JDA Japanese Dermatological Association
THE JOURNAL OF DERMATOLOGY

doi: 10.1111/1346-8138.13948 *Journal of Dermatology* 2017; **44**: 1219–1227

ORIGINAL ARTICLE

Amenamevir, a novel helicase–primase inhibitor, for treatment of herpes zoster: A randomized, double-blind, valaciclovir-controlled phase 3 study

Makoto KAWASHIMA,[1] Osamu NEMOTO,[2] Mariko HONDA,[3] Daisuke WATANABE,[4] Juichiro NAKAYAMA,[5] Shinichi IMAFUKU,[6] Toshiyuki KATO,[7] Tsuneo KATSURAMAKI,[7] for the study investigators★

[1]*Department of Dermatology, Tokyo Women's Medical University, Tokyo,* [2]*Sapporo Skin Clinic, Sapporo,* [3]*Dr Mariko Skin and Dermatology Clinic, Yokohama,* [4]*Department of Dermatology, Aichi Medical University, Aichi,* [5]*General Medical Research Center,* [6]*Department of Dermatology, Fukuoka University Faculty of Medicine, Fukuoka,* [7]*Maruho Co., Ltd, Kyoto, Japan*

ABSTRACT

Amenamevir is a potent helicase–primase inhibitor and a novel class of antiviral agent other than nucleoside compounds, such as aciclovir, valaciclovir and famciclovir. This study is the first randomized, double-blind, valaciclovir-controlled phase 3 study to evaluate the efficacy and safety of amenamevir in Japanese patients with herpes zoster when treated within 72 h after onset of rash. A total of 751 patients were randomly assigned to receive either amenamevir 400 mg or 200 mg p.o. once daily or valaciclovir 1000 mg three times daily (daily dose, 3000 mg) for 7 days. The primary efficacy end-point was the proportion of cessation of new lesion formation by day 4 ("day 4 cessation proportion"). The day 4 cessation proportions for amenamevir 400 and 200 mg and valaciclovir were 81.1% (197/243), 69.6% (172/247) and 75.1% (184/245), respectively. Non-inferiority of amenamevir 400 mg to valaciclovir was confirmed by a closed testing procedure. Days to cessation of new lesion formation, complete crusting, healing, pain resolution and virus disappearance were evaluated as secondary end-points. No significant differences were observed in any of the treatment groups. Amenamevir 400 and 200 mg were well tolerated as well as valaciclovir. The proportions of patients who experienced drug-related adverse events were 10.0% (25/249), 10.7% (27/252) and 12.0% (30/249) with amenamevir 400 and 200 mg and valaciclovir, respectively. In conclusion, amenamevir 400 mg appears to be effective and well tolerated for treatment of herpes zoster in immunocompetent Japanese patients.

Key words: amenamevir, helicase–primase inhibitor, herpes zoster, randomized controlled trial, valaciclovir.

INTRODUCTION

Herpes zoster is a painful rash caused by reactivation of latent varicella zoster virus (VZV) in spinal and cranial nerve ganglia. This reactivation occurs when immunity to VZV declines because of aging or immunosuppression.[1–3] Typical clinical symptoms are pain and burning, followed by a rash, which usually crops vesicles on an erythematous base. The rash turns into clusters of blisters, which fill with fluid and then crust over. New lesion formation usually stops within 3–7 days. However, one of the most common and debilitating sequelae of herpes zoster is postherpetic neuralgia (PHN), defined as pain persisting more than 3 months after onset of symptom.[4] Herpes zoster is estimated to occur at lifetime risk levels of approximately 30% in the general population and more than 50% in those of more than 85 years of age.[5,6] In Japan, herpes zoster is one of the 20 most common dermatological disorders among 85 categories.[7] The incidences of herpes zoster and PHN in Japanese adults increase with age, and the rates are 10.9 and 2.1 per 1000 person-years in those aged 50 years or older, respectively.[8]

The mainstay antiviral therapy for VZV infections over the past several decades is synthetic nucleoside compounds, such as aciclovir (ACV) and penciclovir, and their corresponding prodrugs valaciclovir and famciclovir.[2,9] These compounds require phosphorylation by a herpes virus-specified thymidine kinase (TK) and then by host cellular kinases to form biologically active nucleotide triphosphates, which selectively inhibit viral

Correspondence: Tsuneo Katsuramaki, Maruho Co., Ltd, 93 Chudoji Awata-cho, Shimogyo-ku, Kyoto 600-8815, Japan.
Email: katsuramaki_bby@mii.maruho.co.jp
★A list of principal investigators is provided in Supporting Information.
Received 3 April 2017; accepted 22 May 2017.

DNA polymerase and terminate the growing viral DNA chain.[10] A mutation in the TK gene is the main cause of resistance to these anti-herpes nucleoside analogs.[11,12] Although ACV-resistant VZV is considered much less common than ACV-resistant herpes simplex virus (HSV),[13,14] treating immunosuppressed patients, mainly those who have received prolonged ACV therapy, is an emerging concern.[15] Therefore, there remains a clear medical need to develop novel antiviral agents with an alternative mechanism of action. Much attention has been paid to inhibitors of helicase–primase as a target of antiviral agents.[16–18] The herpes virus helicase–primase, one of the essential proteins for virus replication, is a heterotrimeric protein complex that possesses multiple enzymatic activities, including DNA helicase, ssDNA-dependent ATPase and primase, all of which are essential for viral DNA replication and growth.[19,20]

Amenamevir is an oxadiazolephenyl compound and a novel and potent inhibitor of helicase–primase. Amenamevir has *in vitro* antiviral activities against VZV, HSV-1 and HSV-2 that are more potent than those of ACV.[21] A randomized, double-blind, valaciclovir-controlled, dose range-finding study demonstrated that amenamevir 200 and 400 mg were effective and well tolerated for the treatment of herpes zoster in immunocompetent Japanese patients (data not shown). The objective of this study was to compare the efficacy and safety of these two different doses of amenamevir with valaciclovir in patients with herpes zoster.

