Clinical Pharmacology Review of Alefacept

Indication: Psoriasis
Sponsor: Biogen
STN: 125036

Alefacept is a dimeric fusion protein produced by CHO cells and has an approximate MW of 115 kDa. It is made from the extracellular binding portions of the human leukocyte function antigen-3 (LFA-3) and the Fc portion of human IgG1. The Fc portion in alefacept does not contain the C_H1 domain of IgG1. Alefacept is intended for use in the treatment of patients with chronic plaque psoriasis who are candidates for phototherapy or systemic therapy. Alefacept (LFA3TIF) inhibits the interaction between APC's and T-cells by antagonizing the association of their receptors through LFA-3 and CD2.

The recommended dosing for alefacept given IM is 15 mg/week or 7.5 mg/week for 12 weeks.
Study 722 (comparability of --- BG9273 and --- BG9273)
Study 723 (comparability of --- BG9273 and --- BG9273)

A series of manufacturing changes occurred during development and the pharmacokinetic comparability was assessed in studies 722 and 723. Drug made at ---------- (--- BG9273) was originally used for study and scaled-up for use in phase 3 studies at a different manufacturing site. This latter material was designed --- BG9273 and was produced by same CHO cell line and manufacturing process. Both --- BG9273 and --- BG9273 were [ ]. Latter another series of manufacturing changes occurred. These changes included a [

]. This drug substance was --- BG9273. ------ ------ of ALF3TIF were analyzed with an ----- .

Study 95-701, A Double-blind, Randomized, Placebo-controlled, Dose-escalation Study to Evaluate the Tolerability, Pharmacokinetics and Biologic Activity of BG9273 (LFA-3/IgG1, Fusion Protein) in Healthy Male Volunteers. Lot ------ .

This was a dose response study that characterized the pharmacokinetics, pharmacodynamics and tolerability of LFA3-TIF given as BG9273. The study was placebo controlled with 6 subjects randomized to 1 of 4 doses of BG9273 and 2 subjects to the placebo group per cohort. BG9273 was administered as a single 30 minute IV infusion at doses of 0.005, 0.01, 0.02, 0.04, 0.10, 0.15 and 0.225 mg/kg. The primary pharmacodynamic measure of LFA3TIF was considered to be a change in delayed hypersensitivity. Blood was drawn for pharmacokinetic determinations are the following times: within 1 hour prior to dosing as well as 15 minutes and 30; immediately after the IV infusion; 1, 1.5, 2, 3, 4, 6, 9, 12, 18, 24, 36, 48, 72 hours and 4, 7, 9, 14, 21 and 28 (+/) days after the start of the study. Delayed hypersensitivity testing was accomplished using

a ----------. Skin testing was conducted at day 7 after drug administration and read 48 hours later. No subject developed anergy to skin test antigens.

The results of pharmacokinetic portion of the study are summarized below:

Dose, mg/kg	Cmax, ug/ml	AUC, ug-h/ml	T1/2, h
0.005	0.23	12	156
0.01	0.29	23	125
0.02	0.42	38	159
0.04	0.72	102	206
0.10	2.1	327	294
0.15	2.7	366	205
0.225	5.3	838	287

Table of pharmacokinetic endpoints in healthy volunteers (mean).

Study Number C-722. A Randomized, Open-Label, Crossover Study in Healthy Volunteers Comparing the Pharmacokinetic Properties of Two Formulations of Alefacept (LFA-3/IgG1 Human Fusion Protein) When Given as an Intravenous Injection. Lot ---- for --- BG9273 and lot ----------.

The primary objective of this study was to determine the pharmacokinetic comparability of --- BG9273 versus --- BG9273 at 7.5 mg given by IV administration to ensure that no meaningful differences would arise from different manufacturers of the drug. The study was a single center, randomized, open-label, 2-period crossover study using healthy, male and female subjects within 25% of their ideal body weight. Blood samples for pharmacokinetic assessment were taken 24 prior to the dosing and 0.25, 0.5, 1, 1.5, 2, 4, 6, 9, 12, 24, 36, 48, 72 hours, days 5, 8, 15, 22, and 29. After the first dose an additional blood samples was taken at week 7, day 3. An eight-week washout period occurred between administrations of drug. For each subject the difference, ratio and log of the ratio for the 2 formulations were determined. Using AUC and a two one-sided 90% confidence interval (CI) using boundaries of 80% to 125%, pk comparability was tested (N = 35). The 90% CI for the least squares mean ratio of AUC last for --- BG9273 to ---- --- BG9273 was 107% to 121%. The mean (SD) AUClast (h-ug/ml) for --- BG9273 was 292 (128) and for --- BG9273 was 251 (81).

