Name of Sponsor/Company: Astellas Pharma Global Development, Inc. (APGD)		
Name of Finished Product: Amevive®		
Name of Active Ingredient: Alefacept		

SYNOPSIS

Title of Study: A Phase 2, Single-Arm Study to Evaluate the Safety and Pharmacokinetics of Alefacept in Adolescent Subjects with Moderate to Severe Psoriasis

Investigators/Coordinating Investigator:

[redacted]
[redacted]
[redacted]
[redacted], MD
[redacted], MD

Study Center(s): 5 sites in Bulgaria (1), Latvia (2) and the United States (2)

Publication Based on the Study: None

Study Period:
Study Initiation Date (Date of First Enrollment): 14 April 2009

Study Completion Date (Date of Last Evaluation): 15 February 2012

Phase of Development: Phase 2

Objectives: The primary objective of this study was to establish the safety of alefacept when administered to adolescent patients with moderate to severe psoriasis.
The secondary objectives were to determine the pharmacodynamic effect of alefacept on peripheral blood lymphocytes and lymphocyte subsets when administered to adolescent patients; and to determine the pharmacokinetics of alefacept when administered to adolescent patients in a subset of the study population of adolescent patients.

An additional objective was to determine the efficacy of alefacept when administered to adolescent patients with moderate to severe psoriasis.

Methodology: This was a phase 2, single-arm, multicenter study to assess safety and pharmacokinetics of alefacept in adolescent patients with moderate to severe psoriasis. The first 12 patients received weekly intramuscular injections of alefacept based on body weight, up to a maximum of 15 mg per injection for 12 weeks followed by an additional 12-week observation period, according to a weight-based dose regimen.

Number of Patients (Planned, Enrolled and Analyzed): The number of planned patients was 50; difficulty recruiting appropriate patients limited enrollment to 30 patients. All 30 enrolled patients were analyzed for efficacy, pharmacodynamic assessments and safety. Twenty-three patients were included in the pharmacokinetic analysis.

Diagnosis and Main Criteria for Inclusion: Moderate to severe chronic plaque psoriasis involving at least 10% or greater body surface area (where the patient's hand [palm plus digits] represents approximately 1% of

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the body surface area). Male or female patients, aged 12 to 17 years (inclusive), who were candidates for systemic treatment or phototherapy, were otherwise healthy, had completed all standard childhood immunizations and who had signed an Institutional Review Board/Independent Ethics Committee-approved written Informed Consent/Assent and received documentation of privacy according to national regulations. Female patients of child bearing potential had a negative pregnancy test prior to the first dose of alefacept and agreed to practice effective contraception during the study.

Test Product, Dose and Mode of Administration, Batch Numbers:

Test Product: Alefacept

Dose: 0.15 mg/kg up to 15 mg weekly

Mode of Administration: Intramuscular injections

Batch Numbers: Bulk Lot No./ Packaging Lot No.: [redacted]; [redacted]; [redacted]; [redacted]

Duration of Treatment (or Duration of Study, if applicable): 12 weeks

Reference Product, Dose and Mode of Administration, Batch Numbers: Not applicable.

Criteria for Evaluation: Efficacy was evaluated by measuring the Physician's Global Assessment (PGA) Scale; assessment of the percent body surface area (%BSA) affected and treated psoriatic plaques (excluding the scalp) at baseline/day 1 and at weeks 3, 5, 7, 9 and 11 during treatment and at weeks 14, 18 and 24 during the posttreatment period and the change from baseline to the week 14 visit; assessment of Psoriasis Area and Severity Index (PASI) scores at baseline/day 1 and at weeks 3, 5, 7, 9 and 11 during treatment and at weeks 14, 18 and 24 during the posttreatment period and the change and the percent change from baseline to the week 14 visit.

