Name of Sponsor/Company: Astellas Pharma Global Development, Inc. (APGD) (formerly Astellas Pharma US, Inc.)		
Name of Finished Product: Not yet named		
Name of Active Ingredient: ASP015K		

SYNOPSIS

Title of Study: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Sequential Group, Multiple-Dose Escalation Study to Evaluate the Efficacy and Safety of ASP015K in Subjects with Moderate to Severe Plaque Psoriasis

Investigators/Coordinating Investigator: [redacted]

Study Centers: 11 centers in the United States

Publication (reference): None

Study Period: Up to 70 days, including screening

Date of first enrollment (Study initiation date): March 23, 2010

Date of last evaluation (Study completion date): July 27, 2011

Phase of Development: 2a

Objectives: The primary objective of this proof-of-concept (POC) study was to explore the efficacy and safety of ASP015K when sequentially dosed starting at oral doses of 10 mg twice daily, escalating to 25 mg twice daily, then 60 mg twice daily, 100 mg twice daily and completing with 50 mg once daily compared to placebo in patients with moderate to severe plaque psoriasis.

Methodology: This was a phase 2a, multicenter, randomized, double-blind, placebo-controlled, sequential group, multiple-dose escalation study. Patients were screened up to 14 days prior to randomization to ensure that they met the eligibility criteria. Approximately 120 patients were randomized into 5 cohorts of 24 patients each (18 active, 6 placebo per cohort). The cohorts consisted of 4 sequential twice daily dosing groups (10 mg bid, 25 mg bid, 60 mg bid and 100 mg bid) and one once daily dosing group (50 mg qd). On day 1/baseline, patients were randomized within each cohort to receive ASP015K or placebo at a ratio of 3:1 (ASP015K:placebo). Patients took study drug for 6 weeks, with the first dose of study drug taken on day 1/baseline. Patients returned for a total of 10 study visits after screening on days 1, 4, 7, 14, 21, 28, 35, 42/early termination (ET), 49 and 56/end of study (EOS). Days 49 and 56/EOS were follow-up visits conducted after treatment had been completed.

The primary measure of efficacy was the Psoriasis Area Severity Index (PASI), which was assessed at all visits, except at screening and on day 4. The Physician Static Global Assessment (PSGA) and percent of body surface area (% BSA) with psoriatic lesions were used as secondary measures of efficacy. Prior to Amendment 3, the Physician Global Assessment (PGA) had been specified as an efficacy variable.

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Pharmacokinetic assessments were performed at all study visits except during screening. Pharmacodynamic assessments, which included a lymphocyte subset analysis and a STAT5 phosphorylation assay, were performed at all visits, except at screening and on day 4. Skin punch biopsies were collected on days 1, 14 and 42/ET. An ImmuKnow® assay [redacted] to evaluate immune cell function was performed on days 1, 14, 42/ET and 56/EOS. For patients with a history of psoriatic arthritis, the status of disease activity was assessed at each study visit except on day 4. A single optional pharmacogenomic blood sample was collected at any time during the study after randomization. Vital sign measurements, physical examinations, electrocardiograms (ECGs), and clinical laboratory testing (chemistry, hematology, urinalysis and lipids profile) were performed at predetermined timepoints.

The decision to escalate to the next cohort (up through and including 100 mg bid) was made after a review of all available patient safety data when all patients in the current cohort had completed at least one week of study drug dosing. A safety data review was not planned to guide enrollment decisions and dosing of patients in the 50 mg once daily cohort.

Number of Patients (planned, enrolled and analyzed): A total of 18 patients per ASP015K treatment group and 30 placebo patients were planned, for a total of 120 patients. A total of 124 patients with moderate to severe plaque psoriasis were enrolled. All patients were included in the Full Analysis Set (FAS) and the Safety Analysis Set (SAF). The Per Protocol Set (PPS) included all patients of the FAS who had no major protocol violations and who had baseline and at least one postbaseline assessment for the primary efficacy endpoint. A total of 118 patients were included in the PPS. The Pharmacokinetic Analysis Set (PKAS) consisted of all patients in the FAS who received active treatment (10, 25, 60, 100 mg bid or 50 mg qd of ASP015K) for whom at least one quantifiable plasma concentration of ASP015K was obtained and for whom the dosing and sampling history was recorded. A total of 92 patients, out of 95 patients who received active treatment, were included in the PKAS. The Pharmacodynamic Analysis Set (PDAS) consisted of all patients who received ASP015K and provided an adequate number of blood and skin biopsy samples for the determination of pharmacodynamic parameters. A total of 122 patients were included in the PDAS. The Biopsy Analysis Set (BAS) consisted of all patients who received study drug, including placebo, and provided skin biopsy samples for the assessment of epidermal proliferation, inflammatory cells, lymphocyte subsets, inflammatory cytokines and inflammatory effector molecules. A total of 120 patients were included in the BAS.

Diagnosis and Main Criteria for Inclusion: Patients or their legally authorized representatives must have signed an Institutional Review Board-approved written informed consent form and privacy language as per national regulations. The patients must have been 18 years of age or older at the time of consent, with a clinical diagnosis of moderate to severe plaque psoriasis for 6 months or longer with at least 10% body surface area (BSA) affected with plaque psoriasis at screening and confirmed at baseline. If female, the patient must have been at least 2 years postmenopausal and/or was surgically sterile per documentation provided by a medical professional. The female patient must not have been pregnant, as documented by a negative serum pregnancy

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test at screening, nor lactating. Male patients must also have agreed to no sperm donation during the study and for 60 days after the last dose of study drug.

Test Product, Dose and Mode of Administration, Batch Numbers: ASP015K 10 mg (bulk tablet lot number C1648001) 25 mg (bulk tablet lot number C1649001) and 50 mg (bulk tablet lot number C1650002) was administered orally once or twice daily for total dosing of 10, 25, 60 and 100 mg twice daily and 50 mg once daily. Matching placebo tablets corresponding to 10 mg, 25 mg (bulk tablet lot number C1646001 for both 10 mg and 25 mg) and 50 mg (bulk tablet lot number C1647002) were also administered orally once or twice daily in a corresponding manner.

Duration of Treatment (or Duration of Study, if applicable): 6 weeks

Reference Product, Dose and Mode of Administration, Batch Numbers: None

Criteria for Evaluation: The PASI score was used as the primary measure of efficacy. This evaluation was performed at all study visits except at screening and on day 4. The head, trunk, upper limbs and lower limbs were assessed separately for erythema, induration (thickness of plaque) and desquamation (scaling). The area covered by lesions on each body region was estimated as a percentage of the total area of that particular body part and a composite score was calculated. The PSGA was used as a secondary measure of efficacy and was performed at all study visits except at screening and on day 4. For this assessment, the physician evaluated the condition of the patient's lesions at the time of the visit for induration, erythema and scaling. The % BSA with psoriatic lesions was a key entry criterion and a secondary measure of efficacy; the assessment was performed at all study visits except on day 4. [redacted]

Pharmacokinetic assessments included ASP015K trough levels assessed at each study visit except screening; and ASP015K levels assessed on day 7 at predose (0 hour), 1, 2, 3, 4.5 and 6 hours postdose. The following pharmacokinetic parameters for day 7 were calculated for each patient: area under the concentration-time curve from the time of dosing to 6 hours postdose (AUC_6), area under the concentration-time curve from the time of dosing to the last measurable concentration (AUC_{last}), area under the concentration-time curve in one dosing interval (AUC_{tau}), predose ASP015K concentration (C_0), C_{max} and time to reach C_{max} (t_{max}). The pharmacokinetic assessments were considered exploratory variables.

