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MAJOR ARTICLE

Single-Dose, Patient-Initiated Amenamevir Therapy for Recurrent Genital Herpes: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study

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Background. Amenamevir is a helicase-primase inhibitor with novel mechanisms of antiherpetic action. A patient-initiated single-dose regimen showed clinical efficacy for genital herpes in a phase 2 study.

Methods. In this phase 3 study, adult immunocompetent patients with recurrent genital herpes and able to accurately recognize prodromal symptoms were randomly assigned to administer amenamevir 1200 mg or placebo as a patient-initiated therapy within 6 hours after onset of prodromal symptoms. The primary efficacy endpoint was time to healing of all genital herpes lesions.

Results. In the modified intention-to-treat population, which excluded patients with aborted lesions (amenamevir, n = 89; placebo, n = 97), the median time to all lesion healing was 4.0 days for amenamevir versus 5.1 days for placebo (hazard ratio, 1.60 [95% confidence interval, 1.19–2.15]; $P = .0018$), indicating superiority of amenamevir. All treatment-emergent adverse events in both groups were mild in severity.

Conclusions. Patient-initiated single-dose amenamevir reduced the time to all lesion healing of recurrent genital herpes versus placebo, with no safety concerns, suggesting it could be an effective treatment option for patients with recurrent genital herpes.

Clinical Trials Registration. JapicCTI-194955.

Keywords. amenamevir; ASP2151; herpes simplex virus; patient-initiated therapy; recurrent genital herpes.

Herpes simplex is an infection caused by herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2); globally, it is estimated that 3.7 billion people aged <50 years are infected with HSV-1 and 0.5 billion with HSV-2 [1, 2]. Primary infection with HSV-1 often occurs in childhood and presents with symptoms resembling those of the common cold, such as fever and sore throat [3, 4]. Gingivostomatitis may occur in some patients, and Kaposi varicelliform eruption may develop in children with atopic dermatitis. HSV-2 is generally sexually transmitted, with the primary infection manifesting as multiple vesicles, pustules, erosion, and ulcers on the genitalia [3, 4]. After the primary infection, both HSV-1 and HSV-2 become dormant in the ganglia and can be reactivated by stimuli including fever, ultraviolet exposure, and sexual intercourse, or by impaired cellular immunity [5, 6]. Recurrence of both subtypes may manifest as painful blisters or ulcers, generally on the lips (herpes labialis) and genitalia (genital herpes) [1]; however, HSV-1 most often recurs as herpes labialis and facial herpes, and HSV-2 is more usually the cause of genital herpes. One study reported that 67.1% of patients with genital herpes had >3 recurrences per year [7], and although the symptoms of recurrence are mild compared with those of the primary infection, frequent recurrences can result in impaired well-being, including symptoms of depression [8]. Notably, at the time of recurrence, many patients experience prodromal symptoms prior to lesion eruption; these may include genital pain or localized itching; discomfort in the lower back, hips, or buttocks; or tingling sensations [9].

First-line treatment for recurrent herpes simplex involves oral antiviral drugs [10, 11]. While the nucleoside analogs acyclovir, valacyclovir, and famciclovir have been approved for the treatment of herpes simplex, some patients may not achieve an adequate response to treatment [12, 13]. Amenamevir (formerly ASP2151) is a novel, nonnucleoside, antiviral drug that inhibits herpes helicase-primase, an essential enzyme complex for replication of viral genomic DNA [14]. Amenamevir has an inhibitory effect on varicella zoster virus proliferation [15] and was approved in Japan as once-daily treatment for 7 days for herpes zoster in July 2017 [16]. Of note, amenamevir has also demonstrated efficacy against acyclovir-resistant HSV isolates [17], indicating that it may be a feasible alternative for patients who fail current first-line treatment.

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In preclinical studies, amenamevir showed promise for the treatment of HSV infection [18, 19], and in a phase 2 study of amenamevir for the treatment of genital herpes conducted in the United States, a single 1200-mg dose of amenamevir was demonstrated to be superior to placebo in terms of time to healing (median, 102.1 vs 139.8 hours, respectively; hazard ratio [HR], 1.72; $P = .007$) [20]. In the phase 2 study, patient-initiated therapy was used [20], whereby patients were prescribed oral antiviral drugs before they experienced recurrence, and started the treatment at an early stage at their own discretion after onset of prodromal symptoms. This is a widely used technique for patients with recurrent herpes simplex [10, 11]. The objective of the current phase 3 study was to evaluate the efficacy and safety of a single dose (1-day treatment) of amenamevir 1200 mg to treat recurrent genital herpes using patient-initiated therapy.

