

Table XII-F4. Preliminary PFT results from NAI30008 (continued from previous page)

% decrease from baseline (number of subjects, %)	FEV1, placebo	FEV1, zanamivir	PEFR, placebo	PEFR, zanamivir
Day 28	n=73	n=72	n=77	n=71
No decrease	46 (63%)	51 (71%)	71 (92%)	66 (93%)
Decrease >0-10%	19 (26%)	10 (14%)	3 (4%)	3 (4%)
Decrease >10-20%	6 (8%)	4 (6%)	2 (3%)	1
Decrease >20-30%	2 (3%)	4 (6%)	0	1
Decrease >30-40%	0	0	1	0
Decrease >40-50%	0	1	0	0
Decrease >50-60%	0	2 (3%)		

The data from NAI30008 have been discussed with consultants in the Division of Pulmonary Drug Products who recommended precautionary language for any labeling that may be contemplated. The issue of underlying pulmonary disease may need to be addressed in multiple parts of the label including patient instructions.

Preliminary data from the NIAID Collaborative Antiviral Studies Group study of nebulized zanamivir show two patients with more than 20% decrease in PEFR after the first dose of study medication. Three deaths were reported from this study in this amendment, one apparently associated with influenza pneumonia, one with CVA and pneumonia, one with CHF/CAD (none associated acutely with treatment administration). These reports remain blinded to treatment.

Limited serious adverse event information was provided on an interim basis from study NAI30009 (treatment of influenza in children aged 5-12) and NAI30010 (transmission within families). One SAE was reported from NAI30009 (seven year old patient, noted as having "current influenza infection and hemolytic streptococcus Group A of the throat," with exacerbation of influenza symptoms on second day of blinded study treatment, vomiting, pneumonitis, dehydration, hospitalized for 4 days, resolution over 2 weeks), and one from NAI30010 (46 year old patient with wheezing on first day of blinded study treatment, subsequent pneumonia leading to hospitalization, resolution over 1 to 2 weeks). In both cases it was stated that study medication was continued and not considered related to the SAE.

The submission also contains a section labeled "Drug accountability/compliance information" which is presented as demonstrating "subjects' compliance with the Diskhaler device in an acute setting." This continues the practice of attributing partially punctured medication blisters to noncompliance in subjects who have been selected for ability to use the device at study entry and have received instruction in its use. Data are presented as proportion of subjects considered compliant out of those who returned all medication disks. As subjects cannot be assumed to have correctly used the disks they do not return, if the topic of interest is the proportion of subjects documented to have correctly delivered their medication at least so far as can be ascertained by correct puncture of the Rotadisk blisters, a more appropriate calculation may be number of

BEST POSSIBLE COPY

subjects demonstrated to have correctly punctured all the disks they should have used to complete their treatment course, which appears to be 121/174=70% for NAI30008, 272/337=81% for NAI30009, and 759/888=85% for NAI30010. The implications for likely correct and effective use in the usual clinical setting are not clear.

XII-G. Amendment dated May 21, 1999

This submission contains additional statistical analyses of treatment effect using pairwise comparisons of symptom improvement and relief medication use, and of treatment effect by time after treatment initiation. These are presented as supporting the existence of a treatment effect in NAIA3002.

This amendment also contains requested tabulations of treatment effect in subjects entered before or after 24 hours of symptoms. For influenza positive subjects treated with inhaled drug only (except for NAIA/B2008 in which all subjects received inhaled plus intranasal drug), the point estimate of treatment difference in the group entered before 24 hours versus those entered after 24 hours is less in NAIB3001, identical in NAIA3002, greater in NAIA2005, greater in NAIB2005, less in NAIB2007, greater for BID subjects in NAIA/B2008, and less for QID subjects in NAIA/B2008.

Comment: overall, these analyses do not permit any firm conclusions about relationship of treatment benefit to treatment within 24 hours of symptom onset, although limited analyses discussed earlier in this review had suggested some diminution of effect in subjects entered after 36 hours of symptoms, and although it appears reasonable that the opportunity for treatment benefit would decline as active infection and host response become more established and as the usual course of spontaneous recovery begins. No data are available for subjects treated after 48 hours (except for a very small number of protocol violations).