Pharmacodynamic assessments were considered exploratory variables and included skin punch biopsies and blood samples. One skin punch biopsy was collected on the target plaque (lesional skin) and one skin punch biopsy was collected on uninvolved (normal-appearing) skin for histopathologic and immunohistochemical evaluations on day 1/baseline. On days 14 and 42/ET, one skin punch biopsy was collected only on the target plaque. The skin punch biopsies were obtained for the histopathologic assessment of epidermal proliferation,

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inflammatory cells, lymphocyte subsets, inflammatory cytokines and inflammatory effector molecules. Blood samples for the evaluation of lymphocyte subsets and for signal transducers and activators of transcription 5 (STAT5) phosphorylation were collected predose on days 1, 7, 14, 21, 28, 35 and 42/ET and at any time during the visit on days 49 and 56/EOS. On day 7, serial STAT5 phosphorylation samples were collected predose (0 hr) and at 1, 2, 3, 4.5 and 6 hours postdose. The blood samples were assayed for STAT5 phosphorylation and for peripheral lymphocyte subset quantitation using flow cytometric analysis for the following lymphocyte subsets: B cells (CD3-|CD19+), natural killer (NK) cells (CD3-|CD16+ and CD3-|CD56+) and T cells (CD3+|CD4+ and CD3+|CD8+). Blood samples were also collected for the evaluation of immune cell function [redacted]

Safety was assessed through adverse event (AE) reporting, 12-lead ECG measurements, vital signs measurements, clinical laboratory evaluations (blood chemistry, hematology including absolute neutrophil count [ANC] values, urinalysis including microscopic analysis, lipids and triglycerides) and physical examination findings.

Statistical Methods: All data processing, summaries and analyses were performed using SAS Version 9.1 or higher on Unix. All statistical comparisons were made using 2-sided tests at the alpha = 0.05 significance level, unless specifically stated otherwise. All null hypotheses were of no treatment difference. Data for placebo patients were pooled, assuming variability was similar across the cohorts. No adjustments were made for multiple comparisons.

The primary clinical criterion for efficacy was based on the change in PASI score from baseline to EOT. It was assumed that the SD of the change in PASI score was equal across the ASP015K dose groups and placebo. To test the null hypothesis of equal changes in PASI score across the ASP015K dose groups and placebo, an analysis of covariance (ANCOVA) was used, with baseline PASI score as a covariate. If the covariate was statistically nonsignificant, the analysis was to have been repeated (as a secondary analysis) without this factor. The analysis was displayed for week 6 as well as for EOT. Pairwise comparisons were made between placebo and each ASP015K dose group. If one or more of the dose groups had not completed the study (due to early discontinuation of the study), a secondary analysis would have been performed with just the dose groups that did complete. Plots of the mean PASI score and mean change in PASI score from baseline to EOT for each ASP015K dose group and placebo were produced. The primary efficacy analysis was performed on the FAS; patients without at least one postbaseline efficacy assessment were not included in this analysis. The same analyses of the primary variable were conducted using the Per-Protocol Set (PPS). Subgroup analyses for age, race, ethnicity and sex categories were explored provided the sample size was sufficient to perform the analysis.

The secondary clinical criteria for efficacy was based on the change from baseline to week 6, week 8, EOT and EOS in PSGA score; the proportion of patients achieving success (a score of 1 [almost clear] or 0 [clear]) as measured by the PSGA at weeks 2, 4, 6 and 8, EOT and EOS; and the change from baseline to week 6, week 8,

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EOT and EOS in % BSA affected with plaque psoriasis. For the change from baseline in PSGA, a null hypothesis of equal changes in PSGA score across the ASP015K dose groups and placebo was tested with an ANCOVA with baseline PSGA score as a covariate. If the covariate was statistically nonsignificant, the analysis was repeated without this factor. Pairwise comparisons were made between placebo and each ASP015K dose group. Plots of the mean PSGA score and mean change in PSGA score from baseline to EOT for each ASP015K dose group and placebo were produced. For analysis of the proportion of patients achieving success, the Cochran-Mantel-Haenszel (CMH) procedure was used, controlling for site with modified ridit scores, to determine whether there was any difference between the PSGA success proportions in each ASP015K dose group and placebo. Pairwise comparisons were made between placebo and each ASP015K dose group (using placebo and one dose group). This analysis was performed on the FAS and could have been performed on the PPS. Sites without at least one success and one failure or with fewer than 16 patients were pooled according to their location. Pooling was finalized at the classification meeting held before unblinding. For the change from baseline in % BSA, a null hypothesis of equal changes in % BSA across the ASP015K dose groups and placebo was tested with an ANCOVA with baseline % BSA as a covariate. If the covariate was statistically nonsignificant, the analysis was repeated without this factor. Pairwise comparisons were also made between placebo and each ASP015K dose group. This analysis was performed on the FAS and the PPS. Plots of the mean % BSA by visit and mean change in % BSA from baseline by visit for each ASP015K dose group and placebo were produced.

[redacted]

For the assessment of pharmacokinetics, individual and mean plasma concentrations for ASP015K were listed and summarized by dose group and time point/visit. Plots of ASP015K trough concentration for each patient and overlay plots of ASP015K trough concentration for each dose group (all visits) were produced. For ASP015K concentration on day 7, standard graphics were produced for individual plasma concentration-time profiles, group mean concentration-time profiles, overlay plots of each dose group mean concentration-time profiles and overlay plots of individual patient concentration-time profiles within a dose group. All graphics were presented in both linear and log-linear scale. Descriptive statistics were used to summarize pharmacokinetic parameters for each dose group on day 7. Dose proportionality for C_{max} was evaluated using a

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power model. The power model was analyzed using linear regression on natural logarithm of C_{max} against natural logarithm of dose on day 7. Dose proportionality was concluded if the 95% CI for the slope included 1.

The pharmacodynamic analyses included assessments of STAT5 phosphorylation, peripheral lymphocyte counts, immune cell function and skin punch biopsies. For STAT5 phosphorylation, individual and mean predose and day 7 STAT5 phosphorylation results were listed and summarized by dose group and time point for Janus kinase 3 (JAK3) activity, percent JAK3 activity and percent JAK3 inhibition. In addition, for day 7, peak percent JAK3 inhibition and time to reach peak percent JAK3 inhibition were listed and summarized. Plots of percent JAK3 activity (linear scale only) for each patient and overlay plots of percent JAK3 activity (linear scale only) for each dose group (all visits) were produced. Similar plots were provided for percent JAK3 inhibition. For percent JAK3 activity on day 7, standard graphics were produced for individual percent JAK3 activity-time profiles, group mean percent JAK3 activity-time profiles, overlay plots of each dose group mean percent JAK3 activity-time profiles and overlay plots of individual patient percent JAK3 activity-time profiles within a dose group. All graphics were in linear scale. Similar plots were provided for percent JAK3 inhibition. Plots of individual patient day 7 percent JAK3 inhibition vs ASP015K plasma concentrations, percent JAK3 inhibition vs ASP015K plasma concentrations using all data on day 7 and percent JAK3 inhibition vs change from baseline in PASI score to EOT were provided. The PASI score plot included Pearson's correlation coefficient or Spearman's rank correlation coefficient if the data were not normally distributed. Individual and mean peripheral lymphocyte subset results and their change from baseline were listed and summarized by dose group and time point for total lymphocyte count, peripheral lymphocyte subsets and regulatory, memory and effector cells. Individual and mean immune cell function assay results were listed and summarized by dose group and time point. Individual and mean skin punch biopsy results were listed and summarized by dose group and time point for epidermal proliferation, inflammatory cells, lymphocyte subsets, inflammatory cytokines, inflammatory effector molecules and histopathologic assessments.

