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# Oral brivudin in comparison with acyclovir for improved therapy of herpes zoster in immunocompetent patients: results of a randomized, double-blind, multicentered study

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**Abstract**

Brivudin [(*E*)-5-(2-bromovinyl)-2′-deoxyuridine] is a nucleoside analogue with a high and selective antiviral activity against varicella-zoster virus (VZV) and herpes simplex virus type 1 (HSV-1). The double-blind, randomized study presented here compared efficacy and safety of oral brivudin 1 × 125 mg and acyclovir 5 × 800 mg, both for 7 days, in 1227 immunocompetent patients with herpes zoster. Main results were as follows: brivudin was superior to acyclovir in accelerating the "time to last formation of new vesicles" (primary parameter; risk ratio$_{ITT}$: 1.13, $P = 0.014$). Equivalent effects of brivudin and acyclovir were observed for the secondary parameters "time to first crust" (RR$_{ITT}$: 0.93, $P = 0.004$), "time to full crusting" (risk ratio$_{ITT}$: 1.03, $P < 0.001$), and "time to loss of crusts" (RR$_{ITT}$: 0.95, $P = 0.002$). The incidence of potentially treatment-related adverse events was similar under brivudin (7.7%) and acyclovir (10.0%). In conclusion, brivudin proved to be more effective than acyclovir in terminating vesicle formation, the parameter which reflects the end of viral replication, thus confirming, in the clinical setting, the greater in vitro antiviral activity of brivudin. Compared with acyclovir, brivudin provides a similar safety profile and a significant improvement in efficacy.


*Keywords:* Brivudin; Herpes zoster; Acyclovir; Clinical trials

## 1. Introduction

Herpes zoster, the acute reactivation of latent varicella-oster virus (VZV) infection, is a common ailment with an annual incidence reported to reach values between 1.3 and 4.8 cases per 1000 person-ears (McGregor, 1957; Hope-Simpson, 1965; Ragozzino et al., 1982; Wilson, 1986; Glynn et al., 1990; Helgason et al., 1996). Particularly in the elderly, herpes zoster is often accompanied by acute zoster-associated pain (ZAP) and chronic pain prevailing after resolution of acute signs and symptoms, the so-called postherpeutic neuralgia (PHN). Growing clinical experience with antiviral compounds in zoster therapy has shown that the rapid initiation of treatment with drugs like acyclovir, penciclovir, and their respective prodrugs reduces the duration of zoster lesion formation, accelerates healing of zoster rash, and reduces the duration of acute zoster-related pain (McKendrick et al., 1986; Huff et al., 1988; Wood et al., 1988; Tyring et al., 1995; Beutner et al., 1995). Oral acyclovir is still widely used for the treatment of herpes zoster, although it requires the inconvenient and high dose regimen of 800 mg given five times daily because of its relatively low anti-ZV activity, its poor oral bioavailability, and its short half-life (de Miranda and Blum, 1983; Brigden and Whiteman, 1985). The newer antiviral compounds valaciclovir (prodrug of acyclovir) and famciclovir (prodrug of penciclovir) offer improved oral bioavailability over acyclovir, but still have to be administered three times daily in relatively high doses of 1000 and 250–500 mg, respectively (Degreef, 1994; Beutner et al., 1995; Dworkin et al., 1998; Tyring et al., 2000).

Thus, there is still need for an effective antiviral therapy providing a more convenient dose regimen at lower drug doses, aiming at enhancing compliance and reducing the risk of suboptimal treatment of herpes zoster.

