Study Synopsis

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP2151		
Title of Study: A Phase 2 Dose-Finding Study with ASP2151 in Subjects with Recurrent Episodes of Genital Herpes		
Coordinating Investigators: [redacted], MD, [redacted] and [redacted], MD, [redacted].		
Study Center(s): 26 Centers in the United States		
Publication (reference): There were no publications related to this study at the time of this report.		
Date First Patient Screened: June 15, 2007 **Date First Patient Randomized:** June 21, 2007 **Date Last Patient Evaluated:** August 12, 2008	**Phase of Development:** Phase 2	

Objectives: The primary objective was to compare the safety and efficacy of four (4) different dose regimens of ASP2151 with valacyclovir (VACV) and placebo in the acute treatment of recurrent genital herpes simplex virus (HSV) infection.

Secondary objectives were to characterize the pharmacokinetics of ASP2151 in the study population and to explore pharmacokinetic-pharmacodynamic (PK-PD) relationships. Note: Results of pharmacokinetic assessments will be reported separately in a supplementary report.

Methodology: This was a phase 2, dose-finding, double-blind, double-dummy, randomized, parallel group, active and placebo controlled study comparing the safety and efficacy of four dosing regimens of ASP2151 with placebo and VACV.

Patients were randomized to one of 6 treatment arms: ASP2151 100, 200 or 400 mg every day for 3 days, ASP2151 1200 mg for 1 day, placebo for 3 days, or VACV 500 mg twice daily for 3 days. At the first sign or symptom of a genital herpes recurrence, patients were instructed to obtain swabs of the symptomatic genital area and to initiate self-administered study drug within 6 hours (day 1); thereafter, twice-daily swabs (one patient self-swab and one clinic swab) were to be taken through day 6. Swab samples were assessed via qualitative viral Polymerase Chain Reaction (PCR) and viral culture. Clinical evaluations were performed on days 1 through 6 (and on days 8 and 10, if the lesions had not resolved by day 6 and day 8, respectively).

Throughout the treatment and follow-up periods, patients completed worksheets, recording the dates and times of symptom assessment, study drug dosing, food intake, and swab collection. End-of-study follow-up assessments of efficacy and safety parameters occurred on day 17 (or earlier for those patients who discontinued prematurely).

Blood samples for pharmacokinetic analysis were drawn at the screening visit and on days 1-4.

Number of Patients:

Planned: 650 (to ensure 300 patients who experienced a recurrence [non-aborted] to be included in the final analysis of the primary endpoint)
Randomized: 695
Evaluable in Full Analysis Set (FAS): Efficacy – 437
Safety – 437

Diagnosis and Main Criteria for Inclusion: Patients with history of ≥4 episodes of symptomatic recurrences in the past 12 months, unless on chronic suppression, as well as positive serology for Herpes Simplex Virus (HSV) at screening.

Test Product, Dose and Mode of Administration: ASP2151 capsules, 100, 200, and 400 mg orally every day for 3 days, and 1200 mg orally for 1 day.

Duration of Study/Treatment: 17 days including 3 days of treatment and a 14-day follow-up period.

Reference Product, Dose and Mode of Administration: Valtrex® (valacyclovir, VACV) 500 mg orally twice daily for 3 days (a standard treatment for the indication under study); placebo orally for 3 days, both over-encapsulated.

Criteria for Evaluation:

Efficacy: *Primary efficacy variables:* Time (hours) to lesion healing as determined by the investigator (i.e., time from initiation of therapy to re-epithelialization of lesions, excluding aborted lesions). Aborted lesions were defined by the presence of prodromal symptoms including pain, tingling, itching, or burning, but failure of lesions to develop beyond the macule/papule stage. Re-epithelialization of lesions (healed lesions) was defined as the resolution of crusts, vesicles, or ulcerations; residual erythema in the absence of the preceding was defined as healed.

During the course of the clinical trial, some patients experienced what appeared to be a second recurrence, which was defined as: any lesion (‘macule/papule’, ‘vesicle/pustule/ulcer’ or ‘crust’) which appeared ≥24 hours after the first lesion healed (‘healed/no sign’ after first lesion).

Any efficacy assessment after the time of a second recurrence was excluded from any time to event analysis and for all efficacy summaries, except for viral shedding. Any efficacy assessment which was not resolved before a second recurrence was censored in time to event analysis.