Summary tables were provided for safety variables, including AEs, clinical laboratory test results, vital sign measurements and 12-lead ECG findings. Safety data for individual subjects were provided in the data listings.

Summary of Results/Conclusions:

Population: A total of 124 patients with moderate to severe plaque psoriasis were enrolled; 29 patients were randomized to the placebo group and approximately 19 patients were randomized to each ASP015K treatment group. Six patients (one patient each from the placebo, ASP015K 60 mg twice daily and ASP015K 50 mg once daily groups, and 3 patients from the ASP015K 100 mg twice daily group) were excluded from the PPS due to inadequate treatment duration (< 28 days). For the PKAS, PDAS and BAS, > 94% of patients in each relevant treatment group were included in the analysis populations. Most patients completed treatment (117/124 [94.4%]); 7/124 (5.6%) patients discontinued treatment (3 patients withdrew consent, 3 patients discontinued due to an AE and one patient discontinued for other reasons [decrease from baseline in ANC])

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[Table 1]. Of the 3 patients who discontinued treatment due to an AE, 1/19 (5.3%) patient in the ASP015K 60 mg twice daily group and 1/19 (5.3%) patient in the ASP015K 100 mg twice daily group discontinued due to decreased neutrophil count and 2/17 (11.8%) patients in the ASP015K 100 mg bid group discontinued, one patient due to neutropenia and one due to stomach discomfort and vomiting. A majority of the enrolled patients completed the study (118/124 [95.2%]). Patients could have discontinued treatment, but completed the follow-up visits to complete the study. Six (4.8%) patients discontinued from the study; 5 of these patients had previously discontinued treatment and one patient withdrew consent [redacted]

The majority of the patients were male (97/124 [78.2%]) and most patients were White (116/124 [93.5%]) [Table 2]. Overall, the mean age was 48.10 years, the mean weight was 96.03 kg and the mean body mass index (BMI) was 31.40 kg/m^2. With the exception of age, the demographic and baseline characteristics were not significantly different across the treatment groups. For age, a statistically significant difference among treatment groups at P = 0.0069 was determined from the one-way analysis of variance (ANOVA). Patients in the ASP015K 10 mg twice daily dose group were younger (mean age of 39.11 years) than the other dose groups (mean age range of 46.37 to 53.10 years). The difference in ethnicity across the treatment groups approached statistical significance (P = 0.0527) with a higher percentage of Hispanic patients enrolled in the ASP015K 100 mg twice daily group compared with the other groups.

Study Drug Exposure: Treatment compliance, monitored at each study visit and defined as the percentage of actual doses consumed divided by the expected doses, was > 90% for all patients. Overall, the mean treatment duration was 40.46 days and the median duration of exposure was 42.00 days. There were no meaningful differences among the treatment groups for the treatment compliance or study drug exposure.

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

Efficacy Results: PASI score was used as the primary measure of efficacy. A dose-dependent change from baseline showing an improvement in PASI score was observed over the course of treatment with ASP015K. The primary efficacy criterion was the change in PASI score from baseline to EOT. The overall treatment effect for the primary efficacy endpoint of change from baseline to EOT in PASI score was statistically significant (P < 0.0001) and the improvement in PASI score for each ASP015K dose group was statistically significantly greater than for placebo (all P < 0.05). The results of the ASP015K 50 mg once daily dose group were similar to the ASP015K 25 mg twice daily dose group [Table 3].

PSGA score and % BSA with psoriatic lesions were used as secondary measures of efficacy. Dose-dependent changes from baseline showing an improvement in PSGA score and % BSA with plaque psoriasis were observed over the course of treatment with ASP015K [Table 4 and Table 5]. For PSGA score, the overall treatment effect was statistically significant for the change from baseline to day 42 and EOT (P = 0.0012 at day 42 and P = 0.0002 at EOT). The improvement in the PSGA score for each ASP015K dose group was statistically significantly greater than for placebo (all P values < 0.05) at both day 42 and EOT. The results of

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the ASP015K 50 mg once daily dose group were similar to the ASP015K 25 mg twice daily dose group. For % BSA affected with plaque psoriasis, the overall treatment effect was statistically significant for the change from baseline to each timepoint analyzed (all P values < 0.01). The improvement in the % BSA with plaque psoriasis was statistically significantly greater for the ASP015K 60 mg twice daily, ASP015K 100 mg twice daily and ASP015K 50 mg once daily dose groups compared with placebo (all P values < 0.05) at both day 42 and EOT. Statistically significant differences (P < 0.05) were also observed at the posttreatment follow-up visits on day 56 and EOS for the ASP015K 60 mg twice daily and ASP015K 50 mg once daily groups compared with placebo.

Pharmacokinetic Results: Dose-dependent increases were observed in exposure (C_{max}, AUC_{tau}, AUC_{last} and AUC_6) to ASP015K at doses of 10 mg twice daily to 100 mg twice daily [Table 6]. For the ASP015K 50 mg once daily group, mean C_{max} was approximately 2-fold greater than that observed for the ASP015K 25 mg twice daily group; the mean AUC_{tau} value was approximately 1.7-fold greater compared to AUC_{tau} for the ASP015K 25 mg twice daily group. The median t_{max} for ASP015K ranged from 1.0 hour to approximately 1.8 hours; the mean t_{max} ranged from approximately 1.1 to 1.6 hours. Mean AUC_{tau} values showed exposure to ASP015K increased in a dose-proportional manner over the range of ASP015K 10 to 100 mg twice daily. Dose proportionality for ASP015K was further evaluated using a power model assessing the C_{max} values on day 7. Over the dose range of 10 to 100 mg twice daily, dose proportionality was concluded since the 95% CI for the slope included 1.

Pharmacodynamic Results: ASP015K is a Janus kinase (JAK) inhibitor with moderate selectivity for JAK3. Inhibition of JAK3 inhibits phosphorylation of STAT5, a key intracellular signaling molecule. Phosphorylation of STAT5 is thought to be an integral step in the T cell activation pathway. Peak inhibition of STAT5 phosphorylation increased with increasing doses of ASP015K. JAK3 activity was inhibited in a dose-dependent manner, with a mean inhibition of up to 90% in the ASP015K 100 mg twice daily dose group [Figure 1]. A correlation between plasma concentration of ASP015K and JAK3 inhibition was evident.

Few changes were observed in peripheral lymphocyte subsets (B cells, NK cells, mature T cells, helper T cells or suppressor T cells). No consistent pattern of change was noted with the ImmuKnow assay across dose groups. In skin punch biopsies of psoriatic lesions, histopathologic assessment of marker antigens showed decreases in the mean number of positive staining cells per mm of dermis or epidermis at day 42 (EOT), indicating a general decrease in inflammatory processes in the skin samples [Table 7].

Safety Results: There was no dose-related increase in the incidence of treatment-emergent adverse events (TEAE). For the patients receiving ASP015K, the incidence of TEAE was 57.9%, 42.9%, 36.8% and 64.7% for the 10, 25, 60 and 100 mg twice daily dose groups and 31.6% for the 50 mg once daily dose group. The incidence of TEAE was 37.9% for the placebo group. Overall, 55/124 (44.4%) patients experienced TEAE. No

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deaths or SAE occurred during the study. Overall, 27/124 (21.8%) patients experienced drug-related TEAE. All TEAE were considered to be mild or moderate in severity.