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Brivudin [(*E*)-5-(2-bromovinyl)-2′-deoxyuridine] is a 5′ halogenated thymidine nucleoside analogue with a high and selective antiviral activity against varicella-zoster virus (VZV) and herpes simplex virus type 1 (HSV-1) (De Clercq, 1984, 1993; Snoeck et al., 1994). In cell culture, brivudin proved to be substantially more potent against VZV than acyclovir and penciclovir. In clinical VZV strains, the 50% inhibitory concentration ($IC_{50}$) was 0.0033 μM for brivudin compared to 0.93 μM for acyclovir and 3.6 μM for penciclovir (Andrei et al., 1995). It was therefore anticipated that a once daily dose regimen with brivudin 125 mg once daily for 7 days, may be sufficient for an effective antiviral treatment of herpes zoster. The present Phase III study was conducted to confirm this hypothesis by comparing safety and efficacy of a 7-day treatment course with oral brivudin 125 mg once daily and standard oral acyclovir in immunocompetent adult patients with herpes zoster.

To date, oral brivudin (1 × 125 mg for 7 days) is licensed for the treatment of herpes zoster in several countries of the European Union (Austria, Belgium, Germany, Greece, Italy, Luxembourg, Portugal, and Spain).

## 2. Materials and methods

The study was conducted from February 1997 to August 1997 in compliance with the European guidelines on Good Clinical Practice (GCP).

### 2.1. Patients

Patients eligible for enrollment were Caucasians of either gender aged 18 years or older with untreated herpes zoster showing typical vesicular eruptions in an area of at least 3 $cm^2$ predominantly in one dermatome. Further inclusion criteria comprised the first occurrence of vesicles within the last 48 h and continued formation of vesicles during the last 24 h prior to start of treatment. Main exclusion criteria were ophthalmic and/or CNS complications and/or visceral dissemination during the present or any previous herpes zoster episodes, evidence of congenital, acquired, or drug-induced immunodeficiency (including any malignancy), and any history of intolerance or hypersensitivity to the medication used in the study. Also excluded were patients with impaired renal or hepatic function, pregnant or nursing women, as were patients treated with 5-fluorouracil and/or any other antimetabolites since the main metabolite of brivudin, bromvinyluracil (BVU) is known to interfere with the catabolism of fluorinated pyrimidines (Desgranges et al., 1986; Keizer et al., 1994).

### 2.2. Procedures

A total of 303 study centers in 15 countries (Belgium, The Czech Republic, Denmark, Finland, France, Germany, Great Britain, Hungary, Israel, The Netherlands, Poland, Romania, South Africa, Spain, and the Ukraine) participated in the study. Study centers were general practitioners or dermatologists in private practice, regional treatment centers, and hospital facilities. Each study center was supervised through regular monitoring visits during which the case report forms were checked for completeness and consistency with the corresponding source data. In all participating countries investigator meetings took place at which the investigators were informed in detail on the study procedures. Quality audits were performed by an independent Quality Assurance Unit.

A computer-generated randomization list was provided by an independent institute. A center block randomization was used. The investigator assigned study medication to new patients in ascending order, using the next random number at his/her site. Each investigator was provided with sealed emergency envelopes containing information on the treatment of each patient.

Patients were either assigned to treatment with brivudin 125 mg once daily or acyclovir 800 mg five times daily. All patients received study medication for 7 days. Since brivudin tablets and acyclovir tablets differ in appearance (round tablets versus oblong tablets) and in their dose regimen (drug intake once daily versus five times daily), double-blind conditions were provided by using a double-dummy technique.

Before dosing, patients underwent a physical examination (including taking of blood samples) during which the diagnosis of herpes zoster was clinically confirmed, health status was checked and the time of rash onset was recorded. Clinic visits took place every day during the first week after start of treatment (days 1–8, treatment phase), every other day during the second week (days 10, 12, 14), and once a week during the third and fourth week (days 21, 28, 35). Patients were provided with a diary and were instructed to record five times daily (every 4 h while awake with each intake of study medication) the status of cutaneous zoster symptoms and zoster-related pain. During each clinic visit, diary entries were reviewed by the investigator who, on the basis of his/her own observations and with the help of the patient diary, determined whether any change of zoster lesion stage (appearance of new vesicles, appearance of crusts, encrustation of all vesicles, loss of crusts) and pain (presence/absence of pain, pain intensity, type of pain) had occurred since the last visit. Patients terminated the study when all crusts had fallen off or on day 35 after start of treatment, whichever occurred first.

