Effect of Pritelivir Compared With Valacyclovir on Genital HSV-2 Shedding in Patients With Frequent Recurrences
A Randomized Clinical Trial

Anna Wald, MD, MPH; Burkhard Timmler, MD; Amalia Magaret, PhD; Terri Warren, ANP; Stephen Tyring, MD, PhD; Christine Johnston, MD, MPH; Kenneth Fife, MD, PhD; Stacy Selke, MA; Meei-Li Huang, PhD; Hans-Peter Stobernack, PhD; Holger Zimmermann, PhD; Lawrence Corey, MD; Alexander Birkmann, PhD; Helga Ruebsamen-Schaeff, PhD

IMPORTANCE Current therapy of herpes infections relies on nucleoside analogues. Pritelivir is a well-tolerated novel herpes simplex virus (HSV) helicase-primase inhibitor that reduced genital shedding and lesions.

OBJECTIVE To compare the efficacy of pritelivir with valacyclovir for suppression of genital HSV-2 infection.

DESIGN, SETTING, AND PARTICIPANTS A phase 2, randomized, double-blind, crossover clinical trial at clinical research centers in 4 US cities (October 2012-July 2013) compared daily oral doses of 100 mg of pritelivir with 500 mg of valacyclovir. The planned sample size was 98 adults, allowing for detection of a 50% reduction in viral shedding between the study treatments. Healthy adults with 4 to 9 annual genital HSV-2 recurrences were eligible. Ninety-one participants were randomized: 45 to receive pritelivir and 46 to receive valacyclovir first when the US Food and Drug Administration placed the trial on clinical hold based on findings in a concurrent nonclinical toxicity study, and the sponsor terminated the study.

INTERVENTIONS Participants took the first drug for 28 days followed by 28 days of washout before taking the second drug for 28 days. Throughout treatment, the participants collected genital swabs 4 times daily for testing by HSV polymerase chain reaction assays.

MAIN OUTCOMES AND MEASURES The primary end point was within-participant genital HSV shedding while receiving pritelivir compared with valacyclovir. Secondary end points included the quantity of HSV in positive swabs and the frequency of genital lesions and shedding episodes.

RESULTS Of the 91 randomized participants (median age, 48 years; 57 women [63%]), 56 had completed both treatment periods at the time of the study's termination. In intent-to-treat analyses, HSV shedding was detected in 2.4% (173 of 7276) of swabs during pritelivir treatment compared with 5.3% (392 of 7453) during valacyclovir treatment (relative risk [RR], 0.42; 95% CI, 0.21 to 0.82; \(P = .01\)). In swabs with HSV, the mean quantity of HSV was 3.2 log_{10} copies/mL during pritelivir treatment vs 3.7 log_{10} copies/mL during valacyclovir treatment (difference, −0.1; 95% CI, −0.6 to 0.5; \(P = .83\)). Genital lesions were present on 1.9% of days in the pritelivir group vs 3.9% in the valacyclovir group (RR, 0.40; 95% CI, 0.17-0.96; \(P = .04\)). The frequency of shedding episodes did not differ by group, with 1.3 per person-month for pritelivir and 1.6 per person-month for valacyclovir (RR, 0.80; 95% CI, 0.52 to 1.22; \(P = .29\)). Treatment-emergent adverse events occurred in 62.3% of participants in the pritelivir group and 69.2% of participants in the valacyclovir group.

CONCLUSIONS AND RELEVANCE Among adults with frequently recurring genital HSV-2, the use of pritelivir compared with valacyclovir resulted in a lower percentage of swabs with HSV detection over 28 days. Further research is needed to assess longer-term efficacy and safety.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01658826

Corrected on January 26, 2017.

Copyright 2016 American Medical Association. All rights reserved.

Author Affiliations: University of Washington & Fred Hutchinson Cancer Research Center, Seattle (Wald, Magaret, Johnston, Selke, Huang, Corey); AiCuris Anti-infective Cures GmbH, Wuppertal, Germany (Timmler, Stobernack, Zimmermann, Birkmann, Ruebsamen-Schaeff); Westover Heights Clinic, Portland, Oregon (Warren); University of Texas Health Science Center & Center for Clinical Studies, Houston (Tyring); Indiana University School of Medicine, Indianapolis (Fife).