Three patients discontinued the study due to study drug-related TEAE: one patient in the ASP015K 60 mg twice daily group (decreased neutrophil count) and 2 patients in the ASP015K 100 mg twice daily group (one due to neutropenia and one due to stomach discomfort and vomiting). One patient was discontinued from treatment in the ASP015K 100 mg twice daily group (decreased neutrophil count); the change in the neutrophil count was not reported as a TEAE. The patient continued in the clinical trial without taking ASP015K.

The most frequently reported TEAE were in the infections and infestations and gastrointestinal disorders SOC. The incidence of TEAE in the infections and infestations SOC was 17.2% for the placebo group; for the patients receiving ASP015K, the incidence of TEAE in this SOC ranged from 10.5% to 29.4%. The incidence of TEAE in the gastrointestinal disorders SOC was 24.1% in the placebo group; for the patients receiving ASP015K, the incidence of TEAE in this SOC ranged from 5.3% to 19.0%. Nasopharyngitis (8/124 [6.5%]), diarrhea (5/124 [4.0%]) and flatulence (5/124 [4.0%]) were the most frequently reported TEAE. The incidence of TEAE occurring in ≥ 2 patients in any treatment group was similar across the groups [Table 8].

Few clinically meaningful changes from baseline were observed for any of the clinical laboratory parameters (hematology, chemistry or urinalysis) assessed during this study. The data indicated that anemia was not evident in this study, nor were there clinically significant changes in serum creatinine levels. The clinically relevant changes that were observed included the following clinical laboratory parameters: decreased neutrophil counts, increased creatine phosphokinase (CPK), increased total cholesterol, decreased high density lipoprotein and increased triglyceride levels. Of note, the neutrophil decreases were not associated with infections and there was no case of Grade 3 neutropenia.

Of the abnormal clinical laboratory values reported as AE, the most frequently reported preferred term was blood CPK increased, with single events reported in 4 of the treatment groups, including placebo. Two patients discontinued from the study due to an abnormal laboratory value: one patient in the ASP015K 60 mg twice daily group due to decreased neutrophil count and one patient in the ASP015K 100 mg twice daily group due to neutropenia. No clinically relevant changes from baseline were observed for any of the vital sign measurements. No clinically significant findings were observed for safety ECGs.

CONCLUSIONS: The administration of ASP015K to patients with moderate to severe psoriasis resulted in a statistically significant ($P < 0.0001$) improvement in the primary efficacy endpoint of change from baseline to EOT in PASI score. In addition, the improvement in PASI score for each ASP015K dose group was statistically significantly greater than for placebo (all $P < 0.05$). ASP015K, at doses of 10 to 100 mg twice daily or 50 mg once daily, was well tolerated in this study. These results support further evaluation of ASP015K in patients with psoriasis.

Date of Report: 17 February 2012

Table 1 Patient Disposition at End of Treatment and End of Study

Disposition	Placebo (n = 29)	ASP015K 10 mg bid (n = 19)	ASP015K 25 mg bid (n = 21)	ASP015K 60 mg bid (n = 19)	ASP015K 100 mg bid (n = 17)	ASP015K 50 mg qd (n = 19)	Total (n = 124)
End of Treatment							
Treatment discontinuation, n (%)							
No	28 (96.6)	19 (100.0)	21 (100.0)	17 (89.5)	14 (82.4)	18 (94.7)	117 (94.4)
Yes†	1 (3.4)	0	0	2 (10.5)	3 (17.6)	1 (5.3)	7 (5.6)
Completed treatment	28 (96.6)	19 (100.0)	21 (100.0)	17 (89.5)	14 (82.4)	18 (94.7)	117 (94.4)
Primary reason for discontinuation‡, n (%)							
Adverse event	0	0	0	1 (5.3)	2 (11.8)	0	3 (2.4)
Withdrawal by patient	1 (3.4)	0	0	1 (5.3)	0	1 (5.3)	3 (2.4)
Other	0	0	0	0	1 (5.9)¶	0	1 (0.8)
End of Study							
Study termination, n (%)							
No	27 (93.1)	19 (100.0)	21 (100.0)	17 (89.5)	16 (94.1)	18 (94.7)	118 (95.2)
Yes§	2 (6.9)	0	0	2 (10.5)	1 (5.9)	1 (5.3)	6 (4.8)
Completed study	27 (93.1)	19 (100.0)	21 (100.0)	17 (89.5)	16 (94.1)	18 (94.7)	118 (95.2)
Primary reason for termination‡, n (%)							
Withdrawal by patient	1 (3.4)	0	0	2 (10.5)	1 (5.9)	1 (5.3)	5 (4.0)
Not applicable	1 (3.4)	0	0	0	0	0	1 (0.8)

All randomized patients

† Patients who did not complete study treatment

‡ Only the primary reason for discontinuation or termination for each patient was summarized.

§ Patients who did not complete the study

¶ The patient discontinued treatment due to a decrease from baseline in his absolute neutrophil count, recorded as “other” in the case report form and database. The change in neutrophil count was not reported as a treatment-emergent adverse event. The patient continued in the clinical trial without taking ASP015K.

Source: Table 12.1.2.1 and Table 12.1.2.2

Table 2 Summary of Demographics and Baseline Characteristics

Parameter Category/Statistic	Placebo (n = 29)	ASP015K 10 mg bid (n = 19)	ASP015K 25 mg bid (n = 21)	ASP015K 60 mg bid (n = 19)	ASP015K 100 mg bid (n = 17)	ASP015K 50 mg qd (n = 19)	Total (n = 124)	P Value
Sex, n (%)								
Male	21 (72.4)	16 (84.2)	15 (71.4)	14 (73.7)	14 (82.4)	17 (89.5)	97 (78.2)	0.657†
Female	8 (27.6)	3 (15.8)	6 (28.6)	5 (26.3)	3 (17.6)	2 (10.5)	27 (21.8)	
Race, n (%)								
White	28 (96.6)	15 (78.9)	20 (95.2)	18 (94.7)	16 (94.1)	19 (100.0)	116 (93.5)	0.374†
Black or African American	1 (3.4)	3 (15.8)	1 (4.8)	1 (5.3)	1 (5.9)	0	7 (5.6)	
Asian	0	1 (5.3)	0	0	0	0	1 (0.8)	
Ethnicity, n (%)								
Not Hispanic or Latino	23 (79.3)	18 (94.7)	15 (71.4)	12 (63.2)	9 (52.9)	12 (63.2)	89 (71.8)	0.053†
Hispanic or Latino	6 (20.7)	1 (5.3)	6 (28.6)	7 (36.8)	8 (47.1)	7 (36.8)	35 (28.2)	
Age group, n (%)								
< 65 years	23 (79.3)	19 (100.0)	19 (90.5)	18 (94.7)	16 (94.1)	18 (94.7)	113 (91.1)	0.256†
≥ 65 years	6 (20.7)	0	2 (9.5)	1 (5.3)	1 (5.9)	1 (5.3)	11 (8.9)	
Age, years								
Mean	53.10	39.11	47.52	46.37	51.12	49.11	48.10	0.007‡
SD	14.234	10.440	11.129	13.200	11.699	10.593	12.738	
Median	57.00	40.00	46.00	47.00	54.00	52.00	47.50	
Minimum	23.0	23.0	29.0	21.0	22.0	23.0	21.0	
Maximum	79.0	57.0	78.0	69.0	71.0	66.0	79.0	
Weight, kg								
Mean	92.80	100.54	95.02	96.79	94.45	98.24	96.03	0.822‡
SD	16.807	27.180	16.640	24.366	17.777	14.472	19.572	
Median	92.30	94.00	91.40	90.90	99.50	101.60	94.75	
Minimum	63.6	66.4	66.4	55.9	62.7	71.8	55.9	
Maximum	122.5	170.5	126.8	145.0	119.5	125.0	170.5	
BMI, kg/m^2								
Mean	31.23	31.72	32.06	30.76	31.51	31.14	31.40	0.979‡
SD	5.591	4.969	5.426	6.138	4.757	4.230	5.173	
Median	32.47	32.83	31.29	30.48	32.45	30.58	31.78	
Minimum	20.6	19.9	21.0	19.5	23.6	24.1	19.5	
Maximum	39.1	40.3	40.1	40.0	38.9	38.6	40.3	

