FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE

8:30 a.m.

Wednesday, February 24, 1999

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2 Montgomery Village Avenue
Gaithersburg, Maryland

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C O N T E N T S

Relenza (zanamivir for inhalation)
Glaxo Wellcome Incorporated,
for the Treatment of Influenza A and B

P R O C E E D I N G S

(8:30 a.m.)

DR. HAMMER: Good morning. I'd like to convene this meeting. This is the Antiviral Drugs Advisory Committee. Today we're here to discuss zanamivir, or Relenza, for the treatment of influenza A and B.

I'd like to welcome the sponsor, Glaxo Wellcome, also interested members of the audience, members of the committee, guests, and members of the agency. But I'd also like to welcome two new members to the committee, Drs. Yogev and Wong.

Before proceeding, I would also like the committee to introduce themselves. So, I'll start on the left with Dr. Poland. Please give your name and affiliation.

DR. POLAND: Greg Poland from the Mayo Clinic in Rochester, Minnesota.

DR. KILBOURNE: Ed Kilbourne, New York Medical College.

DR. COX: Nancy Cox, Centers for Disease Control and Prevention in Atlanta.

DR. HENDELES: Leslie Hendeles, University of Florida.

DR. STOLLER: Jamie Stoller, Cleveland Clinic.

DR. LI: James Li, allergy, Mayo Clinic.

DR. STANLEY: Sharilyn Stanley, Texas Department of Health.

DR. HAMILTON: John Hamilton, Duke University and the Durham VA Hospital.

DR. WONG: Brian Wong, Yale University and the Westhaven VA Hospital.

DR. YOGEV: Ram Yogev, Children's Memorial Hospital, Chicago.

DR. DIAZ: Pamela Diaz, Chicago Department of Public Health.

DR. HAMMER: Scott Hammer, infectious disease, Columbia University.

MS. STOVER: Rhonda Stover, FDA.

DR. MASUR: Henry Masur, Clinical Center, NIH.

DR. EL-SADR: Wafaa El-Sadr, Harlem Hospital and Columbia University.

DR. VERTER: Joel Verter, George Washington University.

DR. WITTES: Janet Wittes, Statistics Collaborative.

DR. FLYER: Paul Flyer, FDA.

DR. ELASHOFF: Mike Elashoff, FDA.

DR. STYRT: Barbara Styrt, FDA.

DR. MEYER: Bob Meyer, FDA.

DR. BIRNKRANT: Debra Birnkrant, FDA.

DR. JOLSON: Heidi Jolson, FDA.

DR. MURPHY: Diane Murphy, FDA.

DR. HAMMER: Thank you.

I'd like to turn now to Rhonda Stover who will read the conflict of interest statement.

MS. STOVER: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 United States Code, section 208(b), full waivers have been granted to Dr. Wafaa El-Sadr, Dr. John Hamilton, Dr. Judith Feinberg, Dr. Janet Wittes, Dr. Henry Masur, and Dr. Scott Hammer.

A copy of these waiver statements may be obtained by submitting a written request to agency's Freedom of Information Office, room 12A-30 of the Parklawn Building.

In addition, we would like to disclose that Dr.

Hammer's employer, the Beth Israel Deaconess Medical Center, has received funding from Glaxo Wellcome for clinical trials of products unrelated to Relenza. The agency has determined, notwithstanding these interests, that the interests of the government in Dr. Hammer's participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Dr. Hammer may participate fully in the committee's discussions and vote concerning Relenza.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon.

DR. HAMMER: Thank you.

I'd like to turn now to Dr. Debra Birnkrant for FDA introductory comments.

DR. BIRNKRANT: Thank you very much.

I'd also like to welcome everyone to this morning's advisory committee meeting for zanamivir for

inhalation for the treatment of influenza.

In addition to our Antiviral Advisory Committee members, I'd like to acknowledge the participation from the members of the Pulmonary Drug Products Advisory Committee and invited guests.

I'd also like to recognize Glaxo Wellcome for their efforts in developing this product for influenza.