METHODS

Patients

Inclusion criteria for the study were age ≥18 years to <80 years; prior experience of recurrent genital herpes and the ability to accurately recognize the prodromal symptoms (in the opinion of the investigator); and positive test for anti-HSV antibodies on the day of enrollment. Prodromal symptoms were defined as pain/tingling, discomfort or restlessness, itching, lower back pain, or other symptoms specific to an individual that were known to accurately indicate recurrence. Patients who were immunocompromised or immunodeficient, were pregnant or lactating, or had any serious medical condition making study participation inappropriate were excluded. Concomitant use of cytochrome P450 inducers or inhibitors, antiviral drugs, steroids, immunosuppressants, interferon, or γ-globulin preparations was also prohibited.

Patient Consent Statement

All patients provided written, informed consent prior to study participation. Study procedures were performed in compliance with the Standards for Good Clinical Practice and all other applicable regulatory requirements, the ethical principles based on the Declaration of Helsinki, and the protocol. The institutional review board at each site (Supplementary Table 1 for a full list) reviewed and approved the protocol and all study-related documents prior to study initiation.

Study Design, Treatments, and Blinding

This was a phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group study to demonstrate the efficacy of patient-initiated, single-dose amenamevir to treat recurrent genital herpes. The study was conducted at 53 sites (Supplementary Table 1) between September 2019 and November 2020. The study design is shown in Supplementary Figure 1. Prior to study drug administration, patients were to make routine clinic visits every 28 days. After recurrence of genital herpes and patient-initiated therapy, patients were to visit the study site within 1–2 days (ie, the timeframe in which lesion healing was expected to be observed), and then again between posttreatment days 2–4, 5–7, 8–10, and 11–14 (until healing was complete) to assess lesions and subjective symptoms accompanying genital herpes, and to monitor adverse events (AEs).

Blinded treatment allocation of eligible patients was conducted via a central Web Registration System to achieve a 1:1 ratio. Investigators, study site staff, patients, and the sponsor were all blinded to treatment assignment throughout the study. Patients took a single dose of 6 tablets of the study drug (amenamevir 1200 mg [200 mg per tablet] or placebo) after a meal as a patient-initiated therapy within 6 hours after onset of prodromal symptoms of recurrent genital herpes. The timing of study administration was based on prior studies indicating suppression of rash when antiviral treatment was initiated within 6 hours of prodromal symptoms [20, 21]. Exposure to amenamevir in blood is increased by food intake [22]; thus, to ensure sufficient exposure in blood, treatment in the current study was to be taken after a meal.

Concomitant use of drugs (including topical therapies) for the lesions of genital herpes was prohibited during the period from the onset of prodromal symptoms of recurrence to the time of physical examination at the completion/discontinuation visit. However, use of protection agents (petrolatum-based compounds) and topical anesthetics was permitted.

Patients used a diary to record key details, including prodromal symptoms, skin findings, subjective symptoms, and timing of study drug administration. The diary was to be completed 2–4 times daily starting from the onset of prodromal symptoms of recurrence until the day of the completion/discontinuation visit.

Virologic Examination

Only patients with positive anti-HSV antibodies were included in the study. Prior to enrollment, serum was obtained from prospective participants and tested for anti-HSV antibodies to confirm the presence of HSV infection (either HSV-1 or HSV-2). Viral polymerase chain reaction (PCR) testing was not performed before administration of the study drug. When possible, samples were taken from lesions at the first posttreatment visit (the day of or day after administration of the study drug) and viral PCR testing was performed. Collection was not essential, and samples were not obtained if scabbing or epithelization of the lesions made collection impossible or if crushing blisters or pustules to collect samples would potentially confound the assessment of effectiveness. In addition, no follow-up evaluation was undertaken to measure rates or timing of virus diminution/disappearance posttreatment.

