate the tolerability, pharmacokinetics, biologic activity and efficacy of BG9273 (LFA-3/IgG1 Fusion Protein) when given once every 4 weeks for two doses in subjects with chronic Psoriasis.

Study Design

Multicenter, randomized, double-blind, dose-escalation study of IV infusion of 0.05, 0.10, 0.15 mg/kg BG9273.

Enrollment Criteria

Inclusion: Men and women, aged between 21 and 70, with moderate to severe, chronic plaque-type or palmar plantar psoriasis.

Exclusion: current erythrodermic or palmar pustular psoriasis; fever or symptomatic viral or bacterial infection; serious local or systemic infection; prior treatment with systemic retinoids within 8 weeks or immunosuppressant agents within 4 weeks prior to first dose.

Primary Outcome

Proportion of subjects with at least 50% reduction in PASI at any time during the study.

Clinical and Laboratory Assessments

Alefacept concentration, DTH, anti-alefacept antibodies, clinical labs, adverse events, PASI.

Study Conduct

The study was conducted in Europe (3 sites in UK and two in Hungary) and was run by BRI International. There were several serious protocol violations. There were concerns with timeliness, consistency and quality of flow cytometry measurements of lymphocyte subsets at two study centers. Fifteen subjects received major concomitant antipsoriatic treatment (e.g. PUVA, UVB, systemic corticosteroids) because of lack of psoriasis improvement. This further complicated the interpretation of safety data and confounded the activity data. Four subjects did not receive the intended dose due to pharmacist's errors. Few patients had low baseline PASI scores. The sponsor terminated the study prematurely because of the protocol violations.

Patient Disposition

19 subjects enrolled; 18 were dosed in the following dose groups: 6 with 0.05 mg/kg, 6 with 0.10 mg/kg, 1 with 0.125 mg/kg, 5 with 0.15 mg/kg. 13 subjects completed, 1 was withdrawn due to an adverse event, and 4 were discontinued early following the sponsor's decision to terminate the study early. Participants were Caucasian, aged between 26 and 64, of whom 16 were men. PASI scores ranged from 5 to 38.

Reviewers' comment

Table 14.3.9 of the sponsor’s BLA submission (not shown here) indicates that only five patients received their assigned dose as per treatment allocation. All others received much higher doses.

Results and Discussion

PASI

Treatment response was modest and was confounded by concomitant antipsoriasis medication use. Five subjects who responded were excluded from analysis because of use of antipsoriatic therapy (four received PUVA, one received betamethasone). Five subjects (26%) met the modest response criteria ($\geq 50\%$ reduction in PASI anytime during study). Most of the responders were in the 0.1 mg/kg dose group.

Lymphocyte Counts

Table 5 shows that the incidence and severity of decreased lymphocyte counts were not clearly dose-dependent.

Table 5. Subjects with CD4+ and CD8+ Counts Below Specified Thresholds

	0.05 mg/kg N=6 ^a	0.1 mg/kg N=6	0.125 mg/kg N=1	0.15 mg/kg N=5
CD4 <300	2	2	1	3
CD4 <200	0	1	0	1
CD8 <200	3	3	1	4
CD8 <100	1	1	0	1

^aSubjects dosed

Two subjects in 0.1 mg/kg group had a prolonged depression in CD4+ lymphocyte counts following administration of their second dose of BG9273 (23-92 days below 300×10^6) UV therapy was initiated 4 weeks after end of treatment confounding interpretation.

Infections

One subject in the 0.15 mg/kg group had culture-negative pyuria 2 weeks after the second dose. The pyuria was considered moderate and likely to be related to study drug. The subject was treated with nitrofurantoin. Neutrophils and lymphocytes were normal. Two subjects experienced rhinitis and flu-syndrome.

Serious Adverse Events

There were three serious adverse events, namely hospitalizations for treatment of psoriasis. Subject 05113 and 05204 were hospitalized for “treatment of psoriasis”; both events occurred after the end of the treatment period and were considered unrelated to alefacept. Subject 06305 developed pustular psoriasis four days after his first dose (0.15mg/kg) of alefacept. He had a low lymphocyte count at admission. His skin lesions grew Staph hemolyticus. Alefacept was discontinued and he was treated with antimicrobials, corticosteroids and retinoids. The subject recovered and the lymphocyte count returned to normal. The event was considered likely related to alefacept.

Delayed Hypersensitivity Testing

The sponsor cites only one subject (05302) in the high dose group with a shift from positive to negative for one antigen.

Reviewers' comments

Seven antigens and one control were applied to non-lesional skin before and after alefacept dosing. Overall there were 7 shifts from positive to negative in individual antigens. There were two shifts from negative to positive. These shifts are isolated and are not related to dose. Similar trends in shifts were observed in a previous study.

Anti-alefacept Antibodies

One subject (01102) in the low dose group tested positive at 28 days and at 12 weeks.

Reviewers' comment

Data listings (16.4.26) show a titer of 80 at 28 days but do not confirm that the subject was positive at 12 weeks. At 12 weeks the result is "POSITIVE" but the titer is <5 (below threshold of detection). These results need verification.

PROTOCOL C98-709

Study Title

A Randomized, Multiple-Dose, Dose-Escalation Study to Determine the Relationship of Tolerability to Dose and Plasma Concentration of BG9712 (LFA-3/IgG1 Fusion Protein) in Subjects with Moderate to Severe Plaque Psoriasis

Study Objective

Determine activity safety and PK/PD of a new alefacept drug substance (BG9712) administered in multiple doses as an IV bolus, an IM injection, or an SC injection to patients with moderate to severe plaque psoriasis.

Study Design

Non-controlled, multi-center, randomized, double-blind, dose-escalation study of BG9712. The routes of administration were evaluated in a parallel fashion. The protocol contained appropriate dose-escalation rules.

Dosing

Once weekly for 12 weeks taking into account bioavailability results of previous studies:
IV bolus of 0.15, 0.225, 0.375,
IM injection of 0.15, 0.225, 0.375 mg/kg
SC injection of 0.15, 0.375, 0.75 mg/kg

Enrollment Criteria

Inclusion: Men and women aged between 18 and 70 years with moderate to severe plaque-type psoriasis. Normal absolute CD4+ lymphocyte count.
Exclusion: Erythrodermic, guttate, palmar, or plantar pustular, or generalized pustular psoriasis; fever or serious local or systemic infection (e.g., pneumonia, septicemia); prior

treatment with systemic retinoids or immunosuppressants within 4 weeks prior to the first dose of study drug.

Primary Outcome

Proportion of patients with >75% improvement in PASI at two weeks after the end of treatment.

Clinical and Laboratory Assessments

PASI, PGA, target lesions. Adverse event reporting, physical examination, vital signs, ECG, hematology, peripheral lymphocyte subsets, immunoglobulins, isohemagglutinin, blood chemistry, urinalysis, determination of antibodies to LFA3TIP.

Protocol Amendments

Number of study patients was raised twice to final of 150. Two IV dose cohorts were added: 0.50, and 0.75 mg/kg.

Study Conduct

The study was terminated prematurely because of lower activity and poorer tolerability of BG9712 compared to historical data with BG9273

Patient Disposition

123 patients were enrolled and dosed: 69 received BG9712 IV, 30 by IM injection, and 24 by SC injection. There were 74 men (60%) and 49 women (40%), aged between 19 and 70 years, of whom 80% were Caucasian. Body weight ranged from 47 to 150 kg. In the two highest IV dose group a high proportion of subjects (60-100%) did not complete treatment primarily due to decision to stop study for poor tolerability and lack of activity of BG 9712.

Results

PK/PD

The mean volume of distribution was consistent with blood volume, half-life was around 270 hours, and bioavailability of IM and SC route was approximately 60%.

Reduction in lymphocyte counts induced by BG9712 was less marked than observed for BG9273 and was not dose-dependent. The mean total lymphocyte counts remained above the lower limit of normal at all time points and the proportion of patients with counts below thresholds was smaller. There were only sporadic occurrences of any patient dropping below 600 cells/ μ L. Lymphocyte reductions were greater for the IV route than for the IM or SC routes. On average, counts had not recovered to the baseline level following treatment with BG9712. The SC treatment group was the slowest to recover. Changes in lymphocyte subsets observed with BG 9712 (CD3, CD4, CD8) were qualitatively similar to those seen with BG9273.

Efficacy Results

Few (0-16% in each cohort, 3/39 overall) patients met the PASI 75 endpoint in the IV group. In the IM group 2/28 patients responded. In the SC group 5/22 patients responded. There was no evidence of dose response.

Adverse Events

Up to 60% of patients in route of administration groups developed adverse events classified as infections. The most commonly reported Infection terms were; Infection (not specified), pharyngitis, sinusitis, and flu syndrome. There were 2 cases of herpes zoster and 2 of herpes simplex. Two patients ages 60-70, with long history of psoriasis and major antipsoriatic treatment had diagnoses of malignancy on study (a melanoma in situ and basal cell carcinoma). The lesions were noted at baseline.

Up to 50% of patients experienced symptoms (chills, headache, arthralgia, asthenia, myalgia, and nausea) after dosing in the 0.750 mg/kg IV dose group. Symptoms lasted <24 hrs. Similar symptoms were observed less frequently in the SC and IM groups.

Serious Adverse Events

Two serious adverse events were reported. A 56 year old woman with history of arthritis developed sepsis. Prodromal manifestations 9 weeks after the last dose of 0.750 mg/kg of alefacept with arthritis, followed by diarrhea and rectal bleeding, finally cellulitis, sepsis, renal failure, respiratory failure and pneumonitis. A pathogen was not isolated from joint, skin, fascia or lung. Antimicrobials were given. The patient survived. TSST-1 antibody screen was positive and diagnosis of toxic shock syndrome secondary to cellulitis was made. Relationship to study treatment was judged "not related." The patient's lymphocyte counts had been normal on study.

Reviewers' comments

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

A 59 year old woman developed chills, SOB, severe chest pain and vomiting following administration of alefacept. Gallstones were visualized and cholecystectomy was performed. The patient resumed alefacept dosing without recurrence of symptoms.

Patient Withdrawals

Patient 106-107 a 49-year old woman developed zoster after 10 doses of 0.150 mg/kg IV and discontinued. *H. zoster* resolved in about 10 days. Patient 11-113 discontinued because of fatigue, chills and joint aches after 0.75 mg/kg IV.

Anti-alefacept Antibodies

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

Reviewers' comments

The lower activity of the new product (BG 9712) was unexpected. The safety data raise clinical concerns similar to those in trials of BG9273. The poor tolerability was seen at doses higher than those used in trials of BG 9273. The sponsor stopped development of BG 9712. Questions arose about the reliability of potency assays and have been the focus of discussions with the sponsor.

PROTOCOL 98-710

Study Title

C98-710 (Version 3) "A Blinded, Multiple-Dose Study to Determine the Tolerability of Repeated Courses of LFA3TIP (LFA-3/IgG, Fusion Protein) in Subjects with Moderate, Moderate to Severe, or Severe Plaque Psoriasis

Study Objectives

Determine the tolerability of repeated courses of LFA3TIP administered intravenously. Determine if in subjects who complete study C97-708:

1. Responders (disease severity \leq mild) retreated with the same dose of drug show similar or improved response.
2. Non-responders (disease severity \geq moderate) retreated with a higher dose of drug show a response.
3. Responders whose CD4 cell count was $< 300/\text{mm}^3$ on two consecutive visits show similar response when retreated with a lower dose of drug.

Study Design

Phase 2 multicenter, multiple-dose study in up to 228 subjects with plaque psoriasis who have completed the post-dosing assessment in the C97-708 study (Visit 17). Investigators would be blinded to treatment allocation.

Reviewers' comments

While a randomized controlled study would have been preferable, the study was allowed to proceed. The sponsor agreed to assess safety and efficacy of retreatment in a future randomized blinded trial.

Study Treatment

Subjects received one of the following doses of LFA3TIP as BG9712 (0.0125, 0.025, 0.075, or 0.150 mg/kg) as an IV bolus once a week for a total of 12 doses per treatment course. Treatment allocation would occur by the following criteria.

Group 1: In this group would be responders (received active drug and disease severity by "static" PGA at any time during the 12 week post-dosing period was mild, almost clear or clear) whose weekly CD4 count was not ≤ 300 cells/ mm^3 on two consecutive visits. These subjects will be retreated using the same dose as in the C97708 study: (0.025, 0.075, or 0.150 mg/kg).

Group 2: In this group would be responders (received active drug and disease severity by PGA at any time during the 12 week post-dosing period was mild or better) who had CD4 counts < 300 cells/ mm^3 on two consecutive visits. These subjects would be retreated by dropping their dose to that of the next lower dose level.

Group 3: In this group would be subjects who received placebo during the C97-708 study. These subjects would receive a dose of 0.150 mg/kg of drug.

Group 4: In this group would be non-responders (received active drug and disease severity by PGA at any time during the 12 week post-dosing period remained moderate, moderate to severe, or severe) whose weekly CD4 counts did not drop to less than 300 cells/mm³ on two consecutive visits. These subjects would receive one dose higher than that received during the C97-708 study to a maximum dose of 0.150 mg/kg.

Reviewers' comments

Whereas subjects received alefacept as BG9273 in study 708, in the present study subjects received BG 9712. The objectives of the study would not be realized because the clinical activity of BG9712 would be lower than that of 9273.

Concomitant Medications

No major antipsoriatic medications were allowed.

Modification of Treatment Schedule

1. Continuation of treatment.

The following were required for continuation of treatment

Administration of each dose of study drug separated by at least 7 days.

No clinical evidence of viral or bacterial infection.

Lymphocyte count within 24 h of dosing > 60% of LLN or > 50% of baseline.

Absolute CD4 lymphocyte count from the previous week is >300 cells/mm³.

2. Permanent discontinuation of treatment.

The following conditions required permanent discontinuation of treatment.

Pregnancy, patient's choice, low CD4 count (< 300 cells/mm³) for >38 days between doses, medical emergency, investigator's choice.

Enrollment Criteria

Inclusion: Subjects would be eligible for retreatment following an increased disease severity. Subjects must have completed the C97-708 study (visit 17).

Exclusion: Subjects whose disease never improved to mild or better after the first treatment and whose CD4 count was <300 on two consecutive visits.

Evaluation of Safety

Safety was determined by changes in total lymphocytes and lymphocyte subsets, adverse events including infections, and laboratory abnormalities.

Efficacy Outcomes

Global assessment using both a static and a dynamic scale, PASI score, target lesion assessments, time to response, duration of response.

Clinical and Laboratory Assessments

Physical examination, vital signs, blood chemistry, blood count, urinalysis, lymphocyte subset analysis. Serum samples analyzed for descriptive pharmacokinetic parameters.

Results

Pharmacodynamic Effects of BG9712

The results of the study are confounded by the lower biologic activity of BG9712 and by differences in baseline lymphocyte count between groups due to carry-over effects from alefacept treatment patients received in the previous study. **Table 6** shows the BG 9712 did not lead to drops below normal in lymphocyte counts. Decreases in lymphocyte subsets (CD4+ and CD8+) were qualitatively similar to those seen in study 708. The drops were less pronounced than those seen with BG9273. No changes in B cells or NK cells were observed. The lack of dose proportionality in the decrease in lymphocyte counts is probably due to factors discussed above.

Table 6. Decrease in Lymphocyte Counts at Any Time During Study

		0.025 mg	0.075 mg	0.125 mg
lymphocyte counts	>ULN	0/12	0/37	0/68
	<LLN	2/12 (17)	2/37 (5)	0/68
CD4 Count	>ULN	0/12	0/37	1/68 (1)
	<LLN	3/12 (25)	3/37 (8)	7/68 (10)
CD8 Count	>ULN	0/12	0/37	1/68 (1)
	<LLN	2/12 (17)	3/37 (8)	3/68 (4)

Response to Treatment

The proportion of responders ($\geq 75\%$ improvement in PASI, PGA of “clear” or “almost clear”) was low and dose dependent. Between 0 and 10% of patients were classified as responders in the three dose groups.

Reviewers' comments

In analyzing the efficacy data the sponsor did not consider as treatment failures patients who had received concomitant antipsoriatic therapy. Therefore the actual response rates are likely to be lower. The agency did not reanalyze the efficacy data because the sponsor had stopped development of BG9712. Based on PD and efficacy outcomes it is reasonable to conclude that BG9712 appears to be less active than BG9273.

Safety

There were no deaths. One patient discontinued treatment due to recurrence of gingivitis. One patient developed low titer antibodies to alefacept.

Notable serious adverse events were;

- 27 year old in 0.15 mg group underwent fixation of comminuted tibial fracture 6 weeks after the end of 12-week course of alefacept. He developed infection at the repair site requiring antimicrobials and re-operation. The event was judged to be resolved one week later.
- A 37 year old woman, had psoriasis for 15 years prior to study entry. She had

previously received no systemic agents or phototherapy. She was allocated to the 0.15 mg/kg group and one month after start of dosing, a lesion on her back was biopsied and diagnosed as a squamous cell carcinoma (keratoacanthoma type). The patient's lowest lymphocyte and CD4+ count before the adverse event were 1130 cells/ μ L and 401 cells/ μ L, respectively.

There was a suggestion of dose-dependent increase in the incidence of infections and of serious adverse events (**Table 7**).

Table 7. Incidence of Infections and of Serious Adverse Events

	0.025 mg N=12	0.075mg N=37	0.15 mg N=68
Infectious adverse event	3 (25)	13 (35)	27 (40)
Serious adverse event	0	2 (5)	3 (4)

The more clinically significant infection terms listed were: abscess, cellulitis, conjunctivitis, epididymitis, herpes simplex, otitis externa, periodontal abscess, pneumonia, and urinary tract infection. The serious adverse events were: accidental injury, cholelithiasis, coronary occlusion, dysuria, hemorrhage, bacterial infection, and skin carcinoma.

Reviewers' comments

The safety profile of BG9712 raises clinical concerns similar to those raised by BG9273.

IV. SUMMARY OF CLINICAL STUDIES

PHASE 2 AND 3 STUDIES

Table 8 lists the safety and efficacy studies.

Table 8. Phase 2 and 3 Safety and Efficacy Studies Reported in the Original Submission

Study Title	Design (N)	Dosing	Objectives
C97-708: LFA3TIP in moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled, parallel group, dose-response study	Blinded, randomized, dose-response, placebo controlled. N=229	BG9273 0.025, 0.075, 0.15 mg/kg weekly IV x 12 weeks	Safety, efficacy
C99-711: Randomized, double-blind, comparison of intravenous alefacept versus placebo in subjects with chronic plaque psoriasis	Blinded, randomized, placebo controlled. N=565	BG9273 7.5 mg weekly IV x 12 weeks (two treatment courses)	Safety, efficacy of two 12-week IV treatment courses
C99-712: Randomized, double-blind, placebo-controlled, dose-comparison study of the efficacy and safety of intramuscular administration of alefacept in patients with chronic plaque psoriasis	Blinded randomized, placebo controlled. N=526	BG9273 10, 15 mg weekly IM x 12 weeks	Safety and efficacy of one 12 week IM treatment course
C99-714: Open-label study of tolerability and efficacy of repeat courses of alefacept in subjects with chronic plaque psoriasis who have completed study C97-708 or C98-709	Open label Retreatment. N=27 (ongoing)	BG9273 7.5 mg weekly IV x 12 weeks	Safety of repeated courses of alefacept

Issues Explored in the Efficacy Trials

Use of a Fixed Dose:

In healthy subjects (60-95kg) receiving a range of alefacept doses, clearance appeared to be dose independent. Body weight contributed little (5%) to the variability in alefacept concentration. Data from study C98-707 (N=23, 64-105kg) showed a relationship between body weight and alefacept concentration ($R^2=0.7$). Clearance varied two-fold (20 to 40 ml/hr) over the range of weights studied. In Study C97-708, body weight was not a significant covariate in effects of alefacept on CD4 lymphocyte count or severity of psoriasis determined by PASI score.