Pharmacokinetic analysis was conducted for the first 12 enrolled patients and repeated at each new dose for the first 12 patients at baseline/day 1, week 4 and week 12/ET alefacept doses at hour 0 (predose), 48 hours, 96 hours and 168 hours. Pharmacodynamics was evaluated by assessing total lymphocytes and lymphocyte subsets (CD3+, CD4+, CD8+, CD127, CD45RO+, CD45RA+ for patient 1-12 and the first 12 patients following any dose adjustment at baseline/day 1 and every week inclusive of week 11 and during the posttreatment period at week 14 and 24 and for patients 13 to 30 at baseline/day 1 and every other week until week 11 and during the posttreatment period at week 14 and 24.

Safety was assessed throughout the study via physical examinations, vital sign measurements, clinical laboratory evaluations, adverse event (AE) recording and anti-alefacept antibody sampling.

Statistical Methods:

Analysis of Primary Efficacy Variable: For the primary efficacy variable, the 7-point PGA scale, success was defined as a score of 6 (almost clear) or 7 (clear) at week 14 posttreatment. The frequency and percentage of patients who succeed in having a score of clear or almost clear was determined along with 95% confidence

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intervals. For the Secondary Analysis, PGA success was summarized by visit and at the end of treatment by frequencies and percentages. Summaries were also provided for the posttreatment period. The proportion of patients with a reduction in PASI of at least 50% and at least 75% from baseline to the end of study was summarized. A subgroup analysis was conducted to determine the frequency and percentage of patients with PGA success by visit by baseline PGA score and distribution of PGA scores by baseline PGA score at each visit and at end of treatment.

Analysis of Secondary Variables: Descriptive statistics were determined for %BSA and PASI at each visit. In addition, a within patient change was calculated as the postbaseline measurement minus the baseline measurement for each postbaseline visit. The percent change from baseline to each postbaseline visit for PASI score was also determined.

Pharmacokinetics: For the initial 12 patients and for the first 12 patients after the dose adjustment, the following week 1, 4 and 12 model-independent pharmacokinetic parameters were estimated: T_{max}, C_{max}, $AUC_{0\text{-}168}$, AUC_{tau} and CL/F.

Pharmacodynamics: Quantitative lymphocyte test results were summarized by treatment group and visit, including both actual results and change from baseline. The number and percentage of patients with CD4+ cell counts < 250 cells/mcL were determined along with a listing of all CD4+ cell count data. Shift tables were created for selected lymphocyte subgroups.

Safety: Adverse events were collected from the initial alefacept injection through week 24 and were coded using MedDRA (version 9.1). Treatment-emergent AEs (TEAEs) were defined as AEs that were reported between the first and last dose day of alefacept plus an additional 56 days. Adverse events were presented by system organ class (SOC) and by preferred term. The incidence rates for TEAE were summarized in tables by frequencies and percentages.

Vital signs, including oral temperature, systolic and diastolic blood pressure and pulse rate, were summarized using number, mean, standard deviation, minimum, maximum and median at each visit. Additionally, a within-patient change was calculated as the postbaseline measurement minus the baseline measurement and summarized for each postbaseline visit including the last visit (week 24/end of study [EOS]). Physical examination findings were provided in a listing. No descriptive statistics were provided. Any pregnancy reported during the study was to be captured as a serious adverse event (SAE), summarized in the SAE table and the AE and pregnancy listings. Clinical laboratory variables (hematology, biochemistry and pharmacodynamic assessments) were summarized (in SI units) for each visit using mean, standard deviation, minimum, maximum and median. Additionally, a within-patient change was calculated as the postbaseline measurement minus the baseline measurement and summarized for each postbaseline visit including the last visit (week 24/EOS). Each laboratory result was classified as low (L), normal (N) or high (H) at each visit according to the laboratory supplied reference ranges. Shift tables of reference range changes from baseline to each treatment visit and posttreatment visit were created.

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Summary of Results/Conclusions:

A total of 30 patients were enrolled into the study [Synopsis Table 1]. Of the enrolled patients, 2 patients discontinued study treatment prematurely due to AEs (10 and 15 mg doses). One of these patients completed the protocol-defined study assessments and the other patient withdrew from the study. The patient population was mostly white (not Hispanic or Latino) [Synopsis Table 2].

