Memorandum - BLA Review - Alefacept

To: File, BLA 129036 (----------)
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Date: 2/7/02
Subject: Pharmacology and Toxicology Assessment

Products: Alefacept, manufactured by Biogen, Inc.
(Alefacept; fusion protein binding to CD2; BG9723 or 9723; BG9712 or 9712)

Clinical Indication: Chronic plaque psoriasis

Formulation:
Alefacept drug substance is a protein solution containing 45 to 70 mg/mL alefacept in 25 mM sodium citrate/citric acid with a pH of 6.6 – 7.0. There are no known impurities of toxicologic relevance.

Production history (see Product Review for details):
9723 is the designation for the drug substance that is under consideration for approval. It was utilized in both pivotal phase 3 clinical studies.

9712, a product closely related to 9723 (clinical lots) was prepared ----------, and was utilized in several non-pivotal Phase 1 and 2 clinical studies, as well as the chronic monkey toxicity studies completed to date (reviewed below). Development of the 9712 material was discontinued prior to the initiation of Phase 3 studies due to an evident reduction in clinical efficacy as noted in Phase 2 studies.

New toxicity studies are underway to characterize the chronic toxicity of 9723. However, the toxicity studies using 9712 were discussed prospectively with the Agency, and are adequate to support this BLA filing. Commentary below (drawn from the sponsor's submissions; also see product review) supports that the mechanism of action is the same for the two proteins; [ ]. The safety factor (ratio of plasma levels in humans to that in monkeys) is adequate to assure the studies performed were adequate for human risk assessment. Five mg/kg was the maximum studied in chronic monkey studies. Human doses are approximately 50 lower on a mg/kg basis. However, the pharmacodynamic effects (lymphocyte depletion; which appears to correlate with mild immunosuppression) seen in monkey studies are similar in degree to that seen in the clinic. Therefore, the studies should be seen as just revealing safety consequences of human use of a approximately a year's duration, not for assuring the safety of prolonged, uninterrupted post approval use in psoriasis patients. Note the clinical studies under consideration for the current approval only study the safety of 48 weeks (two cycles of 12 weeks, alternating drug dosed, and drug free periods.

The new toxicologic studies that are currently underway with 9723 will not be reported to the BLA by the intended completion time of the BLA review. This study will evaluate a dose of 20 mg/kg of 9723 in monkeys, out to one year of dosing. An interim report on the results will be submitted in time for presentation to the Advisory Committee.

Introduction- Molecular Pharmacology (See the Product Review for critical analysis)
Alefacept is a glycosylated fusion protein. The molecule is composed of the first domain of the human LFA-3 protein fused to the hinge and the constant regions, CH2 and CH3, of the human IgG1

heavy chain. It is expressed in Chinese hamster ovary (CHO) cells as a disulfide-linked dimer. In vitro experiments have demonstrated that both the LFA-3 and constant region portions of alefacept are functional; the LFA-3 domain can bind to its physiological ligand, CD2, and the constant region is able to bind Fc gamma receptors (CD16, CD64 and possibly CD32). It is believed that both the CD2 and Fc gamma receptor interactions are required for the observed clinical activity of alefacept.

The clinical efficacy of alefacept requires both the LFA-3 and IgG Fc domains of the fusion protein. The LFA-3 domain binds CD2 while the Fc domain engages receptors (CD16, CD64 and perhaps CD32) on NK cells or macrophages. Both of these interactions, as well as their in vitro biological consequences, have been characterized by direct binding assays, cell bridging assays and the monitoring of cell signaling.

The contribution of the simultaneous engagement of CD2 and the Fc receptor to alefacept activity has also been directly assayed using [

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These assays intend to mimic the proposed mechanism of action for alefacept in vivo. Results in this assay showed the specific activity of 9712 to be reduced ---------- relative to batches of 9723.----------. This reduced potency (---- fold) also seemed to mirror the reduced efficacy of 9712 in phase 2 clinical trials.

Clinical Rationale (see Clinical Review for critical analysis):
A number of studies have pointed to T cell activation as a major contributor to psoriatic disease processes. LFA-3/CD2 interactions are widely known to be involved in T cell activation and proliferation. Alefacept has been designed to inhibit binding to and actions of CD2 on T lymphocytes. Since CD2 shows restricted expression on T cells and NK cells, inhibition of LFA-3/CD2 interactions can inhibit T cells and immune processes which rely on T cell activation in a non-selective manner. Alefacept should be recognized as a non-selective immunosuppressant that targets all activated T cells; presence of CD2 on B cells as well is controversial, and not well characterized for human lymphocytes (sparse discussion in the literature).

The sponsor builds arguments regarding alefacept's mechanism of action on the published observation that CD2 is upregulated on activated Ts and CD4+CD45RO+ and CD8+CD45RO+ memory-effector T cells. It is important to clarify that some of these cells are found in active psoriatic plaques, but that they are also likely to be other places as well, such as in lymph nodes, circulation, or at sites of infection or inflammation due to diverse causes. These classes of memory cells are heterogeneous in their antigen recognition, and are recognized to contribute to upregulating any immune responses towards either autoantigens or pathogens.

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Clinical Pharmacology - Sponsor's Rationale for Dosing
(see Clinical Pharmacology Review for critical analysis):
Dose Choice HIstory:
The sponsor cites Study 707 as the basis for the initiation of fixed dosing in the pivotal phase 3 clinical studies (711 and 712). The sponsor chose the dose for pivotal trials based on their clinical results with a 12-week course of 0.075 mg/kg i.v. alefacept. Given that the median body weight for those patients was 98 kg, the sponsor calculated that this i.v. dose corresponded to a total fixed dose of 7.5 mg IV. This is the i.v. dose that was then used in the pivotal trials submitted for consideration for this initial BLA review.

The highest dose ever evaluated in clinical trials was single doses of 0.225 mg/kg, and multiple doses of 0.15 mg/kg. The sponsor chose an i.v. dose similar to 0.075 mg/kg (7.5 mg) for focus in pivotal trials. They felt this dose had a statistically significant clinical effect in early trials, with a limited incidence of marked lymphocyte depletion; the dose of 0.15 mg/kg appeared to cause a higher incidence of marked lymphocyte depletion, without a proportional increase in efficacy.

Intramuscular Route:
Trial 712 used intramuscular route for dosing at doses, which were based on the 7.5 mg i.v. fixed dose and the i.m. bioavailability (approximately 60%). To correct for the reduced i.m. bioavailability, clinical doses of 10 and 15 mg i.m. were chosen to approximate the exposures seen in patients given the i.v. fixed dose of 7.5 mg.

Pivotal Clinical Trials (see Clinical Review for critical analysis):
Two pivotal clinical studies were conducted, 711, and 712, which were randomized, double-blind, placebo-controlled safety and efficacy studies of alefacept, involving adult patients with moderate to severe chronic plaque psoriasis. Trial 711 was designed to explore the effects of two courses of alefacept therapy. Each course consisted of 12 once-weekly i.v. injections of 7.5 mg or placebo, followed by 12 weeks of follow-up. Trial 712 studied i.m. treatment with placebo, or alefacept at 10 or 15 mg given weekly for 12 weeks, with 12 week follow up.