At our last advisory committee meeting, we discussed our rationale for bringing products before the committee. We outlined some of the following reasons: a new chemical entity or first in its class, new mechanism of action, complicated analytic issues, et cetera.

Zanamivir for inhalation fits not only into one, but all of these categories. It is a new chemical entity for the treatment of influenza and also first in its class. Being a neuraminidase inhibitor with in vitro activity against influenza A and B, its mechanism of action differs from the only other marketed drugs for influenza A, that being amantadine, which was approved more than 20 years ago, and rimantadine, which was approved in the 1990s.

Its novel mechanism of action highlights the need to develop more drugs to treat influenza. Recently this became evident in 1997 when a new influenza strain H5N1, which had previously infected chickens, suddenly

infected humans.

Complicated analytic issues from the three phase III clinical trials is another reason why this application is being brought before you today. Keeping in mind that influenza is responsible for a self-limited disease for the most part, treated symptomatically with over-the-counter antipyretics and cough medicine, how do you study it and what type of treatment effect is clinically relevant? This is a key question for this application because the treatment effect among the influenza-positive patients varied across the three phase III studies.

The primary endpoint treatment effect, as measured as a time-to-alleviation analysis, was based upon symptom scores rated by patients as none, mild, moderate, or severe on a scale of 0 to 3 for fever, cough, headache, myalgia, and sore throat, all of which had to be maintained at none or mild with a temperature less than 37.8 degrees Centigrade for the subsequent 24 hours. Aside from temperature, the potential subjective nature of this tool for determining the primary endpoint and the potential confounding by use of allowable relief medications led to many secondary and exploratory analyses which will be presented today by FDA and also by the applicant.

Other issues deserve mention, including the use

of the product in high risk patients and device-related issues.

As the risk of complications from influenza is higher among the elderly and those with certain underlying conditions, such as respiratory disease, it would be important to study these populations. As you have seen, however, in the background material, relatively few subjects entered the phase III trials in the high risk patient category.

Not only does zanamivir have a novel mechanism of action, but it depends on the use of a delivery system which is also novel in the area of antiviral drugs. Points related to the use of the delivery system are critical to today's discussion since appropriate use of the Diskhaler with the Rotadisk is crucial to treating this infectious disease with an inhaled product for the proposed treatment period of 5 days.

Moving to the final reason we brought this application to the committee, it represents a departure from the indications we usually present. Generally we present an application to our committee for a chronic, serious, and life-threatening disease such as HIV or hepatitis B or C. Today we bring an application for a disease which is acute and self-limited in the majority of patients, but one that could potentially infect the entire

population and which accounts for a substantial morbidity from a national and international perspective.

Treatment of a disease with the propensity to affect such a large portion of the population is why we granted this application a priority review. This is also in keeping with the Department of Health and Human Services' efforts to reduce the impact of annual influenza outbreaks and coordinate pandemic preparedness for a potential influenza pandemic.

To help the FDA meet our challenge as we fulfill our regulatory role, we collaborated with our colleagues in the Division of Pulmonary Drug Products in the review of this application. To further help us meet this challenge, we are looking forward to a productive discussion during today's deliberation.

Thank you.

DR. HAMMER: Thank you very much.

We now turn to the sponsor presentation which will be led off by Dr. Marc Rubin.

DR. RUBIN: Thank you and good morning.

We are here today to present data on zanamivir which is an antiviral, the first in its class for the treatment of influenza.

Following my brief introductory comments, we will hear from Dr. Fred Hayden, who will take us through

the spectrum of disease seen with influenza. Dr. Ossi will review the efficacy data from our program, and Dr. Elliott will review the safety data, as well as the data on viral susceptibility that we've gathered.

Let me start by saying and largely echoing the comments of Dr. Birnkrant, that we recognize that this is really quite different than many of the drugs that you have seen us, Glaxo Wellcome, presenting here in the past. And, indeed, it's different than many of the drugs that this committee has focused on in recent years that have typically targeted diseases such as HIV or hepatitis B that are associated with overwhelming morbidity, even overwhelming mortality.

