SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: Not Available		
Name of Active Ingredient: ASP2151		

Title of Study:
Dose-finding Study of ASP2151 in Subjects with Herpes Zoster
A Multi-center, Randomized, Double-blind, Valacyclovir Hydrochloride-controlled, Parallel-group, Comparative Study

Medical Consultant:
[redacted]

Study Center: 53 centers in Japan

Publication (reference): None

Study Period:	**Phase of Development:**
Date of first informed consent: 13 November 2007 Date of last post-study evaluation: 1 September 2008	2

Objectives: To investigate the efficacy and safety of 3 different doses of ASP2151 (100 mg, 200 mg and 400 mg), as compared to valacyclovir hydrochloride in subjects with herpes zoster, and to determine the recommended clinical dose.

Methodology: This study was a multicenter, double-blind, double-dummy, parallel-group comparative study. The study drug was orally administered for 7 days, once daily in the ASP2151 groups at a dose of 100 mg, 200 mg or 400 mg, and three times daily in the valacyclovir (VACV) group at a dose of 1000 mg, and the efficacy and safety of the 3 doses of ASP2151 were assessed and compared with that of VACV.

Planned Sample Size: 400 subjects in total, 100 subjects per group (360 subjects in total, 90 subjects per group, as the analysis population)

Diagnosis and Main Criteria for Inclusion/Exclusion:
Subjects with diagnosed herpes zoster who satisfied all of the following criteria were enrolled:

1. Subjects aged ≥ 20 years and < 80 years on the day informed consent is obtained;
2. Subjects to whom the study drugs can be orally administered within 72 hours after the onset of rash due to herpes zoster;
3. Subjects in whom protocol-specified observations and assessments are considered possible; and
4. Subjects who have given written informed consent.

Subjects who corresponded to any of the following criteria based on the baseline tests/observations were excluded:

1. Subjects in whom the full therapeutic effect of oral antiviral agents cannot be expected;
2. Subjects with extremely compromised immune function due to underlying diseases, treatment with immunosuppressive agents etc., or radiotherapy;
3. Subjects with a serious underlying disease that corresponds to Grade 3 by the "Severity Grading Criteria for Adverse Drug Reactions" (Appendix to Notification No. 80 of

Safety Division, Pharmaceutical Affairs Bureau, MHW 29 June 1992);

4. Subjects who were found to correspond to the following criteria for clinical laboratory tests performed within 2 weeks (14 days) before written informed consent is obtained;
   - Subjects with either aspartate aminotransferase [AST] [glutamic oxaloacetic transaminase (GOT)] or alanine aminotransferase [ALT] [glutamic pyruvic transaminase (GPT)] of ≥ 100 IU/L
   - Subjects with serum creatinine of ≥ 1.5 mg/dL
5. Subjects with concurrent malignant tumors, or those with a history of malignant tumors within the past 5 years;
6. Subjects who used other antiviral drugs (including interferon, anti-influenza drugs and anti-human immunodeficiency virus [HIV] drugs) or immunoglobulin preparations within 2 weeks (14 days) before giving written informed consent;
7. Subjects in whom crusting is clearly observed at the main herpes zoster lesions (subjects in whom only slight crusting at a part of the lesions is observed can be enrolled in the study);
8. Subjects in whom other cutaneous lesions are present at the same site as herpes zoster lesions and appropriate assessment of the study lesions is considered impossible;
9. Subjects with a history of herpes zoster;
10. Subjects who had been inoculated with varicella vaccine in the past 20 years;
11. Subjects with acquired immunodeficiency syndrome (AIDS) or HIV infection;
12. Subjects with a history of serious hypersensitivity or hypersensitivity to ACV and/or VACV;
13. Women who are pregnant or possibly pregnant, lactating mothers, those who wish to become pregnant during the study period, or women in whom the possibility of pregnancy cannot be ruled out based on the pre-treatment pregnancy test results etc. at baseline observation;
14. Subjects who are currently participating in another clinical or post-marketing clinical study, or those who have participated in another clinical or post-marketing clinical study within 12 weeks (84 days) before giving written informed consent; or
15. Other subjects who in the opinion of the investigators are ineligible for the study.