Study Outcomes

The primary efficacy endpoint was time to healing (reepithelialization) of all genital herpes lesions starting from the time of study drug administration. Healing was defined as being when all lesions (erythemas/papulae, vesicles/pustules, and erosions/ulcers) were resolved and complete resolution of crusts or complete epithelialization of the base of crusts was considered to have been achieved.

Secondary efficacy endpoints were time to crusting of all genital herpes lesions; time to resolution of pain accompanying genital herpes; proportion of patients with aborted lesions; and time to resolution of subjective symptoms accompanying genital herpes. An aborted lesion was defined as a herpetic lesion that did not progress beyond the erythema/papule stage. Time of onset of subjective symptoms was obtained from the patient diary, and resolution was confirmed by physical examination, or from the patient diary if resolution occurred prior to a visit.

Safety was evaluated based on treatment-emergent AEs (TEAEs) and laboratory data. TEAEs were classified using the Medical Dictionary for Regulatory Activities/Japanese edition version 22.0. Severity was categorized using the Common Terminology Criteria for Adverse Events Version 5.0 Japanese—Japan Clinical Oncology Group Version. AEs of special interest (AESIs) were platelet count decreased; arrhythmia and related symptoms; renal disorders and related clinical or laboratory events; erythema multiforme; oculomucocutaneous syndrome; and toxic epidermal necrolysis.

Statistical Methods

To confirm the superiority of amenamevir 1200 mg over placebo, with a 2-sided significance level of .05 and a statistical power of 90%, the target sample size of patients with healed lesions was calculated to be 176 in total (88 per treatment group). This was based on herpes simplex treatment data from prior clinical studies [20, 23, 24] and the assumption that the HR for amenamevir over placebo was 1.65. Considering the expected rates of patients with aborted lesions and of patients who would not initiate study drug treatment, approximately 510 patients were required to be randomized in total.

The intention-to-treat (ITT) and safety analysis populations included all patients who received at least 1 dose of study drug. The modified ITT (mITT) population excluded patients with aborted lesions and patients who were confirmed to have no genital herpes recurrence necessitating drug administration (based on the absence of objective and subjective symptoms). The primary efficacy endpoint was evaluated in the mITT population. A supplemental analysis for the primary endpoint was conducted in the ITT population, in which 0 was imputed for the time to healing in subjects with aborted lesions. For the secondary efficacy endpoints, time to crusting of all genital herpes lesions was assessed in the mITT population; time to resolution of pain accompanying genital herpes and proportion of patients with aborted lesions were assessed in the ITT population; and time to resolution of subjective symptoms accompanying genital herpes was assessed in the population of patients with aborted lesions.

For the primary endpoint, data were summarized by the Kaplan-Meier estimation method in the mITT population by treatment group, and expressed with 95% confidence intervals (CIs). The Cox proportional hazard model with treatment as an explanatory variable was performed to compare treatment groups; the HR for amenamevir versus placebo along with the 95% CI and *P* value were calculated. A *P* value less than the 2-sided significance level of .05 was considered to demonstrate the superiority of amenamevir over placebo. For secondary endpoints, no adjustment was made for multiplicity. Time-to-event data were summarized in the same way as the primary endpoint, using Kaplan-Meier methodology and the Cox proportional hazard model. The proportion of patients with aborted lesions was tested by 1-sided Fisher exact test. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina)

RESULTS

Patients

A total of 578 patients were randomly assigned to treatment (Figure 1). Of these, 264 experienced prodromal symptoms and were administered study treatment (ITT and safety populations: amenamevir, n = 124; placebo, n = 140). Two patients in the placebo group discontinued the study (1 had no confirmed recurrence and the other was due to patient request), resulting in 262 patients (amenamevir, n = 124; placebo, n = 138) completing the study. The mITT population comprised 186 patients (amenamevir, n = 89; placebo, n = 97).

Baseline demographic and clinical characteristics of the ITT population are shown in Table 1. Overall, 140 of 264 (53.0%) of patients were female, and the majority (175/264 [66.3%]) were aged between 18 and 44 years. Pain was the most frequent prodromal symptom of genital herpes recurrence (231/264 [87.5%]), and the median number of recurrences in the year prior to enrollment was 4.0 (range, 0–24). Variables were generally comparable between treatment groups. Characteristics for the mITT population are provided in Supplementary Table 2; data were in line with those of the ITT.