In contrast today, we're presenting data on an antiviral for the treatment of influenza. This is a disease, as you know, that routinely affects over 30 million people in the United States each year and even larger numbers worldwide. Perhaps overall this is more analogous to the treatment of herpes simplex infections or even migraine or allergies where, despite the lack of overwhelming morbidity, we feel there's still a need for effective therapy. While influenza certainly can and does cause significant morbidity and even mortality in certain high-risk populations or at-risk populations, the majority of infections each year occur in the otherwise healthy or

the general population.

We do believe, however, that in this population there is an unmet need for symptomatic relief, to shorten the duration of illness, to allow patients and individuals to get back to their functioning quickly, obviously to minimize or avoid potential complications. And while we will be showing you some data today in subsets from our studies in high-risk patients that we believe points towards efficacy in those populations, we will be focusing on the otherwise healthy group where the bulk of the data comes from these studies. Of course, we have ongoing programs specifically designed to gather more data in these other populations.

Just a few words about influenza in the general population, and you'll hear more from Dr. Hayden about this in a few minutes. It's a disease that affects all age groups. It typically has a sudden onset, and it's often temporarily debilitating. Influenza and the pneumonia that parallels it epidemiologically is responsible for up to 300,000 hospitalizations each year, but even more common and I think equally important is the absenteeism from work, from school, and overall the enormous added burden that's placed on families by this disease. I think it goes without saying that each year influenza as a whole has a tremendous economic impact on society.

The hunt for new drugs to treat influenza has been ongoing for a number of years. This cover from Nature in 1983 really heralded a breakthrough in this process with the publication of the structure of the viral neuraminidase as determined by x-ray crystallography. This really was the first step in rational drug design that led to the discovery of zanamivir in the late 1980s.

Well, a few words about the key properties of zanamivir. Again, you'll be hearing much more about this during the course of the presentation. First, from an in vitro perspective, it's potent and it's selective as an inhibitor of the influenza virus neuraminidase with activity against both influenza A and influenza B. And importantly it has activity against strains that are resistant to both amantadine and rimantadine.

As an inhaled product, it is essentially providing topical delivery to the airways, directly to the site of major viral replication. We achieved very high concentrations in the airways, thus minimizing the chances, we believe, of the development of resistance.

In addition, because there really is negligible systemic exposure with this, we would predict for a very favorable tolerability profile in man, and indeed, that has been borne out in the clinical trials, as you'll see.

Well, since zanamivir was and is the first in

its class, in many ways its development really has been a pioneering effort. The design of the clinical development program was very, very challenging. That's clear. There was no road map for us to follow. I think, though, despite those challenges, we've been able to demonstrate antiviral activity and clear clinical efficacy for both flu A and flu B. The proof of concept was first established in the human challenge studies that you'll hear about. Efficacy first was demonstrated in the very large phase II program that enrolled over 2,000 patients, and then in the phase III studies, a global program, enrolling over 1,500 patients.

As can be expected in large global programs with multiple clinical trials, you will see a range of efficacy across these trials today, and Dr. Ossi is going to discuss the differences seen, particularly in the North American study. Nevertheless, we believe the weight of the evidence clearly supports a clinical benefit for this drug.

With respect to safety, as predicted from our preclinical program, zanamivir was very well tolerated. The frequencies of adverse events were essentially the same as that seen in the placebo group, and no zanamivir-resistant isolates were seen during the clinical trial program.

Let me just briefly review some of the important milestones along the way in the development of

zanamivir. In October of 1993, we filed the IND. A year later, we began the phase II clinical program. In May of 1997, we initiated the global phase III program, and in October of last year, submitted the NDA, which was granted priority review status in December. Of course, this brings us up to today's meeting.

Obviously there has been a great deal of interaction, discussion, consultation with the FDA throughout this process, including agreement on many of the protocol analyses that you'll see us present here today. This has been very, very helpful for us and we're certainly very grateful for all of that interaction.