Secondary efficacy variables: Duration (hours) of pain; duration of any symptoms; severity of symptoms; duration (hours) of viral shedding, length (hours) of the episode; and the proportion of patients in each treatment group with aborted episodes.

Safety: Evaluation of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory values, physical examination findings, and vital signs. Adverse events (AEs) starting at any time between the first dose of study drug through 72 hours after the last dose were classified as treatment-emergent. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 9.1.

Statistical Methods:

Primary efficacy endpoint: A proportional hazards model including treatment, gender, and number of recurrences in the 12 months prior to randomization as independent variables was used to analyze time to lesion healing. Additionally, the median time to lesion healing was estimated by means of the Kaplan-Meier method. The primary analysis was repeated by age, gender and number of recurrences in the 12 months prior to randomization.

Secondary efficacy endpoints: Duration of pain, duration of any symptoms, duration of viral shedding and length of episode were analyzed using methods similar to those used for the primary variable. Both primary and secondary analysis methods for the primary variable were applied to these four secondary variables. Severity of symptoms was summarized by visit and treatment group, with shift tables created to show the change from the baseline value (before the first dose) to the value at each visit. The proportion of patients with aborted episodes was analyzed using a Cochran-Mantel Haenszel test, controlling for gender and number of recurrences in the 12 months prior to randomization.

Safety: For patients who received at least one dose of study drug, the incidence of TEAEs and SAEs were summarized and tabulated for each treatment group by body system, preferred term, and severity. AEs considered by the investigator to be related to treatment, or which led to permanent discontinuation from the study, also were tabulated and summarized. Laboratory values and vital signs were summarized using descriptive statistics, including change from baseline by treatment group and time.

Summary of Results/Conclusions:

Demographics: Of the 437 patients included in the FAS, 70.5% were female and 71.4% were white. Patients' mean age was 39.7 years (range: 18-75 yrs). HSV serology was positive for HSV-1 and HSV-2 in 43.2% of patients, for HSV-2 only in 48.7%, and for HSV-1 only in 7.8%. The mean number of recurrences in the 12 months preceding the study was 6.8 (median: 6.0, with a range of 1-31). No statistically significant between-group differences in baseline/demographic characteristics were observed.

Drug Administration: Most patients (92.9%) took all 6 doses of blinded study drug.

Pharmacokinetic/Pharmacodynamic Results: Results to be included in a separate report at a later date.

Efficacy:

Primary Efficacy Variable: The primary efficacy variable was time to lesion healing; results of analysis using the proportional hazard model are shown below in Synopsis Table 1. The hazard ratio for comparison with placebo was 1.40 (P=0.065) for ASP2151 100 mg, 1.40 (P=0.081) for ASP2151 200 mg, 1.25 (P=0.246) for ASP2151 400 mg, and 1.72 (P=0.007) for ASP2151 1200 mg, indicating statistically significant (at α=0.10) improvement over placebo in the time to lesion healing for the 100 mg, 200 mg, and 1200 mg ASP2151 groups. Additionally, the hazard ratio was 1.42 (P=0.077) for VACV compared to placebo in time to lesion healing. The median time to lesion healing in all ASP2151 dose groups and the VACV group was shown to be at least 20 hours shorter than placebo.

Secondary Efficacy Variables: None of the ASP2151 groups showed a statistically significant improvement over placebo in duration of pain. All ASP2151 groups showed a statistically significant improvement over placebo in duration of viral shedding. There was a statistically significant improvement over placebo in length of episode for all ASP2151 groups except the 200 mg group.

A total of 97 patients had aborted lesions, with the 400 mg ASP2151 group showing the highest incidence (25, 33.3%). Statistically significant treatment group differences (α=0.10) were observed between placebo and all but the 100 mg dose of ASP2151, and between placebo and VACV.

Safety Results:

437 (62.9%) patients out of 695 randomized patients received at least one dose of study drug and were included in the safety analysis. Overall, 28.2%, 31.0%, 22.7%, 31.6%, 31.3%, and 28.4% of patients from the placebo, ASP2151 100 mg, ASP2151 200 mg, ASP2151 400 mg, ASP2151 1200 mg, and VACV 500 mg groups, respectively, experienced TEAEs. Overall, there were 126 TEAEs. Only one patient in the study reported a SAE. The patient who received ASP2151 400 mg experienced pyrexia, tremor and tachycardia, with an outcome of recovered, that were considered by the investigator to have a probable relationship to study drug. The patient discontinued the study permanently because of these events. There were no deaths among patients reported to have taken the study drug.