Efficacy, Pharmacokinetics, Pharmacodynamics Results:

Efficacy results: PGA success was defined as a score of 6 (almost clear) or 7 (clear) based on the 7-point PGA scale at week 14. Results of the primary analysis of PGA showed success in 8 of 27 (29.6%) patients in all groups (95% CI of 13.8 to 50.2). Success rates among the treatment groups ranged from 0% in the 10 mg fixed dose group to 41.7% in the 0.15 mg/kg up to 15 mg dose group. The number and percentage of patients with a PGA response to treatment defined as success were determined by visit. The highest success rate was reached at week 14 posttreatment in the 0.15 mg/kg up to 15 mg and 15 mg fixed dose groups and was generally maintained through week 24 posttreatment. None of the 4 patients in the 10 mg fixed dose group attained an improvement defined as success.

Mean PASI results showed the greatest improvement from baseline at week 14 in the posttreatment period overall and for all 3 dose groups [Synopsis Table 3]. Mean (SD) change from baseline in PASI scores at week 14 ranged from -6.50 (1.697) in the 10 mg fixed dose group to -12.95 (8.646) in the 15 mg fixed dose group. The overall mean (SD) change from baseline at week 14 in PASI score was -11.08 (6.900). The percentage of patients with decreases in PASI score of ≥ 75% and ≥ 50% were summarized by dose group and study visit. At week 14, 7 of 12 (58.3%) patients in the 0.15 mg/kg up to 15 mg dose group and 7 of 13 (53.8%) patients in the 15 mg fixed dose group had a decrease in PASI of ≥ 75%, while 9 of 12 (75.0%) patients in the 0.15 mg/kg up to 15 mg dose group and 10 of 13 (76.9%) patients in the 15 mg fixed dose group had a decrease in PASI of ≥ 50%. Decreases of at least 50% seen in the 10 mg fixed dose group ranged from 66.7% at week 11 to 33.3% at week 18 posttreatment.

Mean total %BSA results showed the greatest improvement (decrease) from baseline at week 14 in the posttreatment period. At week 14, change in total %BSA ranged from -10.908 in the 0.15 mg/kg up to 15 mg dose group to -19.665 in the 15 mg fixed dose group. The mean (SD) change from baseline in total %BSA for all patients was -15.131 (14.1618). There was wide variability among patients, and results appeared to be driven by a strong response in a subset of patients.

Pharmacokinetic results: The first 12 treated patients received 0.15 mg/kg up to 15 mg, with a maximum permitted dose of 15 mg alefacept, intramuscularly. Mean AUC_{tau} (AUC_{0-168}) was 35356 hr·ng/mL for week 1, 107149 hr·ng/mL for week 4 and 126926 hr·ng/mL for week 12.

The dose was then changed to a fixed dose of 15 mg per injection for patients who weighed at least 50 kg and 10 mg per injection for patients who weighed less than 50 kg, corresponding to doses used in studies of alefacept in adult patients.

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The 11 patients treated after the dose adjustment consisted of 2 patients who received 10 mg and 9 patients who received 15 mg. The mean AUC_{tau} (AUC_{0-168}) for patients who received 10 mg alefacept was approximately 120173 hr·ng/mL for week 1, 290479 hr·ng/mL for week 4 and 250060 hr·ng/mL for week 12. For patients who received 15 mg alefacept, the mean AUC_{tau} was approximately 76472 hr·ng/mL for week 1, 237752 hr·ng/mL for week 4 and 272164 hr·ng/mL for week 12.

For each of weeks 1, 4, and 12, the mean AUC_{0-168} was larger in the 10 mg and 15 mg dose groups than that of the 0.15 mg/kg up to 15 mg dose group. For both the 10 and 15 mg dose groups, the week 4 mean AUC_{0-168} was within the range of 194000 to 434000 hr·ng/mL, which was used for the dose adjustment criterion for the first 12 patients.