Study Drug, Dose and Mode of Administration, Lot Numbers:

1. Test Drug

Code name: ASP2151 (INN: amenamevir)

Dosage form: ASP2151 100 mg tablets, ASP2151 200 mg tablets, ASP2151 100 mg placebo tablets, and ASP2151 200 mg placebo tablets (lot number: [redacted])

Contents: ASP2151 100 mg and 200 mg tablets contain 100 mg and 200 mg of ASP2151, respectively. Placebo tablets were indistinguishable in appearance from the corresponding active drugs, but do not contain ASP2151.

Dose:

ASP2151 100 mg group: 100 mg/day as ASP2151

ASP2151 200 mg group: 200 mg/day as ASP2151

ASP2151 400 mg group: 400 mg/day as ASP2151

ASP2151 was orally administered once daily after breakfast in all the dose groups.

2. Comparator Drug

INN: valacyclovir hydrochloride

Dosage form: valacyclovir hydrochloride 500 mg tablets and valacyclovir hydrochloride

500 mg placebo tablets (lot number: [redacted])
Contents: valacyclovir hydrochloride 500 mg tablets ([redacted]), which contain 556 mg of valacyclovir hydrochloride (500 mg of VACV), were purchased on the market, and the corresponding placebo tablets were manufactured by Astellas Pharma Inc.
Dose:
VACV group: 3000 mg/day as VACV
VACV (1000 mg/dose) was orally administered 3 times daily after meals.

Duration of Treatment/Study:
Study treatment period: 7 days
Post-treatment period: 85 days

Criteria for Evaluation:

1. Efficacy

Primary endpoint: Cessation of new lesion formation (the proportion of subjects in whom new lesion formation has ceased by Day 4 after the start of study treatment)
Secondary endpoints: 50% crusting, complete crusting, healing, number of rashes, the presence/absence of erosion/ulcer formation and its degree, cessation of viral shedding, resolution of pain, incidence of postherpetic neuralgia (PHN), and discontinuation due to lack of efficacy

2. Pharmacokinetics

Plasma unchanged drug concentrations

3. Safety

Adverse events (AEs), laboratory test values and vital signs

Statistical Methods:

1. Efficacy

Primary endpoint: The cessation rate of new lesion formation on Day 4 and the 95% confidence interval (CI) were calculated. The non-inferiority and superiority of each ASP2151 group to VACV group were assessed using closed testing procedures. The 95% CI for the difference in the cessation rate of new lesion formation was calculated using the Mantel-Haenszel method. The adjusting factor was the time from the onset of rash to the start of treatment and age.
The occurrence of cessation of new lesion formation was regarded as an event, and the cumulative cessation rate was estimated by the Kaplan-Meier method, and plots were prepared. Each ASP2151 group and VACV group were compared using the log-rank test.
Secondary endpoints: For 50% crusting, complete crusting, healing, cessation of viral shedding and resolution of pain, the occurrence of each endpoint was regarded as an event, and the cumulative rate was estimated by the Kaplan-Meier method, and plots were prepared. Each ASP2151 group was compared with VACV group using the log-rank test.
For the number of rashes, summary statistics were calculated for each assessment day.
Concerning the presence/absence of erosion/ulcer formation and its degree, the frequency was tabulated for each assessment day. The incidence of PHN on Day 91 and the 95% CI were calculated. The rate of discontinuation due to lack of efficacy and its 95% CI were calculated.

2. Pharmacokinetics

Estimation of pharmacokinetic (PK) parameters: Population pharmacokinetic analysis was performed using a nonlinear mixed effect model, and the population mean, fixed effects and random effects of PK parameters were estimated. Summary statistics of PK

parameters were calculated by an empirical Bayes method for each treatment group.
Exploratory PK/pharmacodynamic (PD) Analysis: Exploratory PK/PD analysis was performed to assess the relationship between PK and PD parameters. PK parameters were obtained by simulation using the posthoc PK parameters from the final model. PD parameters were cessation of new lesion formation, 50% crusting, complete crusting, healing and cessation of viral shedding.

3. Safety

Incidence of AEs and drug related AEs were calculated. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 9.1) system organ class (SOC) and preferred term (PT).
Summary statistics for laboratory test results and vital signs were calculated.