### 2.3. Efficacy assessments

The primary efficacy endpoint was the time from start of treatment to last eruption of herpes zoster vesicles. Secondary endpoints included the time from start of treatment to start of crusting, complete crusting, and complete loss of crusts, time from start of treatment to cessation of acute ZAP, pain intensity, and use of analgesic medication. For the evaluation of acute pain, patients received a diary to record the intensity of pain daily by the use of a 6-point scale (0: “no pain”, 1: “mild”, 2: “discomforting”, 3: “distressing”,

4: “severe”, 5: “unbearable”). The type of pain could be described as either “constant”, or “shooting”. Any use of analgesic medication was recorded daily.

### 2.4. Safety assessments

Adverse events were recorded during all periods of the clinical study and categorized by intensity, seriousness, and causality. The outcome and the action taken concerning the adverse event were also recorded. On day 1 and day 8, blood samples were obtained for hematology and clinical chemistry and urine samples were obtained for protein, glucose, and bilirubin determination.

### 2.5. Statistical analysis

Kaplan–Meier methods were used to evaluate time-to-event parameters. Primary and secondary efficacy variables were analyzed for both the intent-to-treat (ITT) population and the per-protocol (PP) population using the Cox proportional hazards model which included the covariates “age” (log), “pain at baseline” and “time since first eruption of vesicles”.

The sample size calculations were based on the exponential distribution with proportional hazards and on the assumption that non-inferiority of brivudin towards acyclovir could be stated if brivudin reached 80% of the effect of acyclovir. A previous study indicated that with this non-inferiority limit, superiority towards the spontaneous course of disease (placebo treatment) is still given. The power to detect a difference between the treatment groups was set at 90% (with a one-sided significance level of 0.05). Computation was performed using SAS statistical software, SAS Institute Inc., Cary, NC, USA.

## 3. Results

After giving written informed consent, a total of 1227 patients underwent randomization and were enrolled in the study. Six hundred and fourteen patients were randomly allocated to treatment with brivudin and 613 to treatment with acyclovir. Eighteen brivudin recipients and 21 acyclovir recipients discontinued the study prematurely. Of these, 7 brivudin recipients and 11 patients treated with acyclovir were withdrawn because of adverse events. Altogether, 592 acyclovir recipients and 596 brivudin recipients regularly completed the trial (see Fig. 1).

All patients who were randomly assigned to one of the two treatments, had taken at least one dosage of study medication, and provided data for the primary efficacy variable ($n = 1225$; brivudin: $n = 612$, acyclovir: $n = 613$) entered into the ITT analysis. Of these, 1059 patients (brivudin: $n = 539$, acyclovir: $n = 520$) did not show major protocol violations and entered into the PP analysis.

Demographic and baseline characteristics including herpes zoster findings and pain at baseline were similar in both treatment groups (see Table 1).