All randomized patients who received any amount of study drug (Safety Analysis Set)

BMI: body mass index, BMI = weight (kg)/(height [m^2])

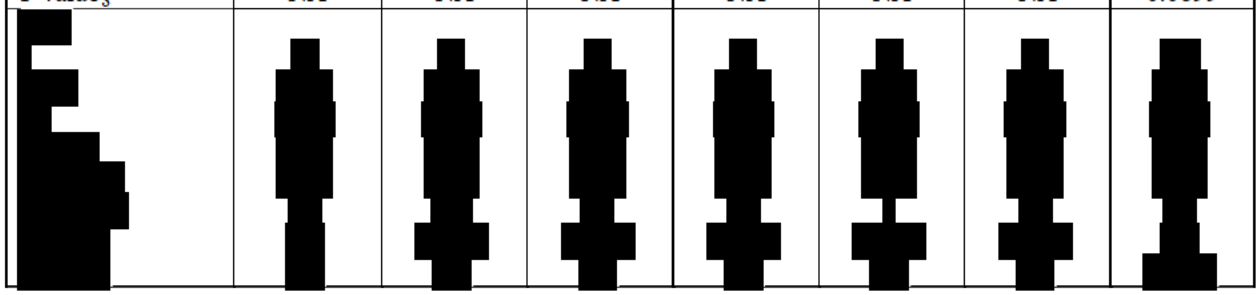
† P value for a discrete variable was from a Fisher's exact test (2-tailed).

‡ P value for a continuous variable was from a one-way analysis of variance.

Source: Table 12.1.3.1 and Table 12.1.3.2

Table 3 Change from Baseline to EOT in PASI Score

Visit† Category/Statistic	Placebo (n = 29)	ASP015K 10 mg bid (n = 19)	ASP015K 25 mg bid (n = 21)	ASP015K 60 mg bid (n = 19)	ASP015K 100 mg bid (n = 17)	ASP015K 50 mg qd (n = 19)	Total (n = 124)
Day 42							
n	27	19	21	17	14	18	116
Mean	-4.44	-6.41	-6.47	-7.79	-12.23	-6.87	-6.94
SD	4.456	2.903	4.803	4.866	6.513	6.967	5.492
Median	-3.70	-6.50	-5.40	-7.50	-12.20	-7.65	-6.60
Minimum	-18.1	-11.6	-18.8	-13.7	-25.8	-16.3	-25.8
Maximum	2.1	0	0.6	1.8	-2.0	6.0	6.0
P value‡	NA	0.0094	0.0480	0.0022	< 0.0001	0.0426	NA
P value§	NA	NA	NA	NA	NA	NA	0.0001
EOT							
n	29	19	21	18	16	19	122
Mean	-4.24	-6.41	-6.47	-8.26	-11.92	-6.59	-6.93
SD	4.383	2.903	4.803	4.999	6.210	6.878	5.497
Median	-3.50	-6.50	-5.40	-8.50	-12.05	-7.60	-6.60
Minimum	-18.1	-11.6	-18.8	-15.3	-25.8	-16.3	-25.8
Maximum	2.1	0	0.6	1.8	-2.0	6.0	6.0
P value‡	NA	0.0053	0.0328	0.0003	< 0.0001	0.0406	NA
P value§	NA	NA	NA	NA	NA	NA	< 0.0001
Day 56							
n	28	19	21	18	17	17	120
Mean	-3.92	-6.09	-4.58	-6.19	-8.24	-7.38	-5.82
SD	6.543	3.576	4.109	5.755	6.095	6.391	5.660
Median	-3.35	-6.20	-4.20	-7.30	-8.60	-7.20	-5.60
Minimum	-25.9	-13.8	-11.5	-16.5	-18.9	-18.6	-25.9
Maximum	6.0	-0.7	2.2	4.6	0	3.7	6.0
P value‡	NA	0.0520	0.4948	0.0790	0.0095	0.0291	NA
P value§	NA	NA	NA	NA	NA	NA	0.0699



All randomized patients who received at least 1 dose of randomized study drug, including placebo (Full Analysis Set)

ANCOVA: analysis of covariance; EOS: end of study; EOT: end of treatment; NA: not applicable; PASI: Psoriasis Area and Severity Index

† EOT was day 42 or the last postbaseline visit during the treatment period. EOS was day 56 or the last follow-up visit after the treatment period.

‡ P value based on pairwise comparisons between each dose group and placebo

§ P value based on one-way ANCOVA with baseline PASI score as a covariate

Source: Table 12.3.1 and Table 12.3.9

Table 4 Change from Baseline in PSGA

Visit† Category/Statistic	Placebo (n = 29)	ASP015K 10 mg bid (n = 19)	ASP015K 25 mg bid (n = 21)	ASP015K 60 mg bid (n = 19)	ASP015K 100 mg bid (n = 17)	ASP015K 50 mg qd (n = 19)	Total (n = 124)
Day 42							
n	25	12	21	17	14	18	107
Mean	-0.48	-1.17	-1.14	-1.35	-1.71	-1.00	-1.07
SD	0.586	0.835	0.727	1.222	1.069	0.907	0.949
Median	0	-1.00	-1.00	-2.00	-2.00	-1.00	-1.00
Minimum	-2.0	-2.0	-3.0	-3.0	-3.0	-3.0	-3.0
Maximum	0	0	0	1.0	0	1.0	1.0
P value‡	NA	0.0121	0.0144	0.0012	< 0.0001	0.0391	NA
P value§	NA	NA	NA	NA	NA	NA	0.0012
EOT							
n	27	13	21	18	16	19	114
Mean	-0.44	-1.15	-1.14	-1.44	-1.69	-0.95	-1.07
SD	0.577	0.801	0.727	1.247	1.014	0.911	0.957
Median	0	-1.00	-1.00	-2.00	-2.00	-1.00	-1.00
Minimum	-2.0	-2.0	-3.0	-3.0	-3.0	-3.0	-3.0
Maximum	0	0	0	1.0	0	1.0	1.0
P value‡	NA	0.0072	0.0093	0.0001	< 0.0001	0.0390	NA
P value§	NA	NA	NA	NA	NA	NA	0.0002
Day 56							
n	26	13	21	18	17	16	111
Mean	-0.50	-1.00	-0.86	-0.94	-1.06	-0.81	-0.83
SD	0.860	0.577	0.910	1.110	0.899	1.047	0.923
Median	0	-1.00	-1.00	-0.50	-1.00	-1.00	-1.00
Minimum	-2.0	-2.0	-3.0	-3.0	-3.0	-3.0	-3.0
Maximum	1.0	0	0	0	0	1.0	1.0
P value‡	NA	0.1031	0.2006	0.1183	0.0605	0.2750	NA
P value§	NA	NA	NA	NA	NA	NA	0.4088
EOS							
n	26	13	21	18	17	18	113
Mean	-0.50	-1.00	-0.86	-0.94	-1.06	-0.78	-0.82
SD	0.860	0.577	0.910	1.110	0.899	1.003	0.918
Median	0	-1.00	-1.00	-0.50	-1.00	-1.00	-1.00
Minimum	-2.0	-2.0	-3.0	-3.0	-3.0	-3.0	-3.0
Maximum	1.0	0	0	0	0	1.0	1.0
P value‡	NA	0.1052	0.1958	0.1170	0.0579	0.3184	NA
P value§	NA	NA	NA	NA	NA	NA	0.3992