METHODS

Study design

This was a multicenter, randomized, double-blind, three-arm, parallel-group, phase 3 study in patients with herpes zoster. The study was conducted at 106 sites in Japan from September 2013 to July 2015.

The study protocol and the informed consent form were approved by the institutional review board at each participating study site. All patients gave written informed consent before initiation of any study-specific procedures. The study was conducted in accordance with the ethical principles originating in or derived from the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice Guidelines, and locally applicable laws and regulations. The study was designed and conducted by the sponsor (Maruho Co., Ltd, Kyoto, Japan) in collaboration with the principal investigators. The sponsor monitored study conduct, collected the data and performed the statistical analyses. This study is registered with www. clinicaltrials.gov (NCT01959841).

Patients and treatment

All enrolled patients were men or non-pregnant women between 20 and 80 years of age, who were clinically diagnosed with localized herpes zoster presenting within 72 h after rash onset. The main exclusion criteria were patients not expected to derive a full therapeutic effect of oral antiviral agents, autoimmune disease, compromised immune function due to underlying diseases, treatment with immunosuppressive agents or radiotherapy, concurrent malignant tumors or a history of malignant tumors within the past 5 years, use of other antiviral agents or immunoglobulin (Ig) preparations within 14 days of informed consent, crusting of the main herpes zoster lesions, other cutaneous lesions present at the same site as the herpes zoster lesions, history of herpes zoster, inoculation with a varicella vaccine in the past 20 years or enrolled in a clinical trial for a herpes zoster vaccine.

The participants were randomly assigned in a 1:1:1 ratio to one of the following three treatment groups by computer-generated randomization with sequencing in blocks of six: amenamevir (200 mg or 400 mg once daily for 7 days) or valaciclovir (1000 mg three times daily for seven 7 days). Randomization was stratified according to age (<65 and ≥65 years). The assigned study drug was administrated p.o. in the fed state. Blinding was carried out using double-dummy method. Compliance was assessed by patient diaries, patient interviews and tablet counting at every patient's visit. After the first administration of the study drug on day 1, participants were scheduled to visit on day 2 or day 3, day 4, day 5 or day 6, day 8, day 11, day 15, day 22, day 29, day 57 and day 92 (total of 11 visits).

Study assessments

The study schedule is shown in Figure S1. The primary efficacy end-point was the proportion of cessation of new lesion formation by day 4 ("day 4 cessation proportion"). Secondary end-points related to other cutaneous lesions were days to cessation of new lesion formation, complete crusting and healing. Other secondary efficacy end-points were days to resolution of pain and cessation of viral shedding.

At each visit up to day 29 or the time of discontinuation, the same investigators, if possible, assessed the cutaneous lesions including the number of rashes (erythemas/papulae and vesicle/pustules), widespread eruption, erosion/ulcer formation, new rash formation, crusting, complete crusting and healing.

Pain was assessed on an 11-point self-report numerical rating scale, which was completed up to day 92 or the time of discontinuation. Days to pain resolution were the number of days until pain was judged to have been relieved (the first day of a period during which the pain score remained ≤2 from the last observation). In this study, PHN was defined as pain localized at a previous herpetic lesion on day 92 after starting the study treatment.

Immunoglobulin G- and M-class antibody titers for VZV were screened by enzyme immunoassay using serum obtained on day 1 before the start of treatment. Virus was identified by polymerase chain reaction (PCR) using samples obtained from the cutaneous lesions on day 1 before start of treatment. A shell vial assay was performed to confirm the disease and cessation of viral shedding, if an adequate rash (e.g. vesicles, pustules) was available on day 1 before the start of treatment and any visit from day 2 to day 29. The day of cessation of viral shedding was defined as the first day on which disappearance of VZV was confirmed and subsequent days were negative up to the last day of testing. VZV isolates successfully obtained at any visit from day 1 to day 29 were used to test the sensitivities to amenamevir and ACV using a plaque reduction assay. The

half-maximal (50%) effective concentration (EC_{50}) against the virus was calculated.

Safety was assessed according to the incidence and severity of adverse events (AE), clinical laboratory (hematology, biochemistry and urinalysis), vital signs and electrocardiogram for all participants who received one or more doses of the study drug (safety analysis set, SAS).

Statistical analyses

Sample size was established based on the expected day 4 cessation proportion. We expected 88% of patients in the amenamevir 400 mg and valaciclovir groups to stop forming lesions on day 4 based on a phase 2 study (data not shown). The limit of non-inferiority was set to 10%. To show non-inferiority of amenamevir to valaciclovir under these conditions, with a one-sided alpha level of 0.025 and 90% power, each treatment group should consist of 240 participants. Therefore, this study planned for enrolment of 250 patients/group (total of 750 patients) taking into account patient dropout.

The efficacy was analyzed in the full analysis set (FAS) as primary and the per protocol set (PPS) as secondary based on the originally assigned arms. The FAS was defined as patients who were diagnosed with herpes zoster at the time of case registration, who subsequently received the study drugs, and had any efficacy variable measured. The PPS was defined as the subset of patients in the FAS who met the inclusion criteria, did not meet the exclusion criteria that affected efficacy assessment, did not receive prohibited concomitant drugs/therapies during the period between randomization and day 4 after start of treatment, and who took more than five of the scheduled study drug administrations by day 4 after starting treatment.

The non-inferiority of each amenamevir dose level versus valaciclovir was assessed stepwise using a closed testing procedure. The 95% confidence interval (CI) for the difference between treatment groups regarding the day 4 cessation proportion was calculated using the Mantel–Haenszel method, adjusted by age (<65 and ≥65 years) and time from the onset of rash to the start of treatment (≤24 h, >24 to ≤48 h and >48 to ≤72 h).