Pharmacodynamic results: Mean lymphocyte and lymphocyte subsets remained above the reference ranges throughout the study. Two patients each had 1 CD4+ value below 250 cells/mcL that was reported as an AE; 1 patient, in the 0.15 mg/kg up to 15 mg intramuscular alefacept group, at week 11 and the other patient, in the 15 mg intramuscular alefacept group, at week 24. The majority of patients began and ended the study with lymphocyte values within the reference range. Between the 10 and 15 mg fixed dose groups, 4 patients had normal CD3+, CD4+ and CD8+ counts at baseline and low counts at end of study. No patients in the 0.15 mg/kg up to 15 mg dose group shifted to low lymphocyte values.

The effect of alefacept on mean lymphocytes and lymphocyte subsets was consistent with what has previously been observed in clinical studies in adult patients treated with alefacept. In most patients, mean lymphocyte count and lymphocyte subset counts remained within the reference range. A few patients experienced 1 or more counts in the low range, and for all of these patients, except patients [redacted] and [redacted] in the 15 mg group, counts had returned to normal range by the end of the full 24 week study.

Safety Results:

Overall 24 of 30 patients (80%) experienced at least 1 AE after being treated with alefacept, including 13 patients (43.3%) with AEs judged to be treatment-related [Synopsis Table 4 and Table 5]. There were 2 SAEs, and 2 patients discontinued study treatment due to an AE, 1 of which was judged to be treatment-related [Synopsis Table 4].

The AEs reported with the highest incidence were in Infections and Infestations System Organ Class (SOC), with 12 patients (40.0%) overall and in Skin and Subcutaneous Tissue Disorders SOC, with 10 patients (33.3%) overall [Synopsis Table 5]. The AEs reported with the highest incidence include headache (4 patients, 13.3% overall) and the following: pharyngitis, tracheitis, upper respiratory tract infection, ecchymosis, psoriasis, pharyngolaryngeal pain and body temperature increase (each in 3 patients, 10.0% overall). Given the small sample sizes, AE reporting appeared similar among the 3 dose groups.

The majority of AEs were mild to moderate in severity, with the exception of 1 severe AE of intermittent pruritus, which was reported for Patient [redacted] (in dose group 0.15 mg/kg up to 15 mg) on study day 12 after receiving study treatment injections on days 1 and 8. The patient was treated with hydroxyzine on day 14, and the pruritus recovered on day 15. There was no interruption in study treatment.

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Overall 13 of 30 patients (43.3%) experienced at least 1 AE that was judged to be treatment-related after being treated with alefacept, including 3 (25.0%) patients in the 0.15 mg/kg up to 15 mg dose group, 1 patient (25.0%) in the 10 mg dose group and 9 patients (64.3%) in the 15 mg dose group.

The treatment-related AEs reported with the highest incidence were in Infections and Infestations SOC (7 patients, 23.3% overall), Skin and Subcutaneous Tissue Disorders SOC (6 patients 20.0%, overall) and Investigations SOC (4 patients, 13.3% overall). Treatment-related AEs with the highest incidence included tracheitis and body temperature increased (each in 3 patients 10.0%) and pruritus and pharyngolaryngeal pain (each in 2 patients, 6.7%).

No deaths occurred during this study. Two patients experienced an SAE, which were judged as not related to study treatment. Patient [redacted] a [redacted], was hospitalized for moderate concussion during the posttreatment period (study day 115) after receiving all injections of 15 mg alefacept; the patient recovered on study day 118 and completed study assessments. Patient [redacted] a [redacted], was hospitalized for moderate, intermittent acute psychosis on study day 12 of treatment after receiving 2 injections of 10 mg alefacept; the patient was discontinued by parents from both further study treatment and assessments.

Two patients were permanently discontinued from study treatment, including the patient hospitalized for acute psychosis and Patient [redacted] a [redacted], who developed a nonserious, moderate, possibly treatment-related erythema multiforme on day 53 after receiving 8 injections of 15 mg alefacept; this patient recovered on study day 73. Treatment was permanently suspended and the patient completed protocol-defined assessments.

One patient had moderate, increased ALT and bilirubin after 6 weekly intramuscular injections of 15 mg alefacept, which were reported as AEs. Treatment was suspended for 3 weeks and resumed with resolution of the AEs. Three patients had mild fever of 37.0°C to 37.4°C, which were reported as AEs (body temperature increase > 37.0°C for Latvian sites). Two of these 3 patients, 1 being treated with 10 mg alefacept and 1 with 15 mg, missed weekly injections, with 1 patient due to fever.