Editorial page 2493
Supplemental content
The treatment for genital herpes simplex virus (HSV) infections relies on the nucleoside analogues acyclovir, valacyclovir, or famiciclovir administered either for each recurrence or daily to prevent recurrences. In addition, valacyclovir, when taken daily by a person with genital herpes has been shown to reduce the risk of HSV-2 transmission to susceptible partners. However, the protection is only partial (approximately 50%), likely because these drugs neither completely inhibit genital viral shedding nor reduce the risk of human immunodeficiency virus (HIV) acquisition conferred by HSV-2 infection. Nucleoside analogues inhibit viral replication by chain termination of viral DNA after monophosphorylation by the viral thymidine kinase followed by phosphorylation to triphosphate by cellular kinases. Drug resistance is uncommon in immunocompetent persons but may occur in immunocompromised hosts in whom treatment is difficult due to lack of safe alternative medications. Therefore, alternative agents to treat HSV infections are needed.

Pritelivir inhibits HSV replication but at the helicase-primase complex and does not require an activation step. In a placebo-controlled study, oral pritelivir was well tolerated and reduced the risk of genital viral shedding in a dose-dependent manner. In the present study, pritelivir was compared with valacyclovir for reduction of genital HSV shedding and lesions in persons with recurrent genital herpes.

Methods

The trial protocol and statistical analysis plan are available in Supplements 1 and 2.

Participants and Procedures

Eligible participants included healthy adults who were aged 18 years or older, HSV-2 seropositive, HIV seronegative, hepatitis B and C negative, and had a history of 4 to 9 genital herpes recurrences in the last year or in the year prior to starting suppressive antiviral therapy. Race information was self-reported. Participants had to agree to use effective contraception, refrain from using any anti-HSV therapy for 7 days prior to and during the treatment period, and be willing to complete all trial procedures. Exclusion criteria were pregnancy, nursing, malignancy or immunosuppression, steroid administration, other immunosuppressive medications, or medications that induced drug-metabolizing enzymes or transporters. In addition, participants had to avoid grapefruit and products containing quinine or quinidine during the study. Participants were required to be free of genital lesions on the first day of each treatment period. Throughout the two 28-day treatment periods, participants obtained swabs from their genital area 4 times during each 24-hour period, approximately 6 to 8 hours apart. The swabs were brought to clinic at the next weekly visit. If a lesion consistent with genital herpes developed, an additional swab was obtained from the lesion at home and participants came to clinic for evaluation. Participants maintained a diary of genital lesions and symptoms, and recorded adherence to the swabbing procedure and the study drugs. Adherence was calculated as the proportion of the expected amount of the drug taken and calculated by pill counts of returned blister pack. Adherence to swabs was defined as the proportion of swabs returned of expected.

The dose of 100 mg of pritelivir daily was chosen based on phase 1 and 2 studies suggesting safety and tolerability of this regimen and also on the high efficacy of 75 mg of pritelivir in suppressing viral shedding in the prior trial. Safety of the study drugs was evaluated with a weekly history and physical examination; laboratory assays for hematology, metabolic panel, and liver function tests; and an electrocardiogram during each treatment period. All adverse events were graded using the division of acquired immunodeficiency syndrome (DAIDS) table of adverse events.

Laboratory Studies

The University of Washington Western blot was used to assess HSV-2 antibody status. Samples of genitalsecretions were tested for HSV DNA with a real-time, quantitative polymerase chain reaction TaqMan assay at the University of Washington Virology Laboratory. Swabs were considered positive for HSV when at least 150 (2.2 log10) HSV DNA copies per mL were detected. To monitor potential signals of drug-resistance, HSV detected during administration of pritelivir at more than 5000 copies of DNA per mL were sequenced in the resistance-associated regions within UL5 and UL52 of HSV-2.
Sample Size
The sample size estimate for the primary efficacy end point was based on the anticipated occurrence of genital shedding, defined as the number of swabs that tested positive for HSV for study participants relative to the total numbers of swabs collected from each participant. We estimated HSV shedding at 5% during valacyclovir administration and 1% to 2% during pritelivir therapy. Using a crossover design with 80% power, 5% type I error, and a discontinuation rate of 6%, we planned to screen 120 volunteers and randomize 90. However, after trial initiation, the decision was made to increase enrollment to 98 because of concern for the possibility that a greater number of participants would drop out given the burden of the study procedures.