Study C-723, A Randomized, Open-Label, Crossover Study in Healthy Volunteers Comparing the Pharmacokinetic Properties of Two Formulations and Two Concentrations of Alefacept (LFA-3/IgG1 Human Fusion Protein) When Given as an Intramuscular Injection. Lot ------- for --- BG9273 and ----------.

The primary objective of this study was to determine the pharmacokinetic comparability of --- BG9273 versus --- BG9273 at 15 mg given by IM administration to ensure that no meaningful differences would arise from different manufacturers of the drug. Two different concentrations of drug were also studied by injecting the drug in either 0.5 ml for --- BG9273 or 1.0 ml for --- BG9273. The study was a two center, randomized, open-label, 2-period crossover study using healthy, male and female subjects within 25% of

their ideal body weight. Blood samples for pharmacokinetic assessment were taken 24 prior to the dosing and 1, 2, 4, 6, 9, 12, 24, 36, 48, 72 hours, days 5, 8, 15, 22, and 29. An additional blood sample was taken at week 7, day 3. An eight-week washout period occurred between administrations of drug. For each subject the difference, ratio and log of the ratio for the 2 formulations were determined. Using AUC and a two one-sided 90% confidence interval (CI) using boundaries of 80% to 125%, pk comparability was tested (N = 80). The 90% CI for the least squares mean ratio of AUClast for --- BG9273 to --- BG9273 was 96% to 106%. The mean (SD) AUClast (h-ug/ml) for --- BG9273 was 402 (105) and for --- BG9273 was 396 (102).

Study C96-704, Tolerability, Pharmacokinetics, and Biologic Activity of BG9273 (LFA-3/IgG1 Fusion Protein) When Given as an Intravenous Infusion or as an Intramuscular Injection: an Open-Label, Randomized, Parallel Group Study in Healthy Male Volunteers. Lot ------.
This study investigated the tolerability and pharmacokinetics of a single dose of BG9273 (0.04 mg/kg) given IM (anterolateral site of injection) or IV (30 minute infusion) to healthy males in a parallel study design with N = 8/route. Pharmacokinetic samples (serum) were collected within 1 hour prior to dosing (and 0.25, 0.5 for the IV route), 1, 1.5, 2, 3, 4, 6, 9, 12, 18, 24, 36, 48, 72 hours after injection as well as days 5, 8, 10, 15, 22 and 29 (+/-4). The pharmacokinetic results are summarized below:

Pharmacokinetic value	IV infusion	IM injection
Cmax, ug/ml	1 (0.92)	0.3 (0.34)
Tmax, h	3 (0.7)	78 (6.2)
AUCt-last, ug-h/ml	163 (7.3)	91 (4.5)
T1/2, h - absorption	---	26 (0.5)
T1/2, h – elimination	254 (9.1)	165 (9.3)

Table of pharmacokinetic endpoints after IM or IV administration. Mean (SEM)

The relative bioavailability of the IM to IV route was determined to be 46% (90% CI of 28% to 78%). Although the terminal elimination T1/2's were reported to be different, a visual inspection of the plots suggests they are not different. It is noteworthy that Cmax for the IV route of injection was not coincident with the first serum sample taken after completing the IV infusion; additionally, after IV administration where appeared to be a plateau like state in serum levels which had a duration of approximately 9 hours. A lag time of approximately 6 hours was reported to follow the IM injection.