Results:

1. Subject disposition and analysis set

The number and percentage of subjects randomized, administered, and completing the study, and the study populations are provided in the following table:

Number (%) of subjects	ASP2151 100 mg	ASP2151 200 mg	ASP2151 400 mg	VACV
Randomized	102	102	97	102
Administered	102	102	97	102
Completed	89	90	89	91
FAS	73 (71.6%)	76 (74.5%)	66 (68.0%)	71 (69.6%)
PPS	71 (69.6%)	73 (71.6%)	65 (67.0%)	69 (67.6%)
SAF	75 (73.5%)	80 (78.4%)	68 (70.1%)	73 (71.6%)
PKAS	75 (73.5%)	80 (78.4%)	68 (70.1%)	73 (71.6%)

2. Demographics and baseline characteristics

Key demographics and baseline characteristics for the FAS are provided in the following table. Approximately 60% of subjects were female in all groups. The percentage of subjects aged 60 years or older was lower in ASP2151 400 mg group compared to other groups. The percentage of subjects with mild herpes zoster was lower in ASP2151 400 mg group than in other groups, and that with fewer numbers of rashes (< 50) on Day 1 was higher in VACV group than in ASP2151 groups. The mean time from the onset of rash to the start of treatment was approximately 50 hours in all groups. Erosion/ulcer was absent in approximately 80% of the subjects in all groups on Day 1. The mean pain score assessed using an 11-point numeric pain scale on Day 1 was 3.7 to 4.0 in all groups.

Variables		ASP2151 100 mg	ASP2151 200 mg	ASP2151 400 mg	VACV
Number of subjects		73	76	66	71
Sex	Male	25 (34.2%)	30 (39.5%)	27 (40.9%)	26 (36.6%)
	Female	48 (65.8%)	46 (60.5%)	39 (59.1%)	45 (63.4%)
Age (year)	<60	41 (56.2%)	43 (56.6%)	31 (47.0%)	40 (56.3%)
	≥60	32 (43.8%)	33 (43.4%)	35 (53.0%)	31 (43.7%)
	Mean ± STD	55.0 ± 15.20	56.4 ± 14.02	57.8 ± 15.35	54.2 ± 15.42
Severity of herpes zoster	Mild	43 (58.9%)	49 (64.5%)	27 (40.9%)	47 (66.2%)
	Moderate	26 (35.6%)	25 (32.9%)	35 (53.0%)	24 (33.8%)
	Severe	4 (5.5%)	2 (2.6%)	4 (6.1%)	0
Number of rashes on Day 1	<50	44 (60.3%)	48 (63.2%)	39 (59.1%)	53 (74.6%)
	≥50, <100	17 (23.3%)	12 (15.8%)	13 (19.7%)	4 (5.6%)
	≥100	12 (16.4%)	16 (21.1%)	14 (21.2%)	14 (19.7%)
	Mean ± STD	68.8 ± 107.05	64.1 ± 75.65	75.6 ± 102.10	55.1 ± 71.60

3. Efficacy

Primary endpoint:

The cessation rate of new lesion formation on Day 4 was 87.7% in ASP2151 100 mg group, 85.5% in ASP2151 200 mg group, 90.9% in ASP2151 400 mg group and 87.3% in VACV group. The 95% CIs of the difference in the cessation rate of new lesion formation between ASP2151 groups (100 mg, 200 mg and 400 mg) and VACV group were greater than −20%, indicating non-inferiority in all ASP2151 groups to VACV group, but no superiority was detected.

For the cumulative cessation rate of new lesion formation, there was no significant difference between the 4 groups by overall log-rank test (P=0.9033), and no significant difference was found in any comparison between each ASP2151 group and VACV group by paired log-rank test (P values when compared to VACV group: 0.5196 in ASP2151 100 mg group, 0.5587 in ASP2151 200 mg group and 0.6466 in ASP2151 400 mg group).