XII-H. Amendment dated June 4, 1999

This one-volume amendment contains a revised version of the draft labeling comprehension protocol dated April 14, 1999. Some recommendations from DAVDP and DDMAC have been incorporated. Of note, this submission contains reports of several pilot pre-tests conducted by a marketing research firm. Findings of the first pre-test were summarized as follows: "The current instructions for the assembly and use of the Relenza Diskhaler are severely limited. Virtually all of the study subjects failed to properly assemble and use the product....A meaningful number of test subjects encountered a problem of comprehension at virtually every stage of the assembly procedure....The subjects found the instructions to be too long, although they agreed they were absolutely necessary for assembly." The market research firm identified some of the same issues covered in previous DAVDP comments, and two iterations of changes in instructions and re-testing were carried out. Findings from the third pre-test (15 subjects)

BEST POSSIBLE COPY

were summarized as follows: "All of the study subjects correctly completed nearly all of the tasks (over 80%) outlined in the instructions relative to the assembly and usage of the product... There were no common areas that elicited error or confusion among the subjects. In fact, the vast majority of consumers said that it was either "extremely or very easy" to follow the instructions when assembling and using the product... In this pretest, most consumers were consistent in keeping the product level when stated in the various steps in the instructions and understood when one needed to advance the medication. These were two areas of confusion in both the first and second pretests." This submission also contains a copy of the "concept statement" to be shown to subjects in the study projected to start June 16, 1999. This "concept statement" was mentioned but not provided with the draft protocol; among the assertions contained in it are "Introducing Relenza Diskhaler. Relenza is a unique product for the treatment of influenza... It is a prescription product that has been clinically shown to: help you get over the flu faster... Reduce the severity of symptoms of the flu, such as headache, fever, cough, sore throat and fatigue.... To work, Relenza must be taken within two days (48 hours) of the start of flu symptoms. So it is important to see your doctor as soon as possible after the onset of flu symptoms."

Comment: The pre-test results are compatible with the hypothesis that patient instructions may severely limit the ability of prospective patients to use this product in a maximally effective manner. The finding of fewer problems on repeat pre-testing after iterative changes to the instructions suggests that improvement in the ability of patients to use the product is possible with better instructions, but it is not clear that performing "over 80%" of use components correctly would necessarily lead to effective use, or that these findings would translate into effective use in the setting of acute illness. The applicant has been encouraged to examine treatment effects using improved instructions under conditions comparable to expected clinical circumstances of use. The applicant was also asked to revise the "concept statement" to avoid the impression of promoting an unapproved drug or making claims not supported by reviewed data.

XII-I. Amendment dated June 15, 1999

This 19-page telephone facsimile communication provides some of the geographic breakdown information from the NAI30008 interim report that was requested in the letter of March 17, 1999, and again on May 17, 1999. The summary table indicates that FEV1 decreases >20% occurred in 1 of 48 placebo subjects and 7 of 42 zanamivir subjects enrolled in the US and Canada, and 4 of 36 placebo subjects and 4 of 37 zanamivir subjects enrolled at other sites.

Comment: This breakdown of information does not suggest a decreased need for information about potential pulmonary adverse events in a North American label, when added to the information previously received.

XII-J. Amendment dated June 24, 1999

This one-volume submission contains responses to requests for additional information on adverse event reports in the nursing home studies and in NAI30008. The two reports of "blindness and low vision" in NAIA3003 are described as transient blurred vision. The reports of bilirubin elevations in NAIA3004 are summarized as follows: "Seven subjects enrolled in NAIA3004 had abnormal elevations of bilirubin reported as drug-related adverse events. With the exception of one patient, the concurrent ALT and AST values were within normal range for 6 of these subjects. The principal investigator reports no evidence of hepatotoxicity in these subjects." Individual case synopses are provided with study therapy blinded; one patient (with baseline elevated bilirubin) also had increased eosinophils during the study, one had elevation of ALT to 53 U/L (ALT and AST values pre- and post-treatment are tabulated for all seven patients and are otherwise normal), five had normal bilirubin on follow-up and the other two did not have repeat values, five had peak bilirubin below 2x ULN and the other two had post-treatment levels about 2.2x ULN. The applicant also provides a table showing elevated post-treatment bilirubin in 3 rimantadine and 2 zanamivir subjects in NAIA3003 (>1.5x ULN, 1 and 2) and in 16 placebo and 13 zanamivir subjects in NAIA3004 (>1.5x ULN, 6 and 4), and concludes, "Available data do not suggest any hepatic effects associated with zanamivir administration." For study NAI30008, tabulations of adverse events for North American and other sites are provided and do not raise salient new safety concerns.

XII-K. Amendment dated July 8, 1999

In addition to proposals for the full package insert, this submission contains an updated version of the color instruction sheet for patients. Some changes have been made in response to the marketing research pre-tests described above. A section containing precautionary information for patients with underlying respiratory disease has also been added.