The primary endpoint was the 14th week (2 weeks after treatment cessation) assessment of response; treatment was scored successful if patients met at least a 75% reduction in PASI scores. Other secondary endpoints were also tracked. The central safety concerns were related to circulating lymphocyte depletion and immunosuppression-related sequela.

Human i.v. Pharmacokinetics (See Clinical Pharmacology review for critical analysis):
In healthy volunteers given a single 0.5 h i.v. infusion of alefacept, $AUC_{0\text{-}inf}$ increased in a manner approximately linear with dose. Half-life increased with dose - at doses of 0.04 and 0.10 (close to pivotal clinical trial uses); interpolating the values to approximate values for 0.075 mg/kg: $AUC_{0\text{-}inf}$, was ~270 ug x h/ml; T ½ , ~10 d; Cmax ~1.4 ug/ml; clearance, 0.28 ml/hr/kg; and Vd, ~100 ml/kg.

Toxicology Summary:
A number of toxicology and toxicokinetic studies were performed which were acute, or interim analyses, or needed for future study design purposes; other studies were conducted in mice (alefacept binds to CD2 on human, baboon, and cynomolgus monkey lymphocytes; CD2 function in mice likely differs from CD2 function in humans). Alefacept is intended for chronic human use, and is associated with only no or minor acute clinical adverse events. Targets of toxicity discovered to date are only those expected to be associated with moderate to marked depletion of CD2 positive mature lymphocytes, and related immunosuppression. To date, depletion of lymphocytes in lymph node and splenic tissue in non-human primate studies is mild in extent, and reversible, and reductions in antibody responsiveness to neo-or secondary antigen exposures are also mild in degree (i.e. 2-3 fold differences in titer). Even so, the extent of immunosuppressive effect of alefacept on cancer or pathogen protection is incompletely understood. In general, the central

safety concern for alefacept, both in monkeys and in humans is lymphocyte depletion; this is carefully monitored in the clinic. Therefore, this review will address only those studies which have bearing on current clinical use and labeling. Other studies will be listed by title as Appendix 1.

The sponsor conducted two genotoxicity studies for this protein, a study of [

] These studies were seen as non-relevant to human risk assessment of a protein of this structure and pharmacologic properties, and are not reviewed here.
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] Alefacept (P9273- 95-05) did not cause hemolysis or flocculation in human blood up to 5 mg/ml.

This compound's cross reactivity to CD2 is limited to CD2 expressed in humans and non-human primates. For this reason, no standard rodent carcinogenicity studies have been performed. For this drug, the chronic monkey toxicity evaluation (one year dosing at 20 mg/kg; known outcome - at least one monkey dosed with 9723 developed B cell lymphoma), will serve this purpose in the carcinogenesis section of the labeling.

Primate Pharmacokinetics and Pharmacodynamics:
1). Pharmacodynamic Assessment following single intravenous administration to cynomolgus monkeys. (P9273-99-02; ----------; GLP; ----------)
A single i.v. dose of 9723 at 0.3, 1, 3, or 10 mg/kg was administered to cynomolgus monkeys (2/sex/group). Flow cytometry was performed over 8 days to determine the time course, and nadir for various T cell subpopulations. Plasma levels were also tracked for comparison.
Maximum depletions were noted at day 2, and were similar across subpopulations CD2, CD3, CD4, and CD8– as expected for an agent that recognizes and depletes CD2 expressing cells. Three baselines samples were evaluated; depletions per lymphocyte subgroup were expressed as percent baseline counts. Effects were very mild at 0.3 mg/kg. Lymphocyte counts in the 3 upper dose groups were sustained past the 8 day tracking limit. The nadir was seen at day 2 (the earliest post dose time point). Nadirs for CD3+ cells across groups on day 2 were 74, 49, 47, and 21% of baseline. PK sampling was limited and approximated values were calculated (5 min, 24 h etc). The Cmax was taken from the 5 min time point; 6.9, 24, 94, and 257 ug/ml, respectively (roughly dose proportional).
0.3 mg/kg was taken from this data as a minimally active dose. No maximally effective dose could be derived here as 10 mg/kg was more active than 3 mg/kg.
Interestingly, CD20 cells were depleted as well, especially in the 10 mg/kg group at day 2 which systematically showed 21-44% of baseline counts. Responses were more variable for CD20 cells across dose groups, obscuring a dose response which was very clear for the other groups. This may reflect a low expression of CD2 on cynomolgus monkey lymphocytes.

2) Pharmacokinetic and Pharmacodynamic comparability of alefacept in cynomolgus monkeys. (P9273-99-03). (GLP).
I.V. injections of 3 mg/kg of 9723 (various lots) and 9712 ---------- were compared for pk and pd differences in groups of cynomolgus monkeys (4/sex/group); drug was given weekly i.v. for 4 weeks; groups of animals (2/sex/group) were sacrificed at day 29 or day 56. PD markers (lymphocyte subsets evaluated by --------- analysis) were tracked over 57 days; the effect size was calculated by taking the area of the curve (decline) showing differences in lymphocyte counts from baseline (% drop from a single baseline value) on an individual animal basis; this was reported as the EAUC. ---------- was performed on the lymphatic and splenic tissues, as well as Peyer's patches.
PK and antigenicity were nearly identical with the two forms of the drug; t1/2 ranged over 136-160 h; Cl, 0.33 to 0.30 ml/hr/kg; and Cmax, 25-29 ug/ml. Variant production lots of 9723 were similar in their effects on lymphocytes and lymphocyte subpopulations; however, 9712 was clearly the less

active preparation, with EAUC of ---------- lower ---------- for any given lymphocyte subset than was 9723. Depletion of CD20 cells were also seen; however, ~ half the effect size was seen when compared with all the other (similar effect size) lymphocyte subset markers (CD3, CD4, and CD8). This is an unexpected effect; immunology texts indicate CD2 is not on B cells.
---------- showed similar and variable lymphocyte effects (based on historical controls) in all groups (there was no concurrent control group for comparison); no systematic scoring was conducted; no conclusions regarding relative potency of 9712 or 9723 could be drawn for this endpoint.
This study sufficed to show that both variants of alefacept affected lymphocyte in qualitatively similar fashion. Overall, the decreased effect of 9712 here is consistent with decreased efficacy of 9712 in clinical trials. In comparing effects of 9712 and 9723 for clinical risk purposes, and in comparing results seen in both chronic monkey studies (one follows, one is not complete yet), the value of --------- difference in potency is well supported (3 mg/kg of 9712 should have similar effects and risks as 1 mg/kg of 9723).