So, in sum, we believe that the efficacy data, the weight of the data across the phase II and III program which enrolled over 3,500 patients, and the safety data in an even larger number of patients support the proposed indication, which is for the treatment of influenza A and B in adults and adolescents.

That concludes my portion of the presentation. I will now turn over the podium to Dr. Hayden. Fred?

DR. HAYDEN: Thank you and good morning.

As a way of background, I would like to point out that I'm an infectious disease trained internist from the University of Virginia and have been involved in the study of antiviral drugs and vaccines for influenza for the

past two dozen years.

I'd also like to point out that I've served as an investigator and consultant to Glaxo Wellcome and other companies involved in the development of neuraminidase inhibitors.

My role this morning is to briefly review for you selected aspects of influenza epidemiology, current management practices, and the need for alternative treatments.

In February of 1991, the Institute of Medicine convened a committee on emerging infectious microbial threats to health in the United States. This was chaired by Joshua Lederberg and Robert Shoop, and I participated in the subcommittee on viral threats.

In the document that was subsequently published in 1992, influenza was recognized as the paradigm of the re-emergent threat. The devastating impact of the 1918 pandemic and the unpredictability of future pandemics were highlighted in this document. Indeed, as you've already heard, the recent cluster of H5N1 cases in Hong Kong is another reminder of the unpredictability of this virus and the need for better tools to confront the threat.

The continuing public health burden of influenza relates to the changing antigenicity of the virus. As you're well aware, the interpandemic form of

influenza causes annual outbreaks and widespread epidemics. This is the result of new strains from point mutations in key antigenic sites in the surface glycoproteins, and it's termed antigenic drift.

The pandemic form results from major changes in the hemagglutinin and sometimes neuraminidase. This antigenic shift results from the acquisition of new gene segments or sometimes interspecies transmission of virus.

The pandemics exact a substantial toll in terms of morbidity and mortality across the age spectrum, and as many who are more expert than I in this room recognize, pandemics are unpredictable, but likely indeed inevitable in the future.

Influenza is spread primarily by droplets and small particle aerosols.

The initial site of infection is the pharynx or upper tracheal bronchial tree, but the virus is capable of replicating throughout the respiratory tract.

The incubation period is short, averaging 2 days, and it's this combination of a very short incubation period and aerosol spread that allows for the explosive outbreaks of febrile respiratory illness that are characteristic of influenza.

The classical clinical syndrome is one of rapid onset with fever, myalgia, malaise, headache, sore throat,

and usually increasingly severe cough.

Now, this constitutional phase is debilitating for usually 2 to 4 days. Fever lasts on average 2 to 3 days, but cough and malaise may persist for several weeks even in previously healthy individuals experiencing influenza.

As any of you who have had a recent bout of influenza know, this is not a trivial illness and has a substantial impact on the individual affected.

It also has a substantial public health and societal impact. During the annual epidemics, which usually last for 6 to 8 weeks in any particular geographic area, the cumulative burden of illness across the United States is considerable. These are CDC estimates of the average effect of interpandemic influenza. These data would indicate that there are 20,000 or more excess deaths per year in this country. In some epidemic periods, it may be as high as 40,000. These figures are greater, for example, than the total exacted by the 1968 appearance of the Hong Kong pandemic virus. Indeed, we continue to see excess mortality despite increasing vaccine use.

These epidemics also translate into roughly 150,000 excess hospitalizations annually, with the broad range indicated here.

With respect to economic effects, in 1986

Schoenbaum indicated that the direct medical costs were between $3 billion and $5 billion, and there were also an associated 15 million lost work days.

Influenza also affects the performance of those who are able to return to work. This observational study assessed the impact of influenza on work place productivity. Among influenza sufferers, the vast majority of them had significant work days lost, as well as days confined to bed, averaging between 2 and 3. Even after return to work, their effectiveness was impaired so that in over 80 percent of these individuals, there were several more days of reduced performance.

Paul Glezen and his colleagues at Baylor College of Medicine have conducted longitudinal surveillance regarding influenza impact in Houston to assess influenza morbidity as it relates to age. Shown below is medically attended illness across the age spectrum. Influenza frequency and the need for medical attention are highest in infants and young children. From adolescence onward, there's an average of about 10 percent of the population that's affected each year and in the form of requiring medically attended illness.