Posttreatment samples for virologic PCR testing were obtained from 54 of 124 patients in the amenamevir group and 53 of 140 in the placebo group. None of these patients were found to be HSV-1 positive; 81.5% (44/54) of patients in the amenamevir group and 73.6% (39/53) of patients in the placebo group were HSV-2 positive. Respectively, 18.5% (10/54) and 26.4% (14/53) of patients tested negative at the first posttreatment visit.

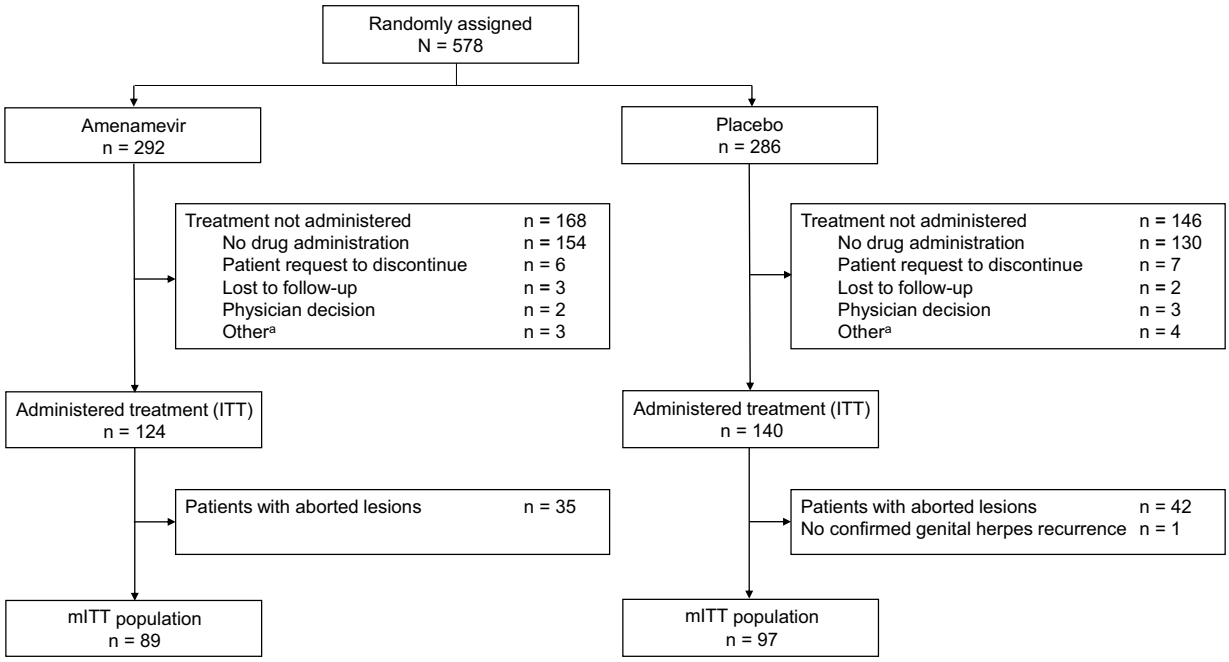

Figure 1. Patient disposition. [a]Includes difficulty in continuing the study due to adverse events, use of prohibited drugs specified in the exclusion criteria, and confirmation of pregnancy. Abbreviations: ITT, intention-to-treat; mITT, modified intention-to-treat.

Treatment compliance was good in both treatment groups. In the ITT population, all patients received the study drug within 6 hours after onset of prodromal symptoms of recurrence, with the exception of 1 patient in the placebo group who received the study drug 8.5 hours after onset of prodromal symptoms. The mean time from onset of prodromal symptoms of

Table 1. Patient Demographics and Clinical Characteristics at Baseline (Intention-to-Treat Population)