The body system with the highest overall incidence of AEs was the gastrointestinal system (46/10.5%). Liver chemistry abnormalities were observed in all study arms without any clear dose relationship.

Conclusions:

- The primary endpoint of time to lesion healing for ASP2151 100 mg, 200 mg and 1200 mg was statistically significantly improved over placebo (α=0.10). The median time to lesion healing in all ASP2151 groups and in the VACV group was at least 20 hours shorter than placebo.
- The 400 mg ASP2151 group had the highest proportion of aborted lesions. Except for the 100 mg ASP2151 group, all ASP2151 groups and the VACV group had a statistically significantly higher proportion of aborted lesions compared with placebo (α=0.10).
- There was a statistically significant improvement over placebo in length of episode for all ASP2151 groups except the 200 mg group.
- No statistically significant dose-response relationship was evident for the primary efficacy variable or other efficacy variables for which a dose relationship was assessed.
- The overall incidence of TEAEs was comparable between treatment groups, ranging between 22.7% and 31.6%; the gastrointestinal system being the most common system in which AEs were reported.
- There was no evidence of a significant dose relationship evident for the incidence of AEs or safety laboratory values.

Date of Report: 08 May, 2009

Synopsis Table 1: Hazard Ratio (HR) for Primary Efficacy Variable (Time to Lesion Healing)

Treatment Group	No. Patients†	Median Time to Healing (hrs)	Hazard Ratio vs. Placebo	P-Value	Hazard Ratio vs. VACV	P-Value
Placebo	61	139.8	N/A	N/A	N/A	N/A
100 mg ASP2151	66	119.6	1.40	0.065‡	0.99	0.940
200 mg ASP2151	54	106.2	1.40	0.081‡	0.98	0.927
400 mg ASP2151	50	115.9	1.25	0.246	0.88	0.548
1200 mg ASP2151	47	102.1	1.72	0.007‡	1.21	0.373
500 mg VACV	50	113.9	1.42	0.077‡	N/A	N/A

Population Base: Full Analysis Set

N/A = Not applicable

†Total n=328, excluding 109 patients with aborted lesions or no assessment.

‡Statistically significant difference (alpha=0.10).

Data Source: Tables 12.3.1.1.1.1, 12.3.1.2.1.

Synopsis Table 2: Treatment-Emergent Adverse Events in ≥2% Patients in Any Treatment Group (FAS Population, MedDRA V9.1)

Body System/ Preferred Term	Placebo (N=71)	100 mg ASP2151 (N=84)	200 mg ASP2151 (N=75)	400 mg ASP2151 (N=76)	1200 mg ASP2151 (N=64)	VACV 500 mg BID (N=67)	TOTAL (N=437)
Nausea	7 (9.9%)	4 (4.8%)	2 (2.7%)	1 (1.3%)	1 (1.6%)	2 (3.0%)	17 (3.9%)
Diarrhoea	0 (0.0%)	5 (6.0%)	2 (2.7%)	4 (5.3%)	0 (0.0%)	2 (3.0%)	13 (3.0%)
Dry Mouth	0 (0.0%)	1 (1.2%)	0 (0.0%)	3 (3.9%)	0 (0.0%)	0 (0.0%)	4 (0.9%)
Vomiting	0 (0.0%)	2 (2.4%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	3 (0.7%)
Headache	3 (4.2%)	4 (4.8%)	5 (6.7%)	5 (6.6%)	1 (1.6%)	6 (9.0%)	24 (5.5%)
Dizziness	0 (0.0%)	1 (1.2%)	1 (1.3%)	1 (1.3%)	2 (3.1%)	1 (1.5%)	6 (1.4%)
Somnolence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	2 (3.0%)	3 (0.7%)
Herpes Simplex†	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	2 (3.0%)	3 (0.7%)
Influenza	0 (0.0%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	3 (0.7%)
Arthralgia	2 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
Back Pain	2 (2.8%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	4 (0.9%)
Fatigue	0 (0.0%)	1 (1.2%)	0 (0.0%)	3 (3.9%)	0 (0.0%)	0 (0.0%)	4 (0.9%)
Pyrexia	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.6%)	0 (0.0%)	0 (0.0%)	2 (0.5%)

†All were episodes of oral HSV, not genital.

Source: Table 12.6.1.2.