The difference in the day 4 cessation proportion between the amenamevir doses and the valaciclovir group was calculated according to the Farrington–Manning test extended to the Mantel–Haenszel type adjustment,[22,23] wherein the non-inferiority margin was set at 10%. If the one-sided *P*-value was less than 0.025 between the amenamevir 400 mg group and the valaciclovir group, non-inferiority of amenamevir 400 mg to valaciclovir was assumed. The analysis was performed in the amenamevir 200 mg group only when non-inferiority of the amenamevir 400 mg to valaciclovir groups was assumed. Similar analyses were performed on the FAS without adjusting for stratified factors and on the PPS to assess stability of the efficacy conclusion. The secondary end-points were days to cessation of new lesion formation, complete crusting, healing, resolution of pain and cessation of viral shedding. The Kaplan–Meier method was used to estimate these time-to-events. Median number of days and the hazard ratio (HR) between the amenamevir groups and the valaciclovir group, and the two-sided 95% CI were obtained using the stratified Cox proportional hazards regression analysis. AE were coded using the Medical Dictionary for Regulatory Activities Japanese Edition version 16.0. All analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC, USA).

RESULTS

Patient disposition and baseline characteristics

A total of 751 patients were randomized, and 750 received one or more doses of the study drug (SAS population). The numbers of participants who completed the study drug administration in the amenamevir 400 and 200 mg and valaciclovir groups were 220, 224 and 226, and the numbers who completed the study were 193, 209 and 206, respectively (Fig. 1). Among the 143 participants who discontinued the study after randomization, major reasons for withdrawal were low platelet count below the lower limit of normal on day 1 (*n* = 26) or day 4 (*n* = 11), use of prohibited/restricted concomitant drug/therapies (*n* = 33, 23.1%), violation of inclusion/exclusion criteria (*n* = 22, 15.4%), withdrawal of consent (*n* = 19, 13.3%) and deviation on a laboratory test defined in the protocol, except platelet count (*n* = 14, 9.8%). The FAS consisted of 735 participants (amenamevir 400 mg group, *n* = 243; amenamevir 200 mg group, *n* = 247; and valaciclovir group, *n* = 245). The reasons for not including the FAS were patients in whom HSV-1 was detected instead of VZV by virus identification test (*n* = 14), did not take any dose of the study drug after randomization (*n* = 1) and no efficacy assessment data after study drug administration (*n* = 1). The PPS consisted of 719 participants after excluding those who received prohibited concomitant drugs/therapies during the period between randomization and day 4 of study treatment (*n* = 3) or those from the FAS with lack of adherence to the study drug (*n* = 13). The reasons for excluding participants from the FAS and PPS are summarized in Table S1.

Baseline patient characteristics in the FAS population were similar across treatment groups (Table 1). More women than men were enrolled in the study. No differences were observed in any of the other baseline characteristics. The mean ages of the amenamevir 400 and 200 mg and valaciclovir groups were 53.0, 52.0 and 52.2 years, respectively. Approximately 28.4%, 27.9% and 27.3% participants were aged 65 years or older in each group, respectively. IgM and/or IgG antibody titers against VZV were positive or equivocal in 99.7% of participants before treatment. VZV was detected in 79.0% of the amenamevir 400 mg group, 81.8% of the 200 mg group and 81.2% of the valaciclovir group by PCR and/or shell vial assay. A total of 312 (41.5%) of VZV isolates were obtained by virus isolation and culture: 107 from the amenamevir 400 mg group, 109 from the amenamevir 200 mg group and 96 from the valaciclovir group. A total of 142 (7.4%) in the FAS population did not take a virological test or the virological test was negative. The proportions of participants who took 10–12 doses during the first 4 days from treatment initiation in the

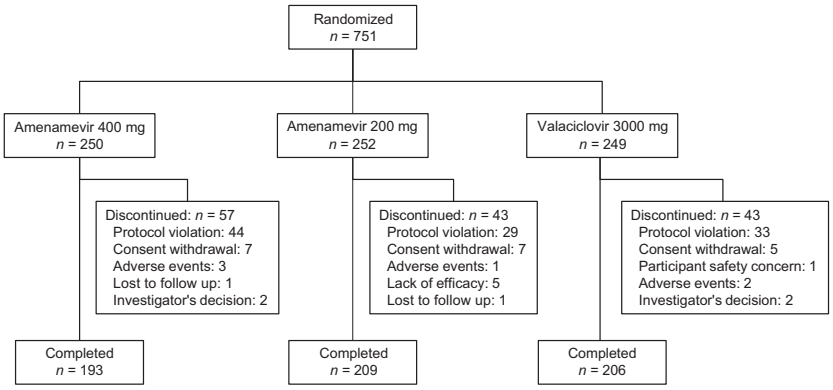

Figure 1. Patient disposition.

amenamevir 400 and 200 mg and valaciclovir groups were 92.2%, 91.1% and 95.1%, respectively.

Efficacy

The day 4 cessation proportions in the amenamevir 400, 200 mg and valaciclovir groups were 81.1%, 69.6% and 75.1%, respectively (Table 2). The 95% CI of the estimated difference in the day 4 cessation proportion between the amenamevir 400 mg and valaciclovir groups was 7.1% (−0.2% to 14.4%). The *P*-value was less than 0.0001, indicating non-inferiority of amenamevir 400 mg to valaciclovir. On the other hand, non-inferiority of amenamevir 200 mg to valaciclovir was not detected ($P = 0.0688$). The 95% CI of the estimated difference in the proportion of the day 4 cessation proportions between the amenamevir 400 and 200 mg groups was 11.8% (4.4–19.1%), and the difference was significant. Sensitivity analyses of the primary end-points were performed in the FAS population without adjusting for stratified factors and in the PPS population, and similar results were obtained (Table S2).