Outcomes
The primary end point was the intent-to-treat comparison of within-participant HSV shedding, defined as the number of swabs that tested positive for HSV per study participant relative to the total number of swabs collected per participant, during pritelivir vs valacyclovir therapy. Secondary end points included a comparison of copy number of the HSV DNA on the days that HSV was detected, HSV shedding on days with and without lesions, frequency of lesions, and frequency of episodes. An episode was defined as an event in which consecutive swabs tested positive for HSV DNA and were preceded and followed by swabs that tested negative. Additional secondary analyses evaluated the duration of pain, shedding episodes, and recurrences.

Statistical Analyses
The analysis was conducted using a nonlinear mixed-effects model with a log link and a random intercept for each participant to account for extra-Poisson variability. Period and carryover effects were examined at a 10% significance level using, respectively, a term for time period and an interaction term between the treatment group and time period. Analyses of duration used Wilcoxon signed rank test.

The intent-to-treat analyses included all randomized participants who received at least 1 dose of the study drug and obtained at least 1 genital swab; per-protocol analyses excluded persons with major protocol deviations, including early dis-}

Results

Study Population
The study was conducted at 4 clinical research centers located in Seattle, Washington; Portland, Oregon; Indianapolis, Indiana; and Houston, Texas, between October 2012 and July 2013. Of 150 screened participants, 91 were randomized (45 to receive pritelivir first) and took at least 1 dose of the study drug (Figure 1). The most common cause of ineligibility was lack of HSV-2 antibody (n = 11). Seventy-five participants received pritelivir and 76 received valacyclovir. On May 9, 2013, the US Food and Drug Administration (FDA) imposed a clinical hold (an order to the sponsor to suspend ongoing investigation), based on hematologic and dermatologic findings such as dry skin, crusty skin lesions, and alopecia in a chronic toxicity study involving monkeys. Because the duration of the clinical hold was uncertain, the sponsor terminated the study on June 24, 2013. At the time of the study termination, 74 participants completed their first treatment period and 56 completed both treatment periods.

The median age of participants was 48 years; 57 (63%) were women; and 66 (72%) were white (Table 1). The median time from HSV-2 acquisition was 17 years and the median number of recurrences in the year prior was 5 (range, 4-9 years). The demographic and clinical characteristics were similar in participants initially randomized to pritelivir and those initially randomized to valacyclovir. Overall, 7276 swabs were collected during pritelivir and 7453 swabs were collected during valacyclovir treatment (Table 2). In both groups, more that 96% of participants collected at least 80% of the expected genital swabs. Adherence to the study drug was very high, as measured by returned study medication, with 93% of persons reporting having taken at least 95% of prescribed doses.

HSV Genital Shedding
Herpes simplex virus was detected in 173 of 7276 swabs (2.4%) obtained during pritelivir treatment and 392 of 7453 swabs (5.3%) obtained during valacyclovir treatment. The frequency of detection of HSV in genital swabs was lower during pritelivir treatment than during valacyclovir treatment (relative risk [RR], 0.42; 95% CI, 0.21-0.82; P = .012; Table 2 and Figure 2A). The HSV copy number on the days that HSV was detected did not differ by group: for a mean 3.2 log10 copies/mL during pritelivir treatment vs a mean 3.7 log10 copies/mL during valacyclovir treatment (P = .83; Figure 2B). The frequency of subclinical shedding was significantly lower during pritelivir treatment than during valacyclovir treatment, 1.8% vs 4.1% (RR, 0.40; 95% CI, 0.20-0.81; P = .01; Figure 2C). The rate of shedding when patients reported genital lesions was not significantly different during pritelivir and valacyclovir treatment, 29.9% vs 37.1% (P = .76).