Table 1
Demographics and baseline characteristics

| | PP | | ITT | |
|---|---|---|---|---|
| | Brivudin (1 × 125 mg) | Acyclovir (5 × 800 mg) | Brivudin (1 × 125 mg) | Acyclovir (5 × 800 mg) |
| Number of patients | 539 | 520 | 612 | 613 |
| % female:male | 58.4:41.6 | 52.3:47.7 | 59.0:41.0 | 53.0:47.0 |
| Mean age ± S.D. (years) | 52.3 ± 17.6 | 53.6 ± 17.8 | 53.2 ± 17.8 | 53.7 ± 17.6 |
| <50 years (%) | 40.3 | 38.8 | 38.1 | 38.7 |
| ≥50 years (%) | 59.7 | 61.2 | 61.9 | 61.3 |
| Location of rash (%) | | | | |
| Cranial | 12.1 | 12.3 | 11.6 | 13.2 |
| Cervical | 17.1 | 17.9 | 17.5 | 17.5 |
| Thoracic | 59.4 | 54.6 | 58.2 | 55.0 |
| Lumbar | 12.2 | 14.6 | 13.4 | 14.0 |
| Sacral | 3.2 | 3.3 | 3.4 | 2.8 |
| Number of affected dermatomes (%) | | | | |
| 1 | 75.1 | 77.1 | 74.7 | 76.2 |
| 2 | 19.9 | 16.3 | 19.6 | 16.2 |
| 3 | 5.0 | 6.5 | 5.7 | 7.7 |
| Maximum pain intensity at baseline (%)[a] | | | | |
| None | 10.6 | 10.2 | 10.9 | 10.8 |
| Mild | 14.8 | 17.9 | 14.1 | 17.9 |
| Discomforting | 26.3 | 25.2 | 26.3 | 24.8 |
| Distressing | 32.3 | 28.8 | 32.5 | 28.7 |
| Severe | 13.4 | 16.2 | 13.6 | 16.3 |
| Unbearable | 2.4 | 1.7 | 2.5 | 1.5 |

[a] No data available for one brivudin recipient (ITT and PP population).

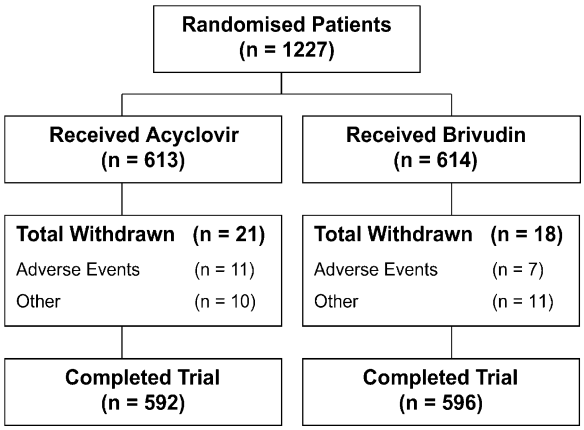


Fig. 1. Study participants' flow. "Other" reasons for withdrawal from the study were: patient's request, lack of patient compliance, non-confirmation of the diagnosis "herpes zoster".

### 3.1. Cutaneous lesion resolution

#### 3.1.1. Eruption of new zoster lesions

The mean time from start of treatment to last eruption of herpes zoster vesicles was 13.7 h in the brivudin group compared to 17.7 h in the acyclovir group (ITT). In the ITT-population, the estimated risk ratio for the comparison of brivudin and acyclovir was 1.13, indicating a 13% better treatment effect for patients treated with brivudin (see Table 2; Fig. 2).

Not only equivalence, but also superiority of brivudin over acyclovir could be demonstrated ($P = 0.014$). Comparable results were found for the PP population (see Table 2). Subgroup analysis in patients aged 50 years and older underlined the superiority of brivudin with regard to the time to cessation of new vesicle formation (see Table 3). In the ITT-subpopulation, the estimated risk ratio was 1.16, indicating a 16% (PP: 19%) better treatment effect for patients treated with brivudin as compared to the acyclovir recipients ($P = 0.022$).

#### 3.1.2. Healing of zoster lesions

Brivudin was found to be as effective as acyclovir in healing herpes zoster lesions as shown by risk ratio analysis of the time from start of treatment to start of crusting, to complete crusting, and to complete loss of crusts. Formation of crusts started within a mean of 65.3 h after initiation of therapy in the brivudin group and within 63.3 h in the acyclovir group (ITT-population, $P = 0.004$).

Full crusting occurred 140.7 h (mean) after start of treatment in the acyclovir group and after 137.8 h in the brivudin group (ITT), again demonstrating comparable efficacy of brivudin and acyclovir ($P < 0.001$). The time to loss of crusts was also found to be comparable in patients receiving brivudin and those receiving acyclovir. The $P$ value for non-inferiority was 0.002 for the ITT-population (see Table 2).