Study C97-706, A Randomized, Placebo-Controlled, Single-Dose Study in Healthy Male Volunteers of BG9712 and BG9273. Lots for BG9712 – ----------
BG9273 – -------)

This is an open-label, randomized, placebo-controlled study with 6 arms. Each arm investigated the pharmacokinetics of a single dose of the study drug (BG9712 or BG9273) by various routes of administration. These arms were: 1) IV infusion (30 minutes duration) of 0.04 mg/kg of BG 9712; 2) IV bolus of 0.04 mg/kg of BG 9712; 3) IV bolus of 0.15 mg/kg of BG 9712; 4) IM injection of 0.15 mg/kg of BG 9712; 5) SC

injection of 0.15 mg/kg BG 9712; 6) IV bolus of 0.15 mg/kg BG9273. A number of comparisons were made based on the route of administration and material used in the study. AUC and Cmax were proportional to dose with IV > IM>>SC. The AUC for 0.04 mg/kg dose was lower than that for the 0.15 mg/kg dose. The levels of LFA3TIP for the BG 9712 material were lower than those for the BG 9273 material. The excipients in BG 9712 formulation (supplied as a lyophilized powder) were citric acid, sodium citrate, sucrose, and glycine. The excipients in the -------- formulation (supplied as a frozen solution) were [

]. Serum samples were taken within 1 hour prior to dosing, 15 and 30 minutes, 1, 1.5, 2, 4, 6, 9, 12, 18, 24, 36, 48 hours (an additional 72 hour sample was taken for subjects given IM or SC injections) after study drug administration and days 5, 8, 15, and 29 (+/-4). These results are summarized below:

Route	Cmax, ug/ml	AUCt-last, ug-h/ml
IV infusion, N = 4	0.7 (0.72)	90 (33)
IV bolus, N = 4	0.6 (0.16)	63 (25.8)

Pharmacokinetics of BG 9712 given IV 0.04 mg/kg. Mean (SD)

Route	Cmax, ug/ml	AUCt-last, ug-h/ml
SC injection, N = 4	0.5 (0.17)	195 (109)
IM injection, N = 4	0.8 (0.25)	312 (42)
IV bolus, N = 4	2.9 (0.55)	446 (76)

Pharmacokinetics of BG 9712 given at 0.15 mg/kg. Mean (SD)

Route	Cmax, ug/ml	AUCt-last, ug-h/ml	Cl, ml/h/kg
IV bolus -BG 9273, N =12	3.4 (0.53)	530 (97.7)	0.2 (0.04)
IV bolus - BG 9712, N =12	2.9 (0.55)	446 (76.5)	0.3 (0.06)

Pharmacokinetics of LFA3TIP given IV at 0.15 mg/kg. Mean (SD)

Study C96-703, 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 Weekly for Eight Doses in Subjects with Chronic Psoriasis. Lot ------.

This double-blind, randomized study using dose escalation primarily investigated the pharmacokinetics, tolerability and pharmacodynamics (delayed-type hypersensitivity of uninvolved skin and quantitation of peripheral lymphocyte subsets) of LFA3TIP (BG9273) in patients with moderate to severe chronic plaque-type psoriasis. The study had 5 arms that differed by dose and route of administration: 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. When the IV route of administration was used, infusions were conducted over a 30 minute period or an IV bolus over 30 to 60 seconds. A total of 8 doses were given to patients as weekly injections. Only a limited number of blood samples were collected for pharmacokinetic analysis. Serum samples were collected within 1 hour prior to dosing, 0.5, 8, and 24 hours after dosing and days 7 (± 12 hours), 14, 28 in addition to week 8. Pharmacokinetic values were calculated using ------. Both outliers (2 data points) and

other data (sampling points from 4 patients after 1512 hours post dosing) were omitted from the analysis. Clearance after IV administration was the only pharmacokinetic values reported by the sponsor. Each value represents a group size of 6 or less patients. The overall average was 0.23 ± 0.015 (mean ± SEM). Serum levels after IM administration were lower than those at comparable time points after IV injection. The relative bioavailability of IM to IV routes of administration is not reported. A visual inspection of the data suggests the relative bioavailability is approximately 50%. The results of the IV portion of the study are presented below:

IV dose, mg/kg	Clearance, ml/h/kg
0.005	0.22 (0.015)
0.025	0.17 (0.021)
0.05	0.3 (0.016)
0.075	0.27 (0.040)

Table of clearance values for various doses of LFA3TIP after IV administration. Mean (SEM)

Study C96-705, 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. Lots ----------.