The frequency of shedding episodes was not found to differ by treatment, with 1.3 per person-months while taking pritelivir and 1.6 per person-months while taking valacyclovir (RR, 0.80; 95% CI, 0.52-1.22; P = .29). The proportion of episodes lasting less than 24 hours was higher during receipt of pritelivir vs valacyclovir (87% vs 69%, P = .005; eFigure 1 in Supplement 3).

Subgroup analyses by sex, age, and duration of genital herpes showed potentially stronger reductions in shedding and lesions for women and for those younger than 50 years. However, this study was not designed to compare efficacy between groups; and group differences were not tested statistically. Per-protocol analyses conducted on 51 persons
who completed study medication without protocol deviations also showed similar results (eTable 1 in Supplement 3), except HSV quantity was significantly lower during treatment with pritelivir (pritelivir, log10 2.9 vs valacyclovir, log10 3.7, P < .001) and median duration of recurrences was not significantly lower during pritelivir treatment (3.0 days vs 6.0 days, P = .050). A sensitivity analysis that excluded the initial week of each group was also consistent (eTable 2 in Supplement 3).

**Genital Lesions and Pain**

The overall frequency of genital lesions was low, with participants reporting lesions on only 2.9% of days. However, genital lesions were reported on 1.9% of days during pritelivir treatment compared with 3.9% of days during valacyclovir administration (RR, 0.40; 95% CI, 0.17-0.96; P = .04; Figure 3).

Twenty participants experienced at least 1 recurrence during the study. The median duration of recurrences did not differ by treatment group. The proportion of days with pain was 4.0% while taking pritelivir and 6.7% while taking valacyclovir (RR, 0.53; 95% CI, 0.30-0.93; P = .03).

No period or carryover effects were found for genital shedding or lesion occurrence.

Fifty-five swabs collected during pritelivir administration contained HSV DNA of more than 5000 copies/mL. Fifty-four were sequenced for UL5 and 55 were sequenced for UL52. No change from the reference sequence (HSV-2

---

**Figure 1. Flow of Patients With a History of Genital Herpes Simplex Virus 2 Recurrences Through Crossover Trial Comparing Priteliver With Valacyclovir for Prevention of Genital Herpes Simplex Virus 2 Shedding**

150 Patients assessed for eligibility

- 59 Excluded
  - 18 Not enrolled due to study termination
  - 11 No HSV-2 confirmation
  - 10 Comorbidity or abnormal laboratory results
  - 6 Unwilling to adhere to study protocol
  - 14 Other

91 Randomized

- Period 1 (pritelivir first)
  - 45 Randomized to receive pritelivir
    - 44 Received ≥1 dose of pritelivir as randomized and contributed ≥1 swab (4247 swabs collected)
    - 1 Did not receive pritelivir as randomized (withdrew consent)
  - 38 Completed period 1
    - 5 Terminated the study early
    - 1 Adverse event

- Washout period
  - 32 Completed the washout
    - 5 Terminated the study early
    - 1 Withdraw consent

- Period 2 (valacyclovir second)
  - 32 Received ≥1 dose and provided ≥1 swab of valacyclovir (3279 total swabs collected)
  - 29 Completed the second period
    - 3 Terminated the study early

Primary analysis
- 75 Received pritelivir
- 76 Received valacyclovir

- Period 2 (valacyclovir second)
  - 31 Received ≥1 dose of pritelivir and provided ≥1 swab (3029 total swabs collected)
  - 27 Completed the second period
    - 4 Terminated the study early

Washout period
- 32 Completed the washout
  - 3 Terminated the study early
  - 1 Withdrew consent

- Period 1 (valacyclovir first)
  - 46 Randomized to receive valacyclovir
    - 44 Received ≥1 dose of valacyclovir as randomized and contributed ≥1 swab (4174 total swabs collected)
    - 2 Did not receive valacyclovir as randomized
    - 1 Disallowed medication
    - 1 Nonadherent
  - 36 Completed period 1
    - 6 Terminated the study early
    - 2 Adverse events

The 88 persons included in primary analysis took at least 1 dose and provided at least 1 swab during the first period. “Terminated the study early” indicates hold imposed by US Food and Drug Administration.
strain HG52, accession No. NC_001798.1) was detected in any of the samples.