A summary of the secondary end-points is shown in Table 3. The median days to cessation of new lesion formation were 4 days in all groups (Fig. 2). The hazard ratios (HR; 95% CI) for the number of days to cessation of new lesion formation in the amenamevir 400 and 200 mg and valaciclovir groups were 1.06 (0.88–1.28) and 0.92 (0.76–1.11), respectively. The median days to complete crusting were 9 days in the amenamevir 400 mg group, and 8 days in the amenamevir 200 mg and valaciclovir groups. The HR (95% CI) for the days to complete crusting in the amenamevir 400 and 200 mg and valaciclovir groups were 0.99 (0.82–1.20) and 1.08 (0.89–1.30), respectively. In all groups, the median days to healing was 11 days with the HR of 1.02 (0.84–1.23) for 400 mg and 0.99 (0.82–1.20) for 200 mg amenamevir and valaciclovir. The median days to pain resolution were 10 days in the amenamevir 400 mg and valaciclovir groups, and 9 days in the amenamevir 200 mg group. The HR (95% CI) of days to pain resolution in the amenamevir 400 and 200 mg and valaciclovir groups were 1.07 (0.87–1.30) and 1.05 (0.86–1.29), respectively. The median days to virus disappearance was analyzed in patients who reached virus-negative status according to the virus isolation and culture assay or whose samples were not available because of complete crusting or healing, resulting in a median of 5 days in the amenamevir 400 mg group, and 4 days in the amenamevir 200 mg and valaciclovir groups. The HR (95% CI) of days to virus disappearance in the amenamevir 400 and 200 mg and valaciclovir groups were 0.92 (0.69–1.23) and 1.14 (0.85–1.52), respectively. The median days to virus disappearance in only the patients who reached virus-negative status according to the virus isolation and culture assay were 4 days in all groups (data not shown). The HR (95% CI) of days to virus disappearance for these patients in amenamevir 400 and 200 mg and valaciclovir groups were 0.99 (0.73–1.34) and 0.77 (0.56–1.04), respectively. No significant differences in these secondary end-points were observed between the treatment groups in an overall stratified Cox proportional hazards regression analysis. The number of rashes decreased time dependently. The incidence rates of PHN in the amenamevir 400 and 200 mg and valaciclovir groups on day 91 were 1.0% (2/193), 1.9% (4/209) and 1.0% (2/206), respectively. Among the VZV isolates, 46 samples were used for the susceptibility assay. The mean $EC_{50} \pm$ standard deviation of amenamevir and ACV were 0.28 ± 0.11 μmol/L (range, 0.08–0.49) and 1.61 ± 0.47 μmol/L (range, 0.78–2.80), respectively.

Subset analyses were performed for age (<65 and ≥65 years), time from onset of rash to first dose (≤24, >24 to ≤48 h, and >48 to ≤72 h) and sex (male and female) (Table S3). The day 4 cessation proportions in subjects aged less than 65 years in the amenamevir 400 and 200 mg and valaciclovir groups were 86.2%, 74.2% and 75.8%, respectively. Those in the subjects aged 65 years or older were 68.1% in the amenamevir 400 mg, 58.0% in the 200 mg group and 73.1% in the valaciclovir group. The day 4 cessation proportions of treatment ≤24 h, >24 to ≤48 h, and >48 to ≤72 h from onset of rash in the amenamevir 400 mg group were 75.0%, 82.7%, and 83.1%, respectively. Those were 50.9%, 72.8%, and 76.5% in the amenamevir 200 mg, and 53.3%, 75.8%, and 83.5% in the valaciclovir group, respectively. The day 4 cessation proportions in males and females were 79.8% and 81.9% in the amenamevir 400 mg group, 77.9% and 62.7% in the amenamevir 200 mg group, and 80.8% and 71.2% in the valaciclovir group,

Table 1. Demographics and clinical characteristics of participants at baseline (FAS)

Variable	Amenamevir 400 mg	Amenamevir 200 mg	Valaciclovir 3000 mg
No. of patients	243	247	245
Sex			
Male	99 (40.7)	113 (45.7)	99 (40.4)
Female	144 (59.3)	134 (54.3)	146 (59.6)
Age (years)			
<65	174 (71.6)	178 (72.1)	178 (72.7)
≥65	69 (28.4)	69 (27.9)	67 (27.3)
Mean (SD)	53.0 (16.2)	52.0 (16.3)	52.2 (15.8)
Minimum, median, maximum	20, 55, 78	20, 56, 78	20, 54, 79
Height (cm)			
Mean (SD)	161.53 (9.31)	162.15 (9.18)	161.08 (9.01)
Minimum, median, maximum	140.0, 161.0, 190.0	140.0, 161.7, 188.0	136.0, 161.0,184.0
Weight (kg)			
Mean (SD)	58.86 (11.79)	59.88 (11.47)	58.82 (12.39)
Minimum, median, maximum	28.0, 57.0, 100.0	37.0, 58.3, 103.0	36.5, 57.0, 116.8
Time from onset of rash to the first dose			
≤24 h	56 (23.0)	53 (21.5)	45 (18.4)
>24 h to ≤48 h	98 (40.3)	92 (37.2)	91 (37.1)
>48 h to ≤72 h	89 (36.6)	102 (41.3)	109 (44.5)
No. of rashes on day 1			
Mean (SD)	85.5 (115.5)	88.0 (145.6)	107.3 (183.0)
Minimum, median, maximum	1, 49, 1070	3, 44, 1450	2, 50, 1400
Lesion site of the underlying disease			
Head or face	42 (17.3)	52 (21.1)	32 (13.1)
Neck	20 (8.2)	20 (8.1)	20 (8.2)
Upper limb	29 (11.9)	25 (10.1)	29 (11.8)
Thoracodorsal site	78 (32.1)	70 (28.3)	85 (34.7)
Ventrodorsal site	88 (36.2)	69 (27.9)	86 (35.1)
Lower limb	19 (7.8)	40 (16.2)	34 (13.9)
Buttocks	15 (6.2)	27 (10.9)	21 (8.6)
Virological tests			
Positive	192 (79.0)	202 (81.8)	199 (81.2)
Negative	51 (21.0)	45 (18.2)	46 (18.8)