3) A pharmacokinetic and toxicology study of CHO cell line derived alefacept following i.v. administration to baboons. (P9273-93-02; GLP,----------). Baboons (3/group) were given a single dose of 0.01, 0.3, 1.0 or 3 mg/kg (groups 1-4, respectively). The study was conducted to determine effects on lymphocytes, and pharmacokinetic parameters. At 3 mg/kg, Cmax was 84 ug/ml, AUC 0-inf was 9355 ug x hr/ml, Vss was 79 ml/kg, Cl was 0.33 ml/hr/kg, and t1/2 was 141 h. Little to no antigenicity of drug was noted over the month of plasma level tracking. Similar effects were noted in studies P9712-97-01 and P9273-94-03. ---------- analysis was not conducted in any of these studies. At 3 mg/kg, decreases in PBLs of ~50% were noted at nadir, with a trend to baseline recovery by day 29. Animals in either study were not sacrificed. Variability in lymphocyte counts and liver serum chemistries was introduced by repeated handling and blood sampling of the animals. When 9712 was compared with 9723 at 3 mg/kg (3 baboons/group), leukocyte counts in 9723 animals showed lower nadirs throughout the 29 day study.

Toxicology Studies:
1) A Three-Month Multiple Dose Toxicity Study of Alefacept In Baboons.
(P9723-95-03) This study was conducted to determine the potential toxicity of alefacept, utilized in initial clinical trials. An early version of this report was submitted with the original IND along with the report of the one month study (P9273-93-03; a comprehensive toxicity study, ----------; GLP; 0, 1, and 10 mg/kg given i.v. twice weekly; 2/sex/group; 1/sex/group sacrificed at day 28; 1/sex/group recovery group to 57 days; ---------- showed sustained declines in CD4, CD8, CD2; CD20 cells increased slightly; ---------- lymphatic and splenic tissue showed depletion in T cell zones; depletion was sustained at day 57; no other toxicities of note).

Baboons were administered twice/weekly i.v. injections for 13 weeks and followed for an additional 7-month post-dose recovery period. Drug treated baboons (3/sex/group) were administered alefacept at 0.05, 1.0 and 20 mg/kg twice weekly. A control group of baboons (3 of each sex per group) was administered sterile saline. After the 13-week dosing period (Day 93), 2 baboons (1M/1F) from each dose group were sacrificed and a complete gross necropsy, histopathologic, and immunocytopathologic evaluation was performed. The remaining recovery phase animals (2M/2F per group) were followed for an additional 7 months. Baboons were sacrificed on Day -------- and a complete gross necropsy, histopathologic, and immunocytopathologic evaluation were performed.

Results:
Dose-or gender-related differences in disposition of the test article were not apparent. Overall mean clearance was 0.54 mL/hr/kg. The mean steady state volume of distribution was 93 mL/kg and the mean terminal half-life was 132 hours. As in the other nonhuman primate studies of alefacept, no antibodies to alefacept were detected. Concentrations expected in the plasma were modeled prior to study start; actual maintained levels were very close. Levels were approximately kept at 200, 10, and 0.5 ug/ml. Levels neither declined nor accumulated with time of dosing.

There were no alefacept-related physical or clinical signs of toxicity observed in food consumption, body weight, body temperature, respiratory rate, heart rate, blood pressure, electrocardiogram, hematology (other than lymphocytes), coagulation parameters, clinical chemistry, or urinalysis during the treatment period.

Alefacept decreased absolute lymphocyte counts at 1 and 20 mg/kg. ---------- analysis of lymphocyte subpopulations also revealed a decrease in both the absolute and relative number of $CD2^+$, $CD4^+$, and $CD8^+$ lymphocytes at 1 or 20 mg/kg alefacept. CD20 B cells were not affected; effects on CD4 cells, as for all these toxicity studies, were the most clear-cut/sensitive, with nadirs of approximately 10% of baseline. The no-effect level for changes in peripheral blood T lymphocytes was 0.05 mg/kg alefacept. Recovery of CD4 lymphocytes occurred over the entire period of 7 months but at the end of study was only to about 50-65% of baseline. At this rate, it would have taken at least another 6 months to possibly see full recovery. Effects on other subpopulations were milder, and recovered more quickly.

Histopathology revealed that dosing at 1 and 20 mg/kg decreased the size and cellularity of the T-cell areas of spleen and selected lymph nodes, and hyperplasia of the B cell (centroblast) and germinal center areas of the spleen. Based on ----------, recovery after 7 months (drug free) was mostly complete at 1 mg/kg alefacept and partially complete at 20 mg/kg. A benign pheochromocytoma was noted by the pathologist in the adrenal medulla of a high dose female. The tumor was described as benign based on lack of mitotic activity, and lack of local invasion, and was therefore disregarded from relationship to test article.

Immunocytopathology analyses was more sensitive, revealing lymphoid depletion in $CD2^+$, $CD4^+$ and $CD8^+$ T-cells in T-cell areas of selected lymph nodes (mid and high dose; reduced paracortical lymphocytes, stromal collapse, and reticuloendothelial hypertrophy) and the (periarteriolar sheath / mantle zone / red pulp sinusoids; most drug dose baboons of the) spleen. An increase in $CD20^+$ cell staining was observed in germinal centers of the spleen at both 1.0 and 20 mg/kg alefacept. At 20 mg/kg, some $CD4^+$ T-cells were also present in the B-cell area of spleen. Based on ---------- all changes which were minimal to mild in degree of change, and were mostly reversed at 1 mg/kg alefacept or less. Changes at 20 mg/kg were only partly reversible with 7 months drug-free recovery; high dose males showed continued reduction of the paracortical lymphocytes in lymph nodes. Thymus, gut associated lymphoid tissue, and bone marrow were unaffected by treatment. No effects on bone marrow myeloid:erythroid ratios or proliferating versus total cell counts were seen. Mild elevations in liver serum chemical parameters were noted (ALT, LDH, chol; approximately 2-4 X increases towards the end of study) in the high dose group. No toxicities (histopathologic findings; malaise) corroborated the significance of these mild and reversible effects.

In conclusion, IV administration of alefacept at 1.0 and 20 mg/kg to baboons caused a decrease in peripheral blood lymphocytes and T-cell subset counts throughout the 3-month dose period and a 7-month dose post-dose study period. Lymphoid tissue changes in the T and B cell regions in animals treated with alefacept were evident immediately following the 3-month dose period. After a 7-month recovery period, these lymphoid tissue changes were reversible at 1 mg/kg or less and partially reversible at 20 mg/kg.

2) 44-Week i.v. toxicity study with alefacept (9712) in cynomolgus monkey with a 1-year recovery period. (P9712-97-03; GLP; ----------)

Design:

Forty-eight cynomolgus monkeys were randomized into four groups each consisting of six males and six females. Group 1 received intravenous injections of sterile saline (control). Groups 2, 3, and 4 received intravenous injections of 9712 at dose levels of 0.005, 0.1, or 1/5 mg/kg, respectively, once weekly for 44 weeks (terminal-sacrifice group) or 47 weeks (recovery-sacrifice

group). Group 4 initially received a weekly dose level of 1 mg/kg; the dose level was increased to 5 mg/kg on Day 57.