In view of the uncertainties regarding the relationship between dose, body weight and CD4 count, monitoring of lymphocyte counts before dosing was an essential component of dosing in the phase 3 studies. Conservative rules for dose interruption and/or discontinuation were used based on decrease in lymphocyte count and persistence of decrease.

Response to Retreatment:

Studies 711 and 712-717 were designed to evaluate the safety and efficacy of a second course of therapy. The response to treatment was evaluated by comparison to baseline before the start of the first treatment and before the start of the second treatment

Duration of Treatment Response:

Following discontinuation of therapy psoriasis recurs. The duration of response varies with different therapies and is important information to include in the package insert. Calculation of duration of response typically begins with the end of the treatment period and ends with the last visit at which response was maintained. The duration of response should not include any interval during the treatment period. The interval between visits should not be used for imputation of duration of response. Patients who used antipsoriatic therapies after the end of study treatment should be declared to have relapsed at the time of start of the antipsoriatic therapy (unless they were previously declared treatment failures).

The criteria for alefacept retreatment (PGA worse than mild) might have resulted in retreatment of a few patients who remained in response (PASI > 75% improvement) but did not achieve PGA score of mild. Rationale for low threshold for retreatment was the reluctance of some patients in previous studies to remain off therapy while deterioration occurred and the desire to explore potential for additional clearing in treatment responders. Patients who remained in remission and did not enter the second treatment period were censored at the last interim visit.

Long-term Treatment:

A conservative approach was used testing repeated courses of therapy separated by a minimum time interval of 3 months for observation of safety and recovery of immune function.

Pediatric Studies:

Treatment of children

Biogen asked for and received a deferral of its obligation to carry out pediatric studies in the phase 3 program. The sponsor will be submitting a proposal for pediatric studies.

Immune Function:

Alefacept induces lymphocyte depletion. There was evidence that complete recovery to baseline of lymphocyte subpopulations did not occur in certain patients. Important safety goals for the phase 3 studies were to follow study patients until adequate recovery of counts occurred (within $\pm 75\%$) and to determine if cumulative depletion of lymphocyte counts occurred upon retreatment. Evidence of clinically significant infections and neoplasms would be carefully sought and correlated with lymphocyte counts. The relationship between decrease in PASI scores and CD4 counts would be explored.

Experimental data: *in vitro*, animal, and human studies were designed to characterize effects of alefacept on immune functions (e.g. humoral and DTH responses).

Clinical Assessments of Psoriasis:

The concordance between various assessments of disease severity would be evaluated in phase 3. At the time the clinical trials were designed questions had been raised about the usefulness of PASI. On March 20, 1998, the Dermatologic and Ophthalmic Drugs Advisory Committee discussed clinical trial design and analysis for studies of psoriasis. The committee discussed shortcomings of clinical scoring of disease severity and recommended that a global physician assessment scoring system be used as primary efficacy outcome. The committee recommended that substantial improvement (defined as $\geq 75\%$) be used to define clinical benefit. A responder analysis was recommended identifying patients with improvement of 100% (completely cleared with restoration of normal skin markings), 90-99% (almost clear with no plaque or scaling and dull erythema, 75% clear (equivalent to a change in severity from severe to mild or from moderate to clear). The committee recommended that photography either of whole body or of target lesions be done. Close ups to show skin markings were recommended. The committee indicated that extended follow up will be needed to assess the safety of immunosuppressive agents.

In the phase 2 study a "static" physician global assessment was used as the primary efficacy measure. A 7-point scale was used to define disease severity and to assess the proportion of responders. The proportion of patients showing a decrease in PASI $\geq 75\%$ was the most important secondary efficacy outcome. A formal analysis of the reliability of the PGA assessments was performed. Analyses of the phase 2 efficacy data showed concordance between PGA and PASI scoring. The PASI score was used as primary efficacy outcome in the phase 3 studies. PGA was used as the principal secondary outcome. Concordance between the two outcomes would be confirmed in the phase 3 studies.

Factors Influencing Psoriasis:

US centers were to be pooled by geographic region: southwestern, midwestern, southeastern, and northeastern. The rationale was that ultra-violet light exposure might be higher at lower latitudes and at higher elevations and therefore influence response to treatment. Data from study C97-708 suggested a higher response rate for individuals who were naïve to prior therapy for psoriasis. Randomization would be stratified by baseline disease: PASI > 20 or < 20 and by previous treatment history (naïve or previously exposed to systemic antipsoriatic therapy).

Concomitant Antipsoriatic Medication:

There was considerable use of major antipsoriatic medications in the phase 2 study. This may have resulted in overestimation of response to treatment. In the phase 3 study patients using major antipsoriatic medications would be considered treatment failures for the purpose of the efficacy analysis.

PROTOCOL C97-708

Study Objectives

The objective of this study was to determine the relationship of clinical response to the dose and plasma concentration of BG9273 when administered once a week for a total of up to 12 doses to subjects with moderate to severe plaque psoriasis.

Study Design

Phase 2, multicenter (25 sites), randomized, double-blind, placebo-controlled, parallel-group, dose-ranging (0.025, 0.075, and 0.150 mg/kg IV once weekly for 12 weeks) study in up to 200 subjects with moderate to severe plaque psoriasis.

The placebo was saline (5 ml) administered by IV bolus. Subjects were randomized by site. The site pharmacists or the investigator's designee were unblinded to prepare doses of drug. One investigator at each site was unblinded only to subjects' hematology results. All other study personnel, including study coordinators and nursing staff, were to remain blinded. The physicians performing the efficacy assessments would remain blinded at all times. All candidates screened for inclusion in the study were logged in. For subjects not enrolled into the study, the reason(s) for exclusion were documented.

Inclusion Criteria

Men or women between 18 and 70 years. Moderate to severe chronic plaque-type psoriasis as defined by a body surface involvement of 10% or greater, previous treatment with systemic or phototherapy and diagnosis for more than 1 year. Must have absolute CD4+ lymphocyte counts at or greater than the lower limit of normal within 14 days before the first dose. Subjects on any prescription medication must be on stable doses of that medication for at least 14 days before the first dose of study drug. Women must be postmenopausal for at least 1 year, surgically sterile, or willing to practice effective contraception.

Exclusion Criteria

Erythrodermic, guttate, palmar, plantar pustular, or generalized pustular psoriasis. Clinically significant abnormal laboratory values for hematocrit, hemoglobin, platelets, serum creatinine, or bilirubin. ALT and AST must not be greater than 3 times the upper limit of normal. History of anaphylactic reactions. History of clinically significant cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, psychiatric, renal, and/or other major disease (other than psoriasis). Serious local or systemic infection (e.g., pneumonia, septicemia) within the 3 months before the first dose of study drug. Fever (body temperature >38 C) or symptomatic viral or bacterial infection (including upper respiratory infection) within 2 weeks before the first dose of study drug. Positive for hepatitis C antibody or hepatitis B surface antigen. Positive for HIV antibody, or known to have risk factors for HIV infection. Morbidly obese (>75% above ideal body weight). Treatment with the following drugs before receiving the study drug: systemic retinoids within 4 weeks; systemic immunosuppressants (e.g., methotrexate, cyclosporine) within 4 weeks; oral prednisone >25 mg/day (or its equivalent) within 2 weeks; high potency corticosteroids, keratolytics or coal tar (other than on the scalp, palms, groin, and/or soles) within the 2 weeks; UV

therapy within 2 weeks or anticipated need for UV therapy during the study period. Poor clinical response to cyclosporine or methotrexate after an adequate regimen and duration of treatment.

Dose Modification Rules

Administration of each dose of study drug would be separated by an interval of at least 6 days, but not greater than 14 days. The absolute lymphocyte count obtained at the site could be no less than 67% of the lower limit of normal within 24 hours before dosing. If study drug is withheld from a subject, placebo would be administered in lieu of the withheld dose of study drug. In the event that the absolute lymphocyte count was not greater than 67% of the lower limit of normal, the physician unblinded to hematology results would notify the pharmacist/designee to administer placebo instead of the study drug. The absolute CD4+ lymphocyte count from the previous week had to be >300 cells/mm³.

Withdrawal of Subjects

Subjects were to be withdrawn for the following reasons: pregnancy, a 20 or more point increase in PASI score from baseline to 4 weeks; subjects' choice.

Concomitant Therapy

Moderate to high potency topical corticosteroids, keratolytics, coal tar, or calcipotriol were not permitted except on groin, scalp, palms, and soles. Low potency (class V) topical corticosteroids could not be used on target lesions. Subjects were instructed not to use emollients within 12 hours prior to visits and prior to evaluation of physician global assessments and PASI. The subject's sun exposure was to be limited during the entire study.

Clinical Efficacy Assessments

All efficacy assessments were to be performed by the same investigator for each subject. The primary efficacy outcome was the proportion of subjects who sustained for at least two weeks during the period between visits 11 and 17 a 75% or greater improvement in skin lesions as measured by physician global assessment.

The secondary efficacy outcomes were: Length of time the PASI remained 50% below baseline after the last dose of study drug; time to reduction in PASI score of at least 50% from baseline; time to 50% improvement in global physician assessment scale.

The tertiary efficacy outcomes were: Proportion of subjects who achieved a reduction of 75% from baseline in PASI sustained for at least two weeks during the interval between visits 11 and 17; proportion of subjects who achieved clear or almost clear on physician global assessment; QOL assessments; 75% improvement of target lesions.

Statistical Analyses

No sample size calculations were provided in the original protocol. The statistical method used to test a positive dose-response relationship for both global assessment and PASI would be a Cochran-Armitage regression. Analysis of covariance would be used to

assess center by group interactions. The components of the PASI would be assessed by Cochran-Mantel-Haenszel test statistic.

Clinical and Laboratory Assessments

All blood samples for hematology and lymphocyte subset analysis would be collected at the same time of the day in order to prevent artifact of diurnal variation.

Baseline:

Complete medical history and physical examination including measurement of vital signs and body weight. Urinalysis, blood chemistries, hematology, pregnancy test for women, HCV and HIV Abs, HBsAg. Skin testing of delayed-type hypersensitivity with reading of results 48 hours later. Collection of blood for determination of antibody formation to BG9273. Analysis of peripheral lymphocyte subsets. Collection of blood for pharmacokinetic assay of BG9273 levels.

On study:

The following testing was done according to the schedule indicated:

Complete physical examination: visits 5, 9, 13, and 17. Vital signs: visits 1-13, and 15-17. Body weight: visits 1-13, and 15-17. Urinalysis: visit 15. Chemistries: visits 5, 9, 13, 15, and 17. Hematology: visits 1-13, and 15-17. Pregnancy test for women: visits 7, 13, and 17. Skin testing of delayed-type hypersensitivity for recall antigen: visits 13 and 17. Antibody formation to BG9273: visits 15 and 17. Photography visits 1, 7, 13, and 17. Investigator and subject global assessments of efficacy, PASI, target lesions, and pruritus: visits 1, 3, 5, 7, 9, 11, 12, 13, 14, 15, 16, and 17. Assessment of any ongoing or new viral, bacterial, or fungal infections: visits 2 through 19. Peripheral lymphocyte subsets: visits 1 through 13, and Visits 15, 16, and 17. BG9273 levels: Visits 3, 7, 12, 15, and 17; also to be obtained 30 minutes after study drug administration on Visit 12. Quality of life assessment: Visits 1, 7, 13, 15, and 17. Telephone monitoring to assess the subject's well-being to be performed weekly during post-dosing period (other than scheduled visits). Subjects would be contacted via telephone (Visits 18 and 19) to assess health status.

Protocol Amendments

The protocol underwent changes in the efficacy outcomes and analytical plan, as described below.

STUDY RESULTS

Patient Disposition

Enrollment occurred between May and November of 1998. The study was completed on December 1999. There were 22 study centers; four centers (117, 121, 122, 127) enrolled about 20 patients each, comprising approximately one third of all study subjects.

Reviewers' comments

In these four study centers, the proportion of responders by treatment group was similar to that seen in the overall study patient population.

For the purpose of data analysis the study centers were pooled using post-hoc criteria. This resulted in grouping of subjects in the following geographic regions: SW, MW, SE, NE each containing approximately 55 subjects.

Table 9. Patient Disposition

	Placebo	0.025	0.075	0.150
RANDOMIZED	59 (100)	57 (100)	55 (100)	58 (100)
DOSED	59 (100)	57 (100)	55 (100)	58 (100)
DID NOT COMPLETE TREATMENT	10 (17)	6 (11)	7 (13)	9 (16)
Lost to Follow-up	1 (2)	2 (4)	0	2 (3)
Voluntary Withdrawal	3 (5)	0	1 (2)	5 (9)
Adverse Event	0	1 (2)	3 (5)	0
Laboratory Abnormality	0	0	1 (2)	1 (2)
Worsening of Disease	5 (8)	2 (4)	1 (2)	0
Other	1 (2)	1 (2)	1 (2)	1 (2)
WITHDRAWN FROM TREATMENT	4 (7)	4 (7)	3 (5)	5 (9)
Lost to Follow-up	2 (3)	2 (4)	0	2 (3)
Voluntary Withdrawal	2 (3)	1 (2)	2 (4)	3 (5)
Other	0	1 (2)	1 (2)	0
EXCLUDED FROM EFFICACY ANALYSIS^a				
Center 117	5	5	5	5
Center 122	4	5	5	5
POPULATION FOR EFFICACY ANALYSIS	50	47	45	48

^aData excluded for violations of Good Clinical Practices.

The proportion of subjects who discontinued study treatment was numerically higher in the placebo (N=17) and high dose (N=16) groups compared to low (N=11) and mid-dose groups (N= 13). Six subjects (five in the mid and high dose groups) discontinued treatment for adverse events or laboratory abnormalities. The proportion of subjects who discontinued study treatment for worsening of disease was numerically highest in the placebo group (**Table 9**). The proportion of subjects who did not receive all 12 treatments was high and was comparable across treatment groups (83-89%). The proportion of subjects who had one or more study treatments substituted with placebo was dependent on dose and was 2% in the placebo group and 8, 27, 51% respectively in the low, mid, and high dose groups.

Demographics

The following demographic factors and baseline disease characteristics were not well balanced across groups: age, ethnic origin gender, severity of psoriasis and history of anti-psoriatic treatments (**Tables 10 and 11**.) These imbalances included factors that do not predict response to treatment ,were not associated with any specific group and were judged to be due to small sample size. Study patients had a median age of around 45 years, were predominantly men 60-80%, mostly Caucasian in origin (82-95%). The median body was 100 kg and ranged from 58 to 158 kg.

Disease Characteristics at Baseline.

Median duration of disease was 15-20 years (range 1-62 years). The proportion of patients treated with various phototherapies and systemic therapeutic agents was numerically lower in the low dose group (**Table 10**).

Table 10. Onset of Psoriasis and Prior Treatment

	Pl acebo	0. 025	0. 075	0. 150
DOSED	59 (100)	57 (100)	55 (100)	58 (100)
AGE: Medi an (yrs)	42	50	44	44
GENDER: Women	24 (41)	12 (21)	14 (25)	16 (28)
Men	35 (59)	45 (79)	41 (75)	42 (72)
ETHNI CITY: Bl ack	1 (2)	0	1 (2)	1 (2)
Caucasi an	56 (95)	50 (88)	45 (82)	48 (83)
Asi an	2 (3)	1 (2)	1 (2)	0
Hi spani c	0	6 (11)	8 (15)	8 (14)
Other	0	0	0	1 (2)
PSORIASIS ONSET				
Medi an (yrs)	18	15	19	18
Min. - Max. (yrs)	1-40	3-48	1-59	2-62
PRIOR TREATMENT				
UVB	22 (37)	24 (42)	20 (36)	29 (50)
PUVA	22 (37)	12 (21)	18 (33)	20 (34)
Methotrexate	15 (25)	9 (16)	14 (25)	13 (22)
Reti noi ds	14 (24)	10 (18)	8 (15)	7 (12)
Cycl ospori n	2 (3)	0	5 (9)	1 (2)
Hydroxyurea	0	1 (2)	0	1 (2)
Thi oguani ne	0	0	0	1 (2)
Rapamyci n	0	0	0	1 (2)
OVERALL	43 (73)	34 (60)	39 (71)	41 (71)

Psoriasis was more severe at baseline in patients in the high dose group as shown by the following criteria (**Table 11**). The median percentage of body surface area affected by psoriasis was 25% in the high dose group compared to 20% in other two treatment groups; the proportion of patients with psoriasis “moderate-to-severe” or worse was 57% in the high dose group compared to 37-46% in the other groups; the proportion of patients with PASI score ≥ 20 was 48% in the high dose group compared to 21-25% in the other groups.

Table 11. Baseline Disease Characteristics

	Placebo (N=59)	0.025 (N=57)	0.075 (N=55)	0.15 (N=58)
% Surface Area Involved ^a	20 (10-80)	20 (10-90)	18 (10-85)	25 (10-85)
Static Global Assessment ^b				
Severe	6 (10)	7 (12)	5 (9)	5 (9)
Moderate to Severe	21 (36)	14 (25)	18 (33)	28 (48)
Moderate	21 (36)	30 (53)	27 (49)	20 (34)
Mild to Moderate	10 (17)	5 (9)	4 (7)	5 (9)
Mild	1 (2)	1 (2)	1 (2)	0
Almost Clear	0	0	0	0
Clear	0	0	0	0
PASI Score ^b				
< 5	2 (3)	4 (7)	1 (2)	0
5 -9.9	11 (19)	11 (19)	12 (22)	12 (21)
10 -19.9	34 (58)	28 (49)	28 (51)	18 (31)
20 -29.9	9 (15)	9 (16)	10 (18)	20 (34)
30 -39.9	1 (2)	2 (4)	3 (5)	5 (9)
40 -49.9	1 (2)	3 (5)	1 (2)	2 (3)
50- 70	1(2)	0	0	1 (2)

^a medians (min- max)

^b N (percentages)

The severity of psoriasis was classified using a five-point global assessment scale (1=mild, 5=severe). About 90% of subjects were classified as having moderate-or-worse disease at baseline. Cross correlation between the global assessment and PASI scores showed broad overlaps between the categories. The greatest heterogeneity was in the “severe” disease category in which individual patient PASI scores ranged from 8 to 72.

STUDY CONDUCT

Table 11 shows that overall about 20% of study patients were not eligible for entry into the study because of mild psoriasis (defined as <10% BSA involvement).

Nearly 80% of patients received one or more antipsoriatic therapies during the study. The protocol allowed use of any topical antipsoriatic therapies (with the exception of retinoids). Application was to be limited to groin, scalp, palms and soles. About 10% of patients received non-allowed anti-psoriatic therapies (including systemic therapy and phototherapy).

Protocol Deviations

The study report (Section 10.4) cites the following violations of study protocol: enrollment of patients with “mild” psoriasis at baseline, missed study treatments, use of non-allowed concomitant medications, schedule evaluations missed or performed outside the allowed time window. The report lists the following individual violations in the placebo group: two subjects had acute infections within 2 weeks of study entry, one subject was morbidly obese, one subject had insufficient washout from systemic retinoid therapy. In the active groups one subject was morbidly obese.

The written report contains no tabulation of protocol deviations. No listing of deviations is found in the study report appendix; section 16.2.2 (Protocol Deviations) contains only

the following statement “Not Applicable”. CRT and statistical data sets and data definition tables do not contain this data set. The statistical programs do not contain a program for deriving these data.

