CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21036

STATISTICAL REVIEW(S)

Statistics Team Leader Memorandum

Drug: Relenza (zanamivir)

Indication: treatment of influenza.

NDA #: 21-036

NDA Date: 12/1998

Statistics Reviewer: Dr. Michael Elashoff

This memorandum is to give my insights and interpretations of the efficacy findings of Dr. Elashoff's statistical review.

The NDA application contains the results of three phase 3 studies, one conducted in European Union (EU), one conducted in the Southern Hemisphere (SH, primarily Australia), and one conducted in North America (NA, primarily the United States). Additionally, the results of 3 smaller phase 2 studies and an influenza prophylaxis study were provided. The phase 3 studies form the basis of Dr. Elashoff's review, although the phase 2 studies do provide some limited supporting information.

For all the phase 3 studies, prospectively agreed upon primary endpoint was the time to symptom alleviation. See Dr. Elashoff's review (page 3) for the details on exact definition of the primary endpoint and the symptom scores on which it was based. The protocols specified the influenza positive subgroup in each trial as the population of primary analysis. Influenza status was generally not known at randomization or during treatment. The prospective analysis plan stipulated that the treatment effect would be quantified by calculating the median time to event on each arm, and taking the difference of those medians. Hypothesis testing would be by the non-parametric Wilcoxon test. The results of these primary analyses as reported by Dr. Elashoff are as follows:

Table 1: Analysis of applicant's primary endpoint

European Union (EU)		Southern Hemisphere (SH)		North American (NA)	
Treatment effect	P-value	Treatment effect	P-value	Treatment effect	P-value
2.5 days	0.001	1.5 days	0.004	1 day	0.078

EU and SH studies show efficacy by prospectively planned analysis. These results are fairly robust by Dr. Elashoff's post-hoc additional analyses (see Dr. Elashoff's review, table 7, page 8).

NA study did not show statistical significance at 0.05 level, but indicates a trend in the right direction (two sided p-value=0.078). However, detailed Post-hoc analyses performed by Dr. Elashoff indicate that the trend noticed in the primary analysis is not

robust. In none of these analyses are the results in North America statistically significant (see Dr. Elashoff's review, table 7, page 8).

A possible reason for a small observed treatment effect and no statistical significance in the NA study is that placebo effect was better in NA study than in the other two studies, particularly, the EU study. This may be due to use of relief medication that was almost twice as much as patients with EU, with SH lying in between. However, as Dr. Elashoff points out, this relationship cannot be tested using the current data since due to the complex interaction between patient's symptoms and patient's use of relief medication.

Though NA study failed to reject the null hypothesis that Zanamirir has no advantage over the placebo, further studies (perhaps phase 4 commitments if the drug is approved) that take into account issues raised above may show efficacy. Since NA study suggests that the treatment effect in North America is small, it may require an enriched design with an appropriate sample size to detect a treatment effect if it exists.

Given the results of the 3 studies, it is difficult to generalize statistically that the treatment will be effective for the US patient population. A clinical overview of the clinical similarities of the 3 patient population may help reconcile the outcomes of these trials (see Dr. Barbara Styrt's review). Dr. Elashoff has mainly addressed the efficacy issues in his review. For a detailed safety review and a risk benefit analysis that takes into account statistical as well as nonstatistical issues such as public health policies, limitations of currently available influenza therapies, evidence from prophylaxis studies, patient familiarity with the drug delivery system, reader is referred to Dr. Styrt's review.

/S/ 7/26/1999

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ON ORIGINAL

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HFD-530/DepDir/Dbirnkrant
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HFD-530/MTL/Skukich
HFD-530/CSO/SLynche
HFD-725/Division file
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HFD-725/ATL/GAras
HFD-700/DepDir/CAnello
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APPEARS THIS WAY
ON ORIGINAL

Statistical Review and Evaluation

Drug: Relenza (zanamivir)

Indication: treatment of influenza.

NDA #: 21-036

NDA Date: 12/98

Medical Reviewer: Dr. Barbara Styrt

Background

Two anti-viral drugs are currently approved for the treatment of influenza: amantadine and rimantadine. These drugs were approved for influenza A, but not for influenza B. Efficacy was demonstrated by showing that the drugs resulted in significantly greater symptomatic relief compared to placebo, where symptomatic relief was quantified by various patient-recorded symptom scores.

Zanamivir is the first drug in a new class of influenza drugs, the neuraminadase inhibitors. In phase I studies, zanamivir was shown to have in vitro and in vivo activity against influenza types A and B, although the activity against type B was more limited than for type A.

For phase 2/3, the applicant proposed a primary endpoint that was different from those used in the prior studies of amantidine and rimantidine. At the protocol stage, there was little information available on which to judge this endpoint, though it was felt that the endpoint was adequate to support the initiation of the phase 2/3 program. It was recognized that the results for this endpoint would need to be robust in order to provide convincing evidence for efficacy.

