Efficacy and Safety of the Neuraminidase Inhibitor Zanamivir in the Treatment of Influenza A and B Virus Infections

A. S. Monto,1 D. M. Fleming,2 D. Henry,4 R. de Groot,1 M. Makela,6,8 T. Klein,7 M. Elliott,8 O. N. Keene,3 and C. Y. Man3

The efficacy and safety of zanamivir, administered 2× or 4× daily over 5 days, was evaluated in the treatment of influenza infections. A total of 1256 patients entered the study; 57% of those randomized had laboratory-confirmed influenza infection. The primary end point, “alleviation of major symptoms,” was created to evaluate differences in clinical impact. In the overall population with or without influenza infection, zanamivir reduced the median number of days to reach this end point by 1 day (P = .012 2× daily vs. placebo; P = .014 4× daily vs. placebo). The reduction was greater in patients treated within 30 h of symptom onset, febrile at study entry, and in defined high-risk groups. Zanamivir reduced nights of disturbed sleep, time to resumption of normal activities, and use of symptom relief medications. It was well tolerated. These results suggest that zanamivir can significantly reduce the duration and overall symptomatic effect of influenza.

Outbreaks of influenza occur every winter in temperate regions of the world, generally accompanied by increased mortality in high-risk groups such as the elderly and those with chronic conditions [1]. Morbidity in the general population also increases, in some years dramatically, resulting in significant time off work or school with loss of productivity, as symptoms can last ≥7 days [2–4]. Recognition of this burden of illness has resulted in increased attention to methods for appropriate treatment and prophylaxis [5].

Vaccination is clearly the standard form of prophylaxis. However, for a variety of reasons, illnesses will continue to occur, especially in children and young adults, the groups at greatest risk for morbidity [6]. Antiviral agents, when given early in the course of infection, can reduce the duration and severity of symptoms and lessen the overall impact of influenza infection [7]. Two antiviral agents, amantadine and rimantadine, are currently approved for the treatment of influenza infections but are not widely used [8, 9]. They are limited in their availability in some countries, and there are questions about risks of side effects and the selection of drug-resistant variants [10, 11]. They are effective against type A viruses alone, which makes use problematic in years when mixed outbreaks occur [12]. Thus, there is a clear need for an effective antiviral agent with a broader spectrum of activity and an improved safety profile.

Zanamivir, formerly termed GG167, is the first of a new class of antiviral agents that acts by inhibiting the influenza neuraminidase, an enzyme essential for viral replication in vitro [13, 14]. It is active against both A and B influenza strains in vitro and in animal models and in young adults challenged experimentally with type A and B influenza viruses [15, 16].

The clinical efficacy of topically administered zanamivir against natural influenza challenge was shown in a placebo-controlled multicenter study involving 417 adults, 262 with confirmed influenza infection [17]. Among the latter group, the drug reduced the median time to alleviation of the major symptoms of influenza by ≥1 day. More recently, more dramatic reduction of duration has been demonstrated [18].

We describe a multicenter study involving 1256 subjects. The study was undertaken to define further the clinical efficacy and safety of zanamivir in a large population that included persons at high risk for developing complications of influenza infection. This study evaluated the effect of therapy both in terms of time to alleviation of symptoms and also by using indicators of illness severity.

Received 28 December 1998; revised 19 March 1999; electronically published 2 July 1999.

All subjects gave written informed consent to participate in the study. The study was conducted in accordance with the ethical principles set out in the Declaration of Helsinki.

Financial support: GlaxoWellcome Research and Development.

Reprints or correspondence: Dr. A. S. Monto; University of Michigan, School of Public Health, Dept. of Epidemiology, 109 Observatory St., Ann Arbor, MI 48109 (asmonto@umich.edu).

The Journal of Infectious Diseases 1999;180:254–61
© 1999 by the Infectious Diseases Society of America. All rights reserved. 0022-1899/99/8002-0002$02.00
Methods

Study design. The study was a double-blind randomized placebo-controlled multicenter parallel-group study that compared the efficacy and safety of zanamivir administered 2× or 4× a day for treatment of influenza A and B infections. The study was double-blind to active treatment versus placebo but not for dosing schedule. Patients were enrolled within 48 h of the onset of symptoms and were followed for 21 days. They recorded their symptoms 2× daily for 10 days. Study sites were located in North America and Europe.