XIII. Additional Comments and Discussion

Definition of endpoints for studies of influenza therapy poses a number of challenges. For the vast majority of patients, influenza is a self-limited disease, and the major objective of therapy is symptom relief and minimization of interference with normal activities. Prevention of minor infectious complications is also a desirable goal, which overlaps to a large extent with the goals of symptom relief and reduction of time lost from daily activities. For the purposes of reducing major morbidity and mortality associated with influenza, a desired objective would be to prevent and/or effectively treat life-threatening complications such as primary influenza pneumonia and secondary bacterial pneumonias. However, extremely large studies would be required to enroll a sufficient number of subjects from the general population to allow meaningful comparisons of serious complications between treatment groups, and most of the

available studies of influenza therapy from the literature and from previous approval reviews do not contain sufficient information to document effects on such complications.

For measurement of effectiveness of treatment of influenza in the general population at relatively low risk of severe complications, numerous approaches have been used, typically involving some type of symptom scoring by the subject combined with some type of assessment by study personnel, either comparing results of different treatment groups at each time point or comparing time required to reach a specified state of improvement. The primary endpoint proposed by the applicant for the Phase 3 treatment studies in this application was a composite endpoint of time to alleviation of major influenza-like symptoms, defined as temperature below 37.8 °C, feverishness symptom score of absent (zero), and symptom scores no greater than mild (1 on a scale of 0=absent, 1=mild, 2=moderate, and 3=severe) for cough, headache, myalgia, and sore throat, all maintained without worsening for the subsequent 24 hours. Assessments of supporting secondary endpoints and of important subgroups were identified as necessary contributors to overall evaluation of study results, because of concerns regarding the use of subjective symptom scores and regarding potential alteration of symptoms by concomitant medications, and because it is likely that use of an anti-influenza drug may be based on clinical judgment when test results are not immediately available and may therefore result in drug exposure for a broader population than the prospectively defined primary efficacy-evaluation group of patients with diagnostic tests positive for influenza.

The efficacy results for zanamivir in the treatment of influenza, in the principal phase 3 treatment studies and in phase 2 studies used for supporting information, are not immediately compelling and can be interpreted in multiple ways. In fact, the basic decision on whether the drug is approvable for influenza treatment using currently available information can be argued in either direction, and a rationale can be constructed either for non-approval or for approval. Some of the principal issues will be briefly outlined below.

Context and background from previously approved drugs

The approvals of amantadine and rimantadine cannot be taken as exact models for a number of reasons including the time periods in which studies and reviews took place and changes in research and regulatory climates during those time periods, as well as individual features of each application which cannot readily be generalized to other settings. In addition, because of differences in study design and description, in populations studied, and possibly in circulating influenza strains when studies were carried out, no direct numerical comparison can be made between study results with those drugs that contributed to approval considerations and study results in the NDA for zanamivir. However, amantadine and rimantadine studies provide most of the available information for assessment of usual outcomes and expectations in the study of influenza treatment, and constitute the background data for widely used public health recommendations; therefore, they should not be disregarded altogether in the assessment of newer drug studies. In the following discussion, points from amantadine and

rimantadine studies considered in the approval process for those drugs will be mentioned where appropriate.

Demonstration of primary treatment effect

There was substantial variability across zanamivir studies in their ability to demonstrate benefit using the primary pre-defined endpoint for phase 3 studies. The smallest phase 3 study (NAIB3002) had both the largest point estimate for treatment effect and the smallest p value, and these results appeared quite resilient to different analytic approaches. Study NAIB3001, with a slightly different study design, also showed what would generally be considered clinically and statistically meaningful positive results, but with more variability among subgroups and among secondary endpoints in the demonstration of effect. The most obvious initial problem in the evaluation of the NDA for zanamivir was the failure to demonstrate a convincing treatment effect using the pre-defined primary endpoint in the largest phase 3 study (NAIA3002). The one-day point estimate for median difference between zanamivir and placebo in time to primary endpoint was at the lower margin of differences that might be considered clinically meaningful; furthermore, with a p value above .05 despite a well-powered, overenrolled study (and correspondingly a 95% confidence interval including the null value), and without strong support from secondary analyses, it could not even be said that the study "showed" a one-day difference in outcomes. Some subgroups showed smaller or even negative point estimates; although further examination did not demonstrate evidence of harm in these populations, these findings reinforced the impression of an estimate of treatment effect that was not clearly differentiable from null effects on the basis of the principal analysis.

Re-examination of additional information from earlier stages in the development program also showed variability and uncertainty regarding whether a treatment effect had been shown. Smaller studies or smaller subgroup analyses of large studies tended to display more instability in treatment estimates and substantial lack of statistical certainty. In particular, NAIA2005, the only study conducted entirely in North America besides NAIA3002, yielded only a 0.75 day difference between treatment groups (with a p value indistinguishable from chance) when analyzed using the same endpoint definition as the phase 3 studies (and no more impressive outcomes according to its original analysis).