The pattern for acute respiratory disease hospitalizations is somewhat different with this U-shaped pattern, again with the primary impact in the young and the

elderly.

This figure is taken from a chapter from Rob Webster and Brian Murphy in Field's Virology text and shows the occurrence of influenza A and B virus activity from the early 1930s, just after the isolation of the first human influenza virus, and continuing to 1990. There are several points I'd like to make from this.

First, as you can see, when one looks at the appearance of influenza A or B virus activity, virtually every year is associated with activity by one or both of these viruses.

Furthermore, most of these years, there's also excess mortality that's seen, although this is somewhat more variable.

Finally, influenza B virus, although less frequent than influenza A, also causes activity roughly 1 in every 3 years on average during the recent years of surveillance, and furthermore, during some of these years, it also is associated with excess mortality so that it's clear that these kinds of data indicate that we need effective treatments against influenza B infections.

The excess mortality observed with influenza relates heavily to age. This figure is taken from a paper by Simonsen and her colleagues at the Centers for Disease Control and shows the percent of excess pneumonia and

influenza deaths among persons aged less than 65 years.

Now, in recent years, as you're well aware, most of the mortality is in older individuals, so that less than 10 percent of mortality is seen in the below 65 age group. But if one looks back at the appearance of the 1968 Hong Kong pandemic virus, the 1957 Asian strain, and particularly the 1918 H1N1 pandemic, you can see that younger individuals were heavily impacted both during the pandemic and for some years afterwards such that in the 1918 experience, approximately 99 percent of the excess mortality occurred in young and middle-age adults. All age groups are impacted by influenza and we need effective means for management.

Current treatment of influenza most commonly involve symptomatic therapies with over-the-counter medications. 30 percent or more of patients receive antibiotics, often for unclear reason. We do have two effective antiviral agents, amantadine and rimantadine, which are approved for treatment of influenza A, and are associated with 1 to 2 day reductions in illness duration if used early in the course of illness.

With respect to prevention, clearly preseason immunization is the primary means of prevention. And there are annual guidelines published in morbidity and mortality weekly reports.

However, there are seasons in which the vaccine strain is a poor match for the epidemic or circulating virus. The 1997-1998 season is a particularly good example of this. The A Sidney drift variant appeared after vaccine had been manufactured, and this virus proceeded to cause widespread outbreaks, including a large number of nursing home outbreaks, across the country. These nursing home outbreaks were associated with attack rates up to as high as 50 percent among patients, and often deaths ensued, despite the extensive use of that year's particular vaccine. In summary, there was little evidence of vaccine efficacy in that particular season.

Now, amantadine and rimantadine are approved for prophylaxis of influenza A and were used for control in many of these outbreaks. Indeed, these are useful drugs, but they do have some limitations that are worth noting.

The most obvious is that their antiviral spectrum is limited to influenza A virus.

With respect to potency, they have relatively modest in vivo antiviral effects, and to my knowledge, their therapeutic use has not been associated with reductions in complications.

Tolerance has also been an issue, especially with respect to central nervous system side effects which occur significantly more often with amantadine as compared

to rimantadine, and this is particularly a problem in elderly individuals. There's also some GI intolerance with each of these agents.

Part of the problem with amantadine administration is that it depends exclusively on renal excretion, and so one has to be cautious about dose adjusting in the setting of renal impairment.

Finally, there have been a number of studies documenting the emergence of drug-resistant virus with the use of these agents. This relates to point mutations in the M2 protein. These resistant variants can appear rapidly, as early as 2 to 3 days into therapeutic administration in up to 30 percent of individuals. Their resistance phenotypically is high level, indicating a complete loss of drug efficacy, and there's no obvious biologic impairment of these viruses such that they're able to cause typical influenza illness and, in conditions of post-contact, have been shown to be transmissible both within households and the nursing home setting, causing failures of drug prophylaxis.