### Adverse Events

Safety was assessed in all 91 randomized persons; the mean number of days of exposure was 26 for both pritelivir and valacyclovir. Overall, 48 participants (62.3%) had a treatment-emergent adverse event while taking pritelivir and 54 (69.2%) while taking valacyclovir (Table 3; eTables 2 and 3 in Supplement 3). No participant had a DAIDS grade 4 treatment-emergent adverse event; 3 participants had a DAIDS grade 3 treatment-emergent adverse event.

### Table 1. Demographic and Clinical Characteristics of Randomized Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Randomized First Period</th>
<th>Total (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pritelivir (n = 45)</td>
<td>Valacyclovir (n = 46)</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>46 (21-66)</td>
<td>50 (21-61)</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>28 (62)</td>
<td>29 (63)</td>
</tr>
<tr>
<td>White, No. (%)</td>
<td>37 (82)</td>
<td>29 (63)</td>
</tr>
<tr>
<td>Antibody status. No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV-2 only</td>
<td>27 (60)</td>
<td>27 (59)</td>
</tr>
<tr>
<td>HSV-1 and 2</td>
<td>18 (40)</td>
<td>19 (41)</td>
</tr>
<tr>
<td>Years since HSV-2 acquisition, median (range)</td>
<td>15 (1-41)</td>
<td>20 (1-42)</td>
</tr>
<tr>
<td>No. of recurrences per year prior to study, median (range)</td>
<td>5 (4-9)</td>
<td>5 (4-9)</td>
</tr>
<tr>
<td>Suppressive therapy prior to study entry, No. (%)</td>
<td>5 (11)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Contributed to efficacy analyses, No. (%)</td>
<td>44 (98)</td>
<td>44 (96)</td>
</tr>
<tr>
<td>Swabs obtained during study, median, No. (range)</td>
<td>213 (2-231)</td>
<td>214 (13-222)</td>
</tr>
</tbody>
</table>

Abbreviation: HSV, herpes simplex virus.

### Table 2. Bivariable Analysis of Virologic and Clinical Efficacy End Points by Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pritelivir (n = 75)</th>
<th>Valacyclovir (n = 76)</th>
<th>Relative Risk or Difference in Copy No., Pritelivir vs Valacyclovir (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic End Points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital HSV shedding, No./total (%)</td>
<td>173/7276 (2.4)</td>
<td>392/7453 (5.3)</td>
<td>0.42 (0.21 to 0.82)</td>
<td>.01</td>
</tr>
<tr>
<td>Subclinical</td>
<td>127/6989 (1.8)</td>
<td>284/6984 (4.1)</td>
<td>0.40 (0.20 to 0.81)</td>
<td>.01</td>
</tr>
<tr>
<td>Lesional</td>
<td>40/134 (29.9)</td>
<td>106/294 (37.1)</td>
<td>0.86 (0.22 to 3.30)</td>
<td>.76</td>
</tr>
<tr>
<td>Episode/person-mo</td>
<td>78/60</td>
<td>97/61</td>
<td>0.80 (0.52 to 1.22)</td>
<td>.29</td>
</tr>
<tr>
<td>Incidence rate per person-mo</td>
<td>1.3</td>
<td>1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV DNA log10 copies/mL, mean (SD)</td>
<td>3.2 (1.2)</td>
<td>3.7 (1.3)</td>
<td>−0.1 (−0.6 to 0.5)</td>
<td>.83</td>
</tr>
<tr>
<td>Overall</td>
<td>2.8 (0.6)</td>
<td>3.3 (1.0)</td>
<td>−0.3 (−0.5 to −0.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>On days with lesions</td>
<td>4.4 (1.3)</td>
<td>4.8 (1.4)</td>
<td>0.7 (0.1 to 1.0)</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Duration of shedding episodes, median (IQR), h</td>
<td>6.0 (6.0 to 12.0)</td>
<td>6.0 (6.0 to 36.0)</td>
<td>.06c</td>
<td></td>
</tr>
<tr>
<td>Clinical End Points, No./Total (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days with lesions&lt;sup&gt;d&lt;/sup&gt;</td>
<td>35/1855 (1.9)</td>
<td>75/1900 (3.9)</td>
<td>0.40 (0.17 to 0.96)</td>
<td>.04</td>
</tr>
<tr>
<td>Recurrences/person-mo&lt;sup&gt;d&lt;/sup&gt;</td>
<td>11/61</td>
<td>18/63</td>
<td>0.65 (0.35 to 1.22)</td>
<td>.18</td>
</tr>
<tr>
<td>Incidence rate per person-mo</td>
<td>0.2</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days with pain</td>
<td>72/1778 (4.0)</td>
<td>123/1878 (6.7)</td>
<td>0.53 (0.30 to 0.93)</td>
<td>.03</td>
</tr>
<tr>
<td>Duration, median (IQR), d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>4.0 (2.0 to 4.0)</td>
<td>4.0 (2.0 to 4.0)</td>
<td></td>
<td>.83&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Recurrences</td>
<td>3.0 (1.0 to 4.0)</td>
<td>5.0 (3.0 to 6.0)</td>
<td></td>
<td>.10&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: HSV, herpes simplex virus; IQR, interquartile range.