The sponsor audited center 122 (Irvine Clinical Research Center) and determined that serious violations of good clinical practice had occurred. As a result, the principal investigator and the study coordinator were withdrawn from the study. The agency conducted its own audit and found missing documentation of the sources for CRF data. Examples were lack of documentation that the physician had attended the clinic on certain patient visit days when assessments of psoriasis were entered in the CRF, and lack of documentation that measurements of vital signs entered in the CRF were performed by the study coordinator.

At center 117, the sponsor found discrepancies between PASI score, static PGA and photography of skin lesions. The sponsor determined that the investigator had misunderstood the procedure for assessing static PGA. Efficacy data from study centers 117 and 122 was excluded from the primary analysis. Sensitivity analyses of the primary efficacy outcomes using data from both study centers revealed the relative proportion of responders across groups similar to the overall study primary efficacy analysis.

Use of Concomitant Medications

Table 12 shows that there was considerable use of potent antipsoriatic medication during the study. This is a significant concern because of potential confounding effects on at least some of the efficacy outcomes.

Table 12. Concomitant Therapy for Psoriasis

	Placebo 59 (100)	0.025 mg 57 (100)	0.075mg 55 (100)	0.15 mg 58 (100)	Total 229 (100)
Concomitant anti-psoriatic use	23 (39)	14 (25)	15 (27)	13 (22)	65 (28)
Topical steroids					
Mild: cortisone	10 (17)	5 (9)	7 (13)	3 (5)	25 (11)
Moderate: derma-smoothe-fs	0	0	1 (2)	0	1 (<1)
Potent:	5 (8)	4 (7)	4 (7)	4 (7)	17 (7)
clobetasol propionate	3 (5)	3 (5)	2 (4)	2 (3)	10 (4)
fluocinonide	1 (2)	0	1 (2)	2 (3)	4 (2)
diflorasone diacetate	1 (2)	0	1 (2)	0	2 (<1)
halcinonide	0	1 (2)	0	0	1 (<1)
Superpotent	1 (2)	0	1 (2)	2 (3)	4 (2)
betamethasone dipropionate	1 (2)	0	0	1 (2)	2 (<1)
ulobetasol propionate	0	0	1 (2)	1 (2)	2 (<1)
Systemic treatment and phototherapy	13 (22)	7 (12)	5 (9)	5 (9)	30 (13)
methotrexate	5 (8)	2 (4)	2 (4)	1 (2)	10 (4)
prednisone	1 (2)	3 (5)	1 (2)	1 (2)	6 (3)
UVB	1 (2)	1 (2)	2 (4)	1 (2)	5 (2)
cyclosporin	2 (3)	1 (2)	0	1 (2)	4 (2)
acitretin	2 (3)	1 (2)	0	0	3 (1)
methylprednisolone	0	0	1 (2)	1 (2)	2 (<1)
PUVA	2 (3)	0	0	0	2 (<1)
methylprednisolone acetate	1 (2)	0	0	0	1 (<1)
methylprednisolone sodium succinate	0	1 (2)	0	0	1 (<1)
psoralens for topical use	1 (2)	0	0	0	1 (<1)

Reviewers' comment

The large number of patients on concomitant antipsoriatic treatments is notable. Accounting for start and duration of treatment, and (in the case of topical therapy) application site(s) was difficult. Certain treatments (e.g. PUVA, UVB, methotrexate, cyclosporin) were not allowed by the protocol.

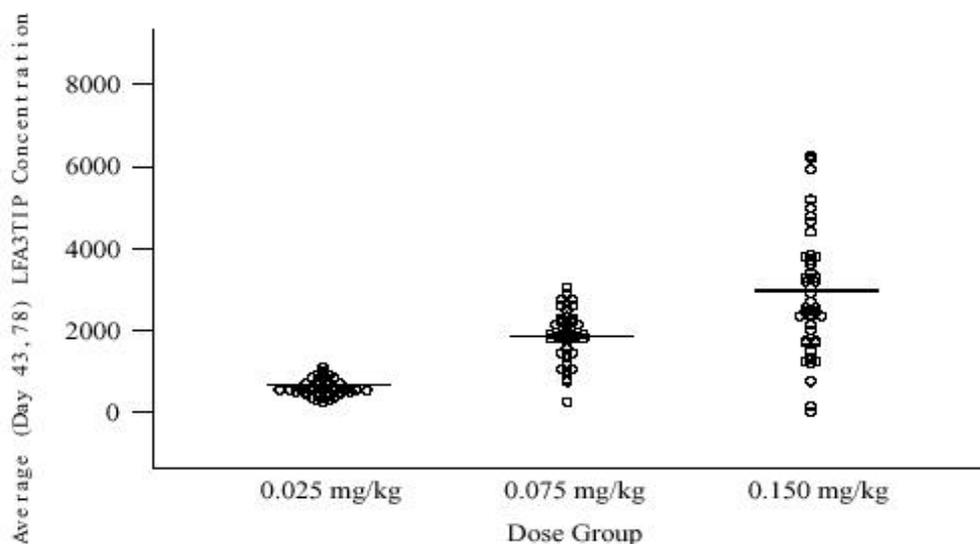
STUDY OUTCOMES: PK, PRIMARY EFFICACYPK data

Comparison of alefacept concentration in paired serum samples obtained at treatment days 43 and 73 showed variability in individual patients within each dose group. Overall the data showed no evidence of alefacept accumulation at the later time point.

With the assumption that steady state was achieved at treatment day 48, the sponsor compared mean alefacept concentrations between treatment groups (See **Figure 3.4-2** below). Serum concentration of alefacept increased with administered dose. There was considerable variability in the mid and high dose groups. Particularly in the 0.15 mg/kg dose group withholding of alefacept dosing due to lymphopenia may have contributed to the variability; in this group 50% of patients did not have paired serum samples available

for analysis. The sponsor also attributes the variability in alefacept concentrations to the wide range in body weight of the study subjects; no supporting data are shown.

Figure 3.4-2 Distribution of alefacept concentrations in Study 708



Each symbol represents value for a single subject (average of Days 43 and 78 pre-dose values), the horizontal line indicates the mean for the treatment group.

Primary efficacy analysis

The primary efficacy analysis was to be performed in the intent to treat population defined as all subjects randomized and receiving at least one dose of study treatment. The evaluable population was defined as all randomized subjects receiving ≥ 8 doses of study treatment. The primary efficacy outcome was the proportion of subjects experiencing sustained (defined as ≥ 2 weeks) improvement of 75% or greater in psoriasis measured by static physician global assessment. The time to achieve endpoint could be anytime between visit 12 (end of treatment) and visit 17 (12 weeks post-treatment). Any center with < 16 randomized subjects was to be pooled into a single center. A Cochran-Armitage regression was used to look for a positive dose-response relationship for the primary efficacy outcome (75% improvement by PGA) and for the principal secondary outcome (75% improvement in PASI). The regression model was: $\text{response} (0,1) = \text{intercept} + \text{slope for dose response} \times \log(\text{dose})$.

On May 14, 1998 the primary outcome was changed to the proportion of subjects whose disease severity was mild or better (mild, almost clear, or clear) as measured by global assessment at 2 weeks after the last dose of study drug. The principal secondary outcome would be an analysis of subjects who improved from: a) “severe” or “moderate-to-severe” to “mild” or b) “moderate” to “almost clear” or “clear”.

The modeling approach presented by the sponsor for the primary analysis differs from the pre-specified plan. The following are the main differences.

1. Baseline characteristics that differed (<0.05) between groups (including newly defined geographic regions) were added to the analysis model.
2. Pooling of centers was based on geographic regions.

Pooling of centers with <16 subjects (as pre-specified) led to one large pooled center and four individual centers. The sponsor developed a post-hoc system of pooling centers based on four geographic regions (Southwest, Midwest, Southeast, Northeast). Each region contained 4-7 individual study centers and 45-62 subjects.

At Week-2 post-treatment the p value for linear dose response = 0.053 with the post-hoc inclusion of geographic region in the analysis model. The sponsor found significant p values for dose-dependency of treatment response using secondary post-treatment time points and/or using secondary efficacy outcomes. However in these analyses the problem of multiplicity is not addressed. The sponsor also analyzed dose response by treatment cohorts defined by measured alefacept serum concentrations. The results of these analyses in general support the notion of a dose-dependent treatment response. The response does not appear to be linear. The hypothesis testing result of sensitivity analysis excluding geographic region from the model are consistent with the primary analysis.

The primary efficacy outcome of improvement in static physician global assessment shows evidence of a modest treatment effect (**Table 13**). The proportion of responders is approximately 20% (absolute) higher in the alefacept treated groups compared to placebo. The presence of a treatment effect of similar magnitude is evident using the secondary efficacy outcome of 75% reduction from baseline in PASI score.

Table 13. Proportion of Responders by Dose Group at Follow-up Week 2

	Placebo	0.025 mg/kg	0.075 mg/kg	0.150 mg/kg
Primary outcome: PGA "mild or better"	5/45 (11) ^a	14/42 (33) ^a	15/41 (37) ^a	14/41 (34) ^a
	5/50 (10) ^b	14/47(30) ^b	15/45 (33) ^b	14/48 (29) ^b
	----	4.3 (1.3, 14) ^c	4.6 (1.5, 14) ^c	3.8 (1.22, 12) ^c
Secondary outcome: PASI \geq 75%	5/55 (9) ^d	10/52 (19) ^d	15/50(30) ^d	14/53 (26) ^d
	----	2.6 (0.8, 8.4) ^c	4.36 (1.4, 13) ^c	3.69 (1.2, 11)) ^c

^aProportions excluding missing data

^bProportions for intent to treat population ; centers 117 and 122 are excluded.

^cOdds ratio (95% C.I.) of the respective treatment group over placebo based on the intent-to-treat population.

^dCenter 122 is excluded

There are minor discrepancies in the proportion of responders based on the definition of intent to treat population and on handling of missing data. **Table 13** shows the proportion of responders using subjects randomized who received at least one dose of study drug, excluding centers 117 and 122 and considering subjects with missing data treatment failures. The proportions meeting the primary efficacy outcome (PGA mild or

better) were 10 % in placebo and about 30% in the alefacept groups. The proportions meeting the principal secondary outcome ($\geq 75\%$ decrease in PASI) were similar. The study captured several secondary outcomes that are based on the same cardinal disease manifestations of psoriasis. As expected these outcomes also showed evidence of a treatment effect.

Reviewers' comment

The protocol did not require that patients who received concomitant anti-psoriatic therapy be considered non responders for the efficacy analyses. This may have led to an overestimate of the response to alefacept treatment. Alternatively, if more placebo patients received concomitant anti-psoriatic treatment on study, it could minimize the magnitude of the treatment difference.

At two weeks post treatment the mean percentage change in PASI compared to baseline was approximately 30% in the placebo group and 40-50% in the alefacept groups. Within each group, the induration, erythema and desquamation components of the score all declined in parallel (**Table 14**). An analysis of change in disease manifestations without weighting for area gave similar results. Assessment of target lesions also confirmed the presence of a treatment effect in the two anatomic regions examined (trunk and limbs). Overall responses were numerically higher in the trunk compared to the limb lesions.

Table 14. Mean % Change in PASI Components at 2 WKS Post Treatment

	Placebo	0.025	0.075	0.150
Number of subjects	49 50	47	45	45 48
% change PASI	-21	-38	-53	-53
Induration	-22	-34	-54	-57
Erythema	-20	-35	-50	-47
Scaling	-17	-38	-48	-52

Study 708 provided evidence of treatment effect. The study did not provide sufficient information about relative activity of the doses tested. The sponsor categorized study patients based on alefacept concentration data into quartiles (0-100, 125-285, 835-2000, and 2250-8100 ng/ml). The sponsor analyzed response variables based on post-hoc allocation of patients to one of four alefacept concentration groups. The results of these analyses were compared to the results of the pre-specified efficacy analyses based on treatment allocation.

Some analyses of treatment response performed by the sponsor suggested overlap in the proportion of responders in the two top dose groups and numerical separation of mid and high dose group from the low dose group. Other analyses (e.g. by drug concentration quartiles) suggested virtual overlap in proportion of responders in low and mid dose groups and numerically higher proportion of responders in the high dose group. (See **Figures 11-3** and **11-4** below).

Figure 11-3 Primary Endpoint (PGA Mild or Better) by Dose and Time

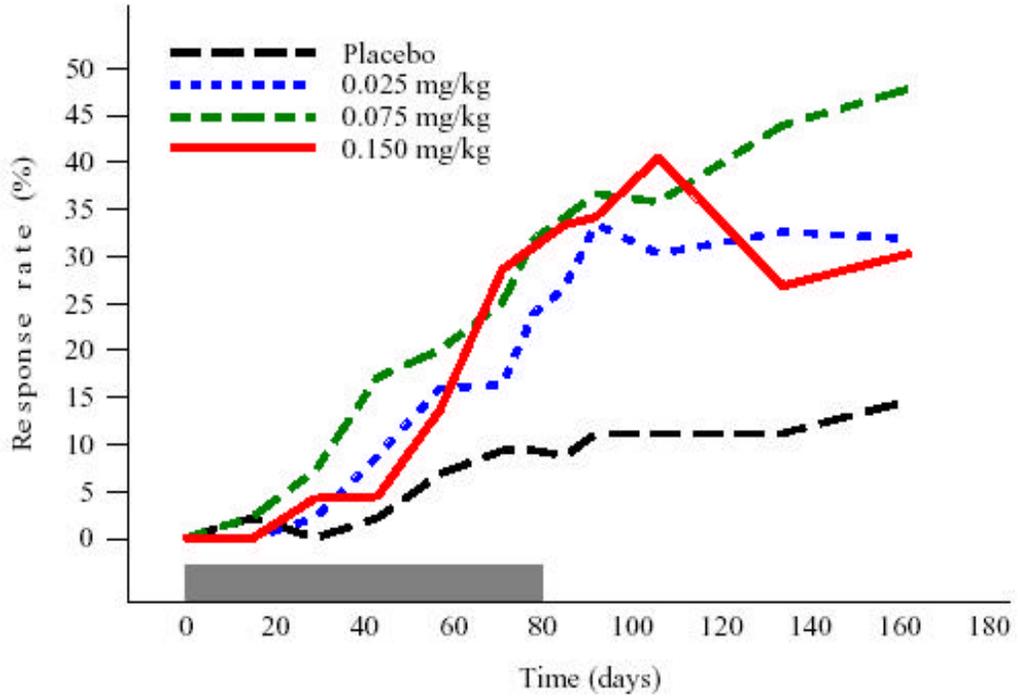
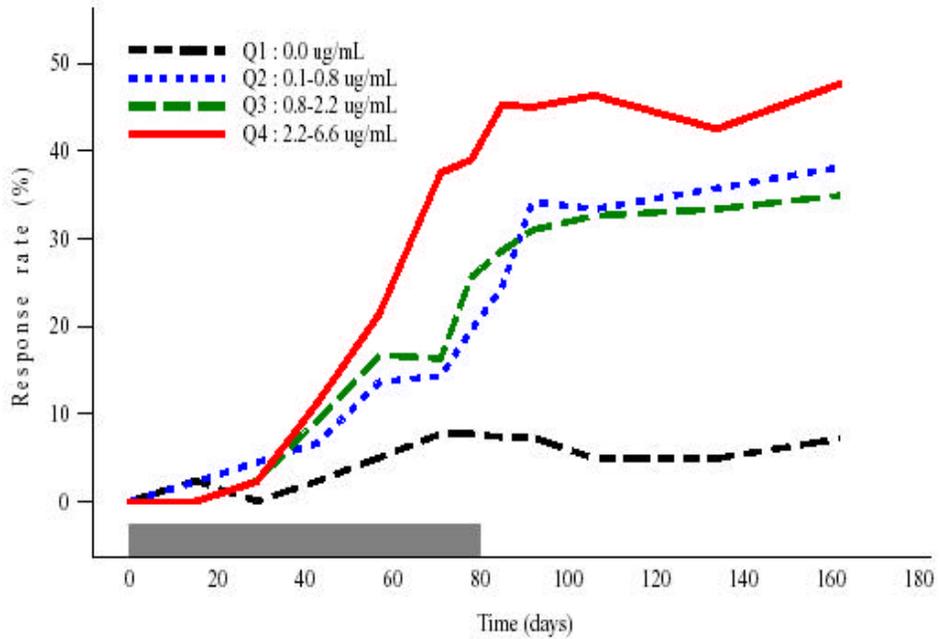


Figure 11-4 Primary Endpoint (PGA Mild or Better) by Concentration and Time

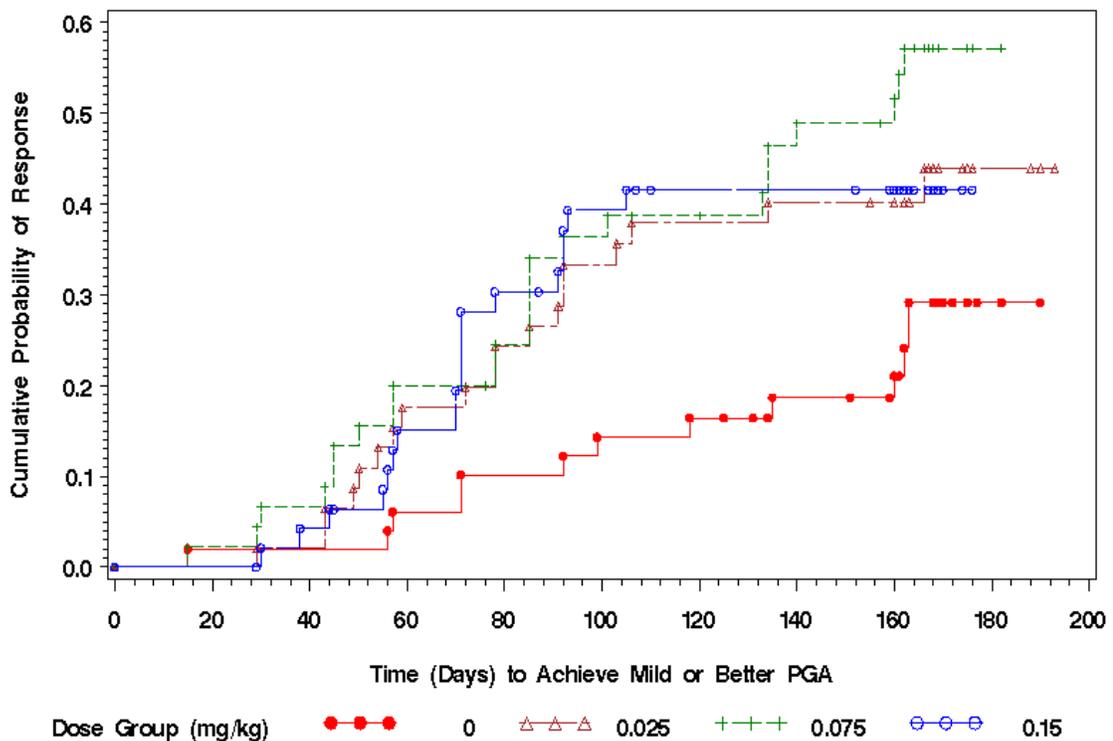


STUDY OUTCOMES: ANALYSES OF SECONDARY EFFICACY OUTCOMES

Time-to-response and duration of treatment response

Additional useful analyses in per-protocol treatment responders is time to response (during the treatment period), and duration of response (after the end of the treatment period) by treatment group. It is worth noting that these analyses may be confounded by the disallowed concomitant medications patients received for psoriasis. The sponsor defines duration of response as the number of days between onset of response and the next observation in which the subject no longer meets the response criteria. The sponsor added 7 days to the duration if the response ended on or before week 2 post treatment and 14 days if the response ended after week 2 post treatment. The sponsor states that the time to onset of response occurs significantly earlier in the alefacept groups compared to placebo (See **Kaplan Meyer plot** below).