Subjects. Otherwise healthy persons ages ≥13 years who presented with symptoms of influenza of ≤48 h duration were enrolled in the study during a single influenza season (November 1995 through March 1996). Symptoms of influenza were defined as feverishness and two or more of the following symptoms: myalgia, headache, cough, or sore throat. In order to increase the likelihood of enrolled patients having confirmed influenza infections, recruitment from a particular center was only started after influenza was confirmed to be circulating in the community, that is after more than 2/5 diagnostic samples collected within a 7-day period were influenza-positive.

Subjects ages ≥65 years or with the following chronic illnesses were included and regarded as being at high risk for developing complications or having more severe or prolonged illness: cardiovascular conditions (excluding hypertension), respiratory conditions, and endocrine or metabolic conditions. However, we excluded persons with any unstable chronic illness, those who had taken other antiviral agents in the previous 7 days, and those with known or suspected hypersensitivity to any component of the study medication. Pregnant or breast-feeding women and women at risk who had received influenza vaccination for the season but had laboratory confirmation of influenza prior to receiving the first dose of medication were included in the study. Subjects received training in the use of the inhaler (Diskhaler) and nasal spray devices; those who were unable to use the devices satisfactorily were excluded from the study.

Study procedure. On the first treatment day, a medical history was obtained, and a physical examination was conducted. Blood samples were collected for clinical laboratory assessments and influenza serology; urine was obtained from female patients for pregnancy testing. In addition, a nasal/throat specimen was collected for influenza diagnosis. All laboratories cultured samples from day 1: some centers also performed rapid tests.

Subjects were randomized in the ratio 2:2:1:1 to receive one of the following treatments for 5 days: zanamivir, 10 mg 2×/day by oral inhalation plus 6.4 mg 2×/day by nasal spray; zanamivir, 10 mg 4×/day by oral inhalation plus 6.4 mg 4×/day by nasal spray; placebo by both routes 2×/day; or placebo by both routes 4×/day. Placebo groups were combined for analysis. Medication was self-administered, and subjects were instructed to take the inhaled medication before the intranasal medication. All were given the first dose of trial medication under supervision during their first visit.

All subjects were provided with acetaminophen tablets and dextromethorphan cough suppressant but were instructed to avoid using these relief medications unless their symptoms became sufficiently severe to warrant them. They were asked to record their usage during days 1–10. All other concomitant medications taken throughout the study were recorded in the case-report form.

For the first 10 days of the study, subjects recorded their oral temperature and the severity of their symptoms on a diary card each morning and evening. Severity was rated on a 6-point scale on which a score of “0” corresponded to no symptoms and “5” corresponded to severe symptoms. They also recorded, on a daily basis, any sleep disturbance, level of ability to perform normal activities, and an overall health-status questionnaire.

On day 6, subjects returned for a posttreatment examination, to provide laboratory samples, and to report any adverse events. On day 21, a repeat laboratory test was performed if there were any abnormal results in the day 6 sample. Adverse events and concurrent medication use were also reported. A serum sample was also obtained for influenza serology.

Influenza diagnosis and assessment of viral shedding. Serum samples collected on days 1 and 21 were assayed for the presence of anti-influenza antibodies by hemagglutination inhibition. These assays were done in one location in North America and at the various research sites in Europe. Pre- and posttreatment drug sera were tested together. Virus isolation from an upper respiratory tract sample collected on day 1 was also used to diagnose influenza. Either primary monkey kidney or Madin-Darby canine kidney cells were used. Persons were defined as being influenza-positive if any of the following laboratory diagnostic tests had positive results: virus antigen detection, virus cell culture, or a 4-fold increase in anti-influenza antibody titer between days 1 and 21.