Characteristic	Amenamevir (n = 124)	Placebo (n = 140)	Total (N = 264)
Female sex	62 (50.0)	78 (55.7)	140 (53.0)
Age, y			
Median (min–max)	36.0 (21–74)	38.5 (20–73)	36.5 (20–74)
18–44	88 (71.0)	87 (62.1)	175 (66.3)
45–64	33 (26.6)	43 (30.7)	76 (28.8)
65–79	3 (2.4)	10 (7.1)	13 (4.9)
Height, cm, median (min–max)	166.2 (147.3–183.0)	164.0 (148.7–186.0)	165.0 (147.3–186.0)
Weight, kg, median (min–max)	62.9 (42.5–100.2)	61.2 (38.9–106.2)	61.8 (38.9–106.2)
Prodromal symptoms of recurrent genital herpes[a]			
Pain	105 (84.7)	126 (90.0)	231 (87.5)
Discomfort	90 (72.6)	107 (76.4)	197 (74.6)
Itching	79 (63.7)	76 (54.3)	155 (58.7)
Lower back pain and/or discomfort	26 (21.0)	33 (23.6)	59 (22.3)
Other symptoms	33 (26.6)	42 (30.0)	75 (28.4)
No. of recurrences in the 1 y prior to enrollment			
Median (min–max)	4.0 (1–24)	4.0 (0–14)	4.0 (0–24)
0	0	3 (2.1)	3 (1.1)
1–3	54 (43.5)	56 (40.0)	110 (41.7)
4–8	58 (46.8)	67 (47.9)	125 (47.3)
9+	12 (9.7)	14 (10.0)	26 (9.8)

Data are presented as No. (%) unless otherwise indicated.

[a]In previous recurrences. Patients could be included in >1 category.

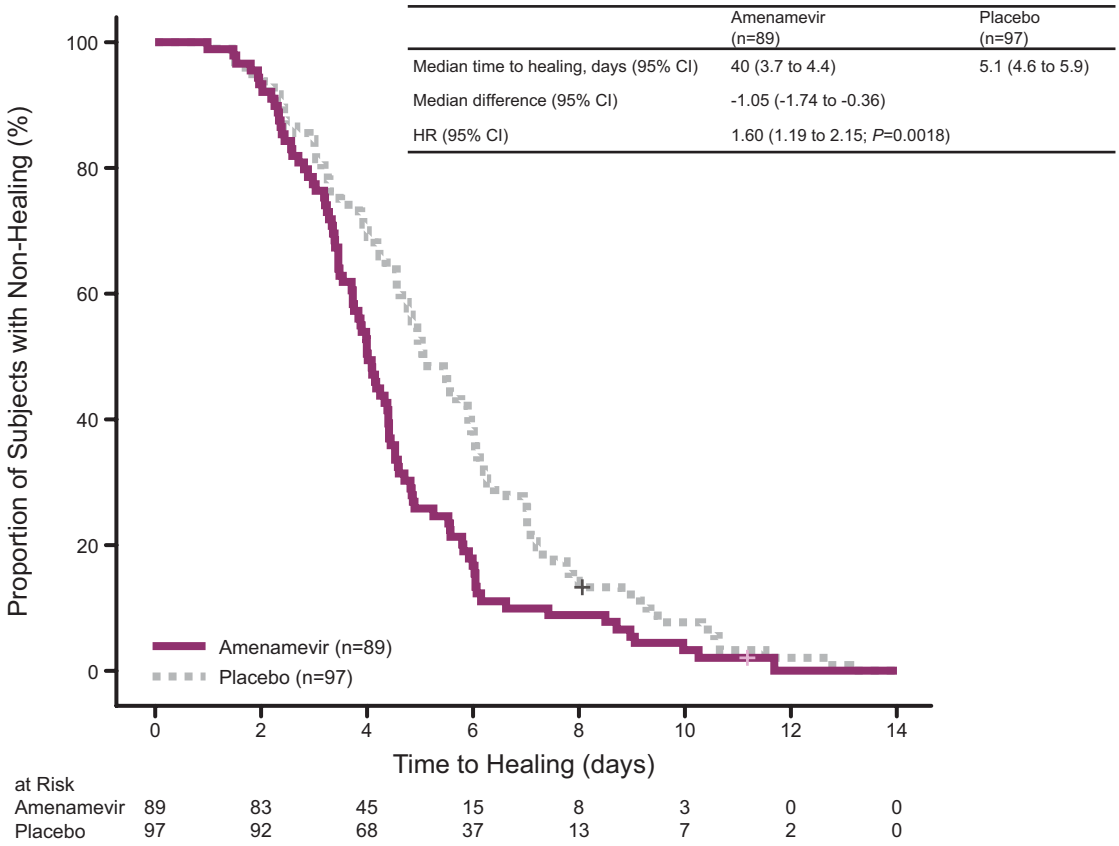

Figure 2. Analysis of time to healing. "+" indicates censoring (1 patient in each group was censored). The 95% confidence interval (CI) of the median was calculated based on the Brookmeyer and Crowley method.

recurrence to study drug administration was 2.73 (standard deviation [SD], 1.65) hours in the amenamevir group and 2.64 (SD, 1.79) hours in the placebo group.