	No. of Animals[a]		Dose Levels	Dose Factor	Dose Concentration	Animal Numbers	
Group	Male	Female	mg/kg/dose	(mL/kg)	(mg/mL)	Male	Female
1 (Control)	6	6	0	1	0	J08588-J08593	J08594-J08599
2 (Low)	6	6	0.005	1	0.005	J08600-J08605	J08606-J08611
3 (Mid)	6	6	0.1	1	0.1	J08612-J08617	J08618-J08623
4 (High)	6	6	1.0 / 5.0[b]	1	1.0/5.0[c]	J08624-J08629	J08630-J08635

[a]Three monkeys/sex in each of the groups underwent a 52-week recovery following termination of dose administration.
[b]Effective March 17, 1998 (Week 9/day 57), the dose level was changed from 1.0 to 5.0 mg/kg/dose.
[c] Effective March 17, 1998 (Week 9/day 57), the dose concentration was changed from 1.0 to 5.0 mg/mL.

Following the Week 44 administration of 9712, three males and three females from each dose group were sacrificed and subjected to a complete necropsy. Organ weights and a complete set of tissues were collected from all animals for gross and histomorphologic evaluation. Immunohistochemical analysis for lymphocyte subsets was performed on selected lymphoid tissues, including spleen, tonsil, thymus, Peyer's Patch, and axillary, inguinal, mesenteric, and mediastinal lymph nodes. The remaining animals were monitored over a one-year recovery period. Animals were evaluated throughout the course of the study for changes in body weights, appetite, clinical signs and behavior, coagulation parameters, complement (C3, C4) levels, hematology, clinical chemistry parameters, urinalyses, ophthalmic examinations, and electrocardiograms. Blood was collected from animals prior to dosing and at designated times throughout the study for determination of serum 9712 concentrations, anti-9712 antibody titers, and flow cytometric analysis of peripheral lymphocyte subsets (CD2+ T cells, CD3+ T cells, CD4+ T cells, CD4+CD45Ro T cells, CD4+CD45Ra+ T cells, CD8+ T cells, CD8+CD45Ro T cells, CD8+CD45Ra+ T cells, and CD20+ B cells).

Immune function testing was performed during the dosing and post dose recovery periods. Humoral immune responses to human serum albumin (HSA) and Keyhole Limpet Hemocyanin (KLH) was evaluated during dosing and recovery periods. Delayed-Type Hypersensitivity (DTH) testing to evaluate cellular immune function was performed prior to dosing and during the dosing and recovery periods. The serum for DTH testing consisted of [

] These novel measures were incorporated into the study to provide some assessment of immune functional performance and to complement information yielded by ---------- and histopathologic examination of the lymph nodes.

Toxicokinetic/Immunogenicity of drug:
9712 serum concentrations were proportional to dose over the dose range studied. Mean maximum serum concentration values for the 0.005, 0.1, and 5 mg/kg dose groups were 0.17, 2.8, and 107 µg/mL, respectively. Overall, the pharmacokinetic parameters were generally consistent between treatment groups. Mean Cl values for the 0.005, 0.1, and 1/5 mg/kg dose groups were 0.45, 0.54, and 0.64 mL/hr/kg, respectively. Mean $t_{½}$ values for those dose groups were 176, 165, and 283 hours, respectively. Both Cl and $t_{½}$ appeared to increase with dose; however, both parameters were within the range of those previously observed. The mean Vss values for the dose groups were 97, 98, and 106 mL/kg, respectively. Transient anti-9712 antibody titers (1/7 to 1/2100) were detected

in the serum of 6/36 animals during the course of the study. The presence of antibodies did not compromise the test system or interpretation of data from affected animals.

Toxicity endpoints:
The repeat-dose intravenous administration of 9712 to cynomolgus monkeys was well tolerated, and no mortalities or clinical signs of toxicity were observed during the dosing period or through the one-year postdose recovery period. There were no changes in clinical observations, body weights, or clinical chemistry or hematology data (with the exception of lymphocyte numbers) that were related to administration of the test article during the course of the study. No trends were noted in the levels of serum complement components C3 and C4 as a function of dose, duration of study, or gender during the treatment or recovery phase. No tumors or other preneoplastic changes were noted on histopathologic analysis; no infections developed in animals on study.

Hematology:
Administration of 9712 resulted in sustained, but reversible, decreases in peripheral and tissue-associated lymphocyte populations. Decreased peripheral lymphocyte counts were observed in increasing proportions of the animals as doses increased. The nadir of the counts was not determined as FACS was conducted twice to get baselines, then not again until day 50 of the study; during study, animals with decreased counts in the high dose group showed CD4 counts that were approximately 30-75% of baseline CD4 (estimate). The data in Appendix 13 is noisy, and would benefit from reanalysis based on per individual, per subset, averaged baseline counts, with subsequent data points calculated as percent baseline to obtain a clear understanding of the quantitative changes in cell counts over time. CD2+ and C4+ T cell subsets in the 5 mg/kg group remained, on an average, 30% below predose baseline in 4 of 6 recovery sacrifice animals throughout the recovery period, so changes in counts, even with a years' recovery, was not always reversible.

DTH:
Animals were sensitized with an antigen cocktail of [
] prior to the initiation of dosing and were subsequently challenged with a low dose of the cocktail not containing ---------- during Week -1 (predose) and Weeks 8, 13, and 25 of the treatment phase. At 24 and 48 hours post-challenge, induration and erythema were measured. The overall DTH scores for each animal were calculated as the average score over the two timepoints. Although there was a slight trend for a decreased response in males during drug dosing, the variability among individuals and over time was too great to discern a significant effect. No other endpoints like CD4 suppression, seemed to suggest any gender-specific effect.

Humoral Immunity:
Humoral immunity was assessed as the immune response to exogenous protein antigens, including KLH and HSA. Animals were immunized with KLH prior to the initiation of dosing and challenged prior to dosing (primary response) and during Weeks -7 (predose) and Weeks 13 and 25 of the treatment phase to examine secondary immune responses. A trend towards reduction (~2x) and a slight delay of boosted anti-KLH titers was noted in the upper two dose groups during drug dosing. This effect was no longer evident following recovery.

Primary and secondary humoral responses to a neo-antigen were also assessed by administration of HSA during the dosing and recovery periods. All animals were administered HSA during Week 32 and tested for anti-HSA titers during Weeks 36 and 37 of the dosing period. All animals tested positive for anti-HSA titers in the 0.005 and 0.1 mg/kg groups and 10/12 animals tested positive in the 5 mg/kg group. In addition, the recovery animals were challenged during weeks 43 (dosing period) and 92 (recovery period). There appeared to be no difference in the anti-HSA titers between the control and treated groups; however, the mean titers for the 5 mg/kg group appeared to be slightly lower at all timepoints compared to the control during the treatment and recovery periods.

Histopathology:
No gross abnormalities were noted in the terminal or recovery sacrifice animals. Microscopic evaluations of ---------- tissues revealed no 9712-related histomorphologic changes in the terminal sacrifice animals.