Thus, there was a tendency across multiple studies to obtain point estimates of treatment effect that slightly favored zanamivir, but only two of the phase 3 studies yielded reasonably convincing statistical support for such an effect. In reviews of previously approved drugs, statistical significance was also noted to be "intermittent" in studies reviewed for rimantadine approval, although the principal studies for both amantadine and rimantadine were so much smaller than the phase 3 zanamivir studies that they might well have been considered underpowered for detection of treatment effect. In general, the amantadine and rimantadine studies were performed in relatively homogeneous populations with little or no use of potentially confounding symptomatic relief medications, characteristics which might have reduced the likelihood of obscuring

treatment effects in contrast to the more heterogeneous subject groups and common use of symptom relief medications in the zanamivir studies.

Although the number of samples obtained and the overall yield were small, positive cultures at day 3 were observed less frequently on zanamivir than on placebo in the two phase 3 studies for which this information is available. These findings provide some support for the existence of a treatment effect, though clear statistical differentiation between treatment groups was not achieved. Additional support for antiviral activity of zanamivir in humans (and in the U.S.) is provided by the challenge studies and by the one completed prophylaxis study: although these have not undergone detailed review for efficacy determination here as that is beyond the scope of this submission, and cannot be translated directly into documentation of treatment efficacy with the proposed regimen in naturally acquired disease, these subsidiary studies provide some supporting information for activity against influenza A and much less supportive evidence for influenza B.

Magnitude of treatment effect

The magnitude of the point estimate for the primary treatment effect was also quite variable across studies. The point estimates for effect in the North American phase 2 and phase 3 studies, 0.75 days and 1.0 day difference between placebo and zanamivir in median time to the phase 3 protocol-defined primary endpoint (both studies failing to reach statistical significance), tended to be at the low end of the range observed across all clinical treatment studies; in particular, for NAIA3002, the combination of low point estimate and lack of statistical significance in the largest phase 3 study, plus lack of clearly demonstrated benefit in several important secondary analyses and subgroup analyses as described earlier in this review, suggested that a numerically precise estimate of benefit could not be described for this study and that any benefit present was marginal. On examination of all of the study results using comparable analyses, it was also evident that study NAIB3002 (the phase 3 study performed in Europe) had a point estimate of treatment effect (2.5 days) well above the other studies: its low p values and relatively large estimates of treatment effect on numerous analyses were not well replicated in any of the other data available from other studies. The equivocal results of NAIA3002 and the "outlier"-like status of the numerical results from NAIB3002 were discussed both internally and with the applicant in the course of the review process.

For most studies, the point estimate of treatment benefit was both less precise than in NAIB3002 and comparatively small. Given the relatively short course of moderate-to-severe symptoms in most cases of influenza, and the institution of treatment after viral replication and the physiologic changes related to infection are presumed to be well established, it is unclear how large a treatment benefit could reasonably be expected. For those time-to-event endpoints that could be located in studies reviewed for amantadine and rimantadine approvals, differences between treatment groups likewise tended to be small in magnitude.

There was not a clear explanation for the discrepancies in magnitude of apparent treatment effect among studies. In the phase 3 studies, it was noteworthy that subjects in NAIA3002 had the highest, and subjects in NAIB3002 the lowest, use of protocol-provided standard symptomatic relief medications. As use of these medications was not controlled and would likely be interrelated with symptomatology, no precise estimate of the effect of such medications on study outcomes could be made, but it would be plausible that any concomitant medications tending to diminish specific symptoms or signs could make the treatment groups within a study more similar and obscure the specific effect on symptoms (or temperature) of the investigational drug. Again, in a number of amantadine/rimantadine studies antipyretic analgesics were not permitted, a condition unlikely to be repeated for current and future studies of anti-influenza drugs unless special circumstances were identified in which such a restriction might be appropriate.