FAS, full analysis set; SD, standard deviation *n* (%).

respectively. Among the subjects aged less than 65 years, the 4-day cessation proportions of treatment for 24 h or less, more than 24 to 48 h or less, and more than 48 to 72 h or less from onset of rash in the amenamevir 400 mg group were 82.1%, 84.5% and 90.6%, respectively. Among the subjects aged 65 years or older, the day 4 cessation proportions from treatment of 24 h or less, more than 24 to 48 h or less, and more than 48 to 72 h or less from onset of rash were 58.8%, 77.8% and 64.0% in the amenamevir 400 mg group, and 35.7%, 66.7% and 61.3% in the amenamevir 200 mg group, respectively. The day 4 cessation proportions of treatment for 24 h or less, more than 24 to 48 h or less, and more than 48 to 72 h or less from onset of rash in the valaciclovir group were 64.7%, 71.4% and 79.3%, respectively.

Safety

Adverse events were coded using the Medical Dictionary for Regulatory Activities. The overall incidence of any AE was similar among the treatment groups (range, 45.4–46.6%). The proportions of patients who experienced drug-related AE were 10.0% (25/249), 10.7% (27/252) and 12.0% (30/249) in the amenamevir 400 mg, 200 mg and valaciclovir groups, respectively. AE with a frequency of 2% or more in any group were nasopharyngitis, beta-N-acetyl-D-glucosaminidase increased, fibrin degradation products increased, alpha-1-microglobulin increased stomatitis, protein urine present, dermatitis contact, glucose urine present, eczema, diarrhea, headache and folliculitis (Table 4). Drug-related AE with a frequency of 2% or more were increased fibrin degradation products in 2.0% (5/249) of the amenamevir 400 mg group and 2.4% (6/249) of the valaciclovir group, and increased α1-microglobulin in 2.4% (6/252) of the amenamevir 200 mg group. Most AE were mild in intensity, and no severe AE were observed of the drug-related AE (Table S4). No death was reported in this study. Six serious AE (SAE) were reported in five patients; one patient (infectious mononucleosis) in the amenamevir 400 mg group, one patient (angina pectoris) in the amenamevir 200 mg group and three participants (loss of consciousness, embolic cerebral infarction, lung neoplasm malignant and tendon rupture) in the valaciclovir group. None of the SAE were considered related to the study

Table 2. Difference in cessation rate (95% CI) of new lesion formation by day 4 between each amenamevir group and the valaciclovir group

Closed procedure	Day 4 cessation proportion	95% CI[†]			P[‡]
		Estimate	LCL	UCL	
Amenamevir 400 mg	81.1% (197/243)	7.1	−0.2	14.4	<0.0001
Amenamevir 200 mg	69.6% (172/247)	−4.3	−12.0	3.4	0.0688
Valaciclovir 3000 mg	75.1% (184/245)	–	–	–	–

[†]Mantel–Haenszel confidence interval adjusted for a stratification factor. [‡]*P*-value for Farrington–Manning test extended to Mantel–Haenszel type adjustment. CI, confidence interval; LCL, lower confidence limit; UCL, upper confidence limit.

Table 3. Summary of secondary efficacy end-points

Event					Hazard ratio		
	Censoring	Time to event (days)				95% CI	
Treatment group	*n*	Q1	Median	Q3	Estimate	LCL	UCL
Cessation of new lesion formation							
Amenamevir 400 mg	8	3	4	4	1.06	0.88	1.28
Amenamevir 200 mg	12	3	4	5	0.92	0.76	1.11
Valaciclovir 3000 mg	6	3	4	4	–	–	–
Complete crusting							
Amenamevir 400 mg	25	7	9	11	0.99	0.82	1.2
Amenamevir 200 mg	29	6	8	11	1.08	0.89	1.3
Valaciclovir 3000 mg	20	7	8	11	–	–	–
Healing							
Amenamevir 400 mg	33	8	11	15	1.02	0.84	1.23
Amenamevir 200 mg	32	8	11	15	0.99	0.82	1.2
Valaciclovir 3000 mg	21	8	11	16	–	–	–
Pain resolution							
Amenamevir 400 mg	26	5	10	19	1.07	0.87	1.3
Amenamevir 200 mg	31	5	9	19	1.05	0.86	1.29
Valaciclovir 3000 mg	19	5	10	19	–	–	–
Virus disappearance							
Amenamevir 400 mg	5	4	5	10	0.92	0.69	1.23
Amenamevir 200 mg	6	4	4	8	1.14	0.85	1.52
Valaciclovir 3000 mg	3	3	4	9	–	–	–

CI, confidence interval; LCL, lower confidence limit; Q1, first quartile; Q3, third quartile; UCL, upper confidence limit.

drug. AE leading to discontinuation of the study treatment occurred in one patient (headache and nausea) in the amenamevir 200 mg group, and two patients (abdominal pain, hepatic function abnormal and encephalopathy) in the valaciclovir group. These were drug-related AE and their grades were mild except moderate encephalopathy. All AE recovered after adequate treatment and termination of the study drug. No notable changes in clinical laboratory (hematology, biochemistry and urinalysis), vital signs or electrocardiogram were observed.

DISCUSSION

The helicase–primase inhibitor amenamevir is a member of a novel class of potent antiviral agents. Amenamevir inhibited replication of clinical VZV isolates in this study several times more potently than ACV, as reported previously in HSV isolated from genital herpes lesions.[24] This randomized, controlled, double-blind study is the first report demonstrating that the efficacy of amenamevir 400 mg once daily for 7 days was non-inferior to that of valaciclovir 1000 mg three times daily (3000 mg daily dose) for the treatment of herpes zoster in immunocompetent Japanese patients. The safety profiles of amenamevir 200 mg and 400 mg were comparable to those of valaciclovir 3000 mg. Patients diagnosed with localized herpes zoster presenting within 72 h after the onset of rash were enrolled in this study. Most were anti-VZV antibody positive, and VZV was identified by PCR and/or shell vial assay.