### 3.2. Zoster-associated pain

A patient was regarded as showing cessation of acute zoster pain if pain intensity reported at the respective visit and during all following visits was "none". For the

Table 2
Resolution of cutaneous lesions and acute phase pain Cox proportional hazards model[a]

| Time from start of treatment | PP | | ITT | |
|---|---|---|---|---|
| | Brivudin ($n = 539$) | Acyclovir ($n = 520$) | Brivudin ($n = 612$) | Acyclovir ($n = 613$) |
| Last eruption of vesicles | | | | |
| Mean ± S.D. (h) | 13.5 ± 20.8 | 18.0 ± 31.0 | 13.7 ± 21.3 | 17.7 ± 29.5 |
| Risk ratio ($CI_{95\%}$) | 1.14 (1.01–1.29) | 1.14 (1.01–1.29) | 1.13 (1.01–1.27) | 1.13 (1.01–1.27) |
| $P$ value$_{(1)}$ | 0.017 | 0.017 | 0.014 | 0.014 |
| Start of crusting | | | | |
| Mean ± S.D. (h) | 65.7 ± 56.3 | 63.9 ± 59.4 | 65.3 ± 55.1 | 63.3 ± 56.5 |
| Risk ratio ($CI_{95\%}$) | 0.92 (0.81–1.03) | 0.92 (0.81–1.03) | 0.93 (0.83–1.05) | 0.93 (0.83–1.05) |
| $P$ value$_{(2)}$ | 0.015 | 0.015 | 0.004 | 0.004 |
| Full crusting | | | | |
| Mean ± S.D. (h) | 138.2 ± 83.8 | 143.1 ± 83.3 | 137.8 ± 88.0 | 140.7 ± 82.0 |
| Risk ratio ($CI_{95\%}$) | 1.04 (0.92–1.17) | 1.04 (0.92–1.17) | 1.03 (092–1.16) | 1.03 (092–1.16) |
| $P$ value$_{(2)}$ | <0.001 | <0.001 | <0.001 | <0.001 |
| Loss of crusts | | | | |
| Mean ± S.D. (h) | 364.7 ± 173.9 | 358.9 ± 170.8 | 360.3 ± 177.7 | 350.2 ± 174.1 |
| Risk ratio ($CI_{95\%}$) | 0.96 (0.85–1.08) | 0.96 (0.85–1.08) | 0.95 (0.85–1.07) | 0.95 (0.85–1.07) |
| $P$ value$_{(2)}$ | 0.002 | 0.002 | 0.002 | 0.002 |
| Cessation of acute pain | | | | |
| Mean ± S.D. (h) | 263.4 ± 208.7 | 260.6 ± 194.6 | 266.0 ± 211.8 | 258.4 ± 197.9 |
| Risk ratio ($CI_{95\%}$) | 1.01 (0.87–1.16) | 1.01 (0.87–1.16) | 0.996 (0.87–1.14) | 0.996 (0.87–1.14) |
| $P$ value$_{(2)}$ | 0.001 | 0.001 | 0.001 | 0.001 |

$P$ value$_{(1)}$ = test for superiority; $P$ value$_{(2)}$ = test for non-inferiority.
[a] Covariates are age (log), pain at baseline, time since first eruption of herpes zoster vesicles.