<sup>a</sup> Shading is defined as the number of HSV-positive swabs per study participant relative to the total number of swabs collected per participant. Subclinical shedding includes only swabs on days without genital lesions and lesional shedding includes only swabs on days when genital lesions were present. Three randomized participants are not included in the intent-to-treat efficacy analyses because they either contributed no swabs or received no study medication.

<sup>b</sup> This result is due to 1 person who started in the pritelivir group during a lesion, a protocol violation. When the person with the lesion at the start was removed, the effect was reversed −0.4 (−0.6 to −0.2; P < .001).

<sup>c</sup> Model-predicted differences (ratios) do not always match raw differences (ratios) due to weighting in correlated regression.

<sup>d</sup> From Wilcoxon rank-sum test, predicted to be shorter on pritelivir, if significant.

<sup>e</sup> These regressions were not adjusted for site and sex because the outcome was too uncommon, and the model did not converge.
Figure 2. Herpes Simplex Virus Detection and Viral Load by Study Group

A, Genital HSV shedding

B, Levels of HSV DNA in positive genital swabs

C, Asymptomatic HSV shedding

A, Genital samples with $150 \log_{10}$ copies/mL of herpes simplex virus (HSV) DNA or more were considered positive for the virus. Of the 63 persons contributing swabs while taking both treatments, 62 contributed at least 15 swabs for both periods and were included in the figure. The median number of swabs contributed was 108 (interquartile range [IQR], 105-109) while taking valacyclovir and was 108 (IQR, 105-109) while taking pritelivir. B, There were 392 positive samples taken during valacyclovir treatment, and 173 positive samples taken during pritelivir treatment. The horizontal bars indicate the median $\log_{10}$ copies/mL of HSV DNA. C, Of 63 persons contributing swabs while taking both treatments, 62 contributed at least 15 asymptomatic swabs during both periods and were included in the figure. The median number of swabs contributed was 105 (range, 93-109) while taking valacyclovir and was 108 (range, 101-109) while taking pritelivir.

during pritelivir administration (elevated lipase, elevated alanine aminotransferase, and migraine); and 3 participants had a DAIDS grade 3 treatment-emergent adverse event during valacyclovir administration (dyspareunia, tooth infection and back pain, and headache and malaise). No deaths or serious adverse events were observed. Potential changes in hemoglobin, white blood cell count, and liver function tests were evaluated statistically. In a paired analysis,
although white blood cell counts were unchanged at every visit, there were statistically significant but not clinically relevant changes in the mean lymphocyte count (110-230100 ×3/μL lower) and creatinine levels (0.03 and 0.05 mg/dL higher [to convert to μmol/L, multiply by 76.25]) during pritelivir administration (eFigure 2 in Supplement 3).

At the week-4 visit following cessation of therapy, only the creatinine levels remained 0.02 mg/dL higher in pritelivir than in the valacyclovir group.