There did not appear to be a relationship between exposure to alefacept and the reporting of AEs. No patients became pregnant during this clinical study.

Anti-alefacept antibodies were assessed throughout the study. Overall, 4 patients (13.3%) were positive for anti-alefacept antibodies at baseline across the 3 dose groups. By week 9 and through the end of the study, 6 of 26 patients (23.1%) were positive for anti-alefacept antibodies [Synopsis Table 6].

CONCLUSIONS:

This was the first study of alefacept in adolescents. Alefacept dosing of 0.15 mg/kg up to 15 mg appeared safe and resulted in a week 4 AUC_{tau} below 67% of the week 4 predicted exposure in adults. When alefacept dosing was changed to fixed doses of 15 mg per injection for patients weighing 50 kg or more and 10 mg per injection for patients weighing less than 50 kg, the resulting week 4 AUC_{tau} was within 67% to 150 % of the predicted week 4 mean AUC_{tau} in adults.

Alefacept appeared to be generally well tolerated. There were no deaths or treatment-related SAEs during the study. Only 1 possibly treatment-related AE (erythema multiforme) resulted in discontinuation from the study.

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Treatment-related AEs occurred in approximately half (13 patients) of the 24 patients who experienced at least 1 AE after alefacept treatment. The SOC of Infections and Infestations and Skin and Subcutaneous Tissue Disorders contained the highest incidence of treatment-related AEs, 7 patients and 6 patients, respectively. The only treatment-related AEs to occur in more than 1 patient are tracheitis (3 patients), body temperature increased (3 patients), pruritus (2 patients) and pharyngolaryngeal pain (2 patients). In the 3 patients who experienced 4 AEs of body temperature increased, all of those 4 AEs were mild in severity, episodic in nature and were judged to be possibly related to study treatment. There did not appear to be a relationship between exposure to alefacept and the reporting of AEs. Anti-alefacept antibodies were detected in 6 of 26 patients (23.1%) at the end of the study; however, 4 of 30 patients (13.3%) were positive at baseline. A small number of fluctuations above and below the reference ranges for hematology and chemistry laboratory evaluations were seen across dose groups, but the majority was not clinically significant and no clinically significant trends were noted. Patient monitoring was required for possible treatment-related AEs including fever (3 patients), decreased CD4+ (2 patients) and other lymphocyte subset counts (1 patient) and increased liver enzymes (1 patient).

Date of Report: 30 October 2012

Table 1 Patient Disposition (All Enrolled Patients)

Population	Intramuscular Alefacept			
	0.15 mg/kg to 15 mg (n = 12)	10 mg (n = 4)	15 mg (n = 14)	Total (n = 30)
Full analysis set, n (%)†	12 (100)	4 (100)	14 (100)	30 (100)
Safety analysis set, n (%)‡	12 (100)	4 (100)	14 (100)	30 (100)
Pharmacokinetic analysis set, n (%)§¶	12 (100)	2 (50)	9 (64.3)	23 (76.7)

†All enrolled patients who were administered study drug.

‡All enrolled patients who received at least one dose of study drug. The safety analysis set will be used for all summaries of the pharmacodynamic data.

§The first 12 patients enrolled at each dose level who have serial blood samples drawn and who have sufficient samples to reliably estimate AUC_{tau} after the week 4 dose.

¶Patients [redacted] and [redacted] were excluded from the PKAS in the 10 mg group; Patients [redacted], [redacted], [redacted], [redacted] and [redacted] were excluded from the PKAS in the 15 mg group.