Statistical analysis. The primary clinical end point was the time to alleviation of clinically significant symptoms, defined as the absence of feverishness, a temperature <37.8°C, and a score of 0 (none) or 1 (mild) for other major symptoms (i.e., headache, myalgia, sore throat, and cough), which had to be maintained ≥24 h. Time to alleviation was measured in half-days from the start of treatment (day 1), with the morning of the first day of treatment corresponding to 0 days. It was assumed that the difference between morning and evening measurements was 1 half-day.

Median times to alleviation were calculated for each treatment group. Confidence intervals (CIs) for differences between medians were calculated using the percentile bootstrap method [19] (because the assumptions required by the more usual Hodges-Lehmann method could not be justified for these data [20]). This resulted occasionally in apparent discrepancies between P values and CIs. Hypothesis testing was performed using an extended Mantel-Haenszel test, with integer scores stratified for investigational center [21]. For the purposes of this test, times were grouped to the nearest day, and patients with no evidence of alleviation were included as the final category.

The primary pairwise comparisons were zanamivir 2×/day against placebo and zanamivir 4×/day against placebo. Adjustments for multiple comparisons for confirmatory claims of efficacy was designed to proceed by using the Hochberg procedure based on Bonferroni adjustments [22]. In summary, if both tests were significant at the 5% level, this would provide confirmatory evidence of efficacy for both treatment arms. A secondary exploratory comparison was made of zanamivir 2×/day against zanamivir 4×/day.

Secondary end points included mean symptom score, sleep dis-
Figure 1. Zanamivir trial profile. Bid and qid, 2× and 4×/day, respectively.

The severity of five symptoms (i.e., feverishness, headache, myalgia, cough, and sore throat) was summarized for each patient by calculating the mean symptom score. This provided a measure of overall severity. This was determined separately for the posttreatment periods, days 1–5 and 1–10. If data were missing, the subject was assumed to have had the symptoms recorded on the previous diary card entry. Persons with no diary cards were excluded. Results are expressed as a percentage of the maximum value achievable. The mean symptom score was analyzed by analysis of variance, allowing for effects due to center and treatment group.

Sleep disturbance was summarized by the number of days during days 2–10 that the subject recorded “moderate” or “severe” symptoms. If data were missing for a particular day, the last value prior to the missing value was carried forward. Persons with no diary
card data were excluded. Time to return to normal activities was defined as the first day on which subjects recorded that they were able to carry out usual daily activities. A person was recorded as having returned to normal activities at the first time point if, and only if, this was maintained over the following 24 h. Persons with no evidence of return to normal activities were included as the final category. Use of relief medication was summarized by calculating the number of administrations of paracetamol and cough mixture during days 1–5. Subjects with no diary card data were excluded.

Analyses of sleep disturbance, time to return to normal activities, and use of relief medication were done as for the primary end point.

Sample size. The calculation of sample size was based on the assumption that 50% of the intention-to-treat (ITT) population in the placebo group would have alleviation of clinically significant symptoms by day 5. A clinically relevant difference was defined as an increase to 65% of patients with alleviation of symptoms by day 5. A sample size of 720 patients (240/group) is required for a two-tailed test of these proportions at the 5% level of significance and >90% power [23].

Analysis populations. Two different patient populations were defined prospectively and used in the different analyses. The ITT population was defined as all randomized patients and was the primary population for assessing efficacy and safety. All persons in this population took 1 dose of study medication. The influenza-positive population was the secondary population for assessing efficacy and was defined as all subjects in the safety population with confirmed influenza infection. Thus, patients were included in this population if their baseline culture or diagnostic test was positive or if their serology results showed a ≥4-fold increase in anti-influenza antibodies (demonstrated by hemagglutination inhibition) between days 1 and 21.

In addition, a subgroup of high-risk patients was identified retrospectively. This population was defined as persons who were at high risk of developing complications if they became infected with influenza or were likely to experience more severe or prolonged illness. It included persons ages ≥65 years or with cardiovascular (excluding hypertension), respiratory, endocrine, or metabolic chronic conditions.

Results

Subjects. In total, 1258 persons were enrolled in the study, and 1256 persons were randomized to one of the treatment groups as follows: zanamivir, 2×/day, 419; zanamivir, 4×/day, 415; placebo, 422 (figure 1). As shown in table 1, all 3 groups in the ITT population were well matched for demographic characteristics. In particular, mean symptom scores for day 1 were comparable for the 3 groups. The average duration of symptoms at the time of enrollment was 29 h for all 3 groups, and 38% of patients were febrile at this time.