Immunohistochemical analysis of lymphoid tissues in the terminal sacrifice animals revealed a depletion of CD4+ T cells in the PALS region of the spleen and in the paracortex of the lymph nodes and Peyer's Patch in the 5 mg/kg dose group. Decreased CD2+ T cells were also observed in the PALS region of the spleen and paracortex of the axillary lymph node in this dose group. Alterations were not observed in the thymus. Following the recovery period, there were no differences in the staining pattern or intensity for any of these markers compared to the control group animals indicating a complete recovery from the effects of 9712. TUNEL analysis showed that the decrease in CD4+ T cells seen in the spleen and lymph nodes of the terminal sacrifice animals was unlikely to be apoptosis-mediated.

Summary:
Chronic treatment with 9712 at dose levels of up to 5 mg/kg for 44-47 weeks was well tolerated in cynomolgus monkeys; clinically relevant drug exposures were maintained in the high dose group. There was no evidence of unexpected target organ change. Decreases in all mature, peripheral blood T lymphocytes were seen, which correlated with slight depletions in T lymphocyte regions of lymph nodes and spleen. Lymphocytes were mostly, but not completely, repleted in animals in the high dose group (25-30% reductions from baseline were still seen in some monkeys allowed to a year to recover). This may reflect an inability of thymically mature animals to replace T cells once they have been substantially and chronically reduced. Mild reductions in primary and secondary humoral immune responses were noted during drug dosing; this effect was completely reversible. These mild effects on lymphocytes and immunity may be compensated for by the redundancy of the immune system (spare lymphocytes/functional coverage) as no instances of opportunistic infection or neoplastic disease were observed.

2) Alefacept intravenous developmental reproduction toxicity study in the cynomolgus monkey. (Study P9712-97-04)

Study Design:

The purpose of this study was to assess the developmental/perinatal and postnatal toxicity of LFA3TIP (9712) when administered to the pregnant Cynomolgus monkey. The table below lists the study groups:

Group Number	Group Designation	Number of Animals	Dose Level mg/kg/occasion	Application Volume (mL/kg)	Dosing Period (once weekly)
1	Control I- cesarean group	8	0	1	Day 20 to 90 p.c.[a]
2	Control II – full term group	8	0	1	Day 20 p.c. until delivery
3	Low I – cesarean group	8	0.005	1	Day 20 to 90 p.c.
4	Low II – full term group	8	0.005	1	Day 20 p.c. until delivery
5	High I – cesarean group	8	5	1	Day 20 to 90 p.c.
6	High II – full term group	8	5	1	Day 20 p.c. until delivery

[a]p.c: *post coitum.*

The control and test articles were administered intravenously into the brachial or saphenous vein to the pregnant Cynomolgus monkeys in the cesarean groups (groups 1, 3, and 5) once weekly from Day 20 to 90 *post-coitum* (p.c.) and in the full term groups (groups 2, 4, and 6) once weekly from Day 20 p.c. until delivery. alefacept was administered as a solution at a dosing volume of 1 L/kg. Control animals received sterile saline (0.9%) according to the same dosing volume and schedule as alefacept-treated animals. For animals assigned to cesarean section groups, pregnancies were terminated on Day 100 ± 1 p.c. and the fetuses collected for evaluation. Day 100 corresponds approximately to a human infant at 5.5 months of gestation. Animals assigned to full term groups were allowed to deliver; the monkey infants were observed for about 16 to 19 months after delivery and then necropsied. During the study all maternal animals were examined twice daily for clinical signs.

Estimated food intake was recorded twice daily from Day 20 of gestation until study termination. Body weights were recorded for the pregnant animals of the cesarean and full term groups on Days 20, 27, 34, 41, 48, 55, 62, 69, 76, 83, 90, 97, 100 ± 1, 104, 111, 118, 125, 132, 139, 146, 153, and 160 of gestation, as applicable. After delivery, body weight (maternal, monkey infant) was recorded on Days 1, 7, 14, 21, and 28 *post-partum* and then at monthly intervals for up to a maximum of 19 months (maternal) or monthly intervals until months 7 to 9 (monkey infants). On June 2, 1999 body weights were taken at two-week intervals for all monkey infants until study termination.

Fetuses removed by cesarean section were weighed, sexed, measured and evaluated for external, visceral and skeletal defects. Fetal organs and the placenta were also weighed. Fetal organs including thymus, spleen, distal ileum (Peyer's patch) and lymph nodes (axillary, mesenteric, and inguinal) were evaluated by immunocytochemistry. Blood samples for maternal immunoglobulin measurements were collected on gestation days 20, 48 and 100 ± 1 for cesarean groups, and 108 for full term groups. Samples for immunoglobulin measurements for the fetus were collected on Day 100 ± 1 p.c. and for monkey infants on Days 35, 360 and 364 *post-partum* (p.p.). Samples of amniotic fluid (at cesarean section) and maternal milk (28 and 88 p.p.) were collected for alefacept concentration measurements. Blood samples for alefacept concentration measurements were collected on Days 20, 83 p.c. (maternal) and Day 100 ± 1 p.c. (maternal and fetal). Post-partum collections for serum concentrations were performed on Days 28 and 58 (maternal and monkey infant) and on Day 88 (maternal). Blood was collected on Days 88, 178, 268 and 360 p.p. (maternal) and 35, and 58 p.p. (monkey infant) for anti-alefacept antibody measurements.

Clinical pathology samples including flow cytometry analyses of peripheral blood lymphocyte subsets were collected during gestation pre-dose and on Days (± 1) 80 and 139 p.c. (full term). Monkey infant clinical pathology samples were collected on Days (± 1) 88, 203, and 357 p.p. Samples for flow cytometry analysis (monkey infants) were collected on Days (± 1) 28, 58, 178, 328, and 360 p.p. The ability of monkey infants to mount a primary antibody response was investigated by an intradermal injection of 100 µg KLH (keyhole limpet hemocyanin) in 0.2 mL of 1:1 emulsion of sterile normal saline and Incomplete Freund's Adjuvant on days 182 and 336 of age. Blood samples were collected for evaluation of anti-KLH antibody titers pre-dose and on Days 196, 203, 210, 343, 350, 357, and 364 p.p. To assess cellular immune function in monkey infants, dermal delayed-type hypersensitivity (DTH) evaluation was conducted at 44 to 54, 63 to 73 and 67 to 77 weeks of age in all monkey infants.

After completion of the final in-life investigation, monkey infants were necropsied and the organs histopathologically investigated. Immunocytochemistry was performed in selected organs (ileum, Peyer's patches, spleen, thymus, and lymph nodes – axillary, mesenteric and inguinal.

Maternal Toxicokinetics:
The half-life (t½), clearance (Cl) and volume of distribution (Vss) were consistent across both dose groups of maternal animals. The mean t½, Cl and Vss were 150 h, 0,74 mL/h/kg and 136 mL/kg, respectively. Maximum observed serum concentration values were 0.37 µg/mL and 106 µg/mL in the 0.005 mg/kg and 5 mg/kg dose groups, respectively. No antibodies to alefacept were observed.

Maternal Toxicity:
No alefacept-related deaths or clinical signs were observed among pregnant animals. Treatment of alefacept did not produce any adverse effects on body weight, hematology, or clinical chemistry data. Peripheral lymphocyte counts and T-lymphocyte subsets in the cesarean and full term maternal animals were decreased by approximately 50% during the gestation period in the 5 mg/kg dose group only. Evaluation of maternal immunoglobulin A, E, G, and M did not reveal any treatment-related changes.