Review Outline

The NDA application contains the results of three phase 3 studies, one conducted in Europe, one conducted in the Southern Hemisphere (primarily Australia), and one conducted in North America (primarily the United States). Additionally, the results of three smaller phase 2 studies and one influenza prophylaxis study were provided. The phase 3 studies form the basis of the review, although the phase 2 studies do provide some limited supporting information. Division advice has been that prophylaxis studies for influenza therapies provide some useful safety and activity information, but that the indications of treatment and prophylaxis are different enough that clinical efficacy does not carry over from one setting to the other.

Part I of the review will summarize the study designs, patient populations, and the applicant's efficacy analyses.

Part II of the review will summarize the FDA analysis of the efficacy data.

Part III of the review will summarize the issues regarding the safety and efficacy of zanamivir, and will provide conclusions and recommendations for the regulatory outcome of the application.

Part I: Applicant Results

Study Designs

Table 1 summarizes the study designs for the three phase 3 studies in the application.

Table 1: Study Designs

	Europe (EU)	South Hemis. (SH)	North America(NA)
Protocol Number	NAIB3002	NAIB3001	NAIA3002
Arms	Zanam/placebo	Zanam/placebo	Zanam/placebo
Zanamivir dose	10mg bid	10mg bid	10mg bid
Treatment duration	5 days	5 days	5 days
Follow-up	14-28 days	14 days	14-28 days
Entry Temp.	>37.8	Any	>37.8
Entry Sx. duration	<48 hours	<36 hours	<48 hours
Flu confirmation	Pcr/serum/cult.	Rapid/serum/cult.	Pcr/serum/cult.
Primary endpoint	Time-to-allev.	Time-to-allev.	Time-to-allev.

The protocol primary analysis was specified as the influenza positive subgroup. Influenza status was generally not known at randomization or during treatment.

Individual symptoms were recorded twice per day. The symptoms were: feverishness, headache, sore throat, aches, cough, weakness, loss of appetite, nasal symptoms. Each of these was measured on a four point scale (0=absent, 1=mild, 2=moderate, 3=severe). At the end of each day, two daily summary scores were recorded, an overall influenza symptom score (0-3 scale) and an activity score (1-5 scale, with 5=normal activity for the day). Temperature was recorded four times per day for the first 5 days and twice daily after that. Use of relief medication (tablets of pain reliever and spoonfuls of cough suppressant) was recorded twice daily.

The primary endpoint was the time to symptom alleviation. The time was defined as the first time at which (headache <2, sore throat <2, cough <2, aches <2, feverishness <1, and temperature <37.8 C), were satisfied for a 24 hour period (encompassing 3 diary cards). Symptoms of weakness, loss of appetite, nasal symptoms, overall score, and activity score did not facto in to the primary endpoint. Secondary endpoints included time to return to normal activity (activity score =5), time to afebrile status (temperature <37.8 C), and time to alleviation with no use of relief medication.

The analysis plan stipulated that the treatment effect would be quantified by calculating the median time to event on each arm, and taking the difference of those medians. Hypothesis testing would be by the non-parametric Wilcoxon test; technically the Wilcoxon test does not test for equality of medians but for equality of distributions.

Study Populations

The following table summarizes the characteristics of the enrolled patients in the Phase 3 studies.

Table 2: Study Populations

	EU	SH	NA
Randomized	356	455	777
Influenza Positive	277	321	569
Influenza Positive Subgroup			
Influenza A	265	214	561
Influenza B	12	107	8
High Risk	30 (11%)	52 (16%)	79 (14%)
Baseline Temp (mean)	38.6 C	38.0 C	38.5 C
Sx. Duration			
0-24 hours	Not reported	40%	37%
24-36 hours	"	60%	47%
>36 hours	"	0%	12%
Smoking status	29% Smokers	21% Smokers	21% Smokers
Race	99% Caucasian	95% Caucasian	87% Caucasian
Age (mean)	38 years	37 years	36 years
Gender	47% Male	54% Male	51% Male
Mean Total Sx Score	9.9	9.3	10.0
Mean Overall Score	2.49	2.43	2.48
Mean Activity Score	1.80	1.95	1.85
Vaccination status	5% Vacc.	5% Vacc.	15% Vacc.

The three studies had generally similar study populations for the factors shown in the table. Some differences included: more minorities in the NA study, more smokers in the EU study, more vaccinated subjects in the NA study, lower baseline temp in the SH study, and more influenza B in the SH study . For an examination of the potential impact of these differences on the study results, see Part II.