Overall, 722 (57%) of the randomized patients had laboratory-confirmed influenza, and a rise in antibody titer was less common than virus identification. Of the 431 subjects with positive serology, 211 (48%) had rises for type A(H3N2), 196 (45%) for type A(H1N1), and 39 (9%) for type B (not mutually exclusive). Influenza-positive patients were distributed evenly among the 3 treatment groups, and the percentages of types A(H3N2), A(H1N1), and B were also well balanced.

In all, 74 persons (6%) were withdrawn from the study; withdrawals were equally distributed among the 3 groups. Of the withdrawals, 35 were due to adverse events, 29 were lost to follow-up, and 10 persons withdrew for other reasons.

Clinical efficacy: alleviation of major symptoms. For the overall ITT population, zanamivir reduced the median number of days to alleviation of clinically significant symptoms by 1 day compared with placebo (6 vs. 7 days; table 2). This difference was statistically significant for both zanamivir treatments ($P = .012$ 2×/day vs. placebo, $P = .014$ 4×/day vs. placebo). The difference between zanamivir and placebo groups was evident by inspection by day 2. It was maintained until the end of treatment. There was no difference between the 2 zanamivir groups ($P = .77$).

A total of 731 persons entered the study within 30 h of the onset of symptoms. Zanamivir reduced the duration of illness by 1–1.5 days when given early in the course of infection ($P = .015$, zanamivir 2×/day; $P = .001$, zanamivir 4×/day). For patients who began treatment >30 h after the onset of symptoms, the difference between zanamivir and placebo groups, although still present, was reduced to 0.5–1 day; this difference was not statistically significant.

In total, 473 patients (38%) were febrile on study entry. Zanamivir reduced the time to symptom alleviation in both febrile and nonfebrile patients but had a greater effect on febrile pa-
Table 2. Median number of days to alleviation of major symptoms for the intention-to-treat population.

<table>
<thead>
<tr>
<th>Population group</th>
<th>Placebo</th>
<th>Zanamivir 2×/day</th>
<th>Differencea</th>
<th>Zanamivir 4×/day</th>
<th>Differencea</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>No.</td>
<td>Days</td>
<td></td>
<td>No.</td>
<td>Days</td>
</tr>
<tr>
<td>Symptom durationb ≥30 h</td>
<td>249</td>
<td>6.5</td>
<td>.015</td>
<td>1.0 (0.0, 2.0)</td>
<td>240</td>
</tr>
<tr>
<td></td>
<td>173</td>
<td>7.0</td>
<td>.222</td>
<td>1.0 (0.0, 2.0)</td>
<td>175</td>
</tr>
<tr>
<td>Feverb ≥37.8°C</td>
<td>170</td>
<td>7.0</td>
<td>.049</td>
<td>1.5 (0.0, 2.5)</td>
<td>148</td>
</tr>
<tr>
<td></td>
<td>246</td>
<td>6.5</td>
<td>.049</td>
<td>0.75 (−1.0, 2.0)</td>
<td>259</td>
</tr>
<tr>
<td>High-risk patients</td>
<td>68</td>
<td>7.8</td>
<td>.137</td>
<td>1.5 (−0.5, 3.5)</td>
<td>42</td>
</tr>
</tbody>
</table>

a Difference from placebo (95% confidence interval).

b At study entry.

tients (table 2). Zanamivir given 2×/day reduced the median time to alleviation of symptoms by 0.75 days in the nonfebrile group (P = .049) and by 1.5 days in the febrile group (P = .049). Similar differences were seen for zanamivir 4×/day, compared with placebo.

Of the persons who were febrile on study entry, 348 (74%) were influenza-positive by isolation and serology; only 57% of that being febrile early in the course of infection may be a good marker to distinguish between influenza and influenza-like illness in the adult population.