Fetal Exposure and Drug Immunogenicity:
Fetuses were exposed to alefacept *in utero*. Approximately 0.7% and 23% of the maternal alefacept serum concentrations were present in the amniotic fluid and cord blood, respectively, at the time of cesarean section (Day 100 ± 1) in the 5 mg/kg dose group. The absolute alefacept concentrations were 0.1 µg/mL and 4.6 µg/mL in the amniotic fluid and cord blood, respectively. These levels were below limits of quantitation in the 0.005 mg/kg dose group. No antibodies to alefacept were observed in fetuses. Alefacept was not detected in the breast milk in either dosed group.

Fetal Outcomes:
The administration of alefacept to pregnant monkeys did not grossly affect the incidence of abortions or stillbirths. One fetus in a group 3 animal appeared to die in utero shortly prior to cesarean section; the cause of this is not known (no know injury to maternal animal 8756 for instance). One fetus was removed by cesarean section from a group 5 maternal animal (8559), which appeared to have died in utero prior to the day 58 ultrasound (no heartbeat detected; no late abortion).

External, visceral, and skeletal examination of live fetuses did not reveal any treatment-related effects. There were no effects on fetal or placental weight, fetal organ weights, or fetal morphometric measurements. Minor abnormalities and variations were detected which were not more frequent in drug-dosed groups, or were within expected incidences for this species.

Immunohistochemical analysis of fetal lymphoid, splenic, or thymic tissues revealed no treatment-related changes. Cells positive for T cell markers including CD2, CD3, CD4, and CD8 were distributed in patterns similar to that observed in adult tissues.

Neonatal Exposure and Health Endpoints:
Alefacept serum concentrations were detected in the neonates from the 5 mg/kg maternal dose group only. Concentrations ranged from 1.1 µg/mL to 4.0 µg/mL 28 days p.p. No antibodies to alefacept were observed. Gestation length, parturition, body weights, and survival and growth of neonates were unaffected by alefacept exposure. Monkey infant hematology and clinical chemistry data did not reveal any adverse treatment-related effects over the 16 to 19 month observation period. No changes in monkey infant peripheral blood lymphocyte counts or lymphocyte subsets were observed which differentiated drug dosed groups from controls.

Monkey Infant Health and Immune Functional Measures:
In general, there were no drug effect on the organ weights nor histopathological evidence in monkey infants of target organ toxicity resulting from in utero exposure to alefacept. However, one monkey infant (8764) died in group 6 on day 245 post birth. The animal had shown anemia at day 88 with low MCH, MCV, MCHC, PCV, HC and high reticulocyte counts; and later, diarrhea, dehydration, and alopecia for days leading up to its death. Necropsy revealed aplasia of the thymus, and an absence of ectopic thymic tissue in either the ethyroid or in the sternum regions. The singular incidence of this finding, and the otherwise normal thymic tissue seen among its cohort of 5 other infants makes this finding particularly difficult to interpret. This animal which died had normal T cell and B cell counts as shown on ---------- at day 203 (a month prior to death), and normal globulin values in the serum samples. However, this finding is notable because this is a small study (n=6/group), and thymic aplasia is not an expected finding based on historical data. Concern is expressed due to the lymphocyte-directed nature of the drug.

Humoral responses to neo-antigens as well as delayed type hypersensitivity (DTH) responses were not affected by the maternal administration of alefacept. Monkey infants were found to generate antibodies to KLH within 7 days of antigen exposure. Delayed type hypersensitivity (DTH) testing was inconclusive. No treatment-related changes were observed in the monkey infants at necropsy. Immunohistochemical analysis of monkey infant lymphoid tissues revealed no treatment-related changes.

In conclusion, administration of alefacept to pregnant cynomolgus monkeys at dose levels of 0.005 or 5 mg/kg weekly from Day 20 to 90 of gestation (cesarean groups) or from Day 20 of gestation until delivery (full term groups; approximately day 160 of gestation) did not produce overt maternal toxicity. Peripheral lymphocyte counts and T-lymphocyte subsets in the cesarean and full term pregnant females were decreased by approximately 50% during the gestation period in the 5 mg/kg dose group only. No evidence of teratology or effects on monkey infant growth and development were observed. However, a monkey infant, delivered from a maternal animal that received 5 mg/kg, developed reticulocytosis, lived to day 245, but then died subsequent to diarrhea and dehydration; necropsy revealed thymic aplasia. The relationship of this finding to study drug is unknown, but is concerning due to the lymphocyte targeted nature of the drug.

<u>Chronic Toxicity Commentary:</u>
The sponsor has developed this new molecular entity specifically for this first clinical indication in psoriatic patients. If approved, this will be the precedent use for a drug of this type. Consequently, numerous discussions with this sponsor have been held over the entire course of IND development to address the program design, and the need for careful and extensive characterization of chronic toxicity and reproductive hazards. Additionally, many discussions have focused attention on the agency's central concern for toxicity, the nonselective down regulation of immune function, mediated by depletion of mature T cells which all express CD2 to varying degrees.

The program for toxicologic investigation was constructed around a series of factors. This drug selectively targets T cells. As a humanized immunoglobulin, alefacept is very unlikely to have any toxic metabolites. Following i.v. administration, pharmacokinetics and distribution of alefacept is very similar in humans and primates. The formulation is simple buffered saline. Immune functional role of CD2 in primates and man is expected to be very similar. Additionally, the drug only binds to CD2 in several species - old world monkeys, chimps, and humans. Therefore, in toto, toxicity is likely to be limited to the immune system, and non human primates are the only species which could usefully model clinical relevant adverse effects. With human chronic use in mind, the toxicity studies were enhanced with additional endpoints to detect immune alterations, especially with regard to chronic use and reversibility of effects. Phase 2 human data was available at the time of the design of the chronic monkey studies, to validate the similarity in human and monkey adverse effect patterns seen with 12 weeks of dosing.

Especially considering that monkeys are the only relevant, available, and reliable species for study and risk assessment, this sponsor should be commended for implementing new methods for detecting immunomodulatory effects of Alefacept; the chronic toxicity studies conducted in primates were modified to incorporate enhanced measures of histopathological changes, as well as pharmacodynamic markers of immunomodulation. These additional tests did not interfere with obtaining data on all the traditional toxicology assessments from these animals.

Specifically, immunohistochemical staining of lymphoid and splenic tissue provided more sensitive and accurate information regarding altered lymphocyte trafficking in lymphoid tissues, than that seen using ---------- Along with these fixed tissue investigations, study primates were challenged with neoantigen and secondary antigens; these challenges offered opportunities to see diminished T cell and B cell functionality. This effort goes beyond current standard measures (such as ---------- analysis) which are oriented at enumeration and depletion of lymphocyte subsets. Both of these investigations were informative; showing subtle changes at dose and effect levels which are likely to be similar to effects in humans. None of these changes showed toxic immune dysfunction, or irreversible changes, which indicated a severe immunosuppressed effect. Another technique employed in the chronic cynomolgus monkey studies was delayed type hypersensitivity testing to a set of antigens administered intradermally. The goal of this testing was to identify a drug effect on cellular immune function. Although this technique has been usefully employed in other laboratories (perhaps using different antigen preparations, or drug challenges), in this case the variability of the skin reactions over time, and among individuals, proved to overshadow any interpretable pattern in the response.