Primary Endpoint

In the mITT population, the median time to all lesion healing of recurrent genital herpes was 4.0 days in the amenamevir group and 5.1 days in the placebo group; the median difference was 1.05 (95% CI, −1.74 to −.36) days (Figure 2). The HR for amenamevir versus placebo was 1.60 (95% CI, 1.19–2.15; $P=$ .0018), indicating superiority of amenamevir over placebo in the time to healing.

The results of the supplemental analysis in the ITT population were similar to those of the primary analysis. The HR for amenamevir versus placebo was 1.36 (95% CI, 1.06–1.74; $P=.016$).

Secondary Endpoints

Secondary endpoints are summarized in Table 2. In the mITT population, use of amenamevir resulted in a statistically significantly shortened time to crusting of all genital herpes lesions vs placebo (HR, 1.59 [95% CI, 1.18–2.13]; $P=.0021$). In the ITT population, the median time to resolution of pain accompanying genital herpes was slightly shorter with amenamevir (2.8 days) versus placebo (3.1 days), but the HR was not significant ($P=.14$).

Overall, 35 of 124 (28.2%) patients in the amenamevir group and 42 of 140 (30.0%) in the placebo group had aborted lesions; these proportions were not significantly different between treatment groups. The median time to resolution of subjective symptoms in patients with aborted lesions was 5.0 days with amenamevir and 3.6 days with placebo (HR, 0.70 [95% CI, .39–1.28]; $P=.25$).

Safety

Safety outcomes are summarized in Table 3. TEAEs were reported in 22 of 124 (17.7%) patients in the amenamevir group and 35 of 140 (25.0%) in the placebo group. TEAEs related to the study drug were reported in 10 of 124 (8.1%) and 13 of 140 (9.3%) patients, respectively. All TEAEs were mild in severity. No deaths or serious TEAEs were reported. The most commonly reported TEAE in the amenamevir group was β-N-acetyl-D-glucosaminidase increased. There was no notable difference between treatment groups in the frequency of these

Table 2. Summary of Secondary Endpoints

Endpoint	Amenamevir	Placebo	Between-Group Difference (Amenamevir vs Placebo)	
Time to crusting of all genital herpes lesions (mITT population), d (median)	3.7	4.8	Median difference, −1.04 (95% CI, −1.71 to −.37)	HR, 1.59 (95% CI, 1.18–2.13); $P = .0021$
Time to resolution of pain accompanying genital herpes (ITT population), d (median)	2.8	3.1	Median difference, −0.33 (95% CI, −1.08 to .42)	HR, 1.24 (95% CI, .93–1.66); $P = .14$
Proportion of patients with aborted lesions (ITT population), % (95% CI)	28.2 (20.3–36.1)	30.0 (22.4–37.6)	Proportion difference, −1.8 (95% CI, −12.7 to 9.2); $P = .67$	
Time to resolution of subjective symptoms accompanying genital herpes (patients with aborted lesions), d (median)	5.0	3.6	Median difference, 1.38 (95% CI, −.05 to 2.81)	HR, 0.70 (95% CI, .39–1.28); $P = .25$

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mITT, modified intention-to-treat.

events. None of the TEAEs reported in the System Organ Class of "Infections and infestations" were judged to be treatment related by the investigator. Regarding AESIs, renal disorder and related events were reported in 5 of 124 (4.0%) patients in the amenamevir group and 8 of 140 (5.7%) in the placebo group. No other AESIs were reported. No abnormal changes in laboratory parameters equivalent to serious or significant AEs were observed.

DISCUSSION

This phase 3, randomized controlled trial aimed to demonstrate the superiority of a single, patient-initiated dose of amenamevir over placebo in patients with recurrent genital herpes. Our data confirmed the superiority of amenamevir for the primary endpoint, with a significantly shorter time to all lesion healing versus placebo. The finding that a single, patient-initiated dose of amenamevir can shorten time to healing by 1 day (calculated via comparison of medians) is a clinically meaningful outcome for patients. The result of time to crusting of all genital herpes lesions also supported the result of the primary endpoint.