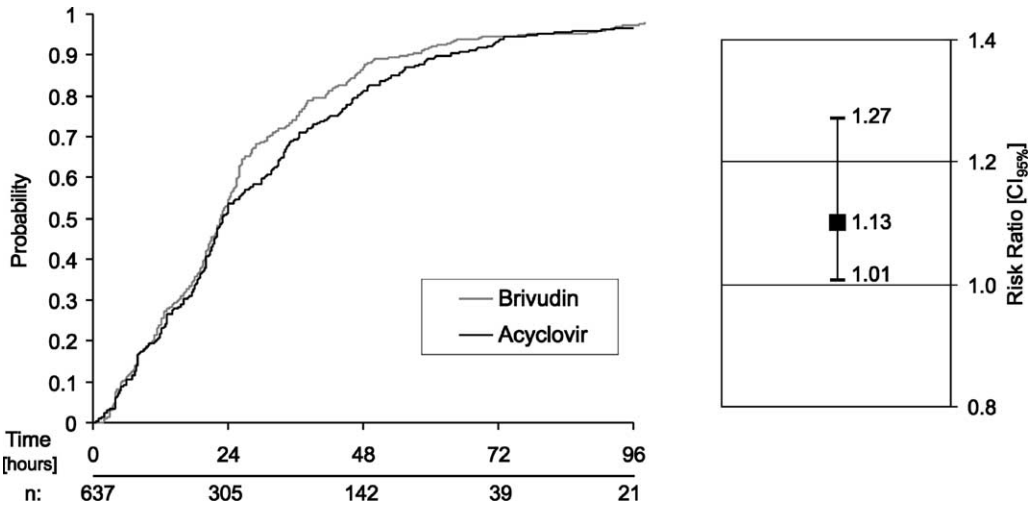


Fig. 2. Intent-to-treat analysis of the primary endpoint "time from start of treatment to last vesicular eruption". Kaplan–Meier curves for herpes zoster patients treated with oral brivudin 125 mg once daily and for patients treated with acyclovir 800 mg five times daily, both for 7 days. The letter *n* indicates the overall number of patients still showing vesicle formation at the respective time points (left). Graphical display of the 95% confidence interval with upper and lower limit (┬) and the point estimate (■) (right).

variables "time from start of treatment to cessation of acute zoster-related pain", it could be shown that brivudin is as effective as acyclovir as indicated by the risk ratio$_{ITT}$ = 0.996 ($P$ = 0.001). Similar results were found for the PP population (see Table 2). Comparable efficacy of brivudin and acyclovir was also demonstrated for the maximum intensity of acute pain during the entire study as measured by weighted mean score values. The mean pain intensity score was 1.25 in both treatment groups (ITT-population).

The use of analgesics was comparable in the two treatment groups. At baseline, 17.3% of the brivudin recipients and 14.2% of the acyclovir recipients required analgesic treatment. The proportion of patients using pain therapy had its maximum at day 2 after start of treatment (brivudin: 33.3%, acyclovir: 35.2%) and steadily decreased thereafter. The most frequently used analgesics were anilides (e.g. paracetamol), low-potency opioids (e.g. tramadol), salicylic acid preparations, and acetic acid derivatives (e.g. diclofenac), with no overt difference between the treatment groups.

### 3.3. Adverse events

During the acute phase, a total of 453 adverse events were reported in 275 (22.4%) of the 1227 patients who had taken at least one dose of study medication (safety population). Most adverse events were mild, transient, and considered not attributable to study medication. Gastrointestinal disturbance and headache were the most frequently reported events in both treatment groups (see Table 4). There was no relevant difference between the treatment groups regarding the percentage of patients reporting adverse events (brivudin: 23.0%, acyclovir: 21.9%). There was no relevant difference between the two groups in the rate of adverse events consi-

Table 4
Potentially treatment-related[a] adverse events reported in ≥0.5% of patients (safety population $n$ = 1227)

| Event | Number of patients (%) | |
|---|---|---|
| | Brivudin ($n$ = 614) | Acyclovir ($n$ = 613) |
| Nausea | 16 (2.6) | 13 (2.1) |
| Headache | 6 (1.0) | 7 (1.1) |
| Abdominal pain | 5 (0.8) | 4 (0.7) |
| Dizziness | 4 (0.7) | 1 (0.2) |
| Vomiting | 3 (0.5) | 7 (1.1) |
| Gamma-GT elevated | 1 (0.2) | 4 (0.7) |

[a] Including definite, possible, and probable relationship to study medication.