Within each study, there was generally good balance of baseline characteristics between the two drug arms. A notable exception was the distribution of high risk subjects in the NA study, where 16.7% of placebo subjects were high risk compared with 11.5% of zanamivir subjects (p=.075).

Study Results

The following table shows the applicant analysis of the primary and secondary endpoints.

Table 3: Applicant Results

	EU		SH		NA	
	Zanam	P	Zanam	P	Zanam	P
ITT[1]: Time to Allev.	5.0	7.5	5.0	6.5	5.5	6.0
	(.75 to 3.5) P=.001		(0.5 to 2.25) p=.011		(-0.5 to 1.0) p=.228	
IP[2]: Time to Allev.	5.0	7.5	4.5	6.0	5.0	6.0
	(1.0 to 4.0) P=.001		(0.5 to 2.5) p=.004		(0.0 to 1.5) p=.078	
ITT:Time to Allev./RM[3]	5.5	8.3	7.0	9.0	7.0	8.0
	P=.001		P=.085		P=.054	
IP: Time to Allev./RM	5.5	8.5	6.5	8.5	7.3	8.0
	P=.001		P=.033		P=.075	
ITT: Time to Norm. Act.	7.0	8.5	7.0	9.0	7.3	7.5
	P=.023		P=.001		P=.336	
IP: Time to Norm. Act.	7.0	8.5	7.0	9.0	7.5	7.5
	P=.025		P=.001		P=.378	
ITT: Time to afebrile			1.0	1.0		
	Not reported		P=.196		Not reported	
IP: Time to afebrile	1.5	2.0	1.0	1.5	1.5	1.5
	Not reported		P=.017		Not reported	
HR[4]IT: Time to Allev.	9.0	11.5	5.5	8.0	7.5	6.5
	P=.178		P=.048		P=.710	
HR IP: Time to Allev.	9.3	11.5	5.0	8.3	6.3	6.0
	P=.210		P=.161		P=.886	

[1]Intent-to-Treat, [2]Influenza Positive [3]Alleviation with no use of Relief Meds,[4]High Risk

For the NA study, no difference was seen in the time to return to normal activity or in the time to afebrile status. Note also that in the analysis of high risk patients, longer times to alleviation were seen for zanamivir compared to placebo in the NA study.

The following table shows the incidence of complications for high risk patients in the phase 3 studies. The number of patients in the high risk groups was relatively small.

Table 4: Complications in the High Risk Subgroup

	EU		SH		NA	
	Zanamivir	Placebo	Zanamivir	Placebo	Zanamivir	Placebo
IP: High Risk	4/12 (33%)	11/18 (61%)	3/24 (13%)	13/28 (46%)	12/36 (33%)	9/43 (21%)
	P=.102		P=.007		P=.095	

Observe that in the largest high risk subgroup (NA study), more zanamivir patients than placebo patients experienced complications.

Part II: FDA Analysis

From the outset, the most notable element of the phase 3 study results was the lack of a significant effect in the largest study, the North American study. Not only was the p-value for the primary endpoint non-significant, but the treatment effect was smaller. In addition, the secondary endpoints also showed minimal treatment effects that were not significant, and were in some case worse than placebo. The focus of the review became deciding whether the results of the NA study were close enough to be consistent with the proven efficacy in the foreign studies. This is especially relevant since this study was the only phase 3 study for the population that FDA regulates, and even the applicant's analyses showed that it could not stand on its own.

The protocol analysis was a comparison of medians using the wilcoxon test. Shown in the table are two alternate methods for analyzing the protocol primary endpoint with different statistical methods.

Table 5: Three Analyses of Applicant Primary Endpoint

Analysis	EU	SH	NA
Median Wilcoxon test (applicant analysis)	2.5 (p=.001)	1.5 (p=.004)	1.0 (p=.078)
Median Logrank test (fda analysis)	2.5 (p=.001)	1.5 (p=.002)	1.0 (p=.156)
Mean t-test (fda analysis)	2.6 (p=.001)	1.3 (p=.001)	0.6 (p=.242)

As the table illustrates, the treatment effects and p-values in the foreign studies are robust to changes in the analysis of the primary endpoint. However, in the NA study, the treatment effects and p-values for the primary endpoint are less robust.

Subgroup Analyses

As noted above, the studies differed in some baseline and demographic variables. To investigate whether these differences may explain the disparate study results, a series of subgroup analyses were done. The table below reports the results for the combined phase 3 study database, after adjusting for treatment and study effects. Results for individual studies were consistent with the overall pattern seen in the subgroup analyses.