Source: Tables 12.1.1.1 and 12.4.1.1

Table 2 Demographic Characteristics

Parameter	Category/Statistic	Intramuscular Alefacept			
		0.15 mg/kg to 15 mg (n = 12)	**10 mg (n = 4)**	**15 mg (n = 14)**	**Total (n = 30)**
Sex, n (%)	Male	8 (66.7)	2 (50.0)	6 (42.9)	16 (53.3)
	Female	4 (33.3)	2 (50.0)	8 (57.1)	14 (46.7)
Race, n (%)	White	11 (91.7)	3 (75.0)	11 (78.6)	25 (83.3)
	Asian	0	1 (25.0)	1 (7.1)	2 (6.7)
	Other	1 (8.3)	0	2 (14.3)	3 (10.0)
Ethnicity, n (%) †	Not Collected	8 (66.7)	2 (50.0)	5 (35.7)	15 (50.0)
	Not Hispanic or Latino	3 (25.0)	2 (50.0)	5 (35.7)	10 (33.3)
	Hispanic or Latino	1 (8.3)	0	4 (28.6)	5 (16.7)
Age Group, n (%)	12-15 years	4 (33.3)	2 (50.0)	6 (42.9)	12 (40.0)
	16-17 years	8 (66.7)	2 (50.0)	8 (57.1)	18 (60.0)
Age (years)	n	12	4	14	30
	Mean	15.75	14.75	15.50	15.50
Country, n (%)	USA	4 (33.3)	2 (50.0)	8 (57.1)	14 (46.7)
	Latvia	8 (66.7)	2 (50.0)	5 (35.7)	15 (50.0)
	Bulgaria	0	0	1 (7.1)	1 (3.3)
Weight (kg)	n	12	4	14	30
	Mean	69.30	47.55	77.09	70.03
	SD	15.919	1.764	20.406	19.418
	Min	52.0	45.5	51.3	45.5
	Median	67.50	47.50	76.90	66.50
	Max	101.5	49.7	111.0	111.0
Height (cm) ‡	n	0	2	11	13
	Mean		162.50	171.43	170.05
	SD		10.607	8.982	9.373
	Min		155.0	154.3	154.3
	Median		162.50	173.00	170.00
	Max		170.0	188.0	188.0
BMI (kg/m^2) ‡	n	0	2	11	13
	Mean		18.47	27.54	26.15
	SD		3.128	6.182	6.653
	Min		16.3	18.3	16.3
	Median		18.47	27.10	26.06
	Max		20.7	37.1	37.1

FAS: Full analysis set; SAF: Safety analysis set

†United States sites only.

‡Height collected per protocol Amendment 4. BMI computed only for patients with height and weight collected. BMI formula kg/m^2 used for all patients.

Source: Tables 12.1.2.1 and 12.1.2.2

Table 3 PASI Week 14 Posttreatment Results Compared to Baseline (FAS)

Alefacept dose (intramuscular) Visit	n	Results					Change from Baseline				
		Mean	SD	Min	Med	Max	Mean	SD	Min	Med	Max
0.15 mg/kg to 15 mg											
Baseline	12	14.64	6.489	9.0	11.80	28.8	--	--	--	--	--
Week 14 PT	12	4.82	6.064	0	2.10	18.8	-9.83	4.592	-17.9	-9.55	-0.3
10 mg											
Baseline	4	13.75	2.565	10.7	13.75	16.8	--	--	--	--	--
Week 14 PT	2	5.35	3.323	3.0	5.35	7.7	-6.50	1.697	-7.7	-6.50	-5.3
15 mg											
Baseline	14	17.17	8.488	7.4	16.15	31.5	--	--	--	--	--
Week 14 PT	13	4.98	4.357	0	5.10	15.2	-12.95	8.646	-31.5	-11.00	-0.4
Total											
Baseline	30	15.70	7.140	7.4	13.10	31.5	--	--	--	--	--
Week 14 PT	27	4.93	4.977	0	3.50	18.8	-11.08	6.900	-31.5	-9.70	-0.3

--: not applicable; FAS: full analysis set; Med: median; PASI: psoriasis area and severity index; PT: posttreatment

Source: Table 12.3.6

Table 4 Overview of Treatment-emergent Adverse Events (SAF)