Studies conducted by the sponsor in nonclinical models provide an adequate basis for assessment of toxicities at this time.

Carcinogenicity:
For chronic drug use in this clinical population, carcinogenicity studies in rodents are ordinarily expected in accordance with ICH documents. However, the principles for nonclinical risk assessment of drugs which are human protein structures (as outlined in the S6 ICH document) point to the primary need for scientific analysis of the utility that such data would serve.

At this point in time, we concur with the sponsor that the scientific limitations of a rodent 2 year bioassay greatly outweigh the utility that the data could serve in terms of human hazard identification. It is already acknowledged that drugs which deplete lymphocytes and are immunosuppressive may decrease immune surveillance for cancers. Factors influencing this case-specific decision were: the availability of the monkey as a research model for human risk; the limited cross-reactivity of alefacept (it does not bind CD2 in rodents); and the partially different roles that CD2 and LFA-3 may serve in man, versus the role of CD2 and CD49 in rodents (different localization of the rodent co-receptor may indicate that CD2 serves a partly different role in rodent immune responses). It was an important factor that the sponsor had studied this molecule over a

long period (9 month drug treatment and 1 year of recovery) in a primate chronic toxicity study, and in primates dosed in utero, and allowed to mature for a full year. In considering these factors, the sponsor was not requested to propose further justifications for not conducting rodent carcinogenicity evaluations.

Subsequent to these program plans, the sponsor identified a lymphoma in a monkey exposed for 20 weeks to alefacept (9723). These new studies (to be reported in the next year) reveal the carcinogenic potential of this agent (likely due to immunosuppression). The drug was dosed at a level which caused similar lymphocyte count changes, as those seen in humans with psoriasis. This finding will be described in the drug labeling, subsequent to the receipt of in life reports which should be submitted to the FDA before the BLA approval period is complete.

Lauren Black, Ph.D.

Attachments:

1) Preclinical Toxicology studies conducted using alefacept.

ATTACHMENT 1:
Preclinical Studies: Comprehensive List

Pharmacology
Primary Pharmacodynamics
In Vitro Binding Studies
Report No. IC-29 - Amino Acid Residues Required for Binding of Lymphocyte Function Associated Antigen 3 (CD58) to its Counter-Receptor CD2

Report No. IC-25 - Binding of LFA3TIP to Dog, Rabbit, Rat, Sheep, and Human Peripheral Blood Lymphocytes

Report No. IC-32 - Specific Interaction of Lymphocyte Function-Associated Antigen 3 (LFA-3) with CD2 can Inhibit T Cell Responses

Report No. IC-46 - Glycols Phosphatidylinositol-Linked LFA-3 Costimulates PHA-p-Activated Proliferation of Cynomolgus Monkey Peripheral Blood Lymphocytes

Report No. IC-47 - Low Affinity Binding of LFA3TIP to CD2+ T Cells is Independent of Cell Activation

In Vitro Pharmacodynamic Studies

Report No. IC-30 - Mechanism of Lymphocyte Function-Associated Molecule-3-Immunoglobulin Fusion Proteins Inhibition of T Cell Responses: Structure/Function Analysis in Vitro and in Human CD2 Transgenic Mice

Report No. IC-53 - The CD2/CD16-Dependent Pharmacology of LFA3TIP Mutants ---------- and --------- and LFA3TIP Variants BG9273 and BG9712

Report No. IC-70 – Biochemical Characterization of LFA3TIP Inhibition of CD2/LFA-3 Interactions and Mediation of CD2/CD16 Interactions

Report No. IC-71 - LFA3TIP Induces Signaling, Activation, and Apoptosis of In Vitro IL-2-Expanded Human Natural Killer Cells

Report No. IC-59 - Costimulation of Human Peripheral Blood Lymphocyte Profileration by LFA3TIP

In Vivo Primary Pharmacodynamics Studies

Report No. IC-28 - The Effects of an Immunomodulatory LFA3-IgG1 Fusion Protein on Nonhuman Primates

Report No. IC-27 - Immunomodulation by LFA3TIP, an LFA-3/IgG1 Fusion Protein: Cell Line-Dependent Glycosylation Effects on Pharmacokinetics and Pharmacodynamic Markers

Report No. IC-26 - Short Course Single Agent Therapy with an LFA-3-IgG1 Fusion Protein Prolongs Primate Cardiac Allograft Survival

Report No. IC-24 - A Novel Murine Model for the Assessment of Human CD2-Related Reagents in vivo

Report No. IC-57 - Blockade of CD2-LFA-3 Interactions Protects Human Skin Allografts in Immunodeficient Mouse/Human Chimeras

Report No. P9273-99-01 - BG9273: Pilot Single Dose, Range Finding Study for Pharmacodynamic Assessment of LFA3TIP Products in ----------Transgenic Mice When Administered Intravenously

Report No. P9273-00-02 - BG9273: Pilot Single Dose, Range Finding Study for Pharmacodynamic Assessment of LFA3TIP Products in ----------Transgenic Mice When Administered Intravenously

Report No. P9273-00-04 - BG9273: Pilot Single Dose, Range Finding Study for Pharmacodynamic Assessment of LFA3TIP Products in ----------Transgenic Mice When Administered Intravenously

Report No. P9273-99-02 - BG9273: Pharmacodynamic Assessment Following Single Intravenous Administration to Cynomolgus Monkeys

Pharmacokinetics
Analytical Methods and Validation Reports
Introduction to Analytical Methods and Validation Reports

SOP 160a.53 – For the Detection of Alefacept by ----------

SOP 160a.58 –- ---------- for Antibodies to Alefacept in ----------

Report No. BA73-002A – Method Validation Report for the --------- for the Determination of Alefacept by ----------

Report No. BA72-003A – Method Validation Report for the ---------- for the Determination of Antibodies to LFA3TIP in ----------

Report No. 6538-162 - Method Validation, and Stability Analyses of LFA3TIP in [
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Report No. 6538-205 - Demonstration and Validation of ---------- to Quantitatively Measure LFA3TIP in ----------

Report No. 6538-132 - Development and Validation of ---------- Procedure for the Determination of Anti-Keyhole Limpet Hemocyanin KLH in Cynomolgus Monkey ----------

Report No. 6538-177 - Demonstration and Validation of ---------- Procedure for the Determination of Antibodies to LFA3TIP in Cynomolgus Adult and Monkey infant Monkey ----------

Report No. 6538-156 - Demonstration and Validation of ---------- to Quantitatively Measure LFA3TIP in Cynomolgus Monkey ---------- and Cross-Validation in Cynomolgus Monkey ----------

Report No. 940903/BG - The Quantitative Determination of LFA3TIP in Baboon ----------