Table 6: Tests for Interaction

Covariate	p-value Main Effect	p-value Interaction Effect
Gender (M/F)	0.001	0.46
Race (Caucasian/Other)	0.180	0.16
Age (linear)	0.001	0.24
Age (<50/>50)	0.001	0.30
Baseline Temperature	0.020	0.18
Baseline Overall Score	0.001	0.23

Smoking Status	0.078	0.12
High Risk	0.002	0.77
Vaccination Status	0.820	0.93

As the table shows, there were no significant treatment by factor interactions.

Alternate Analyses

The next line of investigation was into the behavior of the primary endpoint on a patient-by-patient basis. For each subject, there was a great deal of symptom information. The questions that needed to be addressed were: was the particular algorithm defined as primary robust to modifications in the definition, and did the algorithm accurately reflect the subjects' influenza experience?

On examination of the data, it became apparent that patient's frequently had symptoms rated as moderate or severe after the point at which the primary endpoint had been achieved. In the North American study, 32% of subjects had at least one primary symptom reemerge to moderate or severe after alleviation. The breakdown by symptom indicated that the most common symptom to reemerge was temperature>37.8 (15% of subjects). Next most common were cough and feverishness (11%) and headache (8%). When considering the protocol secondary symptoms (some of which were primary for rimantidine and the Roche neuraminadase inhibitor), 41% of subjects had moderate symptoms after alleviation.

The high level of symptom reemergence is concerning for two main reasons. First, it undermines the confidence in the time-to-event primary endpoint. A time-to-event analysis implies that the event occurs at a specific time, and after that time point the patient is not at risk for the event any longer. An exception is the case of an analysis of time to first occurrence of some event, but these analyses are in settings where the event is deleterious, unlike the current situation, where the event is supposed to represent alleviation. The second reason is that symptoms after "alleviation" do not count in the assessment of efficacy. It results in the awkward situation of moderate/severe symptoms counting if they occur before an arbitrary time point but not after. The symptoms after may be just as important to the patient given that the patients have scored them the same. And the symptoms cannot be dismissed as noise or non-influenza symptoms, since (1) these patients all had influenza, and (2) the time to alleviation was quite long in many patients, meaning that later symptoms are quite consistent with ongoing influenza symptoms.

Where these symptoms isolated spikes that occurred much later than the primary endpoint. The answer is no on both counts. The median duration of symptoms after alleviation was 4 diary cards (2 days). And in the majority of the patients who had a reemergence of their primary symptoms, that reemergence was the first or second diary card after they were considered alleviated.

Of further concern in the NA study, more zanamivir patients compared to placebo patients had reemergent symptoms (36% vs. 27%). These symptoms do not necessarily mean that there is viral rebound, but may simply reflect the fact that

symptoms have substantial variability even as they trend downwards over a one week plus period. This pattern merely highlights the need to examine the full symptom course and not focus exclusively on the point at which patients meet a pre-defined arbitrary definition for the first time.

Since the aim of the primary endpoint was to assess the symptomatic relief due to zanamivir, other ways of examining symptomatic relief were analyzed. These included: mean symptom sores over time, total symptom scores over time, number of days of severe symptoms, number of days of severe/moderate symptoms, days of fever, etc.

The following table shows a series of analysis of the number of mean days where subjects met or did not meet various symptom criteria.

Table 7: Additional Efficacy Analyses

	Treatment Effects		
Analysis	EU	SH	NA
Mean Days w/o Alleviation	1.8 (p=.001)	1.1 (p=.011)	0.3 (p=.256)
Mean Days w/o Alleviation/RM	1.5 (p=.001)	1.1 (p=.006)	0.4 (p=.194)
Mean Days any Sx Mod/Sev	1.8 (p=.001)	0.8 (p=.055)	0.2 (p=.425)
Mean Days any Sx Severe	1.6 (p=.001)	1.0 (p=.011)	0.1 (p=.775)
Mean Days Overall Mod/Sev	1.2 (p=.001)	0.7 (p=.072)	0.1 (p=.647)
Mean Days Overall Sev	0.4 (p=.079)	0.3 (p=.186)	0.1 (p=.469)
Mean Days Temp>37.8	0.9 (p=.009)	0.7 (p=.004)	0.0 (p=.916)
Mean Days Activity<Normal	1.3 (p=.009)	1.5 (p=.001)	0.2 (p=.577)

These analysis exacerbate the efficacy concerns regarding the NA study. In these analyses, the smaller foreign studies consistently outperform the larger NA study both in terms of statistical significance and in terms of treatment effect size. In none of these analyses are the results in North America clinically or statistically significant.

The analysis of activity and overall score are important because they are "meta" symptoms that may be freer from the variation in symptom scores from day to day. Again, we see that the NA study found no real difference between zanamivir and placebo for these analyses. These analyses are consistent with the zero effect found be the applicant (see Part I).