Visit	Intramuscular Alefacept			
	0.15 mg/kg to 15 mg (n = 12) n (%)	10 mg (n = 4) n (%)	15 mg (n = 14) n (%)	Total (n = 30) n (%)
Adverse events	8 (66.7)	4 (100.0)	12 (85.7)	24 (80.0)
Drug-related AEs †	3 (25.0)	1 (25.0)	9 (64.3)	13 (43.3)
Deaths	0	0	0	0
Serious AEs	0	1 (25.0)	1 (7.1)	2 (6.7)
Drug-related serious AEs †	0	0	0	0
Adverse events leading to permanent discontinuation of study drug	0	1 (25.0)	1 (7.1)	2 (6.7)
Drug-related AEs leading to permanent discontinuation of study drug	0	0	1 (7.1)	1 (3.3)

AE: adverse event; SAF: Safety analysis set

† AEs are considered drug-related when they are assessed by the investigator as possibly or probably related or have records where the relationship is missing.

Source: Table 12.6.1.1

Table 5 Treatment-emergent Adverse Events by System Organ Class, Preferred Term (SAF)

MedDRA v. 9.1 System Organ Class† Preferred Term	0.15 mg/kg to 15 mg (n = 12) n (%)	10 mg (n = 4) n (%)	15 mg (n = 14) n (%)	Total (n = 30) n (%)
Any AE	**8 (66.7)**	**4 (100.0)**	**12 (85.7)**	**24 (80.0)**
Any treatment-related AE	**3 (25.0)**	**1 (25.0)**	**9 (64.3)**	**13 (43.3)**
Infections and Infestations	**3 (25.0)**	**1 (25.0)**	**8 (57.1)**	**12 (40.0)**
Pharyngitis	1 (8.3)	0	2 (14.3)	3 (10.0)
Tracheitis	0	1 (25.0)	2 (14.3)	3 (10.0)
Upper respiratory tract infection	1 (8.3)	0	2 (14.3)	3 (10.0)
Furuncle	0	0	1 (7.1)	1 (3.3)
Herpes simplex	0	0	1 (7.1)	1 (3.3)
Nasopharyngitis	0	0	1 (7.1)	1 (3.3)
Otitis media	1 (8.3)	0	0	1 (3.3)
Respiratory tract infection viral	1 (8.3)	0	0	1 (3.3)
Skin and Subcutaneous Tissue Disorders	**4 (33.3)**	**0**	**6 (42.9)**	**10 (33.3)**
Ecchymosis	1 (8.3)	0	2 (14.3)	3 (10.0)
Psoriasis	2 (16.7)	0	1 (7.1)	3 (10.0)
Pruritus	1 (8.3)	0	1 (7.1)	2 (6.7)
Acne	0	0	1 (7.1)	1 (3.3)
Erythema multiforme	0	0	1 (7.1)	1 (3.3)
Hyperhidrosis	0	0	1 (7.1)	1 (3.3)
Rash	0	0	1 (7.1)	1 (3.3)
Nervous System Disorders	**2 (16.7)**	**1 (25.0)**	**3 (21.4)**	**6 (20.0)**
Headache	2 (16.7)	0	2 (14.3)	4 (13.3)
Autonomic nervous system imbalance	0	1 (25.0)	0	1 (3.3)
Syncope vasovagal	0	0	1 (7.1)	1 (3.3)
Respiratory, Thoracic and Mediastinal Disorders	**1 (8.3)**	**1 (25.0)**	**4 (28.6)**	**6 (20.0)**
Pharyngolaryngeal pain	0	1 (25.0)	2 (14.3)	3 (10.0)
Dyspnoea	0	0	1 (7.1)	1 (3.3)
Nasal congestion	0	0	1 (7.1)	1 (3.3)
Tonsillar hypertrophy	1 (8.3)	0	0	1 (3.3)
Gastrointestinal Disorders	**2 (16.7)**	**1 (25.0)**	**2 (14.3)**	**5 (16.7)**
Vomiting	1 (8.3)	0	1 (7.1)	2 (6.7)
Abdominal discomfort	0	1 (25.0)	0	1 (3.3)
Dental caries	1 (8.3)	0	0	1 (3.3)
Diarrhoea	0	0	1 (7.1)	1 (3.3)
Injury, Poisoning and Procedural Complications	**1 (8.3)**	**1 (25.0)**	**2 (14.3)**	**4 (13.3)**
Excoriation	1 (8.3)	1 (25.0)	0	2 (6.7)
Concussion	0	0	1 (7.1)	1 (3.3)
Joint injury	0	0	1 (7.1)	1 (3.3)
Sunburn	0	1 (25.0)	0	1 (3.3)
Thermal burn	0	1 (25.0)	0	1 (3.3)