Study C97–708: Time to PGA 'Mild' or Better



Reviewer's comments

Separation between the alefacept groups and placebo curves began relatively late (after day 60) during the treatment period, the number of responders is very small, there was no difference between the three alefacept groups. For these reasons the significance of the difference in time to response between alefacept and placebo is not clear.

With regard to duration of response, the sponsor found no difference in duration of response during treatment and an overall difference between alefacept and placebo after the treatment period (**Table 15**).

Table 15. Duration of Response (days) PGA Mild or Better

	Placebo	0.025	0.075	0.15	Diff	Linear
DURING TREATMENT PERIOD					0.32	0.67
N	5	11	13	15		
Median	28	28	42	14		
Min – Max	11-41	7-44	7-84	7-58		
DURING FOLLOW-UP					0.025	0.006
N	11	17	23	17		
Median	29	91	89	89		
Min – Max	14-91	7-140	14-101	28-107		

'Diff' represents the p-value for overall treatment differences; 'Linear' represents the p-value for linear dose-response.

Reviewer's comments

Duration of response during the treatment period is not as clinically meaningful an outcome measure as response at the end of treatment or duration of response after discontinuation of treatment. Nevertheless there are no differences between groups. This observation appears to negate the sponsor's argument that there are differences between placebo and active drug in time to onset of response.

The sponsor's definition of response duration is conservative because no loss of clinical benefit is allowed. However in patients with psoriasis it is more appropriate to estimate duration of response starting after the end of treatment. The more relevant clinical question is what is the time interval before retreatment with a potentially toxic drug is necessary. Any interpretation of duration of response should take into account the calculated clearance of alefacept. Finally it is also more conservative to omit the addition of 1- 2 weeks to the last observation of response.

The calculation of $p=0.006$ for linear dose response is not meaningful because of the nearly identical medians (89-91 days) in the alefacept groups. The duration of response in the post-treatment period using different outcome measures is not consistently superior in the alefacept groups and may be confounded by use of concomitant anti-psoriatic treatments

A conservative analysis, which does not add any days to the end of response time, and does not take into account response during the treatment period shows that the duration of response is not different between the placebo and alefacept groups (**Table 16**).

Table 16. Duration of Response (days) PGA Mild or Better

	Placebo	0.025	0.075	0.150	Diff	Linear
During follow-up					0.532	0.272
n (a)	7	16	20	17		
Median	56	77	77	75		
Min - Max	21- 90	7- 140	7- 87	28- 93		

Patient listings were examined to determine if during the post-treatment period variants

of psoriasis (e.g. pustular, erythrodermic) or flares of psoriasis develop. No cases of rebound of psoriasis were identified. Analysis of treatment failures showed a rough inverse dose-response in the proportion and severity of cases of worsening psoriasis with the highest numbers/severity in the in the placebo and low dose groups. For these analyses center 122 was excluded and LOCF was used for missing value at endpoint (See **Table 17**).

Table 17. % Change from Baseline in PASI at 2 Weeks Post Treatment

% change		pl acebo	0. 025	0. 075	0. 15
≥ 75%	Improvement	6 (11)	10 (19)	15 (30)	15 (28)
50- 74. 9 %	Improvement	8 (15)	7 (13)	13 (26)	12 (23)
25- 49. 9 %	Improvement	13 (24)	17 (33)	11 (22)	14 (26)
0- 24. 9 %	Improvement	18 (33)	12 (23)	10 (20)	8 (15)
0. 1- 25%	Worseni ng	3 (5)	3(6)	0	4 (8)
25. 1-50%	Worseni ng	2 (4)	1 (2)	0	0
50. 1- 75%	Worseni ng	3 (5)	1 (2)	1 (2)	0
≥75%	Worseni ng	2 (4)	1 (2)	0	0

Analyses of Other Secondary Efficacy Outcomes

Cross correlations between PASI score at baseline and endpoint were examined and no evidence of dose-dependent worsening of psoriasis was seen in non-responders. The patients who worsened tended to be in the placebo and low dose groups.

Patient photographs were reviewed to confirm the diagnosis of plaque psoriasis and the severity of disease at baseline and at endpoint using scaling, erythema/discoloration, area and whenever possible raised border/elevation.

Pruritus scores (using VAS 0=none 10=maximum severity) were approximately 4.5 at baseline, remained unchanged in the placebo group (-0.33) and declined by about 1.5 points in the alefacept groups.

Cross correlation between the primary efficacy outcome (static PGA with psoriasis mild or better) and the principal PASI outcome ($\geq 75\%$ improvement from baseline) showed good concordance between the two treatment outcomes for patients with PGA scores of severe, moderate-to-severe, and moderate. Nearly all these patients also failed to respond by PASI criteria. Four of 33 subjects classified as moderate (hence treatment failures) by PGA scores were considered responders by PASI scores. All the patients classified as mild, almost clear, and clear by PGA scores were also treatment successes by PASI score. There was a crude overall correlation (correlation coefficient 0.3 as calculated by sponsor) between response to treatment and lymphocyte counts (total, CD4, and CD8).

STUDY OUTCOMES: SAFETY

Incidence of Adverse Events

The incidence of adverse events by body system was numerically higher in the mid- and high-dose groups compared to placebo for the following systems: body-as –a-whole, digestive, nervous metabolic, urogenital and endocrine (See **Table 18**).

Table 18. Incidence of Adverse Events by Body System

	Placebo	0.025	0.075	0.15
Number of Subjects Dosed	59 (100)	57 (100)	55 (100)	58 (100)
Subjects With \geq 1 AE	44 (75)	45 (79)	46 (84)	44 (76)
Body as a Whole	21 (36)	31 (54)	29 (53)	27 (47)
Respiratory	25 (42)	18 (32)	17 (31)	23 (40)
Digestive	9 (15)	13 (23)	8 (15)	10 (17)
Nervous	5 (8)	9 (16)	9 (16)	12 (21)
Skin & Appendages	8 (14)	16 (28)	5 (9)	8 (14)
Musculoskeletal	6 (10)	3 (5)	8 (15)	9 (16)
Special Senses	5 (8)	4 (7)	5 (9)	3 (5)
Cardiovascular	5 (8)	3 (5)	5 (9)	3 (5)
Metabolic/Nutritional	1 (2)	3 (5)	6 (11)	1 (2)
Urogenital	1 (2)	4 (7)	1 (2)	3 (5)
Hemic & Lymphatic	2 (3)	1 (2)	1 (2)	2 (3)
Endocrine	0	0	0	1 (2)

The incidence of most common adverse events was numerically slightly higher in the active arms compared to placebo for the following: accidental injury, dizziness, flu syndrome, diarrhea, nausea, cough, myalgia, and asthenia (**Table 19**). The incidence of infectious events did not appear to be higher in the alefacept group compared to placebo for the following terms: pharyngitis, rhinitis, infection, bronchitis, otitis media, and herpes simplex. Periodontal abscess was numerically higher in the alefacept group.

Table 19. Adverse Events Occurring in \geq 5% of Subjects by Treatment Group

	Placebo	0.025	0.075	0.15	BG9273 Total
Subjects dosed	59 (100)	57 (100)	55 (100)	58 (100)	170 (100)
Subjects with AE	44 (75)	45 (79)	46 (84)	44 (76)	135 (79)
Pharyngitis	16 (27)	10 (18)	12 (22)	15 (26)	37 (22)
Headache	8 (14)	6 (11)	9 (16)	10 (17)	25 (15)
Accidental injury	3 (5)	5 (9)	8 (15)	9 (16)	22 (13)
Rhinitis	7 (12)	5 (9)	4 (7)	7 (12)	16 (9)
Dizziness	1 (2)	3 (5)	5 (9)	7 (12)	15 (9)
Flu Syndrome	3 (5)	6 (11)	4 (7)	4 (7)	14 (8)
Diarrhea	1 (2)	5 (9)	0	6 (10)	11 (6)
Infection	5 (8)	5 (9)	3 (5)	3 (5)	11 (6)
Nausea	0	3 (5)	3 (5)	4 (7)	10 (6)
Chills	0	0	3 (5)	5 (9)	8 (5)
Cough increased	0	5 (9)	2 (4)	1 (2)	8 (5)
Myalgia	2 (3)	1 (2)	2 (4)	5 (9)	8 (5)
Rash	2 (3)	7 (12)	0	1 (2)	8 (5)
Asthenia	1 (2)	0	4 (7)	3 (5)	7 (4)
Bronchitis	2 (3)	1 (2)	2 (4)	3 (5)	6 (4)
Hypertension	3 (5)	1 (2)	3 (5)	2 (3)	6 (4)
Arthralgia	2 (3)	1 (2)	1 (2)	3 (5)	5 (3)
Herpes simplex	2 (3)	1 (2)	1 (2)	3 (5)	5 (3)
Insomnia	0	1 (2)	3 (5)	1 (2)	5 (3)
Periodontal abscess	0	3 (5)	1 (2)	1 (2)	5 (3)
Otitis media	3 (5)	0	2 (4)	0	2 (1)

Table 20 shows that there was no difference in the proportion of adverse events rated as severe across study arms. The incidence of serious adverse events was 7% in placebo and from 2 to 7% in the alefacept groups (not shown).

Table 20. Severe Adverse Events by Body System

	Placebo	0.025	0.075	0.150	Bg9273 Total
Number of subjects dosed	59 (100)	57 (100)	55 (100)	58 (100)	170 (100)
Subjects with at least one event	7 (12)	8 (14)	6 (11)	10 (17)	24 (14)
Body System					
Body as a whole	2 (3)	4 (7)	5 (9)	4 (7)	13 (8)
Respiratory	3 (5)	2 (4)	1 (2)	2 (3)	5 (3)
Skin & appendages	1 (2)	2 (4)	0	2 (3)	4 (2)
Digestive	2 (3)	1 (2)	0	2 (3)	3 (2)
Nervous	0	1 (2)	0	1 (2)	2 (1)
Cardiovascular	0	0	0	1 (2)	1 (<1)
Hemic & lymphatic	0	0	0	1 (2)	1 (<1)
Musculoskeletal	1 (2)	0	0	0	0

Laboratory data**Hematology**

Shifts in PMN, RBC, and platelets were observed; these were not dose dependent. Up to 23% of patients had shift to high PMNs. RBCs tended to shift to low in about 10% of patients. Platelet shifts were to lower or higher counts without apparent pattern.

Lymphocytes declined to low in a dose-dependent manner. The decrease in lymphocyte counts was further characterized. CD3 counts decline in a dose-dependent manner. For CD4 counts the incidence of decreases that are potentially clinically relevant (**Table 21**), the rate of decline and the duration of the decline are all dose dependent. With regard to recovery of counts, three subjects in the 0.075 mg/kg group and five in the 0.15 mg/kg group had CD4 counts lower than the lower limit of normal at the last visit. Subjects were followed until their CD4 counts rose above 300 cells/ μ L (LLN 320 cells/ μ L). The only subject whose CD4 counts did not rise within 6 weeks after the end of the study was diagnosed with metastatic testicular carcinoma, and was placed on chemotherapy and radiotherapy and was withdrawn from study. While the CD4 counts increased during follow up, comparison of the difference between the baseline count and the last recorded count shows that, on average, counts had not recovered to the baseline level after treatment with alefacept.

CD8 counts showed dose-dependent pattern of incidence, rate of decline, and duration of decline similar to that seen with CD4 counts. CD8 counts increased during follow up but did not recover to pre-treatment baseline by the end of the follow up period.

There was some suggestion of slight decrease (?fluctuation) in numbers of natural killer cells (CD16-CD56) with return to baseline. B cells (CD19) did not appear to be affected.

Although there was reasonable correlation between lymphocyte counts and CD4 counts, the CI were wide (not shown) suggesting that in clinical use, CD4 counts should be monitored directly to guide alefacept dosing.

Table 21. Dose-dependent CD4+ T Lymphocyte Depletion

Treatment	N	Cell Counts			
		400	300	200	100
Placebo	(59)	12 (20)	1 (2)	0	0
0.025	(57)	15 (26)	2 (4)	0	0
0.075	(55)	26 (47)	15 (27)	3 (5)	0
0.15	(58)	40 (69)	23 (40)	6 (10)	0

Chemistry:

No evidence of hepatic, renal, endocrine/metabolic abnormalities was seen.

Anti-alefacept Antibodies:

Two subjects in the 0.15 mg/kg alefacept group tested positive: one at baseline with a titer of 5, the other on Day 162 with a titer of 5.

Skin testing for delayed hypersensitivity:

Results are shown in table 14.3.28.of the BLA. The number of - to + shifts was subtracted from the number of + to – shifts by antigen by treatment group to obtain the net number of shifts from positive to negative (see Table 22). There is a suggestion of higher net number of + to – shifts in the alefacept groups compared to placebo . The sponsor’s interpretation is that there is no evidence of development of anergy.

Table 22. Net Number of DTH Shifts from Positive to Negative

Antigen	placebo	0.025	0.075	0.15
Tetanus	7	10	16	6
Diphtheria	0 ^a	0	8	7
Streptococcus	1	2	0	3
Tuberculin	0	4	10	8
Candida	0	5	4	3
Tricophyton	0	0	2	1
Proteus	0	2	0	5
Glycerin	0	2	0	5

^a 0 denotes no net shift or shift from - to + .

Clinical Narratives of Serious Adverse Events

There were no deaths. The following serious adverse events are described in the treatment groups.

Placebo:

- Syncope, bronchitis, cholelithiasis, worsening psoriatic arthritis.

0.025 mg Group:

- Worst asthma exacerbation in patient with average 1 episode /year x 10 years
- Recurrent angioedema with first episode after 10th dose of alefacept, judged to be likely related
- 50-year old with no relevant risk factors developed R facial (forehead, maxilla, ear canal) cellulitis (Staph aureus, B Strep) at the end of 3 months alefacept treatment. Required debridement and antimicrobials. Not associated with abnormal WBC.

- 50-year old with psoriasis for 3 decades treated with phototherapy and systemic therapy, history of two SCC skin. Diagnosis of SCC skin 7 weeks after start of treatment

0.75 mg Group:

- Elective uncomplicated cholecystectomy
- Acute syndrome with nausea vomiting and severe headache following first dosing (resolved, unexplained)
- Worsening psoriatic arthritis
- Abnormal LFTs (present at screening)

1.5 mg Group:

- 25-year old man with diagnosis of testicular teratocarcinoma with pulmonary metastases at about 3 months after the end of a course of alefacept. Treated with orchiectomy, chemotherapy, and radiotherapy. Tumor clinically undetectable following treatment.
- Elective total knee arthroplasty
- MI long after drug clearance
- Post-surgical femoral venous thrombosis
- Borderline transient leukopenia

Reviewer's Comment

The following events in patients treated with alefacept are notable: hypersensitivity reaction, serious infection, and neoplasia.

CONCLUSIONS

Efficacy

- Approximately 20% more patients in the alefacept treated groups have a response compared to placebo.
- There was no discrimination between the two higher doses studied. Lack of difference in response between mid and high dose groups may be attributable to imbalance in baseline psoriasis severity and withholding treatment in the high dose group due to lymphopenia.
- Concomitant use of antipsoriatic therapies may have caused overestimation of the treatment effect.
- Various secondary efficacy outcomes support the primary efficacy outcome and also show evidence of treatment effect.
-
- Alefacept concentration quartiles do not provide additional insights into dose response.
- There was no striking difference between placebo and alefacept in time to onset of response to treatment.

Safety

- Alefacept induces dose-dependent CD2+ lymphocyte depletion (primarily CD4 and CD8).
- CD4 and CD8 counts return to within normal limits. On average, counts do not recover to the baseline level during the follow up period.
- Serious infection and neoplasms were observed, the incidence was too low for meaningful analysis. There was no evidence of opportunistic infections or reactivation of latent/chronic infections. DTH data were inconclusive.
- Rare cases of hypersensitivity reactions occurred.
- No anti-alefacept antibody development was detected.

PROTOCOL C99-711

Study Title

“A randomized, double-blind comparison of intravenous LFA3TIP versus placebo in subjects with chronic plaque psoriasis ” Protocol Number:C99-711; October 21, 1999

Study Objectives

Demonstrate in subjects with chronic plaque psoriasis the efficacy and safety of LFA3TIP administered as a weekly 7.5 mg IV injection for 12 weeks by measuring the proportion of subjects with $\geq 75\%$ reduction from baseline in PASI.

Demonstrate the efficacy and safety of LFA3TIP following two courses of LFA3TIP administered as a weekly 7.5 mg IV injection for 12 weeks per course as measured as the proportion of subjects who achieve a 75% or greater reduction from baseline in PASI.

Design of study

Phase 3, multicenter (approximately 55 sites), randomized, double-blind, parallel-group, placebo-controlled (saline), study of LFA3TIP (7.5 mg IV) in 555 subjects with chronic plaque psoriasis.

Randomization:

Subjects were randomized (centrally) in a 1:1:1 ratio to one of three cohorts. Cohort 1: two courses of LFA3TIP or Cohort 2: an initial course of LFA3TIP followed by a course of placebo or Cohort 3: an initial course of placebo followed by a course of 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.

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 was instructed to not communicate any information to the other investigators, study coordinators, or the sponsor. The only person at each site who should have been unblinded was the pharmacist or designee who prepared study drug.

Open label extension study:

At the end of the second treatment course, study subjects would have had the option to enroll in an open-label retreatment study under a separate protocol.

Study drug

Subjects whose body weight is ≥ 50 kg received 7.5 mg of LFA3TIP or placebo. Subjects whose body weight is < 50 kg received 5.0 mg of LFA3TIP or placebo.

Rationale for fixed dose:

In study C97-708 body weight accounted for a relatively small proportion of variation in LFA3TIP AUC over the body weight range of 60-95 kg.

Treatment course 1 and 2:

Subjects received two courses of study drug separated by a minimum of 12 weeks. Each course consisted of an IV bolus of study drug once a week for 12 weeks. Subjects were followed for 12 weeks after receiving the last dose of study drug.

Subjects were eligible to receive a second 12-week course of study drug if their plaque psoriasis severity was worse than 'clear' on Physician Global Assessment and their peripheral CD4⁺ count was at or above 250 cells/mm³.

Withholding treatment:

Administration of each dose of study drug was to be separated by 7 days. There had to be no clinical evidence of significant viral, bacterial, or fungal infection.

Concomitant Treatments

The sponsor provided low potency topical corticosteroids (hydrocortisone 1% cream) and emollients. If a subject discontinued study drug, systemic medications for psoriasis could have been initiated only after a 4-week washout.

Study Inclusion Criteria

Subjects 16 years of age or older with chronic plaque-type psoriasis for more than 12 months with a body surface involvement of $\geq 10\%$ and CD4⁺ lymphocyte counts above the lower limit of normal were eligible.

Study 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 are 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 not 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.

Eligibility for Treatment Course 2

Patients had to have the following. Disease severity worse than ‘clear’ by Physician Global Assessment, CD4⁺ lymphocyte count ≥ 250 cells/mm³, had not received non-allowed antipsoriatic treatment before visit 8A.

Dose Modification Rules

Dosing was withheld for 2 weeks for body temperature $>38^{\circ}\text{C}$ or clinically significant infection. The study drug was substituted with placebo if the absolute CD4⁺ lymphocyte count from the previous week was below 250 cells/mm³.

The study drug was permanently substituted with placebo if any subject experienced a reduction in number of absolute CD4⁺ lymphocytes below 250 cells/mm³ for 4 or more consecutive visits. Subjects who prematurely discontinued study drug remained in the study and continued 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 were as follows. Absolute: pregnancy; subject’s choice; medical emergency. Discretionary: investigator’s choice (e.g. medical reasons, non-compliance)

Primary Efficacy Endpoint

The proportion of patients with $\geq 75\%$ improvement in PASI score at the end of the first treatment period 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

Target Skin Lesion Assessment.