Exploratory analyses did suggest some patterns across the phase 3 studies in subgroups achieving lower point estimates within a study than the overall study estimate: for example, subjects with lower baseline temperature or investigator-rated severity tended to have lower point estimates of treatment benefit, and a less consistent relationship to age was noted. Baseline severity of disease and temperature were also among the attributes explored as possible factors which could lead to treatment differences between studies. In the sections above it may be noted that fewer subjects reported ability to perform few or none of their normal activities at baseline in study NAIB3001; the proportion of influenza-positive subjects with a baseline investigator rating of "severe" was lowest in NAIB3002 (24%, vs 29% in NAIA3002 and 36% in NAIB3001; no important differences in baseline subject-rated severity were proposed by the FDA statistical reviewer in material provided for the Advisory Committee background document); baseline temperature was lowest in NAIB3001; and baseline symptom scores were similar across the three studies. Where differences were noted, they might have been expected to promote lesser treatment effects in NAIB3001 or in NAIB3002, which in fact showed greater treatment effects than NAIA3002. Differences in the above factors and also in time to various endpoints among the placebo groups of different studies must be regarded with extreme caution because the groups enrolled in the different studies do not have random allocation of baseline demographics or other characteristics, were completing questionnaires which might have slightly different implications in different languages, and were presumably susceptible to differential effects both of differential use of symptom relief medications (which, if they contributed to confusing the interpretation of treatment effects, might do so in part by decreasing symptom scores in placebo recipients) and of any cultural or social predispositions to different reporting of symptoms, different pressures to return to normal activities, etc.; these problems in interpretation acknowledged, the NAIA3002 placebo group had a shorter median time to the primary endpoint than the NAIB3002 placebo group but the same median time to the primary endpoint as the NAIB3001 placebo group, again producing no conclusive explanation of the distinctive results in NAIA3002. Additional exploratory analyses, which also failed to provide an explanation for the between-study differences, are summarized in a previous section of this review. Population familiarity with dry powder

inhalers was also considered as a factor which might have contributed differentially to ability to use the Diskhaler effectively at the beginning of the treatment course. Specific information on such familiarity was not available for the individuals enrolled in the treatment studies, but the marketing-research pilot tests of patient instructions provided in one of the later amendments were compatible with the possibility that some North American subjects might encounter some obstacles to effective first use.

The diversity of estimates of treatment effect across studies, and especially the studies at the extremes of the apparent range, were reinforced by similar patterns in secondary endpoint analyses and subgroup analyses for the principal phase 3 studies where reasonably comparable analyses of such endpoints and subgroups could be performed. These comparisons did not suggest that the studies could reasonably be pooled to derive an overall effect estimate describing an average treatment benefit of zanamivir; in particular, the disparities in multiple components of the analysis suggested that it would be misleading to try to generalize any numerical estimates of effect from NAIB3002 – which appeared uniquely isolated at a particularly high effect estimate – to the population studied in NAIA3002 which did not show a definitely quantifiable treatment effect.

Use of alternative endpoints

Numerous pre-defined secondary endpoints were analyzed in these studies, and numerous additional endpoints were constructed and analyzed in exploratory analyses, both by the applicant and by FDA statistical reviewers. These included endpoints incorporating symptom rises after the primary endpoint, endpoints based on measurements day by day or over a two-week period, endpoints incorporating use of protocol-provided symptomatic relief medication, and endpoints incorporating different selections and combinations of elements from the patient diary cards. Numerical estimates of treatment effect of course changed when the measure of treatment effect was altered; and selected secondary analyses could be presented for NAIB3002 and NAIB3001 that appeared less impressive than the primary analysis, just as selected secondary analyses could be presented for NAIA3002 that appeared more impressive than the primary analysis; but the general pattern of relationships between phase 3 studies tended to be fairly reproducible with relatively resilient treatment effects in a number of salient analyses in NAIB3002, minimal or equivocal treatment effects in NAIA3002, and intermediate findings in NAIB3001.

Description of treatment effect for populations most relevant to this application

Exhaustive comparisons between studies did not suggest that a pooled numerical treatment effect could be derived that would be generalizable to all populations studied. Of particular concern when the discrepant outcomes were observed was the lack of a clear-cut quantifiable treatment effect in the largest phase 3 study, and the evident differences between this and the other phase 3 studies, given that this was the phase 3 study performed in a North American population. From prior principles there was no strong reason to expect influenza illness and its response to specific treatment to differ

between North America, Europe, and Australia, there was no evidence for predictably meaningful differences in circulating influenza strains (including additional information provided by the applicant in a teleconference of February 8, 1999) between North America and Europe, and there was no reason why foreign data should not be considered in the NDA review, but the actual finding of striking differences in study outcomes forced consideration of the extent to which the non-North American studies could or could not be utilized in developing a description of treatment effect for the population which would receive the drug under a U.S. approval. Multiple analyses of NAIA3002 tended to show very small and inconclusive differences between treatment groups which in general tended to favor zanamivir but stopped short of statistical significance, and results in NAIA2005 tended to be similar. Results of non-North American studies appeared applicable as supporting evidence for the activity of zanamivir against influenza virus and influenza disease, as did prophylaxis and challenge study results from North America, but the observed differences in study results did not permit extrapolation of the magnitude of treatment effect in non-North American studies to the North American population. Thus, it appeared that a balanced presentation of likely treatment effect in an intended North American population would have to reflect the marginal and inconclusive nature of the North American treatment study results while noting the existence of some additional supporting evidence for activity.