Table continued on next page

Table 5 continued

MedDRA v. 9.1 System Organ Class† Preferred Term	**0.15 mg/kg to 15 mg (n = 12) n (%)**	**10 mg (n = 4) n (%)**	**15 mg (n = 14) n (%)**	**Total (n = 30) n (%)**
Investigations	**0**	**1 (25.0)**	**3 (21.4)**	**4 (13.3)**
Body temperature increased	0	1 (25.0)	2 (14.3)	3 (10.0)
Alanine aminotransferase increased	0	0	1 (7.1)	1 (3.3)
Blood bilirubin increased	0	0	1 (7.1)	1 (3.3)
CD4+ lymphocytes decreased	0	0	1 (7.1)	1 (3.3)
Musculoskeletal and Connective Tissue Disorders	**0**	**0**	**3 (21.4)**	**3 (10.0)**
Back pain	0	0	1 (7.1)	1 (3.3)
Musculoskeletal discomfort	0	0	1 (7.1)	1 (3.3)
Musculoskeletal stiffness	0	0	1 (7.1)	1 (3.3)
Myalgia	0	0	1 (7.1)	1 (3.3)
General Disorders and Administration Site Conditions	**1 (8.3)**	**0**	**1 (7.1)**	**2 (6.7)**
Asthenia	0	0	1 (7.1)	1 (3.3)
Vessel puncture site bruise	1 (8.3)	0	0	1 (3.3)
Reproductive System and Breast Disorders	**0**	**1 (25.0)**	**1 (7.1)**	**2 (6.7)**
Dysmenorrhoea	0	0	1 (7.1)	1 (3.3)
Menstruation delayed	0	1 (25.0)	0	1 (3.3)
Ear and Labyrinth Disorders	**1 (8.3)**	**0**	**0**	**1 (3.3)**
Eustachian tube dysfunction	1 (8.3)	0	0	1 (3.3)
Eye Disorders	**1 (8.3)**	**0**	**0**	**1 (3.3)**
Vision blurred	1 (8.3)	0	0	1 (3.3)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	**0**	**0**	**1 (7.1)**	**1 (3.3)**
Skin papilloma	0	0	1 (7.1)	1 (3.3)
Psychiatric Disorders	**0**	**1 (25.0)**	**0**	**1 (3.3)**
Acute psychosis	0	1 (25.0)	0	1 (3.3)

AE: adverse event; SAF: Safety analysis set

†Within a system organ class, a patient may have reported more than 1 type of AE.

Source: Table 12.6.1.2

Table 6 Summary of Patients Positive for Anti-alefacept Antibodies (SAF)

Visit	Result	Intramuscular Alefacept			
		0.15 mg/kg to 15 mg (n = 12) n (%)	10 mg (n = 4) n (%)	15 mg (n = 14) n (%)	Total (n = 30) n (%)
Baseline	Positive	2/12 (16.7)	1/4 (25.0)	1/14 (7.1)	4/30 (13.3)
Week 9	Positive	3/12 (25.0)	0/2	3/12 (25.0)	6/26 (23.1)
EOT	Positive	3/12 (25.0)	0/2	3/12 (25.0)	6/26 (23.1)
Week 14 PT	Positive	0	0/1	0/2	0/3
Week 24 PT	Positive	5/11 (45.5)	0/3	2/13 (15.4)	7/27 (25.9)
EOPT	Positive	4/11 (36.4)	0/3	2/13 (15.4)	6/27 (22.2)

EOT: End of treatment; EOPT: End of posttreatment; PT: Posttreatment; SAF: Safety analysis set
Source: Table 12.6.2.1.3