Similar benefits (not shown) regarding symptom alleviation were seen in the corresponding analyses for the influenza-positive population. A reduction of 1.5 days in the time to symptom alleviation was seen in both zanamivir groups for the total influenza-positive population, although the differences were not statistically significant (5.5 vs. 7 days; P = .11 for zanamivir 2×/day, 95% CI, [−0.25, 2.0]; P = .06 for zanamivir 4×/day, 95% CI, [0.0, 2.0]).

A population at high risk of developing complications if infected with influenza or likely to have more severe or prolonged illness was identified after the study was unblinded, and the effects of zanamivir in this subgroup were analyzed. The 158 patients defined as high risk were distributed among the 3 treatment groups as follows: placebo, 68; zanamivir 2×/day, 48; zanamivir 4×/day, 42. Of the high-risk population, 93 (59%) had a concurrent respiratory condition, the most common of which was asthma (n = 69, 44% of high-risk population); 31 (30%) had a concurrent cardiovascular condition; 18 (11%) had a concurrent endocrine and metabolic condition; and 39 (24%) were ≥65 years old. Sixty-one percent of the high-risk population was influenza-positive.

The median duration of symptoms in the high-risk group receiving placebo was almost 1 day longer than for the overall group receiving placebo (7.75 vs. 7.0 days). Zanamivir showed a trend toward a quicker alleviation of symptoms in the high-risk group (ITT population): zanamivir 2×/day, 1.5 days less than placebo, P = .14; zanamivir 4×/day, 2.75 days less than placebo, P = .042. Of the high-risk patients diagnosed as influenza-positive, zanamivir reduced the duration of symptoms by 2.75 days for zanamivir 2×/day compared with placebo (P = .016) and by 3 days for zanamivir 4×/day compared with placebo (P = .009). These results confirm that zanamivir benefits high-risk patients with influenza. However, because of the small number of patients in this analysis, this observation requires confirmation in further studies.

Clinical efficacy: symptom severities. The alleviation outcome involves identification of a single point of improvement at which a case is considered improved. This outcome is useful for comparing different treatment groups, but in reality improvement occurs gradually over time; evaluation of symptom scores over the first 5 and 10 days after starting treatment allows a different assessment of the value of zanamivir to a patient. Results are shown in table 3 for the ITT and influenza-positive populations. There was a clear reduction in symptom scores during the first 5 days, which was more dramatic in the influenza-positive group. Over the longer period, the difference between treatments was reduced, a result of gradual resolution of illness even in those who had received placebo, but the differences remained statistically significant. Review of the severity of each symptom (i.e., headache, sore throat, feverishness, myalgia, cough, nasal congestion, weakness, loss of appetite) showed that zanamivir reduced the mean score for each symptom compared with placebo.

Analysis of additional secondary end points further demonstrated significant benefits of zanamivir therapy to general patient well-being. A reduction in the number of nights of disturbed sleep due to symptoms was reported for both zanamivir groups in the ITT population (mean days: placebo 2.8, zanamivir 2×/day 2.3, zanamivir 4×/day 2.4; zanamivir 2×/day vs. placebo, P = .013; zanamivir 4×/day vs. placebo, P = .026). As shown in figure 2, zanamivir also significantly reduced the time until patients felt able to return to normal activities (P = .005 for zanamivir 2×/day vs. placebo; P < .001 for zanamivir 4×/day vs. placebo). After 5.5 days, 45% of persons in the placebo group were able to resume normal activities, compared with 54% of those in the zanamivir 2×/day group and 59% in the zanamivir 4×/day group.

Zanamivir was also associated with a reduction in the use of acetaminophen and cough mixture. During the first 5 days,
the number of administrations of acetaminophen was reduced by 22% in the zanamivir 2×/day group compared with placebo ($P < .001$) and by 16% in the zanamivir 4×/day group compared with placebo ($P = .007$). Cough mixture use for this period was reduced by 24% in the zanamivir 2×/day group ($P < .001$) and by 14% in the zanamivir 4×/day group ($P = .091$). The increased use of relief medication in the placebo group also means that the effect of zanamivir on symptom severity reported in this study may be an underestimate, since relief medications may have masked the true severity of symptoms in the placebo group.