Safety issues

In general, the safety profile of zanamivir has appeared similar to that of placebo, and few concerns about safety were expressed in Advisory Committee discussions. Most clinical adverse events and laboratory abnormalities have appeared compatible with underlying disease or with sporadic transient findings in the general population, without clear drug relationships. Study reports suggested that some symptoms such as headache, dizziness, and respiratory, ENT, or gastrointestinal symptoms were considered potentially study-drug related. Because placebo subjects received inhaled lactose, the possibility that some of these events were related either to the zanamivir component of the active drug preparation or to the inhaled lactose powder component present in both placebo and active preparations must be considered. No plausible study design for resolving this possibility has been developed, but most such events were not treatment-limiting, and similar dry powder inhalers have not been associated with major safety concerns in use with other drug products. The possibility of additional safety concerns that might arise with wider use in a broader population cannot be ruled out from the size of the database available, but studies have been large enough to provide a reasonable amount of pre-approval information, and the need for postmarketing focused surveillance has been discussed both with the applicant and with FDA postmarketing safety staff.

The principal safety consideration raised by zanamivir studies thus far is the possibility of bronchospasm in asthmatic patients. Although evidence at this time is limited, decreases in PFT results have been noted more frequently with zanamivir than with placebo. These results have not been clearly associated with clinical patterns of adverse events, which have appeared similar between treatment groups in this population, but are of sufficient

concern to require close attention. Available results, and approaches to addressing this issue with precautionary language in labeling and patient instructions and to proposals for obtaining further information, have been discussed with consultative staff from the Division of Pulmonary Drug Products.

Use and instruction issues

Investigators' comments, and comments from the applicant's marketing research studies, suggest that initial use of this drug might be hampered by lack of familiarity with the delivery device and complexity of instructions. Delay in effective use could reasonably compromise treatment effectiveness. Careful attention to instructions (written and in-person) would be needed to optimize initial use; important measures may include both improvement in written instructions and education of healthcare professionals to provide appropriate instruction.

Resistance issues

The susceptibility and resistance results submitted thus far do not demonstrate frequent recrudescence of virus during therapy or rapid routine emergence of resistance, but data are insufficient to demonstrate whether significant problems with resistance will appear or to estimate their likely frequency. Assessment of these possibilities has been limited in part by the use of relatively insensitive sampling methods for on-treatment and post-treatment cultures (leading to low recovery of virus even in the placebo group, at time points when somewhat greater shedding might be expected), and by testing methods for susceptibility and resistance determination (if there is no reliable cell-culture-based means of measuring resistance and only activity of an enzyme is measured, no assurances of lack of resistance can be made, especially given the existence of in vitro resistant variants with mutations in hemagglutinin and not in neuraminidase). Further study in these areas is needed.

Amendments addressing concerns from Advisory Committee discussions

In discussions and submissions after the time of the Advisory Committee, the applicant has provided materials that address a number of the Advisory Committee's concerns. These are discussed in greater detail in the synopsis of each submission but some points will be briefly recapitulated here. In response to concerns about the small magnitude of treatment effect, analyses similar to those used for previously approved influenza drugs have been provided and are compatible with the presence of some treatment effect in all of the principal phase 3 treatment trials; other analyses supporting the existence of a treatment effect, and illustrating the difficulties of attaching a single numerical estimate to such an effect, have been discussed above. Symptom rebound or recurrence has been addressed by the analyses of time to alleviation without subsequent rise in symptoms or rise in symptoms lasting more than one diary card; by the pattern of virologic results over time; by the analysis of activity levels by day; by the analysis showing that proportion of "non-alleviated" diary cards after the primary endpoint did not differ substantially