All randomized patients who received at least one dose of randomized study drug, including placebo (Full Analysis Set)

Eight patients enrolled before protocol Amendment 3 did not have PSGA data collected and were therefore not included in this analysis.

ANCOVA: analysis of covariance; EOS: end of study; EOT: end of treatment; NA: not applicable; PSGA: Physicians Static Global Assessment

† EOT was day 42 or the last postbaseline visit during the treatment period. EOS was day 56 or the last follow-up visit after the treatment period.

‡ P value based on pairwise comparisons between each dose group and placebo.

§ P value based on one-way ANCOVA with baseline PSGA score as a covariate

Source: Table 12.3.4

Table 5 Change from Baseline in % BSA

Visit† Category/Statistic	Placebo (n = 29)	ASP015K 10 mg bid (n = 19)	ASP015K 25 mg bid (n = 21)	ASP015K 60 mg bid (n = 19)	ASP015K 100 mg bid (n = 17)	ASP015K 50 mg qd (n = 19)	Total (n = 124)
Day 42							
n	27	19	21	17	14	18	116
Mean	-3.16	-5.56	-4.84	-10.87	-11.32	-9.35	-6.93
SD	7.761	4.030	5.274	8.772	8.751	9.354	7.957
Median	-1.00	-5.00	-5.00	-9.90	-11.00	-8.08	-6.60
Minimum	-26.0	-15.0	-13.5	-33.5	-31.0	-36.5	-36.5
Maximum	15.0	1.0	5.0	4.0	0	6.0	15.0
P value‡	NA	0.0953	0.4337	0.0004	0.0004	0.0106	NA
P value§	NA	NA	NA	NA	NA	NA	0.0007
EOT							
n	29	19	21	18	16	19	122
Mean	-3.02	-5.56	-4.84	-11.16	-10.84	-8.86	-6.86
SD	7.565	4.030	5.274	8.595	8.412	9.340	7.897
Median	-1.00	-5.00	-5.00	-9.95	-10.50	-8.00	-6.10
Minimum	-26.0	-15.0	-13.5	-33.5	-31.0	-36.5	-36.5
Maximum	15.0	1.0	5.0	4.0	0	6.0	15.0
P value‡	NA	0.0751	0.3962	< 0.0001	0.0003	0.0117	NA
P value§	NA	NA	NA	NA	NA	NA	0.0003
Day 56							
n	28	19	21	18	17	17	120
Mean	-2.21	-5.48	-5.08	-8.09	-6.07	-10.98	-5.90
SD	7.743	3.583	5.594	7.775	8.054	9.377	7.599
Median	0	-6.00	-5.00	-8.50	-8.00	-10.00	-6.00
Minimum	-28.0	-12.9	-13.5	-26.0	-18.0	-40.5	-40.5
Maximum	11.0	0	6.5	5.0	9.0	0	11.0
P value‡	NA	0.0767	0.1732	0.0060	0.0666	0.0002	NA
P value§	NA	NA	NA	NA	NA	NA	0.0063
EOS							
n	28	19	21	18	17	18	121
Mean	-2.21	-5.48	-5.08	-8.09	-6.07	-10.48	-5.87
SD	7.743	3.583	5.594	7.775	8.054	9.340	7.576
Median	0	-6.00	-5.00	-8.50	-8.00	-9.00	-6.00
Minimum	-28.0	-12.9	-13.5	-26.0	-18.0	-40.5	-40.5
Maximum	11.0	0	6.5	5.0	9.0	0	11.0
P value‡	NA	0.0727	0.1735	0.0058	0.0652	0.0004	NA
P value§	NA	NA	NA	NA	NA	NA	0.0087

All randomized patients who received at least one dose of randomized study drug, including placebo (Full Analysis Set)

ANCOVA: analysis of covariance; % BSA: percent body surface area with psoriatic lesions; EOS: end of study; EOT: end of treatment; NA: not applicable

† EOT was day 42 or the last postbaseline visit during the treatment period. EOS was day 56 or the last follow-up visit after the treatment period.

‡ P value based on pairwise comparisons between each dose group and placebo

§ P value based on one-way ANCOVA with baseline % BSA as a covariate

Source: Table 12.3.7

Table 6 Summary of Plasma Pharmacokinetic Parameters for ASP015K

Parameter Statistic	ASP015K				
	10 mg bid (n = 19)	**25 mg bid (n = 21)**	**60 mg bid (n = 19)**	**100 mg bid (n = 17)**	**50 mg qd (n = 19)**
C_{max}, ng/mL					
n	18	21	18	16	19
Mean	34.248	77.589	194.620	415.620	154.693
SD	14.8895	27.2894	48.8064	125.3355	49.6939
CV	43.476	35.172	25.078	30.156	32.124
Median	33.090	74.190	187.980	394.080	131.990
Min–Max	16.260–82.400	38.280–150.350	113.080–297.120	174.810–621.450	83.030–274.760
SE	3.509	5.955	11.504	31.334	11.401
GM	31.783	73.678	188.757	396.412	147.669
t_{max}, h					
n	18	21	18	16	19
Mean	1.131	1.625	1.251	1.504	1.417
SD	0.6471	0.8449	0.7029	0.9066	0.6156
CV	57.240	52.008	56.189	60.274	43.455
Median	1.000	1.783	1.000	1.042	1.000
Min–Max	0–3.017	0.667–4.167	0.583–3.000	0.983–4.500	0.917–3.033
SE	0.153	0.184	0.166	0.227	0.141
GM	1.099	1.450	1.118	1.348	1.312
AUC_{last}, h•ng/mL					
n	18	21	18	16	19
Mean	100.174	249.079	586.315	1228.279	423.791
SD	39.9899	63.6460	148.3736	341.8799	104.6087
CV	39.920	25.553	25.306	27.834	24.684
Median	94.929	254.552	570.086	1235.518	395.346
Min–Max	54.026–213.210	151.745–383.602	339.553–865.291	483.153–1781.448	262.361–614.874
SE	9.426	13.889	34.972	85.470	23.999
GM	93.800	241.318	568.762	1174.402	411.855
AUC_{tau}, h•ng/mL					
n	16	19	16	15	19
Mean	123.622	308.952	734.642	1442.623	539.809
SD	48.7391	75.4040	181.9736	435.1239	156.4202
CV	39.426	24.406	24.770	30.126	28.977
Median	116.364	319.336	724.326	1505.541	506.464
Min–Max	62.294-244.853	190.505-442.066	400.277-1057.806	573.362-2116.707	343.695-979.645
SE	12.185	17.299	45.493	112.349	35.885
GM	115.365	299.761	712.673	1370.076	520.763
AUC_6, h•ng/mL					
n	18	20	17	16	19
Mean	100.351	253.790	597.992	1223.913	423.662
SD	39.8501	61.3198	148.9300	343.4551	104.7114
CV	39.711	24.162	24.905	28.062	24.716
Median	96.477	257.055	590.289	1227.360	396.321
Min–Max	54.026–213.210	168.794–387.293	343.003–873.099	483.153–1781.448	263.665–614.874
SE	9.393	13.712	36.121	85.864	24.022
GM	94.007	246.849	580.398	1169.701	411.702