The proportion of subjects with target lesion score of 0 was assessed. The lesion was located on the trunk, $\geq 2 \text{ cm}^2$, and not sun-exposed. Lesional erythema, induration (thickness), and desquamation (scaling) were graded in half-point increments from 0=none to 4= very marked.

Quality of Life.

Health-related quality of life (QOL) was evaluated in this study using three standard scales, namely the SF-36 Health Survey (SF-36), the Dermatology Life Quality Index (DLQI), the Dermatology Quality of Life Scales (DQOLS). A four-item Treatment Convenience Scale developed by the sponsor was also used.

The SF-36 evaluates health status in eight areas: physical functioning, limitations due to physical problems, bodily pain, general health, vitality, social function, limitations due to emotional problems, and mental health. The SF-36 has been used in studies of psoriasis. SF-36 scale scores range from 0 (worst) to 100 (best).

The DLQI is a ten-item questionnaire designed to evaluate QOL of patients with a variety of skin conditions, including psoriasis. It addresses daily activities, leisure activities, impact on work or school, personal relationships, symptoms and feelings, and treatment-related distress. The Overall DLQI scale score ranges from 0 (worst) to 30 (best).

The DQOLS contains 29 items that represent eight categories: embarrassment, despair, irritability, distress, everyday activities, summer activities, social activities, and sexual activity. The DQOLS also includes 12 symptoms (redness, itch, scarring, flaking, rawness, change in skin color, pain, tiredness, swelling, bleeding, aching, and burning). The DQOLS scale scores range from 0 (best) to 100 (worst).

The Treatment Convenience scale looks at the impact of treatment on patients' daily activities, the time spent managing their psoriasis, the discomfort due to treatment, and patients' overall rating of the convenience or inconvenience of their treatment. The Treatment Convenience scale score ranges from 0 (worst) to 100 (best).

Clinical and Laboratory Assessments:

The schedule for Treatment Courses 1 and 2 was as follows.

- Weekly dosing visits: (Visits 1A-12A); (Visits 1B-12B).
- Follow-up visits: (Visits 13A-17A); (Visits 13B-17B).
- Monthly interim visit(s): After the first treatment course patients had monthly visits.

Assessment of Efficacy and PK:

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

Assessment of Safety:

The following were performed: physical examinations; 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 for infections. Monitoring for adverse events. Adverse events were defined as any sign, symptom, data or medical diagnosis, regardless of relationship to study drug, that begins or is worsened after the start of study drug treatment. AEs were recorded in the subject's adverse event CRF. Definitions of seriousness, severity and causality were included in the protocol. Provisions were made for reporting serious adverse events to sponsor, to IRB, and to FDA.

Assessment Responsibilities 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.

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 group and 10% in the placebo group. A sample size of 370 subjects (2 active:1 placebo) would have 95% power and a type I error rate of 5% to show efficacy.

However to achieve sufficient power for important secondary endpoints (e.g. to demonstrate the efficacy of retreatment with LFA3TIP) additional subject accrual would be needed. The sponsor assumed that 50% of subjects would clear, withdraw, or fail to achieve CD4 counts above 250 between the two dosing periods, therefore the study require an additional 185 subjects for a total accrual of 555 subjects.

Missing data:

The method of last value carried forward was initially proposed 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 to be evaluated using the last endpoint measured. The duration of response endpoint would 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. The sponsor drew a straight line between the last visit when patient was in response and the following visit where loss of response occurred. The cut point was calculated using the time when the straight line cross the horizontal response line (e.g., 75% PASI). The interval between two cut points defined the duration.

Baseline Data:

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

Efficacy Analyses:

All tests were two-sided and were considered statistically significant at the 5% level. Confirmatory analyses were based on an intent-to-treat population defined as patients randomized, receiving at least one dose of study drug, and having at least one post-treatment efficacy assessment. 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, was tested and included in the model if significant at the 5% level.

Primary Efficacy Analysis:

The proportion of subjects with a reduction in PASI of at least 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. The comparison was between active (cohorts 1 and 2) versus placebo (cohort 3) treatment arms. Additional covariates including baseline PASI, gender, race, age, body surface area, and baseline weight will be tested.

Secondary Efficacy Analyses. First Treatment:

The proportion of subjects who achieved a Physician Global Assessment of ‘almost clear’ or ‘clear’ at Visit 13A (Day 92) without the use of phototherapy or other systemic therapy was evaluated with logistic regression using the general analysis model. The comparison was between active (cohorts 1 and 2) versus placebo (cohort 3).

The overall DLQI scale score were analyzed by ANCOVA using the general analysis model and including baseline DLQI score. The interaction between

treatment and baseline DLQI score additionally was tested and included in the model if significant at the 5% level.

Secondary Efficacy Analyses. Retreatment:

The proportion of subjects with a reduction in PASI of at least 75% from baseline (Visit 1A) without the use of phototherapy or other systemic therapy was evaluated at Visit 13B with logistic regression using the general analysis model. The comparison was between subjects who received 12 weeks of active therapy retreatment (cohort 1) and 12 weeks of placebo retreatment (cohort 2). Subjects with a Physician Global Assessment of ‘clear’ at the end of the follow-up after the first course of treatment (Visit 17A) were not included in this analysis if their disease did not worsen and they did not receive retreatment during the study.

The proportion of subjects who achieved a Physician Global Assessment of ‘almost clear’ or ‘clear’ at 2 weeks after the last retreatment dose (Visit 13B) without the use of phototherapy or other systemic therapy was evaluated with logistic regression using the general analysis model. The comparison was between subjects who received 12 weeks of active therapy retreatment (cohort 1) and 12 weeks of placebo retreatment (cohort 2). Subjects with a Physician Global Assessment of ‘clear’ at the end of follow-up after the first course of treatment were not included in this analysis if their disease did not worsen and they did not receive retreatment during the study.

The proportion of subjects whose PASI at 2 weeks post retreatment (Visit 13B) was less than their PASI at 2 weeks post the first treatment (Visit 13A) were compared between subjects receiving 12 weeks of active retreatment (cohort 1) versus those with 12 weeks of placebo retreatment (cohort 2). This analysis was performed with logistic regression using the general analysis model.

Additional Secondary (“Tertiary”) Efficacy Analyses:

- **Target Skin Lesion.**
The proportion of subjects with induration of 0 in the target lesion at Visits 13A were compared between active (cohorts 1 and 2) versus placebo (cohort 3) arms using logistic regression and the general analysis model.
- **50% Improvement in PASI. First Treatment.**
The proportion of subjects (placebo versus active treatment groups) with a reduction in PASI of at least 50% from baseline at Visit 13A evaluated with logistic regression and the general analysis model.
- **50% Improvement in PASI. Retreatment.**
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) were evaluated with logistic regression using the general analysis model. The comparison was between subjects who received 12 weeks of active therapy retreatment (cohort 1) and 12 weeks of placebo retreatment (cohort 2). Subjects with a Physician Global Assessment of ‘clear’ at the end of follow-up after the first course of treatment

were included in this analysis if their disease did not worsen and they did not receive retreatment during the study.

- **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.
- **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 was tested and included in the model if significant at the 5% level.
- **Summation of Response during Treatment, Retreatment, and Follow-up.**
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. The comparison for summation of response was between subjects receiving 12 weeks of active retreatment (cohort 1) versus those with 12 weeks of placebo retreatment (cohort 2).
- **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 was calculated after the last dose as days between the first visit at which response was achieved and the next visit when patients were assessed as either a non-responder, they withdrew, or 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 had 14 days added for the duration of response. The duration of response was assessed for subjects who were first treated with active drug and retreated with placebo (cohort 2) as well as the subset of subjects on cohort 1 achieving and maintaining a Physician Global Assessment of 'clear'.
- **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' was analyzed using Cox Proportional Hazards using the general analysis model. Time-to-event curves were plotted using the Kaplan-Meier method. Subjects who withdrew or did not respond by their last visit or the end of the study were

censored. This analysis was performed for both the treatment and the retreatment courses. Comparison for the first course of treatment was between active (cohorts 1 and 2) and placebo (cohort 3). Comparison for retreatment was between active (cohort 1) and placebo (cohort 2).

Safety Analyses

Any subject who received one dose of study drug and had post baseline data would be considered evaluable for tolerability/safety analyses. The incidence of adverse events would be tabulated by treatment group, severity, and relationship to treatment. The incidence of infections and signs, symptoms, or events associated with infection would be presented by treatment group. For laboratory data shift tables described changes from low, normal, or high. The effect of LFA3TIP on lymphocytes and lymphocyte subsets was examined by calculating the rates of change in subsets over time. The duration that lymphocytes and lymphocyte subsets were below several thresholds was also evaluated.

Study Monitoring

A CRO (Covance) was responsible for study initiation, monitoring, management of adverse event reports, and data management, analysis of all hematology, blood chemistry, and urine samples. ICT Inc. acted as the central randomization service for this study. A blinded sponsor's committee met to monitor subject accrual, non-compliance, and to consider modifications of the protocol. The committee members were Biogen's medical director, program manager, clinical project manager, and project statistician, two study coordinating investigators, and two study principal investigators.

Reviewers' comments

The phase 3 protocol outlined above is designated Version 1 and was the outcome of a series of discussions between the agency and the firm. The agency and the firm reached agreement on the final version (Version 2) of the phase 3 protocol at a teleconference on November 24, 1999. The firm sent to the agency the final revised phase 3 protocol on January 22, 2000. The protocol contained the following modifications and clarifications.

- *Patients must have CD4 counts at or above the lower limit of normal to receive a second course of treatment.*
- *At the end of the study, subjects will be followed until they reach a lymphocyte count of 75% of the original baseline value. At that point lymphocyte subsets will be quantified.*
- *Subjects with missing efficacy data at endpoint will be considered treatment failures in the primary efficacy analysis*
- *The primary efficacy analysis will be performed on the intent to treat population.*
- *The only covariates used in the primary efficacy analysis will be the four stratification criteria and the center's geographic region.*
- *The geographic region will be prospectively defined by dividing the US into 4 quarters by latitude and longitude with roughly the same number of study centers in each quarter.*
- *The secondary efficacy endpoints in order of priority will be as follows:*
 - *Proportion of subjects with PGA of "clear or almost clear" after 1st treatment*

- Proportion of subjects with $\geq 75\%$ improvement in PASI after 2nd treatment
- Proportion with PGA of “clear or almost clear” after 2nd treatment
- Proportion with PASI lower after 1st treatment than after 2nd treatment
- Changes in QOL as measured by DLQI
- Standard definitions for grading PGA using a “static” assessment were added.

In addition the sponsor agreed to conduct additional studies in a small number of subjects to characterize the effects of LFA3TIP on immune function including primary and secondary antibody responses to neoantigens, T-cell proliferative responses and cytokine production in response to antigens.

With these modifications the phase 3 study was judged to be well designed and adequately controlled for the purpose of demonstrating the efficacy and safety of LFA3TIP administered as a weekly 7.5 mg intravenous bolus for 12 weeks to patients with plaque psoriasis.

The study was also designed to provide information on other clinically important questions including the proportion of subjects with complete responses to treatment, the time of onset of the response to treatment, the duration of the response after the end of treatment, the safety and efficacy of retreatment.

Major Protocol Amendments

Amendment 1 dated 01-11-00:

The agreed-upon changes (see above) were added to the protocol.

Amendment 2 dated 11-12-00:

The option to receive open label retreatment. was withheld until more clinical data became available.

STUDY PATIENT DISPOSITION, DEMOGRAPHICS AND BASELINE DISEASE

Discontinued Subjects (Section 16.2.1)

In the cohort never dosed one patient (137206) is listed; he developed AF before randomization. Review of reasons for discontinuations indicates that the principal reasons were lack of improvement or worsening of disease, scheduling conflicts, protocol deviations, and loss to follow up.

Patient disposition

A high proportion of patients entered into the second treatment period at the end of the scheduled follow up period. The criteria for the second treatment were: psoriasis less than clear by PGA, normal lymphocyte count, and no usage of proscribed anti-psoriatic medication. In the two patient disposition tables the following are grouped together under the category adverse event: 1)adverse event, 2)intolerance to drug, 3) laboratory abnormality.

Course 1

Sixty-three (11%) of the 553 patients dosed did not complete the 12-week treatment period (**Table 23**). The percentages of patients not completing the 12-week treatment

period in Course 1 were 17 and 8% for the placebo and combined alefacept groups, respectively. The most common reason for not completing the 12-week treatment period in Course 1 was patient decision (5%). More patients in Cohort 3 (placebo/alefacept) discontinued for this reason (10%) than in the other two cohorts who received alefacept in Course 1 (3% in each). Thirty-nine patients (7%) withdrew from the study during the dosing period, the greatest number (10%) being in Cohort 3 (placebo/alefacept) By study drug, the rates of withdrawal were 10 and 6% for the placebo and combined alefacept groups, respectively. The most commonly reported reason for withdrawal was patient decision with a slightly higher rate in those who received placebo (placebo vs. combined alefacept: 5 vs. 2%).

Course 2

The proportion of non-completion/withdrawal was higher in the control group. The percentages of patients not completing the 12-week treatment period in Course 2 were 3, 13, and 6% for Cohorts 1 (alefacept/alefacept), 2 (alefacept/placebo), and 3 (placebo/alefacept), respectively. The most common reasons for discontinuation of treatment were patient request (3%) and other (2%).

The rates of withdrawal from the study during the treatment period in Course 2 were 3, 12, and 5% for Cohorts 1 (alefacept/alefacept), 2 (alefacept/placebo), and 3 (placebo/alefacept), respectively (**Table 24**). The most commonly reported reasons for withdrawal from the study during the treatment period were “other” (3%) and patient request (2%).

Table 23. Patient Disposition Treatment Course 1

	Cohort 1	Cohort 2	Cohort 3
RANDOMIZED	187	187	188
COURSE 1: DOSED	183 (100)	184 (100)	186 (100)
COMPLETED TREATMENT	172 (94)	164 (89)	154 (83)
Discontinued Treatment	11 (6)	20 (11)	32 (17)
-Loss to Follow-up	1 (<1)	2 (1)	6 (3)
-Adverse Event	1 (<1)	6 (3)	1 (<1)
-Laboratory Abnormality	0	0	0
-Worsening Disease	2 (1)	6 (3)	5 (3)
-Subject Request/Voluntary	5 (3)	5 (3)	19 (10)
-Other	2 (1)	1 (<1)	1 (<1)
Withdrawn during Treatment	8 (4)	13 (7)	18 (10)
-Loss to Follow-up	1 (<1)	1 (<1)	5 (3)
-Adverse Event	1 (<1)	3 (2)	0
-Worsening of Disease	2 (1)	3 (2)	1 (<1)
-Subject Request/Voluntary	3 (2)	4 (2)	9 (5)
-Other	1 (<1)	2 (1)	3 (2)
Withdrawn during F/U	8 (4)	13 (7)	11 (6)
COMPLETED FOLLOW UP	167 (91)	158 (86)	157 (84)

Table 24. Patient Disposition Treatment Course 2

	Cohort 1	Cohort 2	Cohort 3
COURSE 2: ENTERED	167	158	157
Withdrawn before Treatment	13	16	4
-Adverse Event	1	1	0
-Worsening Disease	0	1	0
-Subject Request	1	2	1
-Other	11	12	3
DOSED	154 (100)	142 (100)	153 (100)
COMPLETED TREATMENT	149 (97)	124 (87)	144 (94)
Discontinued Treatment	5 (3)	18 (13)	9 (6)
-Loss to Follow-up	1 (<1)	1 (<1)	3 (2)
-Adverse Event	0	1 (<1)	1 (<1)
-Worsening Disease	1 (<1)	2 (1)	0
-Subject Request	2 (1)	8 (6)	2 (1)
-Other	1 (<1)	6 (4)	3 (2)
Withdrawn during Treatment	4 (3)	17 (12)	7 (5)
-Loss to Follow-up	1 (<1)	1 (<1)	2 (1)
-Subject Request/Voluntary	1 (<1)	9 (6)	1 (<1)
-Other	2 (1)	7 (5)	4 (3)
Withdrawn during Follow-up	7 (5)	7 (5)	6 (4)
COMPLETED FOLLOW-UP	143 (93)	118 (83)	140 (92)
COMPLETED COURSE 1 AND COURSE 2	149(81)	124 (67)	144 (77)

Demographics

Demographic variables at baseline were well balanced across groups (**Table 25**). Median age was 44; nine patients (2%) were between ages 16-20 years and 79 patients (14%) were of age 60 years or greater. Median weight was 90 kg. Study patients were mostly men (70%) of Caucasian origin (90%).

Table 25. Demographic Data

		COHORT 1 (N=183)	COHORT 2 (N=184)	COHORT 3 (N=186)
AGE (yrs):	median (min-max)	45 (16-84)	44 (18-77)	44 (18-76)
BODY WEIGHT (kg):	median (min-max)	90 (49-163)	92 (46-206)	91 (54-170)
GENDER:	women	52 (28)	55 (30)	59 (32)
	men	131 (72)	129 (70)	127 (68)
ETHNIC GROUP:	Caucasian	165 (90)	167 (91)	162 (87)
	Black	4 (2)	5 (3)	8 (4)
	Asian	3 (2)	2 (1)	1 (<1)
	Hispanic	5 (3)	8 (4)	11 (6)
	other	6 (3)	2 (1)	4 (2)

Disease Characteristics at Baseline

By a variety of criteria it is clear that nearly all study patients can be classified as having moderate to severe disease. All patients had chronic disease (median duration nearly 20 years), all had $\geq 10\%$ BSA involvement, and nearly 80% had history of major anti-psoriatic treatment (**Table 26**). By PGA only 7% of patients had less than moderately severe disease.

Table 26. Disease Severity at Baseline

		COHORT 1	COHORT 2	COHORT 3
Disease Duration (yrs):	median (min-max)	18 (3-54)	20 (2-60)	17 (2-55)
PASI:	median (min-max)	15 (4-51)	15 (4-56)	15 (4-56)
BSA involvement (%):	median (min-max)	22 (10-98)	22 (10-95)	22 (10-85)
Major Anti-psoriatic Treatment:	N (%)	141 (77%)	141 (77%)	147 (79%)
PGA \geq moderately severe:	N (%)	181 (94%)	181 (93%)	175 (93%)

As judged by the patients based on a 3-point scale, the proportion of patients who failed (unchanged or worsened) a specific major anti-psoriatic therapy ranged from about 20 to 50% (Table 27).

Table 27. Response to Previous Major Anti-psoriatic Treatment

		COHORT 1 (N=183)	COHORT 2 (N=184)	COHORT 3 (N=186)
METHOTREXATE	Worsened	4/ 64 (6)	2/ 69 (3)	1/ 55 (2)
	No Change	21/ 64 (33)	21/ 69 (30)	16/ 55 (29)
	Improved	39/ 64 (61)	46/ 69 (67)	38/ 55 (69)
CYCLOSPORIN	Worsened	0/ 22	2/ 23 (9)	0/ 14
	No Change	5/ 22 (23)	5/ 23 (22)	4/ 14 (29)
	Improved	17/ 22 (77)	16/ 23 (70)	10/ 14 (71)
RETINOIDS	Worsened	2/ 32 (6)	3/ 32 (9)	2/ 28 (7)
	No Change	15/ 32 (47)	13/ 32 (41)	12/ 28 (43)
	Improved	15/ 32 (47)	17/ 32 (53)	14/ 28 (50)
PUVA	Worsened	3/ 61 (5)	2/ 70 (3)	2/ 56 (4)
	No Change	23/ 61 (38)	20/ 70 (29)	18/ 56 (32)
	Improved	36/ 61 (59)	48/ 70 (69)	36/ 56 (64)
UVB	Worsened	6/ 89 (7)	8/ 89 (9)	8/101 (8)
	No Change	31/ 89 (35)	32/ 89 (36)	39/101 (39)
	Improved	52/ 89 (58)	49/ 89 (55)	54/101 (53)

STUDY CONDUCT

Study Centers

51 principal investigators participated in the trial. All the principal investigators had experience with clinical trials and with few exception they were board-certified dermatologists. At every center the examining physicians were qualified dermatologists. A contract research organization (Covance) managed most aspects of the trial including clinical laboratory measurements.