between treatment groups; and by the analysis of mean symptom scores by day which shows a monotonic decrease in both treatment groups in all three studies for both the 5-symptom and the 8-symptom score. The analysis of symptom scores by day also illustrates why averaging symptoms over a 14-day period may yield misleadingly small differences between treatments for a usually brief self-limited disease in which improvement is sufficiently rapid in most patients that no treatment can be expected to show major effects on more than a few days' worth of symptomatology. Additional analyses of both phase 2 and phase 3 studies, as well as the preliminary results of the completed prophylaxis study, are compatible with an effect of the drug against influenza in a North American population, and the subgroup analyses suggest some options for selecting patients most likely to have a treatment benefit, although these should be acknowledged as exploratory analyses and there remain open questions about how to ensure that the drug is prescribed and used appropriately to maximize the likelihood of benefit. The viral shedding results submitted suggest some difference between treatment groups in the phase 3 studies; although statistical significance was not demonstrated and conclusions are limited by methodologic concerns as noted above, the quantity and quality of these data should be enhanced by results from ongoing studies and are open to interpretation in the context of the information available for other influenza drugs. The applicant has presented a plan for resistance surveillance and information to address concerns about any possible relationship of zanamivir use to antigenic drift. Furthermore, if substantial as yet undetected resistance risks exist, non-approval could not be expected to prevent emergence of resistant virus, because the drug is approved in other jurisdictions and any resistant strain of major public health importance could potentially enter the United States from other parts of the world, as new influenza strains routinely do. Additional safety information for high-risk groups has been provided; when all phase 3 and phase 2 studies are taken into account, there is more suggestion of promise for at least some high risk populations (*e.g.* older patients) than had been compiled for other drugs, and further information collection is ongoing for these population groups. The need for provider education regarding patient selection, and the possibility of toxicity in patients with underlying respiratory disease, have been reviewed in discussions of labeling language and phase 4 commitments. Subgroup analyses have been provided for a more systematic overview of the relationship of treatment effect to attributes such as age and symptom duration, and studies are in progress to provide more information on treatment effects in children and effect on transmission within families. Other ongoing studies could also provide additional information on efficacy in a U.S. population. Reports from pilot pre-tests indicate that some problems with the instructions have been identified and corrected, so there is the possibility that proposed marketed versions of the instructions would be associated with more effective use than hitherto; proposals have been submitted for additional study of the patient instructions.

Possible impact on therapeutic choices

The magnitude of effect demonstrated for any of the drugs studied for treatment of influenza has been relatively modest, perhaps because most patients treated in clinical trials have self-limited disease with spontaneous resolution over a fairly short time

period. However, a rationale for making therapeutic options available has been recognized even where benefit to the average patient may be small, as a small average benefit could translate into potentially important impact at the population level, especially in the setting of widespread epidemic or pandemic influenza activity. Discussions of these general issues with experts continued during the review period and contributed to the internal discussion process. For previously approved drugs for influenza treatment, efficacy and safety information available for approval was based on more narrowly defined patient groups in smaller studies, and endpoints were varied and were not always clearly defined prospectively. Concerns about potential use of zanamivir in patients who do not have influenza, based on intent-to-treat analyses of all randomized subjects in clinical trials, may be issues of education and judgment more appropriately addressed in labeling than in approval deliberations; it was agreed during end-of-phase-2 discussions that primary efficacy analyses would use the influenza-positive population, and only subjects with confirmed influenza were considered in treatment efficacy analyses of previous anti-influenza drugs. In addition, the two drugs already on the market for influenza are active only against influenza A, have not shown time-to-improvement benefits notably better than zanamivir from the limited amount of information available, have not been shown in reviewed efficacy studies to reduce complications or improve outcomes in particularly high-risk patients, and are associated with safety and resistance concerns. When efficacy results for zanamivir are re-analyzed using outcome measures similar to those used in studies of amantadine and rimantadine, the phase 3 studies tend to show plausible treatment effects: for example, differences in symptom scores by day, although small, have very low p values for at least part of the time period when a drug effect might be anticipated. Overall the efficacy-plus-safety profile of zanamivir has appeared no worse and may be better than that demonstrated in earlier trials of amantadine and rimantadine, despite study of a more heterogeneous population with more risk factors for adverse outcomes. In addition, although sufficient information is not yet available for direct comparisons, it is likely that the adverse event spectrum will be different from the adamantane derivatives (in particular, aggregate results of studies to date do not suggest that the types of central nervous system adverse events that have aroused particular concern with the adamantane derivatives would be as much of a problem with zanamivir), and even limited *in vitro* and clinical shedding data may suggest that the rapid and common emergence of resistance observed with the earlier drugs is unlikely to be replicated with zanamivir.

Perhaps the most conclusive demonstration of clinical benefit of an antiviral drug in the treatment of acute influenza would be achieved if initial controlled trials happened to be carried out in a season and location where a highly virulent strain circulated in a poorly protected population, leading to high morbidity and mortality as a background for discerning treatment effects. However, once a drug has been shown to have some effect in milder disease and to have potential advantages as an addition to other available choices, it is open to question what case could be made for waiting for such a situation to perform additional trials before making the drug available: the predictably unpredictable nature of influenza would make it difficult to find the appropriate situation and complete such studies within feasible resource limits and practicable timelines, and many

physicians and patients would likely consider clinical equipoise to be lacking for such a trial. Once there is adequate information to support the existence of a therapeutic effect that is expected to be clinically meaningful in appropriately selected circumstances, it is a matter of judgment whether more definitive information applicable to a larger range of circumstances is required before making therapy available at all, or whether adequate information can be made available to guide appropriate use based on the initial evidence while additional evidence-collecting is under way.