Report No. 940905/BG - Qualitative Determination of LFA3TIP in Baboon ----------

Pharmacokinetics
Single Dose Pharmacokinetics
Report No. P9273-00-01 - BG9273: Single Dose Pharmacokinetic Assessment of LFA3TIP Products in C57BL/6 Mice When Administered Intravenously

Report No. P9273-00-03 - BG9273: Single Dose Pharmacokinetic Assessment of LFA3TIP Products in C57BL/6 Mice When Administered Intravenously
Report No. P9273-00-05 - BG9273: Single Dose Pharmacokinetic Assessment of LFA3TIP Products in C57BL/6 Mice When Administered Intravenously

Report No. P9273-92-01 - A Pilot Pharmacokinetics and Toxicology Study Comparing CHO and ---------- Following Intravenous Administration to Baboons

Report No. P9272-93-01 - A Comparative Pharmacokinetics Study of CHO Cell Line Derived LFA3TIP with and without ---------- Following Intravenous Administration to Baboons

Report No. P9273-93-02 - A Pharmacokinetics and Toxicology Study of CHO Cell Line Derived LFA3TIP Following Intravenous Administration to Baboons

Report No. P9273-94-03 - A Single Intravenous Dose Pharmacokinetics and Toxicity Study of BG9273 in Baboons

Report No. P9273-96-01 - BG9273 Intramuscular Tolerability and Toxicity Study in Baboons

Report No. P9712-97-01 - LFA3TIP (LFA-3 IgG1 Fusion Protein): A Single Intravenous Dose Pharmacokinetics Comparability Study of BG9712 and BG9273 in Baboons

Report No. P9273-92-02 - A Pharmacokinetic Study of ---------- in Cynomolgus Monkeys

Report No. P9273-99-02 - BG9273: Pharmacodynamic Assessment Following Single Intravenous Administration to Cynomolgus Monkeys

(*This report also listed in In Vivo Studies*)

Repeat Dose Pharmacokinetics

Report No. P9273-92-04 - A Study to Provide Distribution Information of LFA3TIP in Baboons

Report No. P9273-93-03 - A Toxicology Study of BG9273 Following Multidose Intravenous Administration to Baboons

Report No. P9273-93-05 - Pilot Escalating Dose Toxicity Study of CHO Cell Line Derived LFA3TIP Following Intravenous Administration to a Baboon

(Note: Report inadvertently labeled as No. P9272-93-05 instead of No. P9273-93-05; see Memo to File in Report)

Report No. P9273-95-01 - BG9273: An Intermittent Repeat Dose Toxicity and Pharmacokinetic Study in the Baboon

Report No. P9273-95-02 - BG9273: An Intermittent Repeat Dose Toxicity and Pharmacokinetic Study in the Baboon

Report No. P9273-97-03 - LFA3TIP (BG9273 and BG9712) An Exploratory Evaluation of Activity Pharmacokinetics Tolerability and Antigenicity in Cynomolgus Monkeys

Report No. P9273-99-03 - Pharmacokinetic and Pharmacodynamic Comparability of LFA3TIP in Cynomolgus Monkeys

Report No. P9273-00-06 - BG9273: Comparative Assessment of Commercial BG9273 in Cynomolgus Monkeys - Pharmacokinetics and Pharmacodynamics after Intravenous Injection

Report No. P9273-00-07 - BG9273: Comparative Assessment of Two Different Formulations of BG9273 ---------- BG9273 and ---------- BG9273 in Cynomolgus Monkeys - Pharmacokinetics and Pharmacodynamics after Intravenous Injection

Toxicology
Single-Dose Toxicity
Report No. P9712-97-02 – A Single Dose Intravenous Toxicity Study of BG9712, Manufactured with the ----------, in Male CD Rats

Report No. P9273-96-01 - BG9273 Intramuscular Tolerability and Toxicity Study in Baboons

(*This report also listed in Single-Dose Pharmacokinetics*)

Report No. P9273-92-01 - A Pilot Pharmacokinetics and Toxicology Study Comparing CHO and ---------- LFA3TIP Following Intravenous Administration to Baboons

(This report also listed in Single-Dose Pharmacokinetics)

Report No. P9273-93-02 - A Pharmacokinetics and Toxicology Study of CHO Cell Line Derived LFA3TIP Following Intravenous Administration to Baboons

(This report also listed in Single-Dose Pharmacokinetics)

Report No. P9273-94-03 - A Single Intravenous Dose Pharmacokinetics and Toxicity Study of BG9273 in Baboons

(This report also listed in Single-Dose Pharmacokinetics)

Report No. P9273-99-02 - BG9273: Pharmacodynamic Assessment Following Single Intravenous Administration to Cynomolgus Monkeys

(This report also listed in In Vivo Studies)

Report No. P9712-98-01 - Assessment of Formulation Effect on LFA3TIP (BG9712) Pharmacokinetics and Activity in Cynomolgus Monkeys

Repeat-Dose Toxicity

Report No. P9273-93-05 - Pilot Escalating Dose Toxicity Study of CHO Cell Line Derived LFA3TIP Following Intravenous Administration to a Baboon

(This report also listed in Repeat-Dose Pharmacokinetics)

Report No. P9273-93-03 - A Toxicology Study of BG9273 Following Multidose Intravenous Administration to Baboons

(This report also listed in Repeat-Dose Pharmacokinetics)

Report No. P9273-95-01 - BG9273: An Intermittent Repeat Dose Toxicity and Pharmacokinetic Study in the Baboon

(This report also listed in Repeat-Dose Pharmacokinetics)

Report No. P9273-95-02 - BG9273: An Intermittent Repeat Dose Toxicity and Pharmacokinetic Study in the Baboon

(This report also listed in Repeat-Dose Pharmacokinetics)

Report No. P9273-95-03 - A Three Month Multiple Dose Toxicity Study of BG9273 in Baboons

Report No. P9273-97-03 - LFA3TIP (BG9273 and BG9712) An Exploratory Evaluation of Activity Pharmacokinetics Tolerability and Antigenicity in Cynomolgus Monkeys

(This report also listed in Repeat-Dose Pharmacokinetics)

Report No. P9712-97-03 - 44-Week Intravenous Toxicity Study with LFA3TIP (BG9712) in Cynomolgus Monkeys with a 1-Year Recovery Period

Genotoxicity
Report No. P9273-95-04 - Evaluation of BG9273 in the [

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Report No. P9273-95-06 - Test for BG9273 Induction of Chromosomes Aberrations in Cultured Human Peripheral Blood Lymphocytes With and Without ----------

Reproductive and Developmental Toxicity
Report No. P9712-97-04 - LFA3TIP (BG9712) Intravenous Developmental Reproduction Toxicity Study in the Cynomolgus Monkey

Other Toxicity Studies
Report No. P9273-94-01 – Pilot Tissue Cross-Reactivity Study of LFA3TIP – (BG9273; LFA-3 IgG_1 Fusion Protein) – Determination of Conditions for the Assay with Human Tissues
Report No. P9273-95-05 – Evaluation of BG9273 to Induce Hemolysis in Human Blood and Flocculation in Human Plasma and Serum