One participant was randomized in error and discontinued from the study due to a prolonged QT interval that was noted prior to initiating therapy with pritelivir. One participant receiving pritelivir developed urticaria without angioedema and was discontinued on day 10, and one participant receiving valacyclovir discontinued treatment on day 7 because of a constellation of mild symptoms that included headache, insomnia, and anxiety; these treatment-emergent adverse events were considered probably or possibly related to the trial medication. The percentage of participants with skin and subcutaneous tissue disorders were similar during pritelivir (10.4%) and valacyclovir (9.0%) treatment.

### Discussion

Among adults with frequent recurrences of genital HSV-2, the use of pritelivir compared with valacyclovir resulted in a lower percentage of swabs with HSV detected over 28 days.
Pritelivir decreased the number of days of overall genital shedding, subclinical shedding, and genital lesions over the total number of positive swabs and days with lesions, respectively, compared with valacyclovir in intent-to-treat analysis. The frequency of pain was also reduced. In addition, in per-protocol analysis, quantity of virus shed was also decreased significantly during pritelivir treatment compared with valacyclovir treatment. No sequence variation in the UL5 and UL52 regions associated with resistance to pritelivir in vitro was detected in genital swabs obtained during pritelivir therapy.

A crossover design of the trial allowed participants to be their own controls. This design is more efficient relative to a parallel group study of the same size because in patients with established genital HSV-2 infection, shedding and recurrence rates have been shown to be stable over months and shedding rates are highly variable between persons; thus, studying within-person changes allows for a more precise estimate of treatment efficacy. In addition, each study participant in a crossover trial is treated with both drugs. A potential drawback to this design occurs if either there are temporal trends that affect shedding rates over time, if the effect of the first drug remains after the second drug is initiated, or if there are high dropout rates, which would make within-participant comparisons unfeasible. The placebo-controlled trial of pritelivir suggested that a month-long washout period is sufficient because shedding rates returned to baseline within 2 weeks of drug cessation.

Currently available nucleoside analogues improve the clinical outcomes in genital herpes and improve the quality of life of those who choose suppressive therapy. However, breakthrough viral shedding and recurrences still occur, as well as sexual and perinatal transmission. Furthermore, nucleoside analogues only partly mitigate the more severe HSV syndromes such as neonatal HSV or HSV encephalitis, and the options for immunocompromised patients who develop resistance to acyclovir are severely limited. In addition, the availability of nucleoside analogues has not affected the prevalence of HSV-2, likely because most patients are not diagnosed or not treated and because the drugs are insufficiently potent to completely abrogate viral shedding and transmission. Whether a more potent regimen would have the potential to reduce HSV-2 infection on the population level requires further study, akin to the work currently conducted on HIV incidence by lowering the community viral load.

Conclusions

Among adults with frequently recurring genital HSV-2, the use of pritelivir compared with valacyclovir resulted in a lower percentage of swabs with HSV detection over 28 days. Further research is needed to assess longer-term efficacy and safety.
Effect of Pritelivir vs Valacyclovir on Genital HSV-2 Shedding

Original Investigation  Research

University of Washington from Gilead, Vical, and Genocere, and travel funds from Admedus.

Dr Magaret reports consulting for Acicuris and Immune Design. Ms Warren and Drs Fife and Tyring report receiving clinical trial support through their institutions from Acicuris. Dr Johnston reports receiving clinical trial support through her institution from Acicuris and Sanofi Pasteur. Dr Corey reports holding stock in Immune Design and being a coinventor on several patents associated with the development of an HSV-2 vaccine. Dr Birkmann reports contributing to patents related to galenic and the synthesis of drug substances through Acicuris. Drs Timmler, Stobernack, Zimmermann, Birkmann, and Ruebsamen-Schaeff are employees of Acicuris. Drs Timmler, Zimmermann, Birkmann, and Ruebsamen-Schaeff report holding stock options in Acicuris. No other disclosures are reported.

Funding/Support: This study was supported by Acicuris GmbH & Co KG.

Role of the Funder/Sponsor: The study was designed collaboratively by investigators at University of Washington and Acicuris. Acicuris had a role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The sponsor did not have the right to prevent submission or publication of the data. The statistical analyses reported herein were conducted independently at the University of Washington.


REFERENCES