Tolerability. There were no differences between the active therapy and placebo groups with regard to number of persons reporting adverse events or the types of adverse event. During treatment, 378 subjects reported adverse events. These were distributed among the 3 groups as follows: placebo, 139 (33%); zanamivir 2×/day, 118 (28%); zanamivir 4×/day, 121 (29%). After treatment, 277 patients reported adverse events. These were also distributed evenly among the 3 treatment groups.

The most commonly reported adverse events during treatment were nasal signs and symptoms, headaches, bronchitis, and gastrointestinal events (table 4). The incidence of these events was low and similar among the treatment groups. Headaches; nasal signs and symptoms; ear, nose, and throat infections; bronchitis; and sinusitis and throat-tonsil discomfort/pain were the most common adverse events reported in the post-treatment period. Again, there was a similar incidence in each treatment group.

Possible drug-related adverse events were reported by 158 subjects during treatment and were evenly distributed among the 3 groups: placebo, 59 (14%); zanamivir 2×/day, 46 (11%); zanamivir 4×/day, 53 (13%) (see table 4). After treatment, only 17 patients reported drug-related events, and the incidence of any adverse event was >1%.

Thirty-five persons were withdrawn from the study due to adverse events, with about equal numbers from each treatment group (table 4). Most adverse events were possibly related to influenza-like illness. Nine serious adverse events occurred during the study, only 1 of which was considered related to treatment. This person was in the placebo group. No clinical differences in laboratory data were observed among the 3 groups.

Discussion

Since the introduction of amantadine and rimantadine in the United States, there has been debate regarding the role of these antivirals in the therapy of influenza infections [24]. This debate was limited geographically, because the drugs were either unavailable or little used in much of the world. Gradually a consensus arose that antiviral therapy with these drugs had an appropriate role in the treatment of influenza [25]. This consensus was supported by the recognition that even uncomplicated influenza is a disease with a relatively long duration with significant restriction of daily activity. However, the consensus was tempered by concerns regarding side effects (especially with

Table 3. Comparison of mean symptom scores in the influenza-positive and intention-to-treat population for days 1–5 and 1–10, expressed as a difference in mean symptom scores.

<table>
<thead>
<tr>
<th>Group</th>
<th>Days 1–5</th>
<th>Days 1–10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Difference from</td>
</tr>
<tr>
<td></td>
<td></td>
<td>placebo (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention-to-treat population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>32.3 (15.8)</td>
<td>—</td>
</tr>
<tr>
<td>Zanamivir (2×/day)</td>
<td>29.0 (15.4)</td>
<td>3.2 (1.1–5.3)</td>
</tr>
<tr>
<td>Zanamivir (4×/day)</td>
<td>29.6 (15.6)</td>
<td>2.5 (0.4–4.7)</td>
</tr>
<tr>
<td>Influenza-positive population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>33.7 (15.6)</td>
<td>—</td>
</tr>
<tr>
<td>Zanamivir (2×/day)</td>
<td>29.1 (14.7)</td>
<td>3.9 (1.1–6.7)</td>
</tr>
<tr>
<td>Zanamivir (4×/day)</td>
<td>28.8 (14.3)</td>
<td>4.6 (1.8–7.3)</td>
</tr>
</tbody>
</table>
amantadine), the possible emergence of resistance, and the need to ensure that the disease being treated was caused by type A virus [10, 26, 27]. These concerns, as well as difficulties in determining the precise level of efficacy of amantadine and rimantadine from the small studies conducted in the past, have been at least partially responsible for the negligible use of the drugs outside North America.

The development of zanamivir provides an alternative antiviral therapy for the management of influenza infection. This agent has convincing efficacy against influenza caused by different types of influenza viruses, as is shown in the study described here and in a previous smaller study [17]. The first study on treatment of natural infection involved 417 healthy adults and was done at a time when both type A and B influenza viruses were circulating. The effect of treatment was also measured by using the end point median time to alleviation of major symptoms of influenza. By taking into account the main symptoms of the disease, this end point provides a valuable means of comparing various subgroups with a single outcome measure. In the first study [17], the effect of zanamivir therapy on time to symptom alleviation was evident among those who were positive for influenza infection, as determined by virus isolation or rise in antibody titer, but not in the ITT population. The difference of 1 day between treated and placebo groups in median time to alleviation became greater when the patients under consideration were limited to those with documented fever or a shorter duration of illness before therapy was begun.