One strength of this study was the large sample size, which was representative of the wider Japanese community. In this study, we used cessation of new lesion formation by day 4 as a primary outcome instead of time to crusting. Crusting of rashes is a healing process after VZV replication stops. On the other hand, new lesions form due to VZV replication. Antiviral agents are recommended for patients in whom new lesions form after onset of a rash.[9] The amenamevir doses of 400 and 200 mg used in this study were selected based on a

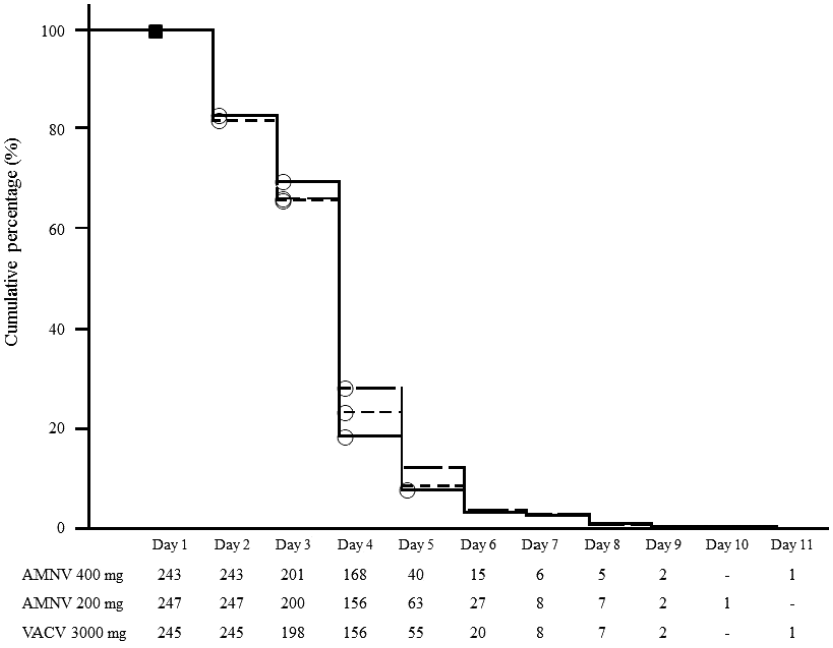

Figure 2. Time changes of cessation of new lesion formation by amenamevir (AMNV) 400 mg (—), amenamevir 200 mg (– –) and valaciclovir (VACV) (**- - -**) are shown by the Kaplan–Meir plot. Censorings are shown with (○).

Table 4. Number and percentage of patients with adverse events classified by primary system organ class and preferred term (preferred term incidence ≥2% in any group)

	All adverse events			Adverse events related to study drug		
(SOC) PT	Amenamevir 400 mg	Amenamevir 200 mg	Valaciclovir 3000 mg	Amenamevir 400 mg	Amenamevir 200 mg	Valaciclovir 3000 mg
Safety analysis set	249	252	249	249	252	249
Adverse events	116 (46.6)	115 (45.6)	113 (45.4)	25 (10.0)	27 (10.7)	30 (12.0)
(Gastrointestinal disorders)						
Diarrhea	2 (0.8)	1 (0.4)	5 (2.0)	1 (0.4)	0	3 (1.2)
Stomatitis	7 (2.8)	1 (0.4)	0	0	0	0
(Infection and infestations)						
Folliculitis	0	5 (2.0)	5 (2.0)	0	0	0
Nasopharyngitis	22 (8.8)	19 (7.5)	17 (6.8)	0	0	0
(Investigations)						
Beta-N-acetyl-D-glucosaminidase Increased	11 (4.4)	7 (2.8)	8 (3.2)	3 (1.2)	4 (1.6)	2 (0.8)
Fibrin degradation products increased	9 (3.6)	7 (2.8)	10 (4.0)	5 (2.0)	4 (1.6)	6 (2.4)
Glucose urine present	3 (1.2)	3 (1.2)	5 (2.0)	1 (0.4)	2 (0.8)	0
Protein urine present	5 (2.0)	2 (0.8)	5 (2.0)	0	1 (0.4)	3 (1.2)
Alpha-1-microglobulin increased	9 (3.6)	11 (4.4)	10 (4.0)	3 (1.2)	6 (2.4)	4 (1.6)
(Nervous system disorders)						
Headache	2 (0.8)	9 (3.6)	7 (2.8)	0	1 (0.4)	2 (0.8)
(Skin and subcutaneous tissue disorders)						
Dermatitis contact	5 (2.0)	4 (1.6)	5 (2.0)	0	0	0
Eczema	3 (1.2)	7 (2.8)	6 (2.4)	0	0	0

Adverse events were coded using the Medical Dictionary for Regulatory Activities Japanese Edition version 16.0. PT, preferred term; SOC, system organ class *n* (%).

randomized, double-blind, valaciclovir-controlled, dose range-finding phase 2 study (data not shown). Amenamevir 100, 200 and 400 mg p.o. once daily were compared with valaciclovir 1000 mg three times daily for 7 days in immunocompetent Japanese patients with herpes zoster, resulting in non-inferior efficacy of amenamevir to that of valaciclovir at all dose levels.

In this study, the day 4 cessation proportion with amenamevir 400 mg was relatively high and the non-inferiority to valaciclovir was assumed. However, non-inferiority of amenamevir 200 mg to valaciclovir was not assumed. Furthermore, a significant difference in efficacy was found between the amenamevir 400 and 200 mg groups. Robust effectiveness of amenamevir 400 mg was confirmed by sensitivity analyses in the FAS without adjusting for stratified factors, such as age (<65 and ≥65 years) and time from onset of rash to start of treatment (≤24 h, >24 to ≤48 h, and >48 to ≤72 h), and in the PPS.