There were no significant differences between treatment groups in the other secondary outcomes. In the prior US study [20], the proportion of aborted lesions was higher in the amenamevir group than in the placebo group; in the current study,

Table 3. Summary of Safety Outcomes (Safety Population)

	All TEAEs, No. (%)		Treatment-Related TEAEs, No. (%)	
Outcome	Amenamevir (n = 124)	Placebo (n = 140)	Amenamevir (n = 124)	Placebo (n = 140)
Any TEAE	22 (17.7)	35 (25.0)	10 (8.1)	13 (9.3)
Serious TEAE or death	0	0	0	0
TEAEs occurring in ≥2% in any treatment group				
Infections and infestations				
Vulvovaginal candidiasis	2 (1.6)	4 (2.9)	0	0
Nasopharyngitis	2 (1.6)	3 (2.1)	0	0
Folliculitis	1 (0.8)	3 (2.1)	0	0
Investigations				
α-1-microglobulin increased	2 (1.6)	5 (3.6)	2 (1.6)	3 (2.1)
NAG increased	3 (2.4)	2 (1.4)	3 (2.4)	2 (1.4)
Adverse events of special interest				
Platelets decreased	0	0	0	0
Arrhythmia and related symptoms	0	0	0	0
Renal disorder and related events	5 (4.0)	8 (5.7)	4 (3.2)	6 (4.3)
α-1-microglobulin increased	2 (1.6)	5 (3.6)	2 (1.6)	3 (2.1)
NAG increased	3 (2.4)	2 (1.4)	3 (2.4)	2 (1.4)
Protein urine present	1 (0.8)	2 (1.4)	0	2 (1.4)
Blood creatinine increased	0	1 (0.7)	0	1 (0.7)
Renal impairment	0	1 (0.7)	0	1 (0.7)
Erythema multiforme	0	0	0	0
Toxic epidermal necrolysis	0	0	0	0
Oculomucocutaneous syndrome	0	0	0	0

TEAEs were classified using the System Organ Class and Preferred Term from the Medical Dictionary for Regulatory Activities/Japanese edition version 22.0. Severity was categorized using the Common Terminology Criteria for Adverse Events Version 5.0 Japanese—Japan Clinical Oncology Group Version.

Abbreviations: NAG, β-*N*-acetyl-D-glucosaminidase; TEAE, treatment-emergent adverse event.

there was no increase in proportion of aborted lesions in the amenamevir group, even though both trials were broadly comparable in terms of design and patient characteristics. Studies of patient-initiated famciclovir show similar discrepancies [23, 24]. Interestingly, both Japanese studies were characterized by a similarly high placebo rate of aborted lesions (about 30%); however, while regional/ethnic differences are possible, it remains unclear why there was no additional effect on aborted lesions in the amenamevir group in our study and further investigation will be needed to elucidate this point. Patient-initiated single-dose amenamevir was also not observed to suppress the development of rash (erythema/papules) in the early stages of recurrence in our study.

With regard to the patients who experienced prodromal symptoms without rash, active drug may have halted recurrence in the amenamevir group. In the placebo group, just 9 of 140 patients (6.4%) reported prodromal symptoms without subsequent development of erythema/papules (data not shown); these patients were categorized as having aborted lesions. This small group may have included patients who had real prodromal symptoms, but some may have mistakenly recognized other sensations as prodromal symptoms of recurrent herpes. It is not possible for us to retrospectively distinguish between these 2 possibilities. Overall, these findings suggest that the majority of patients were able to properly recognize subjective symptoms and take medication, supporting the use of this self-initiated regimen for patients with genital herpes and appropriate understanding of their prodromal symptoms.