LFA3-TIF was administered at dose of 0.05 (N = 6), 0.10 (N = 6) or 0.15 (N = 6) mg/kg as a 30-minute infusion to patients with moderate to severe, chronic psoriasis. The study was primarily intended to investigate the tolerability, pharmacokinetics and pharmacodynamics (effect on delayed type hypersensitivity on uninvolved skin) of LFA3TIF (BG9273). The pharmacokinetics are summarized below:

Pharmacokinetic endpoints	Dose 1	Dose 2
Cl, ml/h/kg	0.42	0.38
T1/2 alpha, h	13	13
T1/2 beta, h	200	226

Study C97-707, An Open-label, Single-dose Study to Compare the Pharmacokinetics of BG9712 (LFA-3/IgG1 Fusion Protein) IV Bolus in Healthy Lean and Obese Volunteers and to Estimate the Bioavailability of BG9712 as an IM and SC Injection in Healthy Obese Volunteers. Lot -------.

The purpose of the study was to investigate the pharmacokinetics of LFA3TIF (BG9712) when given as an IV bolus, IM or SC injection at a dose of 0.075 mg/kg. The study population was composed of healthy lean and obese volunteers. Lean subjects had to be within 20% of their ideal body weight. Obese subjects had to be greater than 50% of their ideal body weight.

Subjects were allocated to dosing groups in accordance with the following table:

Group	Population	Number of subjects	Route of administration
1	Lean	6	IV
2	Obese	6	IV
3	Obese	6	IM
4	Obese	6	SC

The bioavailability of the IM relative to the IV bolus was 49% based on AUClast; bioavailability between the SC injection and the IV bolus was 25.7% based on AUClast.

C97-708, LFA3TIP in Moderate to Severe Plaque Psoriasis: Clinical Results from a Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study
The primary objective of this study was to measure the clinical response of LFA3TIP in a when administered once a week IV for 12 weeks. Doses of LFA3TIP (BG9273) were 0.025, 0.075, or 0.15 mg/kg q weekly. Limited sampling was performed in this study. Serum samples were obtained immediately prior to doses 1, 3, 7 (day 43) and 12 (day 78). Also on day 78, a sample was obtained 30 minutes after drug administration. Other samples were collected on weeks 4 and 12 after the final dose of drug. The number of serum samples suitable for pharmacokinetic analysis was low due to time of collection being close to trough and limitations of the assay. Serum levels derived from these time points were incorporated into a ---------- analysis and reported in descriptive statistics that are summarized below. Since a patient's dosage may have been adjusted for reasons of safety, the dosage groups represent the treatment assigned rather than the actual one given over the dosing interval.

Sampling time, N	Placebo	25 ng/kg	75 ng/kg	150 ng/kg
Baseline, N = 50 - 55	22 (62.9)	31 (66.6)	197 (648.1)	145 (625.5)
Prior to 3rd injection, N = 50 - 54	15 (44.8)	509 (373.4)	1724 (1124.4)	2491 (815.8)
Prior to 7th injection, N = 47 - 53	28 (66.4)	716 (1051.5)	1876 (694.4)	2993 (1571.0)
Prior to 12th injection, N = 47 - 51	20 (60.4)	625 (262.3)	1848 (805.0)	2952 (1808.8)
30 min after injection 12, N = 45 - 48	20 (57.7)	1580 (384.2)	5509 (8058.3)	10668 (21609.5)
4 weeks after injection 12, N = 48 - 53	49 (118.8)	234 (242.2)	793 (809.8)	954 (708.7)
12 weeks after injection 12, N = 51 - 56	21 (70.8)	16 (49.8)	91 (327.4)	52 (127.8)

Table of mean serum levels of LFATIP at various treatments and times. Mean (SD) ng/ml.