In addition to analysis that focused on days meeting various symptom criteria, several analyses were done that looked at mean symptom scores over time. Figures 1-3 in the appendix show the mean symptom score, overall score, and activity score over time for the phase 3 studies. These graphs indicate that analyses based on days may overstate

the true benefit of zanamivir on symptoms. This is because the symptom score curves are relatively flat in the area where the alleviation definition was typically met: 4 to 8 days. The alleviation times are roughly equivalent to the time at which the mean symptom score curves cross 1.0. Thus, the two treatment groups may cross this line 1 or 2 days apart, but the actual scores on those days were very similar. That is, placebo patients with a mean score of 1.1 might be considered unalleviated while zanamivir patients with a mean score of 0.9 might be considered alleviated. In this way, small symptom score differences were magnified into 1 or 2 day differences. This problem is particularity acute in the analyses of median days, such as the primary analysis, since median times are so coarse (0.5 day increments). This effect explains why in Europe a difference of 0.2-0.3 symptom score units translated into a 2.5 day difference, and in NA a difference of 0.1 symptom score units translated into a 1.0 day difference.

Summary of Analyses

On the basis of the spectrum of analyses performed, it is apparent that the primary endpoint and method of analysis lead to misleading estimates of treatment effect. In the foreign studies, while statistically significant, the results indicated a much more modest effect on symptoms than suggested by the 1.5-2.5 days of effect in the initial analysis. And in the NA study, the results indicated a fraction of a day of effect or a fraction of a point on symptom scores, and did not support a finding of statistical significance or of a "trend".

Treatment/Study Interaction

The additional analyses found that the treatment effect size in both NA and non-NA studies was smaller than the applicant's analysis suggested. However, the results in non-NA studies were still clearly statistically significant, while the results of the NA study were clearly non-significant. To formally test for a treatment by study interaction, the phase 3 data were pooled.

Table 8: Study/Treatment Interaction

Analysis	Pooled Trt Effect	Study Effect	Interaction Effect
Median time to alleviation	1.0 (p=.001)	0.5 (p=.023)	0.5 (p=.019)
Mean days w/o alleviation	0.9 (p=.001)	0.5 (p=.005)	0.5 (p=.015)

These results confirm what was seen above, that the studies exhibit a heterogeneity of effect that do not allow for an overall estimate of treatment effect.

The NA study included both Canadian and US centers. An analysis of focusing on the US centers found that the US centers were consistent with the study as a whole:

Influenza Positive: Median time to alleviation 1.0 days (p=.07), Mean 0.6 days (p=.10)
Intent-to-Treat: Median time to alleviation 0.5 days (p=.20), Mean 0.3 days (p=.30)

Phase 2

The lack of efficacy in North America was also suggested by the results in phase 2 studies. Study AB2005 and had both North American and non-North American components. The following table shows the results of this broken down into these components.

Table 9: NAIAB2005

Analysis	Treatment Effects	
	Non-NA (N=197)	NA (N=220)
Median time to allev.	1.0 (p=.141)	1.0 (p=.120)
Mean days w/o allev.	1.3 (p=.111)	0.8 (p=.373)
Mean days w/o allev/RM[1]	1.2 (p=.121)	0.5 (p=.557)
Mean days overall mod/sev	0.4 (p=.469)	0.3 (p=.653)

[1]Alleviation without use of relief medications

As the results indicate, the lack of efficacy seen in the phase 3 NA study was consistent with the lack of effect in the North American part of NAIAB2005.

Intent-to-Treat

The previous discussion has focused on the influenza positive analysis. This subgroup answers the biologic question of whether the treatment is effective in only those patients for which it could be expected to work. As seen above, the result was that zanamivir appears to be effective in foreign treatment settings but not in the population in North America. The subgroup analysis, though, does not address the question of what treatment can be expected for the group of patients who take zanamivir without prior knowledge of their influenza status. This is the intent-to-treat population, composed of all subjects in the trials. The treatment effect estimates for this population are much more reflective of the average benefit that a patient can expect from zanamivir therapy. The following table shows the treatment effects for the intent-to-treat analysis.

Table 10: ITT (All Treated) Analyses

Analysis	Treatment Effects		
	EU	SH	NA
Median time to alleviation (Wilcoxon)	2.5 (p=.001)	1.5 (p=.011)	0.5 (p=.228)
Median time to alleviation (logrank)	2.5 (p=.001)	1.5 (p=.011)	0.5 (p=.492)
Mean time to alleviation	2.2 (p=.001)	1.0 (p=.001)	0.2 (p=.565)
Mean Days w/o Alleviation	1.5 (p=.001)	1.0 (p=.008)	0.1 (p=.692)
Mean Days w/o Alleviation/RM	1.4 (p=.001)	0.9 (p=.013)	0.3 (p=.201)
Mean Days any Sx Mod/Sev	1.6 (p=.001)	0.8 (p=.033)	0.0 (p=.957)
ean Days anySx Sev	1.5 (p=.001)	0.7 (p=.043)	0.0 (p=.882)