In subset analyses, amenamevir 400 mg was more effective than amenamevir 200 mg and valaciclovir in subjects aged less than 65 years, but no difference was observed in subjects aged 65 years or older. Starting the amenamevir 400 mg treatment early (≤24 h onset of rash) was significantly more effective than that with amenamevir 200 mg and valaciclovir. Amenamevir 400 mg was significantly more effective in female patients than amenamevir 200 mg and valaciclovir, but no efficacy differences were found in male patients in each group. No statistical differences in efficacy were observed in the time from onset of rash to the start of treatment (>24 to ≤48 h and >48 to ≤72 h). These results were sufficient to account for the clinical effect of amenamevir 400 mg once daily.

It was difficult to determine the absolute impact of amenamevir on herpes zoster in the absence of a placebo group, although amenamevir has been reported to be as effective as valaciclovir and was more effective than placebo for the treatment of episodes of recurrent genital herpes in a placebo-controlled, double-blind, randomized study.[25] The favorable efficacies of valaciclovir for the treatment of the patients with herpes zoster and herpes zoster-associated pain have been established by high-quality trials that include randomized, double-blind, active- and/or placebo-controlled studies.[26] Valaciclovir has also been demonstrated to be significantly superior to ACV with respect to the time to cessation of new lesion formation in a Japanese clinical study.[27] This suggests that amenamevir would be superior to ACV for the treatment of the patients with herpes zoster.

The most common complication of herpes zoster is PHN. Vander Straten *et al.*[28] suggested that antiviral agents appear to be effective in reducing PHN severity and duration in the acute phase of herpes zoster, but not its incidence. Initiating antiviral therapy as early as possible during the course of an acute zoster episode, and definitely within 72 h of onset, is effective in alleviating acute pain and preventing PHN in most patients.[29–31] In our study, the incidence of PHN in all treatment groups was extremely low (1.0–1.9%), which might have been due to early initiation of treatment followed by inhibition of virus replication.

Amenamevir is administrated once daily, unlike the three times daily dosing schedule required for valaciclovir, and the five times daily for ACV. Claxton *et al.*[32] reported that medication adherence with once-daily regimens was significantly higher than with three- and four-times-daily regimens across a variety of therapeutic classes. Higher adherence is particularly required to ensure antiviral therapeutic success.[33] Once daily amenamevir would be expected to respond more favorably to antiviral activity than multiple daily dosing of valaciclovir and ACV followed by higher adherence in routine clinical practice.

Our results suggest that amenamevir is a satisfactory alternative treatment option to nucleoside antiviral agents in patients with herpes zoster.

Amenamevir and valaciclovir were well tolerated in this study. Most AE were mild in intensity, and no SAE were observed among the drug-related AE. No deaths were reported. Six SAE were reported in five patients, but none of the SAE were related to the study drug. No notable changes in clinical laboratory (hematology, biochemistry and urinalysis), vital signs or electrocardiogram were observed. Although a certain number of drugs were prohibited as concomitant use with amenamevir during the study, the risk of AE-related drug–drug interaction would be limited, because drugs used with amenamevir in routine clinical practice affecting activation/inhibition of main metabolic enzymes of amenamevir have not been found. Concomitant medication for treating pain was also prohibited in the study, and the study to evaluate the risk of AE caused by the combination with amenamevir is needed in post-marketing surveillance.

In conclusion, we demonstrated that amenamevir 400 mg once daily for 7 days provided efficacy comparable with that of valaciclovir 1000 mg three times per day (daily dose, 3000 mg) for 7 days in the treatment of immunocompetent Japanese patients with herpes zoster. Amenamevir was generally well tolerated and no major safety issues were identified. This is the first report demonstrating that a helicase–primase inhibitor is efficacious in the treatment of herpes zoster.

ACKNOWLEDGMENTS: This study was funded by Maruho Co., Ltd. We thank all participating patients and their families, the study investigators (Supporting Information), study nurses, study monitors, data manager and all other members of the study team. We thank Dr Tetsuji Asao (SunFlare Co., Ltd, Tokyo, Japan) for medical writing services, which were funded by Maruho Co., Ltd.

CONFLICT OF INTEREST: Maruho Co., Ltd, covered all of the expenses for this study. All drugs used for this study were provided by the company. M. K. was the medical advisor of the study and O. N., M. H., D. W., J. N. and S. I. were coordinating investigators of the study. M. K. received fees from the company for consultation, lectures and writing. M. H. received fees from the company for consultation, lectures, writing and research grants. D. W. and S. I. received fees from the company for consultation, lectures, writing, as well as from research grants. J. N. received fees from the company for lectures and research grants. T. K. and T. K. are employees of the company.