The availability of a more diverse list of anti-influenza agents would give physicians and patients a greater degree of choice in situations where treatment of influenza is warranted, and expand the range of options for public health professionals preparing to deal with potential epidemic or pandemic strains, and decisions about appropriate use in individual situations would then depend on the informed judgment of the health care provider and patient. These reasons, and its different mechanism of action and broader spectrum of activity, can be proposed as contributing to a clinical rationale and public health advantage to having zanamivir available as part of the treatment armamentarium against influenza, provided it can be made available with appropriately balanced labeling, and provided there are adequate commitments to phase 4 studies which would lead to better definition of patient selection and treatment outcomes and improvement in the patient instructions.

XIV. Labeling Issues

It is considered important that the package insert should appropriately represent the magnitude and the level of certainty of the treatment effect seen with zanamivir in an appropriate presentation for the population intended for use under the terms of this application, and that appropriate information should be made available concerning populations in which benefit has not been proven and greater risks may exist. Furthermore, where data to support more definite label language might be obtainable through appropriate further studies, such studies should be encouraged. Suggestions regarding the label language were conveyed to the applicant on two occasions before the Advisory Committee meeting. After consideration of the information submitted by the applicant in follow-up to the Advisory Committee meeting, the review team provided further suggestions regarding characteristics of label language that might be compatible with approval if the overall decision after further discussion was that approval could be justified. Discussions of salient points of potential labeling were continued throughout the remainder of the review process.

APPEARS THIS WAY
ON ORIGINAL

XV. Phase 4 commitments

The following topics were suggested phase 4 commitments after initial discussions.

A large rectangular area with a hand-drawn border, containing several horizontal lines for writing. The area is currently blank, intended for the user to list suggested phase 4 commitments.

XV. Recommendations

After review of the information made available both before and after the Advisory Committee, it appeared that the balance of evidence could be considered to weigh marginally either against or in favor of approval based on the studies submitted thus far. It is clear that further studies are needed for optimal understanding of the appropriate role of zanamivir in treatment of influenza, but such studies might alternatively be performed prior to approval, or after approval with appropriate label language to reflect the incomplete state of information at this time and phase 4 commitments to expand future availability of information. Issues of consistency and public health priorities need to be considered in any approval decision, and may contribute to the totality of evidence under consideration. Because the best approach is not absolutely clear-cut and the decision is subject to many influences related to policy as well as quantitative comparisons, contents of this application were the subject of intensive discussions within the Agency. Extensive consideration was given to concerns raised at the Advisory Committee meeting and to determining adequate responses to those concerns through additional information submitted, labeling agreements, and phase 4 commitments. After discussion of the totality of the information available over the ensuing five months of ongoing submissions and review, it was considered that approval could be justified if the expected benefits and risks for the expected treatment population could be appropriately described in the package insert and if appropriate phase 4 commitments could be constructed and agreed upon.

Iterative discussions of label language and phase 4 commitments were carried out with the goal of achieving adequate descriptions to guide and provide a useful choice to reasonably prudent prescribers and prospects of additional data to clarify outstanding

questions. On the basis of study results showing treatment effects (albeit modest and variable) in numerous studies, a safety profile that has shown few causes for concern from a reasonably extensive database, and the prospect of expanding the useable treatment options for a widespread disease with pandemic potential where even a small average benefit may carry substantial public health importance, the overall conclusion was that this application could be considered to provide adequate evidence for approvability in the context of the understandings reached regarding label language and phase 4 commitments.

APPEARS THIS WAY
ON ORIGINAL

/S/

Barbara Styr, M.D., M.P.H.
Medical Officer, HFD-530

XVI. Concurrence:

HFD-530/Dir/HJolson /S/ 10/15/99
HFD-530/DepDir/DBirnkrant /S/ 11/3/99
HFD-530/MTL/SKukich 9/13/99

cc:

HFD-530/NDA21036
HFD-530/Division File
HFD-530/Pharm/Wu
HFD-530/Micro/Battula
HFD-530/Chem/Boring
HFD-530/Stat/Aras
HFD-530/Biopharm/Rajagopalan
HFD-340
HFD-530/MO/BStyr
HFD-530/MTL/SKukich
- HFD-530/DepDir/DBirnkrant
HFD-530/CSO/Lynche

APPEARS THIS WAY
ON ORIGINAL