Table 3
Subpopulation of patients ≥50 years of age: Cox proportional hazards model[a]

| Time from start of treatment | PP | | ITT | |
|---|---|---|---|---|
| | Brivudin ($n$ = 322) | Acyclovir ($n$ = 318) | Brivudin ($n$ = 379) | Acyclovir ($n$ = 376) |
| Last eruption of vesicles | | | | |
| Mean ± S.D. (h) | 14.7 ± 21.3 | 19.1 ± 27.3 | 15.3 ± 22.3 | 18.8 ± 26.2 |
| Risk ratio (CI$_{95\%}$) | 1.19 (1.02–1.39) | 1.19 (1.02–1.39) | 1.16 (1.01–1.34) | 1.16 (1.01–1.34) |
| $P$ value$_{(1)}$ | 0.015 | 0.015 | 0.022 | 0.022 |

$P$ value$_{(1)}$ = test for superiority.
[a] Covariates are age (log), pain at baseline, time since first eruption of herpes zoster vesicles.

dered to be related (including definitely, possibly, and probably related events) to study medication [7.7% (brivudin) versus 10.0% (acyclovir)]. In both treatment groups, gastrointestinal disturbances and headache were the most frequently reported adverse events. Nine brivudin-treated patients and 13 acyclovir recipients discontinued the treatment due to adverse events. Serious adverse events were reported for three brivudin recipients and for four patients of the acyclovir group. None of these serious adverse events could be attributed to the treatment-study medication. No deaths occurred during the study.

## 4. Discussion

The study described here compares efficacy and safety of brivudin 125 mg once daily and standard acyclovir 800 mg five times daily, both for 7 days, in the treatment of herpes zoster in immunocompetent patients and introduces oral brivudin as a new option in herpes zoster therapy.

The rationale of antiviral treatment in herpes zoster is to stop viral replication as quickly as possible, first to limit the acute disease, and second to prevent neurological damage which can result in troublesome sequelae such as PHN (Wassilew, 1987). As viral replication leads to continued formation of new zoster vesicles, the time to cessation of new vesicle formation is generally regarded as the most suitable parameter to evaluate the ability of an anti-VZV agent to stop viral replication. With regard to this parameter, which was used as primary endpoint in many previous herpes zoster studies, brivudin proved to be superior to acyclovir by showing a 13% better treatment effect in all patients according to the intention-to-treat principle. In the PP population the risk ratio was 1.14 indicating a 14% better treatment effect of brivudin as compared to acyclovir. Therefore, it can be concluded that brivudin treatment stops viral replication significantly faster than treatment with acyclovir. Subgroup analysis in patients $\geq$50 years of age corroborated these findings by showing a 16% (ITT) better treatment effect (PP: 19%) of brivudin as compared to acyclovir.

Furthermore, brivudin has been shown to be as effective as acyclovir in accelerating healing of zoster lesions as measured by the time to first crust, time to full crusting, and time to loss of crusts. Results for lesion healing under acyclovir obtained in this study largely correspond to those previously published (McKendrick et al., 1986). A unique advantage of brivudin treatment is its convenient dose regimen, offering effective herpes zoster treatment with only one daily drug intake. This advantage of brivudin is likely to enhance compliance and reduce the risk of suboptimal treatment of herpes zoster. Overall, brivudin was well tolerated with a safety profile comparable to that of acyclovir, a drug which proved to be very safe in broad clinical use.

To conclude, the present study demonstrated in a large patient population that brivudin offers significant advantages over acyclovir, particularly in shortening the viral replication phase of the disease. This result confirms in clinical conditions the significantly higher antiviral activity of brivudin demonstrated in vitro in comparison with acyclovir. It is of particular clinical relevance that superiority of brivudin over acyclovir with regard to stopping the formation of new vesicle was also demonstrated in patients aged 50 years or older, those who are most frequently affected by herpes zoster (Ragozzino et al., 1982) and show a higher risk of developing complications such as PHN (Whitley et al., 1998). Treatment with brivudin 125 mg offers a convenient once daily dose regimen and is well tolerated. Therefore, brivudin represents a valuable new option in herpes zoster therapy.

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