For quality assurance purposes a CRO (ClinAudits LLC) audited the following components at 13 study centers during the course of the trial:

- Investigator file and project management file at Biogen and Covance
- GCP documentation in the Investigator's files at the site
- All informed consent and serious adverse event documentation
- Source documents and CRF for a sample of subjects

The record contains audit certificates for each of the 13 centers. There is no information on what the audits showed.

Randomization Codes (Section 16.1.7)

Nine subjects are listed in the cohort “never dosed”. Presumably these patients were randomized but the treatment allocation is not given.

Two formulations of BG9273 are listed: Creative Biomolecules (CMB) and Biogen (Cambridge). The first treatment course used the CMB formulation exclusively. The second treatment course used either the CMB or the Cambridge formulations.

Adequacy of the blind

The FDA inspector confirmed the identity, qualifications and procedures used by: Laboratory Assessing Physician (evaluates and maintains lab data, communicates changes in study drug treatment to the pharmacist, may communicate with Examining Physician if required by patient safety), and by Pharmacist (unblinded, maintains randomization log). The inspector also determined if other study personnel or monitors had access to information maintained by laboratory assessment physician and by pharmacist.

Protocol Deviations

The incidence of protocol deviations was not strikingly different among study centers. A few patients were not stratified correctly due to errors in history of previous systemic treatments obtained at screening; this did not affect the efficacy outcome. Other common deviations were in the following categories: study visits outside specified window, omission of portions of physical examination (e.g. genitalia), clinical laboratory, study drug administration, admission criteria, and other medication.

The use of other medications was further examined. During the course of the study a number of patients received potent anti-psoriatic treatments. The principal reasons were worsening of psoriasis, lack of response to study treatment, presence of psoriasis variant (e.g. psoriatic arthritis), insufficient wash-out of antipsoriatic therapy. **Table 28** shows rationale for use of various antipsoriatic therapies. Lack of improvement/worsening of psoriasis was the most common reason for starting antipsoriatic treatment.

Table 28. Use of Anti-psoriatic Therapies by Study Patients

Patient #	cohort	course	day	event	Treatment
116205	1	2	93 121	-- flare 78% BSA	temovate cyclosporine
124202	1	1	3-9	withdrawn	cyclosporin, temovate
129202	1	1	107	--	methotrexate
129209	1	1	94	High severity psoriasis	Cyclosporin x 5 weeks
130203	1	1	90	Poison ivy	prednisone
135211	1	1	67	sunburn	UV (sunlight)
132201	1	1 2	120 106-134	-- worsening psoriasis	Kenalog sc in plaques Kenalog SC, UVB
142205	1	2	107 120	severe psoriasis flare	Targretin, prednisone
142206	1	2	92 120 134	psoriasis flare pustular psoriasis flare severe psoriasis guttate flare	Targretin triamcinolone .01% UVB narrow band
142210	1	2	134	severe psoriasis	trimacinolone 0.1%
154206	1	1	150	--	PUVA

		2	116	lack of improvement	methotrexate
154207	1	1	120	--	Kenalog, ultravaite
154209	1	1	87	Lack of improvement	ultravaite
161208	1	1	163	--	Prednisone,diprotene
201201	1	2	1	--	Bethametasone valerate
201207	1	1	103	--	UV (tanning salon)
		2	106	--	Moderate potency steroid
205209	1	1	78	Lack of improvement	Metothrexate, cyclosporin
205212	1	1	106	--	UVB
		2	109	--	Elocom
206209	1	1	157	Worsening psoriasis	prednisone
103207	2	1	78	Psoriatic arthritis	Systemic steroids methotrexate
106206	2	2	106	--	methotrexate
129210	2	2	158	Lack of improvement	cyclosporin
129211	2	1	69		UV (sun), face forearms
129212	2	2	77 119	Painful psoriasis plaques	Elocon diprolone
135204	2	1	18	Herpes zoster	prednisone
137201	2	2 2	99 135	Flaring of psoriasis “”	Dovonex, diprolene tazovac
137203	2	2	121	flaring	TAC Eucerin
137204	2	2	92 144	Flaring of psoriasis extensive flaring	TAC Eucerin ---
137211	2	1	1	Inadequate washout	Systemic retinoid
138201	2	2	-63 (pre 2 nd treatment)		Cyclosporin, dovonex, temovate
142203	2	2	92-134	Severe psoriasis flare	Soriatane, prednisone, temovate, UVB
142204	2	1	106-176	Psoriatic arthritis	Methotrexate, kenalog IM
142207	2	2	106	Worsening psoriasis	Targretin, temovate, dovonex
142211	2	1 2	134 interim visit	Psoriasis flare --	Methotrexate metothrexate
142213	2	2	78 134	Inflamed plaques Severe psoriasis	Triamcinolone UVB
144203	2	2	131	Painful lesions	Embeline E CR
149209	2	1	92 120		Psorcon E Ultravate
153203	2	1	135	Skin discomfort	Triamcinolone 0.1%
154212	2	2	43	Psoriasis exacerbation	elocon
160209	2	2	79	--	temovate
205202	2	2	88	--	UV (tanning salon)
205211	2	1	92	--	Dovonex diprososne
210205	2	2	92	--	UVB
210206	2	2	121	Treatment of psoriasis	UVB, bethamethasone
210207	2	2	106	Treatment of psoriasis	Acitretin, halcinonide
106210	3	1	9	Worsening psoriasis	triamcinolone
108208	3	1	16	Flaring psoriasis	cyclosporin
110202	3	2	149	psoriasis	thioquanine
114210	3	1	-27	Palmar plaques	temovate
116203	3	2	153	“Upper respiratory infection”	prednisone

127206	3	2	162	psoriasis	cyclosporin
129201	3	2	106	--	cyclosporin
135205	3	1	70	sunburn	UV (sunlight)
136204	3	2	83 (Post-discontinuation)	<4 weeks washout of study drug	methotrexate
136210	3	2	-260		UVB
137207	3	2 2 2	88 129 142	Psoriatic arthritis " scalp lesions	Medrol dose pack Cortisone injection Dovonex clobetasol
137208	3	1	134	Severity of psoriasis	cyclosporin
137209	3	1 2	48 106	Flare Worsening psoriasis	None listed Psoriatane, UVB, triamcnl
137212	3	2 2	1 49	-- --	TAC Eucerin UVB
137213	3	2	92	Flaring psoriasis	Dovonex, clobetasol
142202	3	1 1 2 2	59 107 107 134	Psoriatic arthritis " " "	Prednisone methotrexate methotrexate prednisone
142215	3	1 2	110 135	Psoriasis Severe psoriasis	Methotrexate psoriatane
144201	3	1	102	--	temovate
145205	3	1 2	156 107	Back pain --	Cortisone injection Ultravate, tazorac
146201	3	2	60	Occipital neuralgia	depomedrol
146202	3	1	45	Sunburn	UV (not coded as non-allowed therapy)
149204	3	1 1	106 134	-- --	Psorcon Temovate
156201	3	1	134	--	diprolene
160204	3	1	57	Lack of improvement	Ultravate, triamcinolone
201202	3	1	70	--	betamethasone
201204	3	1	10	Sun tanning	UV
201210	3	1	169	--	methotrexate
201212	3	2	-7	Sun tanning	UV
201214	3	2	137	Sun tanning	UV
205203	3	1	77	Lack of response	dovonex
205205	3	1	106	--	elecom
205206	3	1 1	56 77	-- Lack of response	Diprosone, dovonex cyclosporin
210201	3	1	69	--	UVB
210202	3	2	106	--	Calcipotriol

Comments:

Concerning the use of antipsoriatic medications, the following work is ongoing: confirm the time- period of use and (for topicals) the application sites, determine how such patients were treated for the purpose of the efficacy analyses. Use of concomitant antipsoriatic treatment during course 1 and in the interval between course 1 and 2 argues for using PASI score at visit 1B (instead of 1A) as baseline for assessment of response to course 2.

Table 29 shows the proportion of patients using concomitant antipsoriatic therapy by specific treatment and by dose group. The majority of patients used emollients and low

potency corticosteroids. As for concomitant non-allowed antipsoriatic treatment, the proportion of users during course 1 was similar across treatment groups (approx. 15%).

Table 29. Concomitant Antipsoriatic Therapies

	IV Bolus		
	Placebo	7.5 mg	Total
NUMBER OF PATIENTS DOSED IN COURSE 1	186 (100)	367 (100)	553 (100)
NUMBER OF PATIENTS TAKING ANY CONCOMITANT MEDICATION IN COURSE 1	42 (23)	71 (19)	113 (20)
Topical Steroids: Mild	1 (<1)	4 (1)	5 (<1)
CORTATE	0	3 (<1)	3 (<1)
CORTISONE	1 (<1)	1 (<1)	2 (<1)
Topical Steroids: Moderate	6 (3)	6 (2)	12 (2)
DERMA-SMOOTH- FS	5 (3)	6 (2)	11 (2)
TRIAMCINOLONE ACETONIDE	1 (<1)	0	1 (<1)
Topical Steroids: Potent	7 (4)	19 (5)	26 (5)
TEMOVATE	3 (2)	5 (1)	8 (1)
PSORCON	2 (1)	3 (<1)	5 (<1)
CORMAX	1 (<1)	3 (<1)	4 (<1)
CLOBETASOL PROPIONATE	0	3 (<1)	3 (<1)
LIDEX	1 (<1)	2 (<1)	3 (<1)
CLOBETASOL	1 (<1)	1 (<1)	2 (<1)
DERMOVATE	0	1 (<1)	1 (<1)
TIAMOL	0	1 (<1)	1 (<1)
Topical Steroids: SuperPotent	16 (9)	26 (7)	42 (8)
BETAMETHASONE VALERATE	9 (5)	7 (2)	16 (3)
CELESTODERM	3 (2)	5 (1)	8 (1)
ULTRAVATE	2 (1)	6 (2)	8 (1)
BETAMETHASONE	1 (<1)	2 (<1)	3 (<1)
VALISONE	1 (<1)	2 (<1)	3 (<1)
BETNOVATE	1 (<1)	1 (<1)	2 (<1)
DIPROLENE CREAM	0	2 (<1)	2 (<1)
DIPROSONE	1 (<1)	1 (<1)	2 (<1)
BETADERM	1 (<1)	0	1 (<1)
BETAMETHASONE DIPROPIONATE	0	1 (<1)	1 (<1)
Systemic Treatment & Phototherapy	21 (11)	40 (11)	61 (11)
UVB	6 (3)	10 (3)	16 (3)
PREDNISONE	3 (2)	10 (3)	13 (2)
METHOTREXATE	4 (2)	5 (1)	9 (2)
NEORAL	2 (1)	4 (1)	6 (1)
PUVA	2 (1)	3 (<1)	5 (<1)
CICLOSPORIN	1 (<1)	2 (<1)	3 (<1)
DECADRON	1 (<1)	2 (<1)	3 (<1)
KENALOG	1 (<1)	2 (<1)	3 (<1)

Table 29. (Cont'd) Concomitant Antipsoriatic Therapies

	IV Bolus		
	Placebo	7.5 mg	Total
NUMBER OF PATIENTS DOSED IN COURSE 1	186 (100)	367 (100)	553 (100)
NUMBER OF PATIENTS TAKING ANY CONCOMITANT MEDICATION IN COURSE 1	42 (23)	71 (19)	113 (20)
MEDROL	1 (<1)	1 (<1)	2 (<1)
ADAPALENE	1 (<1)	0	1 (<1)
ARAVA	0	1 (<1)	1 (<1)
GOLD	0	1 (<1)	1 (<1)
KENALOG- 40	1 (<1)	0	1 (<1)
PRED- FORTE	0	1 (<1)	1 (<1)
PREDNISOLONE	1 (<1)	0	1 (<1)
PREDNISOLONE ACETATE	1 (<1)	0	1 (<1)

The following patients were excluded from the efficacy analyses.

Table 30. Patients excluded from efficacy analysis

Patient Number	Investigator	Study Site
112-210	Sherer	New York
116-204	Menter	Dallas
123-210	Savin	New Haven
128-201	Hampel	New Braunfels (TX)
131-205	Cognetta	Tallahassee
136-201	Goffe	Seattle
137-206	Gordon	Chicago
156-201	Aton	Martinez (GA)
156-202	Aton	Martinez
156-203	Aton	Martinez
156-204	Aton	Martinez
156-205	Aton	Martinez
156-206	Aton	Martinez
156-207	Aton	Martinez
160-202	Hahn	Indianapolis
201-205	Bissonnette	Montreal

Study Drug Accountability

This section was reviewed to identify patients who underwent changes in study treatment due to safety issues. The following patients were notable for persistent decrease in CD4 counts occurring during alefacept treatment or for discontinuation of alefacept due to adverse event.

123205 (cohort 1, course 1) permanent placebo substitution due to persistently low CD4, after visit 5

104201 (cohort 2, course1) permanent placebo substitution due to persistently low CD4
105201 (cohort 2, course2) received alefacept on visit 1B by mistake.
123209 (cohort 2, course 1) permanent placebo substitution due to persistently low CD4,
concomitant clinically significant infection.
134201 (cohort 2, course 1) permanent placebo substitution due to persistently low CD4
135206 (cohort 2, course 1) study treatment stopped prednisone started for temporal
arteritis
139202 (cohort 2, course 1) permanent placebo substitution due to persistently low CD4
150208(cohort 2, course 1) permanent placebo substitution due to persistently low CD4
131202(cohort 3, course 2) permanent placebo substitution after visit 6 due to error
145215 (cohort 3, course 2) persistently low CD4 visit 9-12
201202(cohort 3, course 2) visit 9 SAE episcleritis, study treatment discontinued

PK data

Examination of PK data (drug concentration over time) showed that in all three study groups some of the measurements were in error. For example from visit 1A to 17 A approximately seven percent of patients in the placebo/alefacept group had measurable concentration of alefacept at a time when they were to have received placebo. This observation was unexplained and was taken as an unfavorable indication of the quality of the study conduct.

Case Report Forms

Baseline: History of previous antipsoriatic therapy

The screening visit captured response to previous psoriatic treatments on a 3-point scale (worse, improved, unchanged). Duration of treatment and date of the last treatment were also recorded.

In-treatment visit. Clinical assessments before administration of study drug:

At each visit during the treatment periods the CRF listed all the required testing and assessments. At a minimum the following were required.

Visit 10A

The following tests and evaluations should be performed at this visit prior to administration of study drug:

- Concomitant Therapies
- Adverse Events
- Hematology
- Lymphocyte Subset Analysis
- New or Ongoing Infection Assessment
- Study Drug Administration

Adverse events:

At every visit the CRF prompts the investigator to assess the patient for presence of infection as shown below.

NEW OR ONGOING INFECTION ASSESSMENT

Evaluate if a new infection has occurred since the last visit. If an infection has occurred, record on the adverse event page. Study drug should be withheld if the subject has a clinically significant infection.

On visits requiring a physical examination, the CRF also prompts the investigator to record new or worsening physical signs as an adverse event. However for most study visits the CRF has no prompt and does not document that the patient was assessed for treatment-emergent adverse events. The CRF contains an adverse event section after the in-treatment and post-treatment data for course 1 (pages 4-83 to 4-86) and for course 2 (pages 4-173 to 4-175). At the end of each treatment course the CRF asks if a patient experienced an adverse event during the study as shown below

ADVERSE EVENTS REPORT-Treatment Course 2

Did the subject experience any adverse events during the study? Y Yes N No
Is the event a new infection? Y Yes N No

Reviewer's Comment:

The CRF was not optimally designed to capture treatment emergent adverse events. A check box at each visit would have been useful for confirming that the investigator had assessed the patient for adverse events.

Eligibility criteria for treatment course 2

The CRF indicates that the protocol allowed the use of antipsoriatic medications in the post-treatment period. This use is expected to influence the estimates of duration of response to first treatment and the assessment of response to retreatment.

Protocol No.: C99 - 711	Subject Initials [][][]	Subject No.: [][][] - [][][][]	Visit 1B
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ELIGIBILITY CRITERIA FOR TREATMENT COURSE 2**EXCLUSION CRITERIA**

YES NO

Y N

Treatment History

- | | | |
|--------------------------|--------------------------|---|
| <input type="checkbox"/> | <input type="checkbox"/> | 11. Subject has had treatment with another investigational drug or approved therapy for investigational use within 4 weeks prior to study drug administration. |
| <input type="checkbox"/> | <input type="checkbox"/> | 12. Subject has had treatment with systemic retinoids, systemic steroids, methotrexate, cyclosporine, azathioprine, or thioguanine within the 4 weeks prior to study drug administration. |
| <input type="checkbox"/> | <input type="checkbox"/> | 13. Subject has had treatment with high potency corticosteroids (Class I and II) within the 4 weeks prior to study drug administration. |
| <input type="checkbox"/> | <input type="checkbox"/> | 14. Subject has had treatment with moderate potency topical corticosteroids (Class III and IV) (other than on the scalp, palms, groin and/or soles) within the 2 weeks prior to study drug administration . |
| <input type="checkbox"/> | <input type="checkbox"/> | 15. Subject has had treatment with vitamin D analogues and topical retinoids (other than the scalp, palms, groin and/or soles) within 2 weeks prior to study drug administration. |
| <input type="checkbox"/> | <input type="checkbox"/> | 16. Subject has had treatment with keratolytics or coal tar (other than the scalp, palms, groin and/or soles) within 2 weeks prior to study drug administration. |
| <input type="checkbox"/> | <input type="checkbox"/> | 17. Subject has had phototherapy within 4 weeks prior to study drug administration. |

QUESTIONS 11 - 17 MUST BE ANSWERED "NO" FOR THE SUBJECT TO BE ELIGIBLE FOR PARTICIPATION IN THE STUDY.

Past medical history

During the study a few patients developed variants of psoriasis or required non-allowed medications for control of psoriatic arthritis. Line listings were reviewed for all patients to look for evidence of these conditions at baseline or in past history. Very few patients had history of psoriasis variants. A notable number of patients had history of psoriatic arthritis.

The line listings confirm the presence of common chronic medical conditions in the study patients. For some patients few or no adverse events were captured during the study. The incidence of adverse events over the two treatment and follow up periods (a total time span of one year) is somewhat lower than might be expected based on waxing and waning or new manifestations of chronic diseases.

STUDY OUTCOMES: PRIMARY EFFICACY**Response to first treatment course**

The study met its primary endpoint, namely the proportion of patients with $\geq 75\%$ improvement in PASI score from baseline to the end of the first treatment period (visit 13)

A) was greater in the alefacept group. The absolute difference in the proportions was 11%.

Table 31 shows that response to treatment was not affected by the stratification variables of severity of psoriasis or history of previous major antipsoriatic therapy. Response was also not affected by age or gender. Response to treatment was numerically higher in non-Caucasians compared to Caucasians, however the number of non-Caucasians was small. This was not confirmed in study 712. With regard to geographic region, treatment response was numerically lower in region E (Southern); this trend was also seen in study 712.