Mean Days Overall Mod/Sev	1.0 (p=.002)	0.7 (p=.046)	-0.1 (p=.542)
Mean Days Overall Sev	0.4 (p=.068)	0.2 (p=.313)	0.0 (p=.785)
Mean Days Temp>37.8	0.8 (p=.009)	0.3 (p=.097)	0.1 (p=.594)
Mean Days Activity<Normal	1.1 (p=.014)	1.2 (p=.001)	0.1 (p=.693)

The typical patient in the North American study gained no more than half a days benefit from zanamivir, and in many analyses gained nothing. Further, these analyses exclude any meaningful differences due to the high power and consequent narrow confidence intervals.

Relief Medications

The following table shows the relief medication use in the phase 3 studies.

Table 11: Use of Relief Medication

		Europe	South Hemis.	North America
Tablets Acetomin. Days 1-14	Total	10	17	21
	Placebo	11	17	22
	Zanamivir	9	17	21
Spoons Cough Syrup Days 1-14	Total	13	15	18
	Placebo	15	17	20
	Zanamivir	11	14	17

Two points can be made. First, that the use of relief medication use was similar between zanamivir and placebo. Second, that patient in NA used almost twice as much relief medication as patient in EU, with SH lying in between. Since this pattern in relief medication use parallels the overall study results, it is suggestive of a relationship. However, this relationship cannot be tested since due to the complex interaction between patient's symptoms and patient's use of relief medication. In any case, even if this association were proved, that would not mitigate the lack of efficacy in NA, since we cannot tell patients not to use relief medications.

Influenza B

The NA and EU studies had very few subjects with influenza B (8 and 12 patients respectively), so the SH study was the only meaningful Phase 3 source from which to draw inference about the efficacy in influenza B versus that in influenza A. In addition, the phase 2 study NAIAB2005 also had a substantial number of subjects with influenza B.

The following table gives a breakdown of the results by influenza type.

Table 12: Results for Influenza A vs. Influenza B

		Treatment Effects in days (p-value)	
Study	Analysis	Influenza A	Influenza B
SH (N=214 A, 107 B)	Mean Days w/o Alleviation	1.4 (p=.007)	0.3 (p=.617)
SH (N=214 A, 107 B)	Mean Days w/o Alleviation/RM	1.4 (p=.005)	0.5 (p=.461)
NAIAB2005 (N=147 A, 115 B)	Mean Days w/o Alleviation	1.5 (p=.053)	0.6 (p=.489)
NAIAB2005 (N=147 A, 115 B)	Mean Days w/o Alleviation/RM	1.5 (p=.042)	0.3 (p=.781)

As the table indicates, there were no significant effects for any analysis in influenza B infected patients. The table also indicates that this lack of significance was not due to fewer subjects than influenza A but was due to much diminished treatment effects. Given that prior influenza drugs have been given indications restricted to influenza A, the results seen for zanamivir necessitate a similar restriction.

Part III: Discussion And Conclusions

The only phase 3 study in the US population did not find evidence of efficacy. Lack of statistical significance does not by itself constitute a proof that a drug has no efficacy. However, small observed effects, lack of significance, and very high power to exclude clinically relevant treatment effects, were all seen over the broad spectrum of endpoints in this study. The US study therefore, when looking at the combined weight of evidence, is considered to be negative. Analyses of Phase 2 North American centers support this conclusion. Further, the results of the foreign studies, while convincing evidence of efficacy in those populations, only heighten the concern over the US study results. These studies proved that any of variety of analyses of symptoms can find significant differences in favor of zanamivir, *if such differences exist.* Extensive examination of the study results did not identify any firm reasons why the US failed to show efficacy, other than the null hypothesis of the study, that zanamivir has no advantage over placebo.

The level of evidence for new drugs is generally two positive clinical trials. But this criteria has to be examined more closely if: 1) there is a negative study as well, 2) that study is as large as the other two studies combined, 3) that study was the only Phase III study in the US, and 4) there is empiric evidence that the clinical efficacy in these foreign studies cannot be extrapolated to the US population in this case, since there was a significant treatment/study interaction and the use of relief medication varied so widely between studies..

The median time to alleviation in the placebo arm was 6-7 days in the phase 3 studies, with median times to alleviation with no use of relief medications and median times to normal activity several days beyond that. So there was room for treatment to show reductions in these times, and indeed in the European study large differences were seen that were highly significant. In North America, the preponderance of evidence from multiple different analyses not only failed to find differences, but the very high power means it is likely that meaningful differences do not exist.