Closed procedure	Cessation rate		95% CI of difference in cessation rates	Non-inferiority	Superiority
	ASP2151 group	VACV group			
1. ASP2151 400 mg vs. VACV	90.9% (60/66)	87.3% (62/71)	(-5.85%, 14.51%)	Yes	No
2. ASP2151 200 mg vs. VACV	85.5% (65/76)	87.3% (62/71)	(-13.16%, 9.39%)	Yes	No
3. ASP2151 100 mg vs. VACV	87.7% (64/73)	87.3% (62/71)	(-10.86%, 10.70%)	Yes	No

Secondary endpoints:

- For the cumulative rates of 50% crusting, complete crusting, healing, cessation of viral shedding, and resolution of pain, there was no significant difference between the 4 groups by overall log-rank test, and no significant difference was found in any comparison between each ASP2151 group and VACV group by paired log-rank test.
- The number of rashes reached a peak on Day 2 or 3 in all groups. It subsequently decreased to 10 or less by Day 8 or 11.
- A peak of the number of subjects with erosion/ulcer formation was found on Day 2 to Day 4, and decreased thereafter in all groups. Most of the erosion/ulcer was mild in degree.
- The incidence of PHN was low in all groups (0.0% to 3.0%).
- The rate of discontinuation due to lack of efficacy was low in all groups (1.5% or low).

3. Pharmacokinetics

- PK in Japanese zoster patients was well described by 1-compartment model with first-order absorption.
- Non-linear PK of ASP2151 could be modeled by dose-dependent decrease in bioavailability.
- Volume of distribution increased with body weight.
- CL decreased in elderly subjects 65 years of age or older.
- No exposure parameter was found to be correlated with any PD endpoints.

4. Safety

The incidence of AEs was almost comparable across the 4 treatment groups. There was no trend indicating an increase in AEs with increasing dose of ASP2151. The majority of AEs were mild in intensity.

Variables	Treatment group	Number and percentage of subjects	95% CI for incidence
Adverse event	ASP2151 100 mg	45/75 (60.0%)	(48.04, 71.15)
	ASP2151 200 mg	44/80 (55.0%)	(43.47, 66.15)
	ASP2151 400 mg	39/68 (57.4%)	(44.77, 69.28)
	VACV	43/73 (58.9%)	(46.77, 70.29)
Serious adverse event	ASP2151 100 mg	2/75 (2.7%)	(0.32, 9.30)
	ASP2151 200 mg	0/80	(0.00, 4.51)
	ASP2151 400 mg	1/68 (1.5%)	(0.04, 7.92)
	VACV	0/73	(0.00, 4.93)
Adverse event leading to permanent discontinuation	ASP2151 100 mg	1/75 (1.3%)	(0.03, 7.21)
	ASP2151 200 mg	0/80	(0.00, 4.51)
	ASP2151 400 mg	1/68 (1.5%)	(0.04, 7.92)
	VACV	0/73	(0.00, 4.93)

- AEs that occurred at a higher incidence of 3% or more than in VACV group were as follows: ASP2151 100 mg group; constipation, blood potassium increased, blood alkaline phosphatase increased, ASP2151 200 mg group; beta-N-acetyl-D-glucosaminidase increased, ASP2151 400 mg group; beta-N-acetyl-D-glucosaminidase increased, blood alkaline phosphatase increased, back pain and dermatitis contact.
- No subject died during this study. SAEs occurred in 2 subjects (uterine cancer and gastric cancer) in ASP2151 100 mg group and 1 subject (appendicitis) in ASP2151 400 mg group. AE which met the criteria for SAEs after the last observation were reported in 1 subject (spinal osteoarthritis) in ASP2151 200 mg group. Neutrophil count decreased that occurred in 1 subject in ASP2151 100 mg group was considered as non-serious by the investigator but serious by the sponsor. Any causal relationship between the study drug and all SAEs was ruled out.
- AEs leading to permanent discontinuation occurred in 2 subjects (neutrophil count decreased in ASP2151 100 mg group and dermatitis contact in ASP2151 400 mg group). Both events were mild or moderate in intensity, and considered as not related to the study drug by the investigators.
- Laboratory test values did not show clinically relevant changes from the baseline in any groups. Moreover, no specific patterns of changes from baseline were noted in individual subjects, either.
- No notable changes from the baseline were observed in blood pressure and pulse rate in any groups.

Conclusions:

ASP2151 at all doses of 100, 200 and 400 mg appeared to have at least similar efficacy compared to VACV in subjects with herpes zoster. There were no apparent safety concerns at doses up to 400 mg in the target population.

Date of Report: 7 March 2017