The current study involved more than 3 times the number of persons in the earlier study, and the increased numbers are at least partially responsible for the new observations. First, a significant difference in time to alleviation was seen between the treatment and placebo groups, even in the ITT population. Further improvements in the benefit of zanamivir when the analysis was restricted to the influenza-positive population are generally limited in this study, suggesting that there may have been some lack of precision in the detection of influenza by the laboratory procedures. As in the previous study, there was a greater difference in time to symptom alleviation among those with illnesses of shorter duration at the beginning of treatment and those with fever \(\geq 37.8^\circ C\). The latter indicator was found in previous studies to be a surrogate for influenza positivity. There were no significant differences between the 2 zanamivir-treatment groups in time to symptom alleviation for the total ITT or influenza-positive populations or for the subanalyses.

Recently, a third study [18] showed a benefit for zanamivir in both the ITT and influenza-positive populations. Both studies included a proportion of patients with a high risk of developing complications. The effect of zanamivir in this subgroup was analyzed separately, because such persons are expected to experience more severe or prolonged illness and might therefore derive a greater benefit from zanamivir. This expectation was borne out in both studies: zanamivir reduced the time to alleviation of symptoms by about 3 days in high-risk patients with confirmed influenza. In both studies, the numbers of patients included in this analysis were necessarily small and thus firm conclusions cannot be drawn, but this represents the first evidence of a role for an antiviral in this vulnerable population.

The main results of the present study are based on the median symptom alleviation time. However, other measures, such as symptom scores, sleep disturbance, use of symptom-relief medications, and effect on activities, also support the therapeutic benefits of zanamivir, even before the primary end point is reached. Further support for the antiviral effects of zanamivir comes from a subset of subjects in the current study. When virus titers in daily nasal wash samples from patients in a single center in Rotterdam, The Netherlands, were determined, a reduction in both the duration and degree of viral shedding was found [28]. Zanamivir dramatically reduced viral titers by day 2 of treatment. Median viral titers fell below detectable limits on days 2–3 in groups receiving zanamivir, while this was only achieved by day 4 in the placebo group. This more rapid reduction of viral shedding may be expected to decrease infectivity and hence the risk of transmission. This may also result in decreased transmission because of a shorter period of infectivity.

It took many years for a consensus on use of amantadine and rimantadine to be reached in North America [25]. This was partly due to the fact that the studies, especially those involving treatment, were small and differed in design, making assessment of the precise therapeutic benefit difficult [7–9]. In contrast, studies with zanamivir have all used the same well-defined end point and a similar design. The benefits of zanamivir appear to be greatest where the illness is most severe, as would be expected from the natural history of influenza infection, and when treatment is given early. There are also benefits on patient quality of life and functioning. The results of all studies with zanamivir indicate that it is well tolerated, with a reported side-effect profile comparable to placebo. This was evident in both otherwise healthy persons and in those at high risk of complications. The fact that zanamivir can be used to treat all strains of influenza A and B viruses and that resistance has not been detected during acute therapy [29] also suggests that it has definite advantages over the older antiviral agents. Thus,

### Table 4. Adverse events reported during treatment with an incidence \(\geq 1\%\) in any treatment group.

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (2×/day)</th>
<th>Zanamivir (2×/day)</th>
<th>Zanamivir (4×/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>11 (3)</td>
<td>11 (3)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>14 (3)</td>
<td>7 (2)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Nasal signs and symptoms</td>
<td>14 (3)</td>
<td>7 (2)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Headaches</td>
<td>9 (2)</td>
<td>8 (2)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>11 (3)</td>
<td>3 (1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Withdrawal due to possible adverse events</td>
<td>12 (3)</td>
<td>13 (3)</td>
<td>10 (2)</td>
</tr>
</tbody>
</table>

**NOTE:** Data are no. (%).
there seems to be a clear role for zanamivir in the treatment of type A and B influenza infections.

References