Table continued on next page

Parameter Statistic	ASP015K				
	10 mg bid (n = 19)	25 mg bid (n = 21)	60 mg bid (n = 19)	100 mg bid (n = 17)	50 mg qd (n = 19)
AUC_6/dose†, (h•ng/mL)/mg					
n	18	20	17	16	19
Mean	10.035	10.152	9.967	12.239	8.473
SD	3.9850	2.4528	2.4822	3.4346	2.0942
CV	39.711	24.162	24.905	28.062	24.716
Median	9.648	10.282	9.838	12.274	7.926
Min–Max	5.403–21.321	6.752–15.492	5.717–14.552	4.832–17.814	5.273–12.297
SE	0.939	0.548	0.602	0.859	0.480
GM	9.401	9.874	9.673	11.697	8.234

All patients in the Full Analysis Set who received at least one dose of active treatment (10, 25, 60, 100 mg bid or 50 mg qd of ASP015K) and for whom at least one quantifiable plasma concentration of ASP015K was obtained and for whom the dosing and sampling history was recorded (Pharmacokinetic Analysis Set)

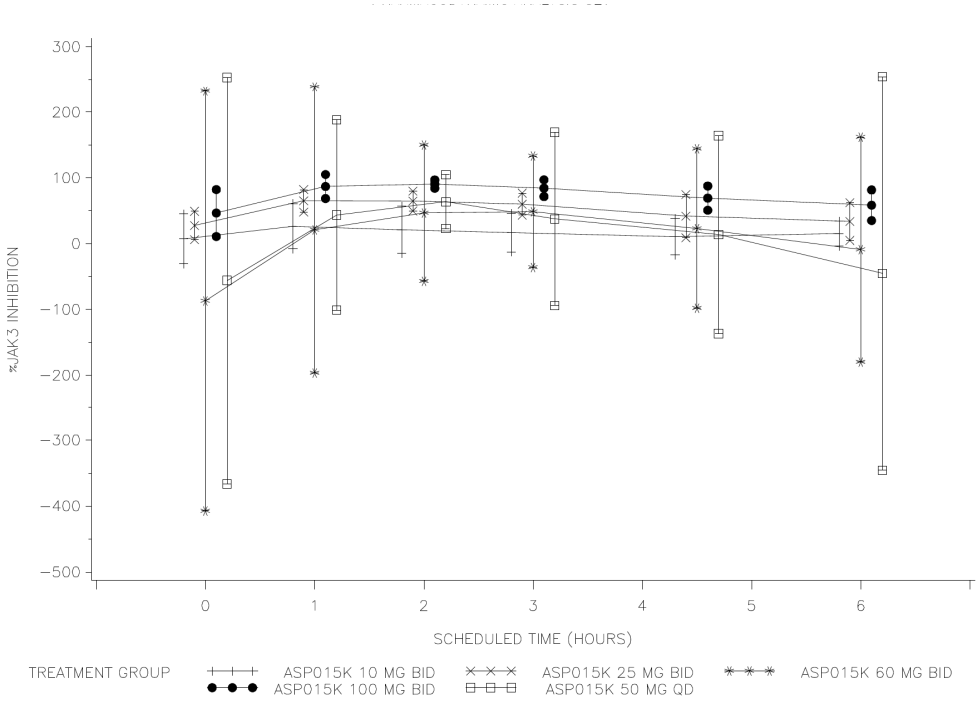
The pharmacokinetic parameters were assessed on day 7.

AUC_6: area under the concentration-time curve from the time of dosing to 6 hours postdose; AUC_{last}: area under the concentration-time curve from the time of dosing to the last measurable concentration; CV: coefficient of variation; GM: geometric mean; Max: maximum: Min: minimum; t_{max}: time to reach C_{max}

† AUC_6 represented exposure after one of the doses for patients receiving twice daily administration of ASP015K; therefore, AUC_6/dose was calculated based on the mg dosage for each group.

Source: Table 12.4.3

Figure 1 Mean (SD) Day 7 % JAK3 Inhibition



All patients who received ASP015K and provided an adequate number of blood and skin biopsy samples for the determination of pharmacodynamic parameters (Pharmacodynamic Analysis Set)

% JAK3:percent Janus kinase 3

Source: Figure 12.5.4.4

Table 7 **Mean (SD) Change from Baseline to Day 42 in Pharmacodynamic Parameters Derived from the Skin Punch Biopsies**

Parameter Statistic	Placebo (n = 27)	ASP015K 10 mg bid (n = 19)	ASP015K 25 mg bid (n = 21)	ASP015K 60 mg bid (n = 17)	ASP015K 100 mg bid (n = 14)	ASP015K 50 mg qd (n = 17)
Ki67, number of positive cells/mm lesion						
Dermis						
Mean	-10.270	-14.995	13.152	-40.059	-69.469	-85.465
SD	60.4971	44.7110	87.0419	185.7843	79.8248	116.6131
Epidermis						
Mean	-61.085	-158.847	-114.829	-208.165	-269.921	-238.476
SD	202.5671	116.8976	175.2088	280.1699	205.4781	182.5199
CD14, number of positive cells/mm lesion						
Dermis						
Mean	-23.411	-27.979	-12.848	-37.929	-66.234	-37.594
SD	119.7758	93.8036	59.9633	92.1822	73.8879	90.3305
Epidermis						
Mean	11.930	-6.168	-2.238	0.024	-9.421	-3.418
SD	75.9629	11.0194	7.4852	21.1403	10.0635	4.6971
CD207, number of positive cells/mm lesion						
Dermis						
Mean	-1.981	-2.189	-5.586	35.529	-24.345	-15.100
SD	17.3927	21.1846	26.3790	101.2990	67.0716	29.6216
Epidermis						
Mean	-4.548	6.237	17.148	12.447	-8.264	0.318
SD	32.1409	26.1641	149.2856	40.7135	21.2328	35.4961
CD11, number of positive cells/mm lesion						
Dermis						
Mean	-139.433	-75.995	-84.200	-193.994	-349.521	-412.035
SD	320.7086	110.5957	400.7897	579.4178	225.5267	552.3663
Epidermis						
Mean	-28.870	-31.747	-59.995	-58.035	-69.437	-53.435
SD	56.8144	31.0390	92.2986	105.3414	39.6756	70.4189
CD3, number of positive cells/mm lesion						
Dermis						
Mean	-26.063	-150.342	-123.719	-155.494	-243.418	-325.941
SD	251.3254	226.8561	286.9622	330.9704	188.2001	424.2741
Epidermis						
Mean	-20.626	-57.842	-49.667	-20.282	-52.508	-34.924
SD	51.2900	61.5790	71.3602	41.4332	51.7229	48.2829
CD8, number of positive cells/mm lesion						
Dermis						
Mean	-17.663	-52.995	-14.643	-63.447	-100.707	-129.835
SD	97.6321	91.7463	166.2822	100.2306	97.2451	228.9979
Epidermis						
Mean	-12.730	-17.589	-23.510	-10.118	-18.294	-20.371
SD	20.1905	28.4059	26.3432	13.5663	15.7912	23.7704