REFERENCES

1 Arvin AM. Varicella-zoster virus. *Clin Microbiol Rev* 1996; **9**: 361–381.

2 Cohen JI. Herpes zoster. *N Engl J Med* 2013; **369**: 1766–1767.
3 Marin M, Harpaz R, Zhang J, Wollan PC, Bialek SR, Yawn BP. Risk factors for herpes zoster among adults. *Open Forum Infect Dis* 2016; https://doi.org/10.1093/ofid/ofw119
4 Johnson RW, Rice AS. Clinical practice. Postherpetic neuralgia. *N Engl J Med* 2014; **371**: 1526–1533.
5 Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc* 2007; **82**: 1341–1349.
6 Johnson R, McElhaney J, Pedalino B, Levin M. Prevention of herpes zoster and its painful and debilitating complications. *Int J Infect Dis* 2007; **11** (Suppl 2): S43–S48.
7 Furue M, Yamazaki S, Jimbow K *et al.* Prevalence of dermatological disorders in Japan: a nationwide, cross-sectional, seasonal, multicenter, hospital-based study. *J Dermatol* 2011; **38**: 310–320.
8 Takao Y, Miyazaki Y, Okeda M *et al.* Incidences of herpes zoster and postherpetic neuralgia in Japanese adults aged 50 years and older from a community-based prospective cohort study: The SHEZ study. *J Epidemiol* 2015; **25**: 617–625.
9 Dworkin RH, Johnson RW, Breuer J *et al.* Recommendations for the management of herpes zoster. *Clin Infect Dis* 2007; **44** (Suppl 1): S1–S26.
10 Elion GB. The biochemistry and mechanism of action of acyclovir. *J Antimicrob Chemother* 1983; **12** (Suppl B): 9–17.
11 Morfin F, Thouvenot D. Herpes simplex virus resistance to antiviral drugs. *J Clin Virol* 2003; **26**: 29–37.
12 Reusser P. Herpesvirus resistance to antiviral drugs: a review of the mechanisms, clinical importance and therapeutic options. *J Hosp Infect* 1996; **33**: 235–248.
13 Morfin F, Thouvenot D, De Turenne-Tessier M, Lina B, Aymard M, Ooka T. Phenotypic and genetic characterization of thymidine kinase from clinical strains of varicella-zoster virus resistant to acyclovir. *Antimicrob Agents Chemother* 1999; **43**: 2412–2416.
14 Reyes M, Shaik NS, Graber JM *et al.* Acyclovir-resistant genital herpes among persons attending sexually transmitted disease and human immunodeficiency virus clinics. *Arch Intern Med* 2003; **163**: 76–80.
15 Andrei G, Topalis D, Fiten P *et al.* In vitro-selected drug-resistant varicella-zoster virus mutants in the thymidine kinase and DNA polymerase genes yield novel phenotype-genotype associations and highlight differences between antiherpesvirus drugs. *J Virol* 2012; **86**: 2641–2652.
16 Davison AJ, Scott JE. The complete DNA sequence of varicella-zoster virus. *J Gen Virol* 1986; **67**: 1759–1816.
17 Kleymann G, Fischer R, Betz UA *et al.* New helicase-primase inhibitors as drug candidates for the treatment of herpes simplex disease. *Nat Med* 2002; **8**: 392–398.
18 James SH, Larson KB, Acosta EP, Prichard MN. Helicase-primase as a target of new therapies for herpes simplex virus infections. *Clin Pharmacol Ther* 2015; **97**: 66–78.
19 Crute JJ, Tsurumi T, Zhu LA *et al.* Herpes simplex virus 1 helicase-primase: a complex of three herpes-encoded gene products. *Proc Natl Acad Sci USA* 1989; **86**: 2186–2189.
20 Cavanaugh NA, Ramirez-Aguilar KA, Urban M, Kuchta RD. Herpes simplex virus-1 helicase-primase: roles of each subunit in DNA binding and phosphodiester bond formation. *Biochemistry* 2009; **48**: 10199–10207.
21 Chono K, Katsumata K, Kontani T *et al.* ASP2151, a novel helicase-primase inhibitor, possesses antiviral activity against varicella-zoster virus and herpes simplex virus type 1 and 2. *J Antimicrob Chemother* 2010; **65**: 1733–1741.
22 Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. *Stat Med* 1990; **9**: 1447–1454.
23 Yanagawa T, Tango T, Hiejima Y. Mantel-Haenszel-type tests for testing equivalence or more than equivalence in comparative clinical trials. *Biometrics* 1994; **50**: 859–864.
24 Katsumata K, Weinberg A, Chono K, Takakura S, Kontani T, Suzuki H. Susceptibility of herpes simplex virus isolated from genital herpes lesions to ASP2151, a novel helicase-primase inhibitor. *Antimicrob Agents Chemother* 2012; **56**: 3587–3591.
25 Tyring S, Wald A, Zadeikis N, Dhadda S, Takenouchi K, Rorig R. ASP2151 for the treatment of genital herpes: a randomized, double-blind, placebo- and valacyclovir-controlled, dose-finding study. *J Infect Dis* 2012; **205**: 1100–1110.
26 McDonald EM, de Kock J, Ram FS. Antivirals for management of herpes zoster including ophthalmicus: a systematic review of high-quality randomized controlled trials. *Antivir Ther* 2012; **17**: 255–264.
27 Niimura M, Nishikawa T, Kawashima M *et al.* Phase III study of valaciclovir hydrochloride tablets in patients with herpes zoster – double-blind comparative study with aciclovir tablets. *J Clin Ther Med* 1998; **14**: 2867–2902.
28 Vander Straten M, Carrasco D, Lee P, Tyring SK. Reduction of postherpetic neuralgia in herpes zoster. *J Cutan Med Surg* 2001; **5**: 409–416.
29 Wood MJ, Kay R, Dworkin RH, Soong SJ, Whitley R. Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster: a meta-analysis of placebo-controlled trials. *J Clin Infect Dis* 1996; **22**: 341–347.
30 Wood MJ, Shukla S, Fiddian AP, Crooks RJ. Treatment of acute herpes zoster: effect of early (< 48 h) versus late (48-72 h) therapy with acyclovir and valaciclovir on prolonged pain. *J Infect Dis* 1998; **178** (Suppl 1): S81–S84.
31 Whitley RJ, Volpi A, McKendrick M, van Wijck A, Oaklander AL. Management of herpes zoster and post-herpetic neuralgia now and in the future. *J Clin Virol* 2010; **48**(Suppl 1): S20–S28.
32 Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001; **23**: 1296–1310.
33 Wójcik K, Piekarska A, Jabłonowska E. Adherence to antiviral therapy in HIV or HBV-infected patients. *Przegl Epidemiol* 2016; **70** (27–32): 115–118.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Full analysis set (FAS), per protocol set (PPS) and the reasons excluded from the sets.

Table S2. Sensitivity analyses of cessation rate of new lesion formation by day 4 between each amenamevir group and the valaciclovir group.

Table S3. Subgroup analyses of cessation rate of new lesion formation by day 4 between each amenamevir group and the valaciclovir group.

Table S4. Summary of adverse events (safety analysis set).

Figure S1. Study schedule.