Study C98-709, 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. Lot ----------. This study determined serum levels and pharmacokinetics of LFA3TIF in psoriatic patients after IV bolus, IM and SC injections. Blood was collected for pharmacokinetic analysis with 24 hours prior to dosing as well as 30 minutes and 4 hours after the first dose; within 24 hours prior to the second, fourth and eighth doses; within 24 hours prior to as well as 30 minutes and 4 hours after the twelfth dose; 1, 2, 4, 8 and 12 weeks after the last dose. For a subset of patients additional samples were collected at 8, 24, 48, 72 hours after the first and last injection of LFA3TIF. As the pharmacokinetic collection plan followed a sparse sampling technique, data were analyzed using ----------. Pharmacokinetic analyses were pooled by the route of administration. For the IV bolus route, clearance was reported to be 0.27 ± 0.05 ml/h/kg and t1/2 276 ± 46 hours; for the IM route, clearance was 0.28 ± 0.05 ml/h/kg and t1/2 259 ± 72 hours; for the SC route, clearance was 0.30 ± 0.05 ml/h/kg and t1/2 262 ± 87 hours. Bioavailability was computed to be 63% for the IM route relative to IV and 57% for the SC route relative to IV. Dosing, numbers of patients in the analysis and routes of administration are summarized below:

Dose, mg/kg	Route	Number pts
0.15	IV bolus	15
0.225	IV bolus	9
0.375	IV bolus	15
0.5	IV bolus	15
0.75	IV bolus	15
0.15	IM	15
0.225	IM	9
0.375	IM	6
0.15	SC	12
0.375	SC	6
0.75	SC	6

C98-710, A Blinded, Multiple-dose Study to Determine the Tolerability of Repeated Courses of LFA3TIP (LFA-3/IgG1 Fusion Protein) in Subjects with Moderate, Moderate to Severe, and Severe Plaque Psoriasis. Lot ---------- (BG9712)

This study was primarily aimed at determining the tolerability of LFA3TIP in patients. A sparse sampling technique was employed to gather limited insight into the pharmacokinetics of the biological product after IV administration of 0.0125, 0.025, 0.075, or 0.150 mg/kg. Pharmacokinetic data were analyzed using ----------. For all doses, clearance was ranged from 0.33 to 0.39 ml/h/kg and t1/2 from 241 to 277 hours. Little difference was observed between the pharmacokinetic endpoints at the various doses studied. The mean and SD for clearance and half-life of three highest doses are presented below:

Dose, mg/kg	Clearance, ml/h/kg	T1/2, h
0.025, N = 12	0.39 ± 0.06	241 ± 20
0.075, N = 37	0.33 ± 0.09	277 ± 75
0.15, N = 68	0.33 ± 0.08	272 ± 49

Table of pharmacokinetic values after IV bolus administration to patients. Mean ± SD.

C99-711, A Randomized, Double-Blind, Comparison of Intravenous Alefacept Versus Placebo in Subjects with Chronic Plaque Psoriasis.

The purpose of this study was to assess the efficacy of LFA3TIF when given weekly at a dose of 7.5 mg in two 12 week courses separated by 12 weeks. Blood samples were collected during the course of the study prior to dosing on days 1 and 78 as well as on days 92, 106, 120, and 162. Two versions of LFA3TIF were used which were --- BG9273 and ---- BG9273. Their pharmacokinetics were measured in 3 cohorts over 2 courses. Values for various pharmacokinetic endpoints were reported as the range of observed means for half-life, the values were 262 hours to 281 hours and clearance they were 0.23 ml/hr/kg to 0.26 ml/hr/kg.

C99-712, A Randomized, Double-Blind, Placebo-Controlled, Dose Comparison Study to Evaluate the Efficacy and Safety of Intramuscular Administration of Alefacept in Patients with Chronic Plaque Psoriasis.

The primary objective of this study was to determine the efficacy of LFA3TIF when given weekly at either 10 or 15 mg IM over a 12 week period. Sampling was performed on days 78, 92, 106, 120 and 162. An absolute bioavailability was reported to be 60% for the IM route of administration. Day 78 pre-dose samples were used to calculate serum steady-state trough values (Cmin). Pharmacokinetic endpoints are summarized below:

Dose, mg	Cmin, ng/ml	Cl, ml/h/kg	T1/2, h
10	1325 (739)	0.45 (0.14)	264 (100)
15	1970 (955)	0.46 (0.14)	270 (79)

Table of pharmacokinetic endpoints after IM administration. Mean (SD)

Martin D. Green, Ph.D.