Prior to carrying out the study, it was thought that the currently approved anti-viral therapies for influenza were lacking, and that zanamivir might provide a meaningful alternative to patients who need influenza treatment. These areas included "high risk" patients, patients with more severe disease, patients who did not want the safety risks of the older drugs, and patients with influenza B. Patients in the "high-risk" influenza positive group in the NA study actually did numerically worse in the treated group than in the placebo group for the primary endpoint (-0.3 days) and had more complications as well (33% to 21%, p=.09). In the NA study, patients with severe disease did not show any more evidence of treatment effect than patients with milder disease, and in secondary analyses showed less treatment effect. Preliminary results from an active control trial did not find any safety advantage for zanamivir (see Medical Review). And finally, no significant effect was seen for Influenza B.

The drug has been studied in fewer than 3000 patients. The adverse event rule of three allows us only to conclude that the rate of serious adverse events attributable to zanamivir is on the order of 1 in 1000 or less. This may be small when compared to the

HIV setting, but is worrying when compared with the number of people in this country who get influenza or *influenza like symptoms.* Since the drug has no proven efficacy for the treatment of influenza in the US population, no proven effect on reducing person-to-person transmissibility, and no proven impact on preventing influenza (with the exception of an unreviewed study for another indication that the applicant has not applied for). These factors should be considered when assessing the potential impact of zanamivir on public health.

If approved, the number of patients in this country who take zanamivir who do not have influenza can be reasonably expected to be very large. In controlled clinical trials, which were subject to strict entry criteria and an in-person clinic visit, 25-35% of patients who received zanamivir did not have influenza. When these conditions are relaxed, this proportion can only increase. These patients will be exposed to the risks of zanamivir, while deriving no benefit from it. The Intent-to-Treat treatment effect estimates, the most relevant for determining the expected benefit for the typical patient, show no treatment effect in North America across a wide range of analyses. Further, these analyses exclude meaningful effects due to the very high power in the North American study. And as discussed above, outside of a controlled clinical trial the proportion of influenza negative patients will be higher, meaning the expected benefit for patients who take zanamivir will be even less than the ITT estimates in the study.

The advisory committee meeting for zanamivir was held on February 22, 1999. The advisory committee voted 13-4 against approval. The primary reason members cited for recommending that zanamivir not be approved was that efficacy not been established, particularly for the US population, since it was felt that the NA study was a negative study. Further, the majority felt that while the foreign studies appeared to be well conducted, the results in those studies could not be applied to the US population because of the disparate study results.

Following the advisory committee, the applicant provided several additional analysis of the efficacy results, however, these analyses did not alter the efficacy picture in a meaningful way. The applicant also provided the results of a study for influenza prophylaxis. This study provided further evidence of activity, but activity was never an issue to begin with, the issue has been clinical efficacy. There has been consistent Division advice for influenza drug development programs that prophylaxis studies are non-contributory for treatment efficacy.

The unambiguous advisory committee vote and comments support the findings of this review. Zanamivir has not been shown to be effective in this country for the treatment of influenza, and in my opinion therefore should not be approved.