The median time to lesion healing in this study (4.0 days in the amenamevir group) was consistent with that reported for the same dose (1200 mg) in the prior US study (4.25 days [102.1 hours]) [20]. At the time that this study was planned, no patient-initiated regimen of anti-HSV drug was approved in Japan, so we could not include an active comparator arm. However, data from the US study, in which the median times to healing in the amenamevir 1200 mg, valacyclovir, and placebo groups were 102.1, 113.9, and 139.8 hours, respectively, with between-group differences of 1.57 days (amenamevir and placebo) and 1.08 days (valacyclovir and placebo) [20], were in line with the findings reported in our study. The early initiation and short duration of treatment in the current study demonstrated that amenamevir 1200 mg was highly effective when administered as patient-initiated therapy, suggesting it could be a highly beneficial treatment option for recurrent genital herpes. Types and frequencies of TEAEs in patients receiving amenamevir were similar to those observed in the placebo group. Given that laboratory-related TEAEs were mild in severity, and no clinically relevant changes in laboratory data were found in subjects without laboratory-related TEAEs, no major safety concerns associated with amenamevir treatment were identified.

For patients whose symptoms are resistant to or who have an inadequate response with first-line nucleoside analogs, the helicase-primase inhibitor amenamevir may offer an alternative therapeutic approach [25]. Drug-resistant HSV has been an issue since the first use of acyclovir, particularly in immunocompromised patients [26]. Since most resistance results from deficiencies in thymidine kinase (required to phosphorylate acyclovir to the active metabolite acyclovir triphosphate), increasing the dose or switching to a related antiviral that also requires activation by thymidine kinase is not recommended [27]. As such, the use of a treatment with an unrelated mechanism of action is likely to be more successful. Moreover, in Japan, the use of valacyclovir to suppress recurrence of genital herpes is recommended only for patients who experience recurrence ≥6 times per year [28]. Given that one survey indicated that 67.1% of patients experience ≥3 recurrences per year, including 26.9% who experience ≥6 annual recurrences [7], this leaves approximately 40% of patients who experience frequent recurrences (3–5 episodes per year) without the ability to access patient-initiated valacyclovir treatment. The patient-initiated amenamevir regimen offers a high level of convenience for patients and may be an appropriate option to fill current treatment gaps and support excluded patients.

The main limitation of this study was the single-dose design. Ongoing virologic monitoring was not conducted, since we anticipated that collecting samples (via crushing blisters or pustules) could impact the accurate assessment of effectiveness. No data relating to efficacy and safety following repeated treatments for additional recurrent episodes are available, and real-world clinical practice data will be needed to assess the long-term clinical outcomes following multiple patient-initiated single-dose administrations due to repeated recurrences of genital herpes. The eligibility criteria used in this study excluded patients who were immunocompromised or had decreased immunofunction; it would be desirable to collect additional clinical data from such patients following treatment with amenamevir, to better understand efficacy and safety outcomes in individuals with a more complex medical background. In addition, although many patients with genital herpes are able to identify recurrences, this identification is not always accurate; as a result, misidentification of prodromal symptoms within a small sample size has the potential to confound the results. When considering the selection of patients for whom the amenamevir patient-initiated single-dose regimen is most suitable, it is important for clinicians to ascertain that patients with repeated recurrences are able to accurately recognize true prodromal symptoms.

CONCLUSIONS

In this study, the time to all lesion healing of recurrent genital herpes was significantly shortened by patient-initiated single-dose amenamevir versus placebo with no clinically notable safety concerns, suggesting that amenamevir could be an

effective treatment option for patients with recurrent genital herpes.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. M. K., S. I., K. F., and H. K. were responsible for the study design. K. F. was responsible for the conduct of the study. K. F. and H. K. were responsible for data analysis and interpretation. M. K., S. I., K. F., and H. K. were involved in writing and critically reviewing the manuscript; all authors provided final approval of the manuscript for submission.

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Data availability. The study protocol will be made available on request. However, due to the laws governing use of patient data, and the wording of the informed consent form used in this study, it is not possible to provide even de-identified patient data from this study to other researchers for analysis.

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Potential conflicts of interest. M. K. reports receiving grants, consulting fees, and honoraria from Maruho Co, Ltd, honoraria from Sanofi K.K., Sato Pharmaceutical Co, Ltd, Nippon Zoki Pharmaceutical Co, Ltd, and Takeda Pharmaceutical Co, Ltd, and has also participated in an advisory board for Maruho Co, Ltd. S. I. reports receiving grants and honoraria from Maruho Co, Ltd, and has also participated in an advisory board for Maruho Co, Ltd. K. F. and H. K. are employees of Maruho Co, Ltd.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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