Table 31. Responders by Strata, Geographic Region, Age, Gender, and Race

	Placebo (N=186)		7.5 mg (N=367)	
PASI > 20, No prior systemic therapy	0/ 8	0	3/ 18	(17)
PASI > 20, Prior systemic therapy	1/ 48	(2)	9/ 93	(10)
PASI <= 20, No prior systemic therapy	0/ 38	0	13/ 74	(18)
PASI <= 20, Prior systemic therapy	6/ 92	(6)	28/182	(15)
No prior systemic therapy	0/ 46	0	16/ 92	(17)
Prior systemic therapy	7/140	(5)	37/275	(14)
PASI > 20	1/ 56	(2)	12/111	(11)
PASI <= 20	6/130	(5)	41/256	(16)
GEOGRAPHIC REGION: A	0/ 37	0	9/ 68	(13)
B	3/ 39	(8)	14/ 79	(18)
C	1/ 30	(3)	16/ 66	(24)
D	1/ 41	(2)	9/ 90	(10)
E	2/ 39	(5)	5/ 64	(8)
AGE: <30	1/ 26	(4)	6/ 41	(15)
30-39	2/ 42	(5)	14/ 90	(16)
40-49	1/ 48	(2)	12/ 96	(12)
50-59	3/ 41	(7)	14/ 90	(16)
>59	0/ 29	0	7/ 50	(14)
GENDER: Women	4/ 59	(7)	20/107	(19)
Men	3/127	(2)	33/260	(13)
ETHNIC GROUP: Non-caucasian	1/ 24	(4)	8/ 35	(23)
Caucasian	6/162	(4)	45/332	(14)

Response to treatment was also examined by study center. Taking into consideration the small number of patients enrolled at each center, there was no evidence that responses to study treatments differed between centers.

Statistical analyses to identify baseline prognostic factors and potential interaction with treatment confirmed the observation of the summary data. Age, ethnic group, baseline CD4 and CD8 counts, and randomization stratum were not important predictors of response. The treatment responses were consistent across the strata of these factors. For this analysis the percentage change in PASI score at endpoint was used. There was no interaction between treatment and baseline CD4, or CD8 lymphocyte counts. The

adjusted difference in % reduction in PASI between drug and placebo groups was approximately 20% at endpoint (visit 13A).

Effect Of Body Weight on Treatment Response

Patients whose body weight at screening was 50 kg or more were to receive placebo or 7.5 mg alefacept. Patients whose body weight at screening was less than 50 kg were to receive placebo or 5.0 mg alefacept. The distribution of body weights and the relationship between body weight and response were explored. Only five patients (< 1% of total, all women) weighed < 50 kg. The mean body weight was 92 kg (median 91 kg LQ 77 and UQ 105).

Comment

The sponsor confirmed that patients weighing less than 50 kg received 5 mg of alefacept.

There was a suggestion that patients weighing > 85 kg (approximately 60% of total) had lower response rates compared to patients weighing < 85 kg. (**Table 32**) This trend of lower response rates in patients with higher body weight would also be observed in study 712.

Table 32. Relationship between Body Weight and Response to Treatment in Course 1

	Placebo	7.5 mg
WEIGHT (kg)		
<50 kg	0	1/ 5 (20.0)
50-69 kg	1/ 18 (5.6)	10/ 51 (19.6)
70-84 kg	1/ 53 (1.9)	22/ 89 (24.7)
85-99 kg	3/ 53 (5.7)	9/ 96 (9.4)
100-114 kg	0/ 44	7/ 76 (9.2)
115+ kg	2/ 18 (11.1)	4/ 50 (8.0)

Comment

There is insufficient information to recommend a specific dose for patients weighing <50 kg. There is a suggestion that patients with BW> 85 kg may be under-dosed.

The relationship between body weight and response was explored further by examining the relationship between % change in PASI score, change in CD4, and dose over lean body mass (LBM) in the alefacept-treated patients. Lower dose/LBM was associated with lower % reduction in PASI score. Even though this relation was statistically significant (not multiplicity adjusted), the R² for the regression fit was only 0.035 Therefore only 3.5% of the variation in % reduction in PASI was contributed by dose/LBM. Lower body weight was associated with larger % reduction in PASI. However only 3.7% variation in % change in PASI is explained by body weight. Change in CD4 count was significantly related to % change in PASI. However, only 1.7% variation in % change in PASI was contributed by the variation in change in CD4. Finally dose/LBM did not affect the change in CD4 count. Note that none of these associations were statistically significant for the placebo patients

STUDY OUTCOMES: SECONDARY EFFICACY

First Treatment Course: Secondary Outcomes

Various other secondary outcomes support to the primary efficacy outcome. They show similar, modest increases in the proportion of responders in the alefacept group compared to placebo (**Table 33**). By criterion of proportion of patients achieving clear to nearly clear skin by PGA, the absolute difference in response between placebo and alefacept groups was 7% in favor of alefacept. Using a less clinically meaningful outcome measure (proportion of patients with $\geq 50\%$ improvement in PASI) the absolute difference in response between placebo and alefacept groups was 28% in favor of alefacept. The percentage decrease in PASI from baseline was $19 \pm 30\%$ in the placebo group and $39 \pm 36\%$ in the alefacept groups.

Table 33. Efficacy Endpoints Based on Proportions Responding in the First Course

	Placebo	7.5 mg
PATIENTS DOSED IN FIRST COURSE	186 (100)	367 (100)
Primary Endpoint: PASI $\geq 75\%$ Reduction from Baseline	7 (4)	53 (14) ^a
Secondary Endpoints:		
-PGA 'almost clear' or 'clear'	7 (4)	42 (11)
-PASI $\geq 50\%$ Reduction from Baseline	18 (10)	138 (38)
-Target lesion induration of zero	15 (8)	78 (22)

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

Response to Second Treatment Course

Patients who received alefacept in the second course of study treatment showed a greater proportion of responses compared to patients who received placebo (**Table 34**). The absolute difference in proportions for the PASI-75 outcome was 15% using the pre-specified comparison between PASI at Visit 13 B (end of course 2) and PASI at Visit 1 A (baseline of course 1). Other secondary measures were also supportive. The percentage decrease in PASI (mean \pm S.D.) from baseline was -31 ± 32 in placebo and -50 ± 35 in the alefacept group. Eighteen patients in cohort 1 responded for the 1st course. Among these 18 patients, 12 (2/3) of them responded for the 2nd course. One hundred and thirty-six (136) cohort 1 patients did not respond to the 1st course but 24 (18%) of them responded to the 2nd course.

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 \geq 75% Reduction from Baseline	10 (7)	34 (22) ^a
Other Secondary Endpoints:		
-PGA 'almost clear' or 'clear'	7 (5)	30 (19)
-PASI \geq 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 \geq 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.

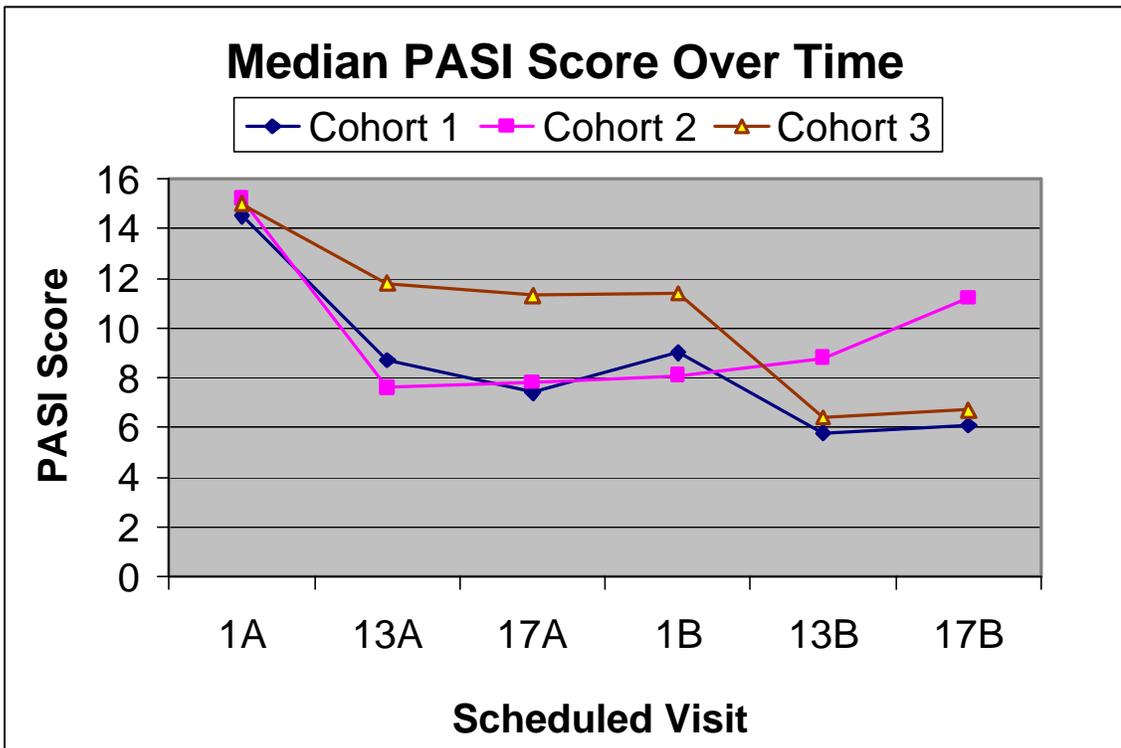
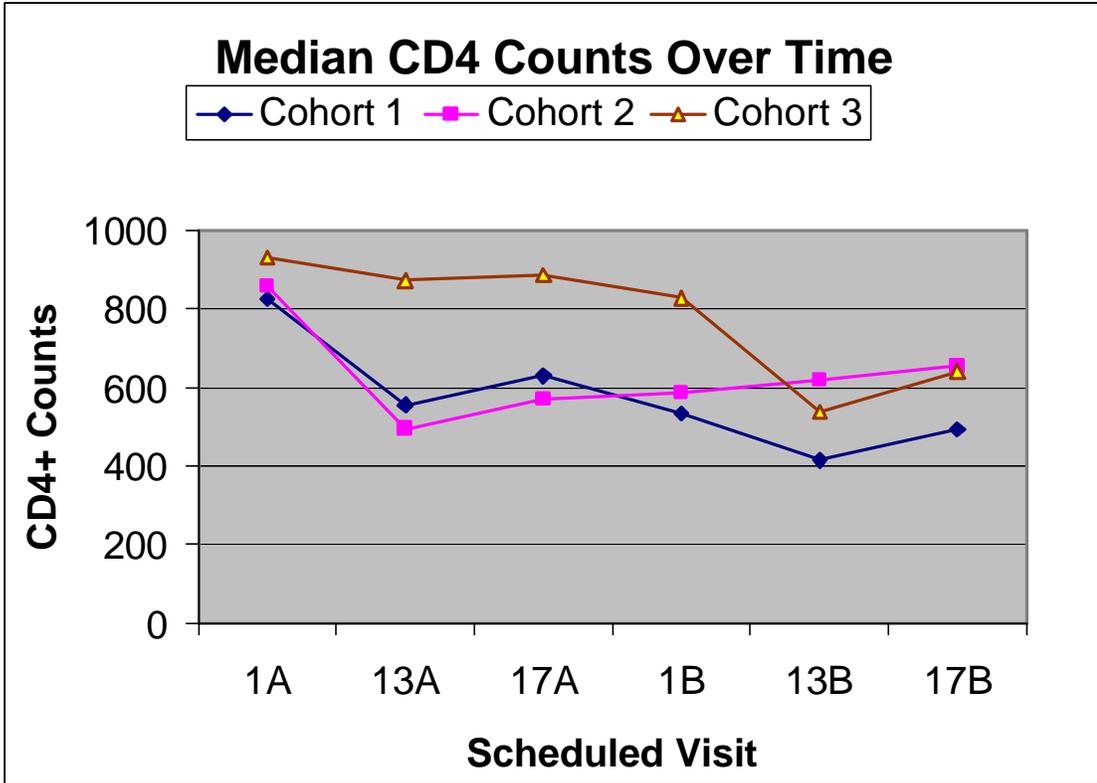
Table 35. Response to Second Course (Visit 13 B) Using Visit 1B as Baseline

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

Correlation between PASI Scores and Lymphocyte Counts

The two figures below shows that 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.

In cohort 2 (alefacept /placebo) PASI scores and CD4 counts decline after the first treatment course. There are no further declines in PASI or CD4 counts in the second treatment (placebo) course. CD4 counts 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 PASI without change in CD4 counts at the end of course 1. At the end of course 2 there is a further decline in PASI that is accompanied by a drop in CD4 counts.



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.

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

Table 36. 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	
DQOLS	Psychosocial	0-100	Higher: worse QOL
	Activities	0-100	
	Symptoms	0-100	
Treatment Convenience	Treatment Convenience	0-100	Higher: better QOL

Table 37 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 are 3-5% in favor of alefacept. For the SF-36 there is no discernible trend at all.

Table 37. Observed Mean Change in QOL Scores

QOL Scale	Cohort 1		Cohort 2		Cohort 3	
	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

Table 38 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 38. Adjusted Mean Change in QOL From Visit 1A to Visit 13B.
Treatment Course 2: Cohort 1 versus Cohort 2**

QOL Scale	Placebo	7.5 mg
	Mean Change (SE)	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 39**) 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 (14 vs. 9%).

Table 39. 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 ($\geq 5\%$) 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 39**) and of severe adverse events (**Table 40**) 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 40. 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

Table 40. (Cont'd) Incidence of Severe Adverse Events in the First Exposure

	First Course		Second Course	
	Cohort 3	Cohort 1 and 2	Cohort 3	
	Placebo N=186	LFA3TIP N=367	LFA3TIP	N=153
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 40** 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 41. 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 41 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 42 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)
Sympt/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 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 41**). There were very few discontinuations due to adverse events ≤ 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 (**43-46**) show that there is persistent lowering of CD4+ and CD8+ lymphocyte counts in patients treated with alefacept compared to placebo.

Table 43. 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
E _{max} (b): No. of Patients Evaluable (c)	154 (100)	154 (100)	142 (100)	139 (100)	153 (100)	153 (100)
Time to E _{max} (days) median (min max)	65 (8,99)	58 (8, 99)	70 (8,96)	36 (7,94)	43 (7,95)	65 (7,99)
Count at T _{max} (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 44. 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 00 for explanation of variables

Table 45. Depletion of CD8+ 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.	511 +/- 272	376 +/- 227	488 +/- 271	315 +/- 239	462 +/- 222	469 +/- 265
E _{max} (b): No. of Patients Evaluable (c)	154 (100)	154 (100)	142 (100)	139 (100)	153 (100)	153 (100)
Time to E _{max} (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 T _{max} (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 00 for explanation of variables

Table 46. Recovery of CD8+ 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.	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 00 for explanation of variables

Comparison of first and second treatment in cohort 1 (**Tables 43-46**) suggests that by criteria of cell counts and proportion of patients with counts lower than normal, there may be some cumulative effects 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 43-46**) and clinical chemistry.

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
- 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

Selected Narratives of Patients with Serious Adverse Events

The following serious adverse events were selected to illustrate the clinical features of events with suspected relationship to alefacept.

Surgical wound infection:

A 58-year old man (135-203), had psoriasis for 10 years. Medical history included non-insulin dependent diabetes mellitus, hypertension, and obesity. 15 weeks after his first dose of alefacept, a full-thickness R rotator cuff tear was diagnosed. He underwent shoulder arthrotomy with decompression acromioplasty and rotator cuff repair. The patient received 5 doses of alefacept until six weeks post-operatively, he complained of right shoulder pain and redness. The patient's total lymphocyte and CD4+ counts were 1540 and 616 cells/ul. Incision and drainage of a surgical wound abscess was done in the operating room. Cultures grew *Propionibacterium* species. Antimicrobial therapy was given. The patient received 3 further doses of alefacept until the drug was withdrawn because of persistent wound drainage.

Four months post-operatively the patient underwent a third wound drainage and irrigation. Necrotic purulent debris extended down to the humerus. The wound was left open. Intra-operative cultures were negative. Clindamycin and metronidazole were administered. Five months post-operatively the patient underwent debridement, and reconstruction of the right shoulder with flaps. Breakdown of the original repair and a large fistula extending to the humeral joint was noted. Cultures grew *Serratia marcescens* sensitive to ciprofloxacin. He received levofloxacin post-operatively. At last follow-up 9 months post-operatively, the patient had pain and some loss of right arm function, his wound was healed and he was no longer receiving antibiotics. The investigator graded both the infection events as moderate. The relationship to study drug was 'unlikely'. The investigator graded the skin disorder as mild and classified the relationship to study drug as 'none'.

Infection of skin burn:

Patient ID: 150-218. A 55-year old man, had had psoriasis for 7 years, diabetes mellitus, hypertension, hypercholesterolemia, and obesity. One month after his first alefacept dose, he developed erythema and pain associated with a 18 x 24 cm burn to the mid abdomen. The patient's most recent total lymphocyte and CD4+ count were 1890 and 1014 cells/ul. He was hospitalized and treated with cephalosporin, debridement, silver sulfadiazine, and meperidine. He recovered and went on to receive 7 further doses of alefacept in Course 1 and 12 doses in Course 2. The investigator graded the serious adverse event as severe and classified the relationship to study drug as 'unlikely'.

Skin carcinoma:

A 64-year old man (145-209), had psoriasis for 32 years and had received PUVA (for 2 months, last dose 1980). The patient received alefacept 12 doses in Course 1 and seven and a half months after his first dose of alefacept, a left shoulder cyst biopsy revealed a 1 cm squamous cell carcinoma that was eventually completely excised. The total lymphocyte and CD4+ counts before the onset of the event were 1180 and 336 cells/ul. The patient was not eligible to enter Course 2 because his CD4+ count was below the lower limit of normal, and therefore, was withdrawn from study. The investigator graded the serious adverse event as mild and classified the relationship to study drug as 'unlikely'.

Pancreatitis:

Patient 133-201. The patient's past medical history included abnormal liver function tests, hypercholesterolemia, exercise-induced asthma, and chronic low back pain. During Course 1, 8 weeks after her first dose of alefacept she was hospitalized for abdominal pain, nausea, vomiting, and dehydration. Her serum amylase rose to maximum of 513 u/L (23-85 WNL). The gastroenterologist's diagnosis was acute pancreatitis of unknown etiology. She had no history of alcohol abuse, a normal lipid profile, and a normal ultrasound. She did, however, report similar symptoms twice in the past 2 years. She was treated with IV fluids, meperidine, hydroxyzine, prochlorperazine, and ceftriaxone sodium. On discharge one week later, her amylase and lipase had decreased to normal. She was subsequently lost to follow-up. The investigator graded the serious adverse event as moderate and classified the relationship to study drug as 'unlikely'.

COMPARISON OF EFFICACY OF DRUG PRODUCT MANUFACTURED BY CREATIVE BIOMOLECULES (CBM) AND BIOGEN

Alefacept administered in Course 1 was derived from the material manufactured by Creative Biomolecules and labeled CBM BG9273. In Course 2, alefacept from both CBM BG9273 and from BIO BG9273, manufactured by Biogen, was administered. Patients received alefacept from either source but not from both within a given course. CBM BG9273 from lot 73G01ZA 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 CBM 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 47. CD4+ T Cell Count: Alefacept Naive Patients Who Received CBM or BIO BG9273

	CBM 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 48. CD8+ T Cell Count: Alefacept Naive Patients Who Received CBM or BIO BG9273

	CBM 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 00 for explanation of variables

Clinical Criteria

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

SUMMARY OF STUDY C99-711

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 ($\geq 75\%$ 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 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 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.
- The lymphocyte subsets, CD4+, CD8+, and CD16/CD56 (NK cells) are the cell populations primarily affected. B cells also express CD2 on the cell surface; however at least at the dose levels studied, B cell depletion was not seen.
- 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 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 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, 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 Objective

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 $\geq 75\%$ 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) to be administered IM in the present study, the sponsor is

assuming an IV: IM equivalence ratio of about 1.5. The sponsor proposes to evaluate 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 will be followed for 12 weeks after the end of treatment. Subjects who prematurely withdraw from the study will not be replaced.