/S/

Michael Elashoff, PhD
Division of Biostatistics III

Concur: Dr. Aras

Figure 1

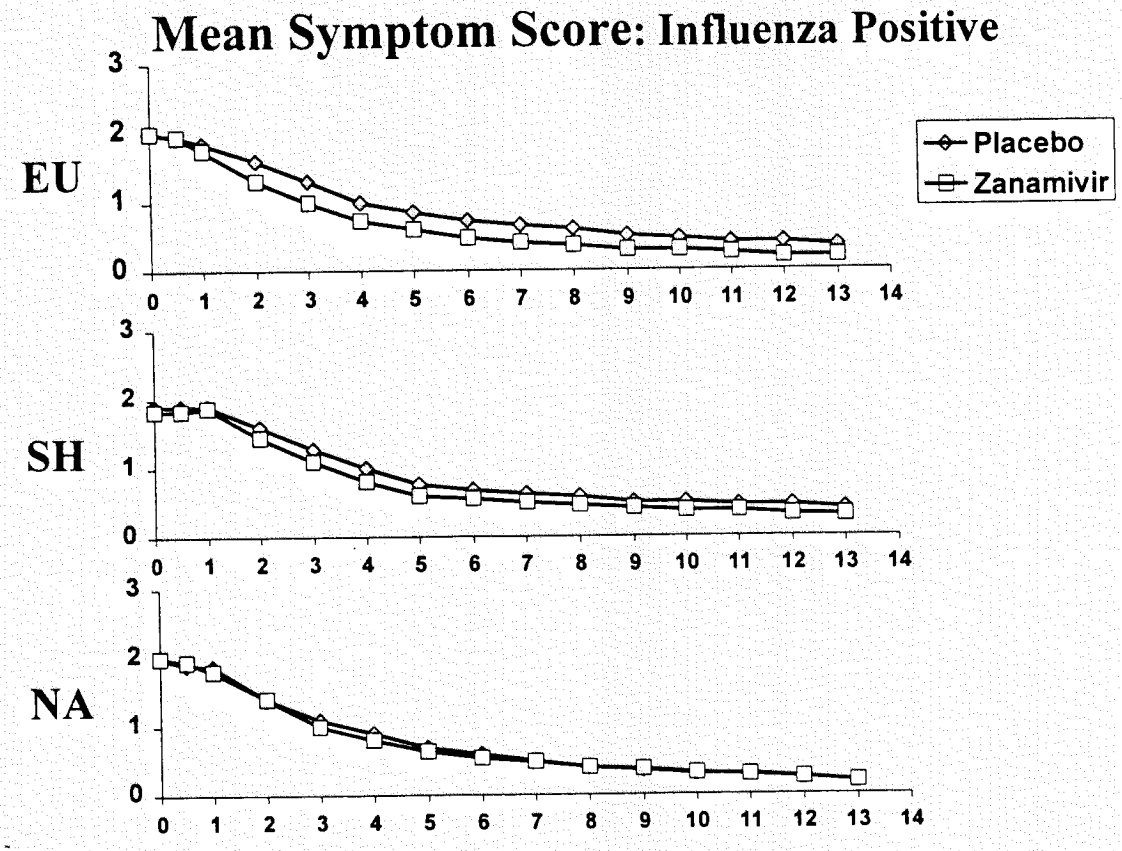

Figure 2

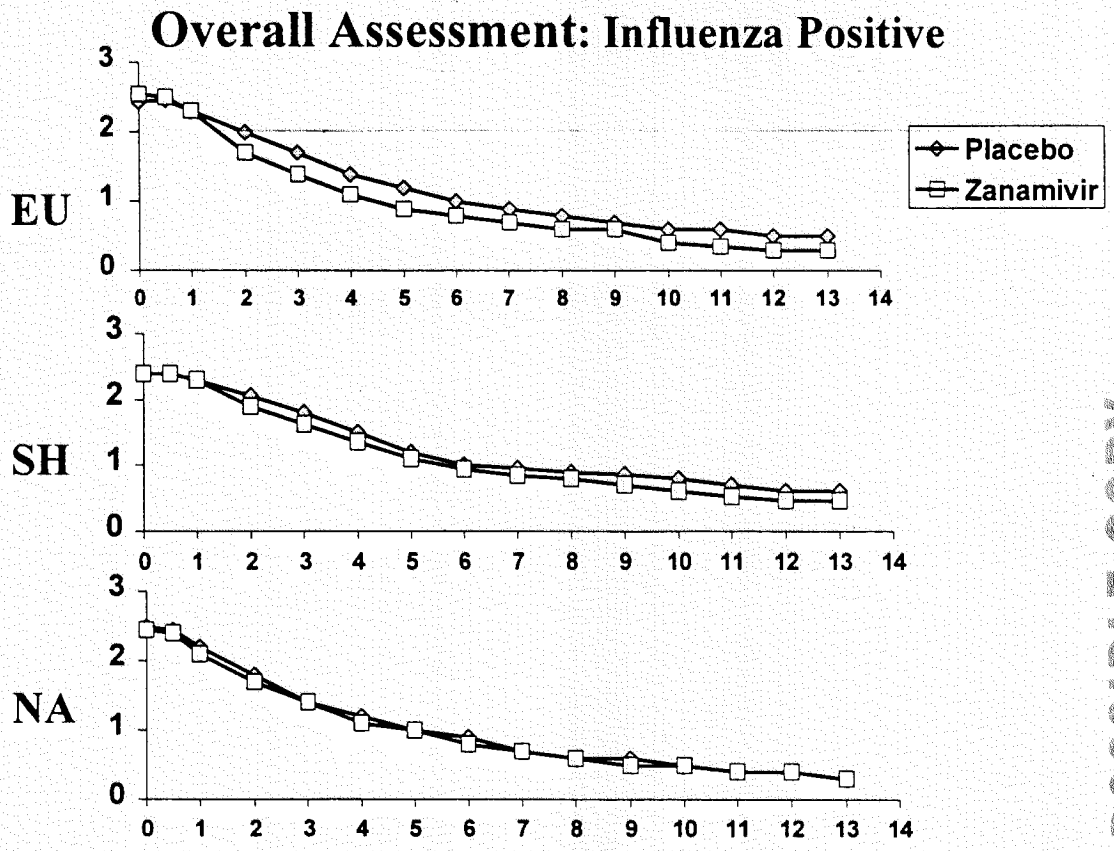

Figure 3