Table continued on next page

Parameter Statistic	Placebo (n = 27)	ASP015K 10 mg bid (n = 19)	 25 mg bid (n = 21)	 60 mg bid (n = 17)	 100 mg bid (n = 14)	 50 mg qd (n = 17)
IFN-g, number of positive cells/mm lesion						
Dermis						
Mean	-21.681	-12.411	-4.500	-109.200	4.698	-120.724
SD	82.7833	26.6010	14.8540	367.8730	111.8777	168.8935
Epidermis						
Mean	-1.189	-0.442	-0.095	-4.400	0.863	-3.694
SD	2.8707	1.0303	0.4260	11.4465	4.7600	5.3717
IL-12, number of positive cells/mm lesion						
Dermis						
Mean	9.648	-0.853	7.914	-3.859	-1.241	-39.318
SD	71.2407	2.3073	27.0621	14.9364	7.5360	149.8338
Epidermis						
Mean	-0.022	-0.242	2.876	-0.271	-0.206	-2.776
SD	7.2850	0.5521	14.2907	1.0445	0.8863	26.5176
IL-22, number of positive cells/mm lesion						
Dermis						
Mean	3.059	55.958	-114.214	-19.582	-35.455	-18.288
SD	122.8884	168.6667	265.9589	221.6974	73.2495	72.1694
Epidermis						
Mean	-1.333	2.053	-3.752	-6.112	-2.886	-0.841
SD	6.5473	5.1629	33.3258	35.8764	9.6914	4.5468
iNOS, number of positive cells/mm lesion						
Dermis						
Mean	0.17	13.66	2.30	-0.15	0	-0.53
SD	0.828	38.155	11.758	0.606	0	2.183
Epidermis						
Mean	-11.700	-11.411	-20.419	-26.418	-21.191	-33.676
SD	60.1569	36.5270	35.0591	38.5494	36.0972	49.3408
TNF-a, number of positive cells/mm lesion						
Dermis						
Mean	0.189	0.379	0.719	-0.559	0.060	0.594
SD	0.7910	2.2100	1.9260	3.9230	1.3495	1.1929
Epidermis						
Mean	0.05	-0.04	0.11	-0.19	0.04	0.04
SD	0.214	0.146	0.332	0.536	0.139	0.086
Epidermal thickness, mm						
Mean	-0.041	-0.091	-0.048	-0.094	-0.124	-0.075
SD	0.0860	0.0927	0.0894	0.1007	0.0667	0.0668

All patients who received study drug, including placebo, and provided skin biopsy samples for the assessment of epidermal proliferation, inflammatory cells, lymphocyte subsets, inflammatory cytokines and inflammatory effector molecules (Biopsy Analysis Set)

IL: interleukin; IFN-g: interferon gamma; iNOS: inducible nitric oxide synthase; TNF-a: tumor necrosis factor alpha

Source: Table 12.5.1

Table 8 TEAE Occurring in ≥ 2 Patients by SOC and Preferred Term

MedDRA (v. 9.1) SOC† Preferred term	Placebo (n = 29)	ASP015K 10 mg bid (n = 19)	ASP015K 25 mg bid (n = 21)	ASP015K 60 mg bid (n = 19)	ASP015K 100 mg bid (n = 17)	ASP015K 50 mg qd (n = 19)	Total (n = 124)
	n (%)						
Any TEAE occurring in ≥ 2 patients in any group	**9 (31.0)**	**9 (47.4)**	**8 (38.1)**	**6 (31.6)**	**9 (52.9)**	**5 (26.3)**	**46 (37.1)**
Gastrointestinal disorders							
Diarrhoea	2 (6.9)	1 (5.3)	0	0	1 (5.9)	1 (5.3)	5 (4.0)
Flatulence	1 (3.4)	0	1 (4.8)	1 (5.3)	1 (5.9)	1 (5.3)	5 (4.0)
Dyspepsia	1 (3.4)	0	1 (4.8)	0	0	1 (5.3)	3 (2.4)
Abdominal pain	1 (3.4)	0	1 (4.8)	0	0	0	2 (1.6)
Dry mouth	0	0	2 (9.5)	0	0	0	2 (1.6)
Nausea	0	0	0	0	1 (5.9)	1 (5.3)	2 (1.6)
Stomach discomfort	1 (3.4)	0	0	0	1 (5.9)	0	2 (1.6)
Vomiting	0	0	0	1 (5.3)	1 (5.9)	0	2 (1.6)
General disorders and administration site conditions							
Fatigue	0	0	1 (4.8)	0	0	1 (5.3)	2 (1.6)
Oedema peripheral	0	1 (5.3)	1 (4.8)	0	0	0	2 (1.6)
Pain	0	1 (5.3)	0	0	1 (5.9)	0	2 (1.6)
Infections and infestations							
Nasopharyngitis	3 (10.3)	0	1 (4.8)	1 (5.3)	3 (17.6)	0	8 (6.5)
Postoperative wound infection	0	2 (10.5)	0	0	0	1 (5.3)	3 (2.4)
Upper respiratory tract infection	0	0	0	1 (5.3)	1 (5.9)	1 (5.3)	3 (2.4)
Sinusitis	0	0	1 (4.8)	1 (5.3)	0	0	2 (1.6)
Investigations							
Blood creatine phosphokinase increased	1 (3.4)	1 (5.3)	1 (4.8)	0	1 (5.9)	0	4 (3.2)
Neutrophil count decreased	0	1 (5.3)	0	1 (5.3)	0	0	2 (1.6)
Metabolism and nutrition disorders							
Hyperlipidaemia	0	0	1 (4.8)	0	1 (5.9)	0	2 (1.6)
Musculoskeletal and connective tissue disorders							
Back pain	0	0	0	1 (5.3)	2 (11.8)	0	3 (2.4)
Nervous system disorders							
Headache	1 (3.4)	0	1 (4.8)	1 (5.3)	0	1 (5.3)	4 (3.2)
Psychiatric disorders							
Abnormal dreams	1 (3.4)	0	1 (4.8)	0	0	0	2 (1.6)
Renal and urinary disorders							
Haematuria	0	0	1 (4.8)	0	0	1 (5.3)	2 (1.6)

Table continued on next page

MedDRA (v. 9.1) SOC†	Placebo (n = 29)	ASP015K 10 mg bid (n = 19)	ASP015K 25 mg bid (n = 21)	ASP015K 60 mg bid (n = 19)	ASP015K 100 mg bid (n = 17)	ASP015K 50 mg qd (n = 19)	Total (n = 124)
Preferred term	n (%)						
Respiratory, thoracic and mediastinal disorders							
Pharyngolaryngeal pain	1 (3.4)	1 (5.3)	0	1 (5.3)	0	1 (5.3)	4 (3.2)
Nasal congestion	0	2 (10.5)	0	0	0	0	2 (1.6)
Skin and subcutaneous tissue disorders							
Acne	0	0	0	0	3 (17.6)	0	3 (2.4)
Dermatitis contact	2 (6.9)	1 (5.3)	0	0	0	0	3 (2.4)

All randomized patients who received any amount of study drug (Safety Analysis Set)

TEAE: treatment-emergent adverse event

† Within an SOC, a patient may have reported more than one type of adverse event.

Source: Table 12.6.1.11