Randomization:

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

Stratified randomization will be 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 will be used in this study.

Blinding:

Laboratory data from the central laboratory will be sent directly to an independent (blinded) investigator at each site (the “laboratory assessing physician”). The laboratory-assessing physician will be able to change or withhold dosing with study drug (substitution with placebo). He will not communicate any information to the other investigators, study coordinators, or the sponsor. The only person at each site who will be unblinded is the pharmacist or designee who prepares study drug.

Retreatment protocol:

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

Screening Log

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

Dose Modification Rules

Withholding dose:

Dosing will be withheld for 2 weeks for body temperature >38°C or clinically significant infection.

Switching from study drug to placebo:

The study drug will be substituted with placebo if the absolute CD4⁺ lymphocyte count from the previous week is below 250 cells/mm³.

Discontinuation of study drug:

The study drug will be permanently substituted with placebo if any subject experiences a reduction in number of absolute CD4⁺ lymphocytes below 250 cells/mm³ for 4 or more consecutive visits. Subjects who prematurely discontinue study drug should remain in the study and continue the protocol-specified follow-up evaluations. All subjects will be followed until their absolute CD4⁺ lymphocyte counts return 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)

Withholding treatment:

Administration of each dose of study drug must be separated by 7 (∓2 days). There must be no clinical evidence of significant viral, bacterial, or fungal infection.

Concomitant treatments

Moderate potency topical corticosteroids, keratolytics, coal tar or vitamin D are allowed on groin, scalp, palms and soles only. Low potency topical corticosteroids are allowed everywhere but on target lesions. Subjects should not apply topical treatments to skin within 12 hrs of a scheduled study visit. If a subject discontinues study drug, systemic medications for psoriasis may 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 are eligible.

Exclusion Criteria

The following are 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 are 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 are not 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 $\geq 75\%$ improvement in PASI score at the end of the treatment period (visit 13 on day 92) will be the primary efficacy endpoint. A standard Psoriasis Area and Severity Index will be used.

Principal Secondary Efficacy Endpoint

The proportion of patients with a score of clear to almost clear by Physician Global Assessment will be the principal secondary endpoint. The following 7 point scale will be 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 will be measured: PASI, Physician Global Assessment, target lesion assessment, body surface photography, and quality of life assessment. LFA3TIP serum concentrations will be measured.

Assessment of Safety

The following will be 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) will collect and evaluate all clinical data.

Treatment and Follow Period:

The examining physician will perform 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 will evaluate all lab data and in particular hematology and analysis of peripheral lymphocyte subsets.

Safety Analyses

Any subject who receives one dose of study drug and has post baseline data will be considered evaluable for tolerability/safety analyses.

Statistical Analysis Plan

Sample size considerations:

The sponsor assumes that at endpoint the proportion of responders ($\geq 75\%$ improvement in PASI after the first treatment) will be 25% in the active groups and 10% in the placebo group. A sample size of 402 subjects will 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 will be summarized for each treatment group. Study centers will be pooled by geographic regions. Subjects will be stratified by screening PASI and prior systemic therapy into four strata.

Efficacy Analyses:

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

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

Subjects who discontinue study medication and/or use non-allowed therapies will be evaluated using the last endpoint measured. The duration of response endpoint will be truncated 12 weeks after the last retreatment injection of study drug. Subjects in response at the end of the study will have 14 days added for the duration of response.

Binary outcomes will be 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 will include terms for geographic region, strata, and treatment. The interactions of treatment group and geographic region, plus treatment group and strata, will be 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 will be tested.

Primary Efficacy Analysis:

The proportion of subjects with a reduction in PASI $\geq 75\%$ from baseline without the use of other systemic therapies will be 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 will 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) will be evaluated with logistic regression using the general analysis model.

Percentage Change in PASI:

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

Quality of Life:

SF-36, DQOLS scale, and Treatment Convenience scores will be analyzed by ANCOVA using the general analysis model and including baseline QoL score. The interaction between treatment and baseline QoL score will be 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) will be evaluated with ANOVA using the general analysis model. Only subjects who

responded to treatment are included in the analysis. The summation of response will be calculated as days between the first visit at which response was achieved and the next visit they are assessed as either a non-responder, the subject withdraws, or the subject reaches the end of the study, whichever comes first. The summation of response endpoint will be truncated at the end of the study. Subjects who are in response at study end will have 14 days added for the summation of response

Duration of Response:

Duration of response for each of three definitions will be evaluated with summary statistics. Only subjects who responded to treatment are included in the analysis. The duration of response will be calculated after the last dose as days between the first visit at which response was achieved and the next visit they are assessed as either a non-responder, the subject withdraws, or the subject reaches the end of the study, whichever comes first. The duration of response endpoint will be truncated at the end of the study. Subjects who are in response at study end will 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' will be analyzed using Cox Proportional Hazards using the general analysis model. Time-to-event curves will be plotted using the Kaplan-Meier method. Subjects who withdraw or do not respond by their last visit or the end of the study will 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: PATIENT DISPOSITION, DEMOGRAPHICS AND BASELINE DISEASE

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 49. 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 49**). 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 50**).

Table 50. 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 51**).

Table 51. 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 52**. 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 52. 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)

^amedians (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 53** shows that a substantial proportion of patients (1/3) in each of the study arms the study received non-allowed major anti-psoriatic treatment.

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 53. 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-SMOOTH- 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)
DI PROGENTA	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)

Table 53. (Cont.) Concomitant Major Anti-psoriatic Treatments

	IM Injection			Total
	Placebo	10 mg	15 mg	
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)
CYCLOSPORIN	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)
MX	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 54 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 ($\geq 75\%$ 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 54. Efficacy Outcomes: Proportions Responding

	Placebo (n=168)	10 mg (n=173)	15 mg (n=166)
Primary: $\geq 75\%$ Reduction from Baseline PASI	9 (5)	21 (12)	35 (21)
Secondary: PGA 'almost clear' or 'clear'	8 (5)	18 (10)	23 (14)
$\geq 50\%$ 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 55**).

Table 55. Percentage Responding to Treatment¹ 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 $\geq 75\%$ 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 56). Caucasians had numerically higher proportions of response than non-caucasians. However, the number of non-caucasians in the study was small.

Table 56. Percentage Responding to Treatment¹ 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 57. Percentage Responding to Treatment¹ 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 higher than those weighing at least 85 kg (**Table 57**).

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 influenced the overall results for efficacy.

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 58**).

Table 58. Treatment Response by Geographic Region

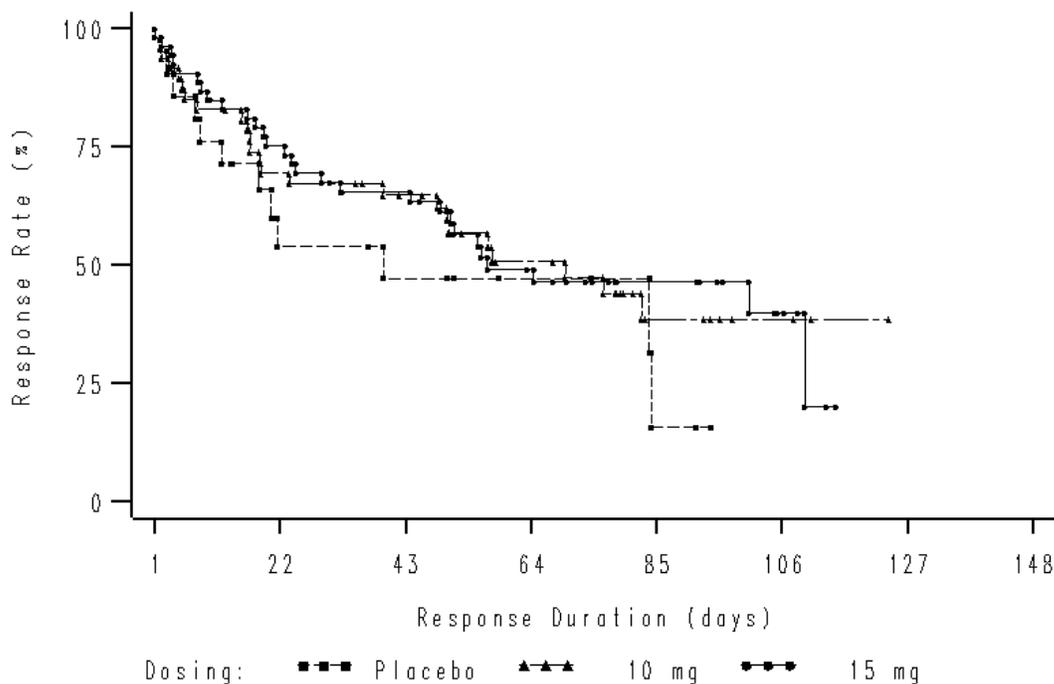
	Group											
	10 mg				15 mg				Placebo			
	% Change in PASI				% Change in PASI				% Change in PASI			
	<75% Reduction		75%+ Reduction		<75% Reduction		75%+ Reduction		<75% Reduction		75%+ Reduction	
	N	%	N	%	N	%	N	%	N	%	N	%
Region												
Europe	64	83.1	13	16.9	55	76.4	17	23.6	67	94.4	4	5.6
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 OUTCOMES

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 were 21, 49, and 50 days for placebo, 10 and 15 mg groups respectively (See **Figure below**).

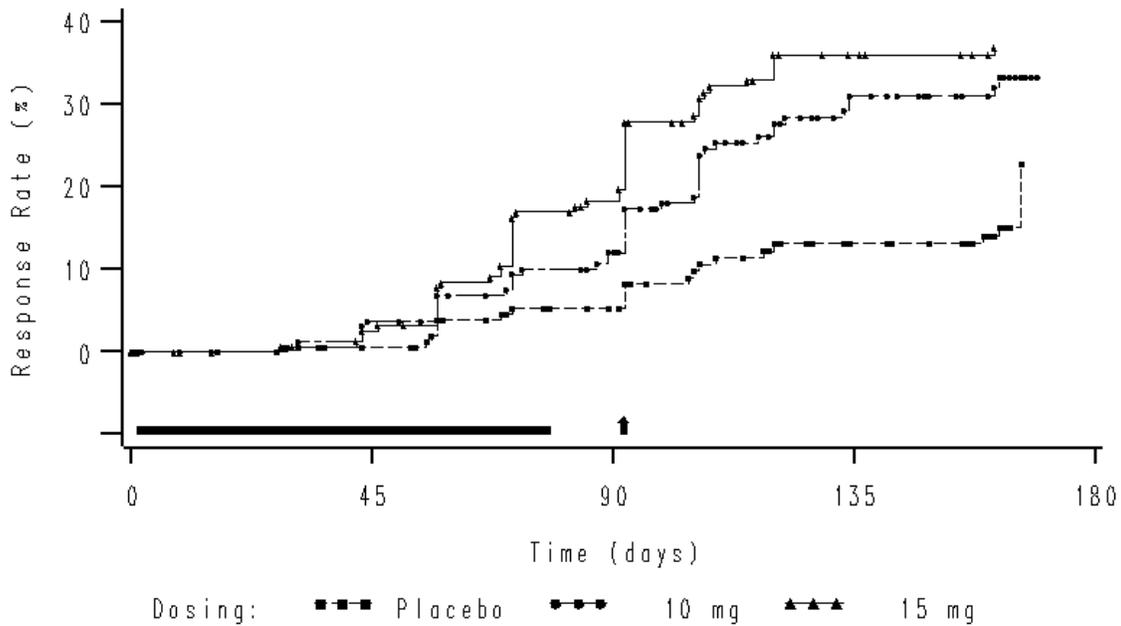
Duration of a 75% Reduction from Baseline PASI
in Those Who Achieved a 75% Reduction



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.

Time to Reduction in PASI of 75% or More from Baseline



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

Quality of life measures

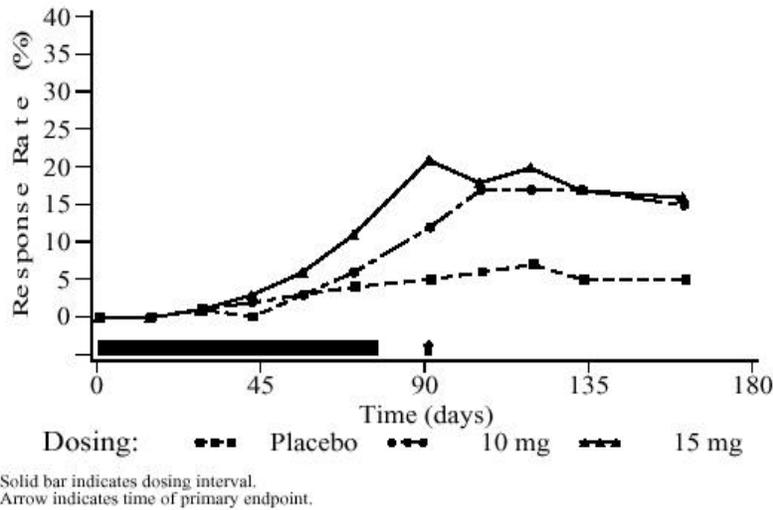
The DLQI overall scale was the principal QOL outcome. The mean change was 2.7, 3.8 and 4.9 in the 0, 10 and 15 mg groups respectively. The difference between placebo and 15 mg groups was significant; this represents a 7% improvement in the score. Examination of the DQOLS and SF-37 scales shows that for 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 (ranged from 4 to 9% improvement).

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



SAFETY OUTCOMES

All Adverse Events

Few events had higher incidence in the alefacept groups compared to placebo as shown by **Table 59**. 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 59. Adverse Events $\geq 5\%$ 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 were 19 (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 60. 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 61**).

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 62-64 show dose-dependent decreases in total lymphocyte, CD4+ counts that persist in some patients up to the last study visit

	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.

patient's lowest lymphocyte and CD4+ count prior to onset was 1300 cells/ μ L and 457 cells/ μ L,. The patient was treated with augmentin, steroids, and topical anesthetics and he made a full recovery. he went onto receive 2 further doses of alefacept. No sequelae during follow up. The investigator graded the serious adverse event as severe and classified the relationship to study drug as 'likely.'

Cellulitis:

A 52-year old man (144-305), had psoriasis for 21 years treated with methotrexate and UVB. Medical history included myocardial infarction, hyperlipidemia, obesity, hypertension, asthma, and hypothyroidism. The patient received 1, 15 mg dose of alefacept. When seen one week later he reported flu-like symptoms 2 hours after his injection and swelling of both legs. His concomitant therapy was zafirlukast, albuterol, salmeterol xinafoate, and 1% hydrocortisone cream. His lower extremities showed "2+ pitting edema "without signs of infection." That evening, the patient complained of chills, fever, and nausea and chest pain and was hospitalized with diagnosis of possible cellulitis of psoriatic lesions of extremities. He was afebrile, blood cultures and a venous Doppler were negative. The patient's lowest lymphocyte and CD4+ count were 990 cells/ μ L and 312 cells/ μ L, the patient was treated with ampicillin/sulbactam, dicloxacillin, nitrates, and diuretics. His hospital course was uncomplicated and he made a full recovery. On follow-up on his right leg had trace pitting edema without tenderness, and his left leg showed psoriatic plaques. The investigator graded the serious adverse event as severe and classified the relationship to study drug as 'likely.'

Psoriasis:

A 50-year old man, 325-306 had had psoriasis for 14 years previously treated with cyclosporin, methotrexate , systemic retinoids, and PUVA (last dose 4 weeks before study treatment) . He received 7 doses of alefacept (15 mg) . His psoriasis gradually worsened by 65% with up to 80%BSA involvement. He developed a fever of 38.6 C, pustular lesions on his arms and legs, and right wrist pain. He was hospitalized with a diagnosis of erythrodermic psoriasis and arthralgia. The patient's lowest lymphocyte and CD4+ count were 950 cells/ μ L and 378 cells/ μ L, respectively, the investigator eventually withdrew the patient from the study and started cyclosporin, and anti-inflammatory agents. On last follow-up psoriasis had improved on cyclosporin, but arthritic symptoms persisted. The investigator graded the serious adverse event severe and classified the relationship to study drug as 'unlikely.'

Pancreatitis:

A 57-year old man (370-307) had psoriasis for 24 years treated with cyclosporin , PUVA, systemic fumarates and systemic retinoids . He had pancreatitis before possibly due to alcohol consumption, hypercholesterolemia and hyperlipidemia biliary sludge. He was consuming a "moderate amount of alcohol" before the current event. The patient was hospitalized with pancreatitis three days after his first alefacept dose (amylase 111, U/L, lipase 976 U/L, AST 52 U/L, ALT 79 U/L, and triglycerides 306 mg/dl, ultrasound showed "an edematous pancreas."). The patient recovered with conservative management went onto receive 11 further doses of alefacept with no further pancreatic symptoms. The

investigator graded the serious adverse event as moderate and classified the relationship to study drug as ‘unlikely.’

Comment: This report is significant because of negative alefacept rechallenge.

Pancreatitis:

A 42-year old man (156-314), had had psoriasis for 11 years and had received UVB treatment. Medical history included pancreatitis, alcohol abuse, gallstones, type 5 hyperlipidemia, and hypercholesterolemia. The patient received 4, 10 mg doses of alefacept. Two weeks after his last dose he was hospitalized diagnosis of acute pancreatitis with amylase 599 U/L, lipase 308 U/L, LDH 229 U/L, GGT 480 U/L, alkaline phosphatase 99 U/L, total bilirubin 0.9 mg/dL, ALT 208 U/L, AST 64 U/L, total cholesterol 711 mg/dL, triglycerides 5943 mg/dl, abdominal CT scan with “pancreatic inflammation and a gallstone without evidence of obstruction.”. The patient’s lowest lymphocyte and CD4 counts were 1240 cells/ μ L and 771cells/ μ l. He had an uncomplicated hospital course. The event was attributed to a combination of his alcohol abuse and hypertriglyceridemia, and possibly occult passage of a gallstone. On discharge his amylase and lipase levels were normal. The investigator graded the serious adverse event as severe and classified the relationship to study drug as ‘not related’.

SUMMARY OF STUDY C99-712

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 not superior to the response in 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
- Evaluations of “quality of life” outcomes showed only small degrees of improvement in the 15 mg group compared to placebo.

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.

V. CONCLUSIONS RE: EFFICACY AND SAFETY OF ALAFACEPT FOR THE TREATMENT OF PATIENTS WITH MODERATE-SEVERE 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%), and some lack of consistency and did not provide strong support for efficacy of alefacept.
- 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 a cumulative treatment effect of alefacept across two treatment courses.
- 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 depletes total lymphocyte counts: The lymphocyte subsets, CD4+, CD8+, and CD16/CD56 (NK cells) are the cell populations primarily affected
- Studies consistently showed that lymphocyte counts decrease and do not recover to baseline in a substantial proportion of patients even after a prolonged observation period.
- 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.
- B cells also express CD2 on the cell surface; however at least at the dose levels studied, B cell depletion was not seen.

- The studies 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.
- 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.
- There was a somewhat higher number of serious adverse events including infections and malignancy in the alefacept treated groups. However the incidence of these events was too low to draw definitive conclusions.
- There was a suggestion of alefacept-induced hypersensitivity reaction (rare cases 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.
- 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. The clinical consequence of this is not known.
- 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.