Now, this cartoon depicts for you the replication cycle of influenza virus. The initial events are made by the viral hemagglutinin which is critical in terms of binding to cell surface receptors containing sialic acid and also infusion of viral and host cell

membranes. The M2 protein is involved in mediating influx of hydrogen ions into the interior of the virion which releases the viral nucleic acid segments, and it is at this site that amantadine and rimantadine exert their principal antiviral effect.

Release of the virus occurs by assembly and then budding at the cell surface, and it's here that viral neuraminidase plays a key role.

The primary function of the neuraminidase is to cleave sialic acid residues from various glycoconjugates. In essence, this eliminates the virus receptor for the hemagglutinin and, by doing so, promotes release of virus from the infected cell and prevents aggregation of virus at the cell surface.

In addition, because respiratory mucus also has sialic acid bearing moieties, this action of the neuraminidase can prevent inactivation of viral infectivity by respiratory secretions.

These activities together then, in terms of release and prevention of inactivation by respiratory mucus, promote spread of virus within the respiratory tract.

The fact that neuraminidase appears essential for virus replication has been established by various techniques, including the use of anti-neuraminidase

antibodies, nonspecific chemical inhibitors, temperature sensitive mutants, as well as more recently neuraminidase-deficient influenza viruses. When one uses one of these kinds of interventions, as shown in this photoelectron micrograph, the effect is that virus particles aggregate at the cell surface and with each other, and there is an inhibition of subsequent rounds of viral replication.

In addition to performing an essential role in viral replication, what was learned in the crystallographic studies by Peter Coleman, Graham Labor, and their colleagues was that the active enzyme site of influenza neuraminidase is conserved across influenza A and B viruses. This schematic depicts a view of the active enzyme site shown in yellow and the actual substrate, sialic acid.

Now, the solution of this crystal structure allowed these workers to recognize that there were sites, indicated by the pale blue, where the inclusion of positively charged substitutions might enhance binding affinity and lead to the development of inhibitors. In fact, in the case of zanamivir, what was done was a substitution at the fluorocarbon position leading to a very potent and selected inhibitor. So, we have an essential viral function and a highly conserved active enzyme site and optimal target for antiviral drug development.

Thank you for your attention.

DR. OSSI: Thank you, Dr. Hayden. Good morning.

The purpose of this next part of the presentation is to describe the efficacy of zanamivir that has been established in our clinical trial program.

By way of introduction, I'll first summarize results briefly of an extensive program of investigations in a step-wise fashion, as you see on this slide, starting with in vitro data that led then to the animal studies and then first in human studies before then describing the efficacy results in our clinical trials in more detail.

These investigations or the results illustrate features of zanamivir that make it an important advance in the chemotherapeutic options available for treatment of influenza.

Zanamivir demonstrates potent enzyme inhibition of both influenza A and B virus neuraminidase in EIC50 ranges in very low nanogram per ml concentrations you see here. This activity also has been demonstrated for all nine known neuraminidase subtypes.

Selectivity of inhibition has been demonstrated as well in terms of negligible activity shown for other respiratory virus neuraminidases, as well as bacterial mammalian neuraminidases and human lysosomal neuraminidase.

Inhibition of viral replication has been shown in in vitro cell culture assays and human respiratory epithelial cell explants, and this activity extends to, as you've heard before, viruses resistant to amantadine and rimantadine.

There are excellent animal models of influenza in terms of the fact that as in humans, viral replication is confined primarily to the respiratory tract, and this allows the opportunity to evaluate administration of drug to the site where virus is replicating. In these models, significant antiviral effects have been shown both with inhaled and intranasal administration in the mouse and ferret, and in addition, in the ferret, reduction of pyrexic response has also been shown.

Also in the mouse model, activity was shown -- this has been published in the Journal of Infectious Diseases -- for the H5N1 avian strain that appeared in Hong Kong that has been previously alluded to.

In addition, the comprehensive preclinical toxicology program has been carried out where extremely high doses, giving systemic exposures far in excess of expected clinical exposure, were well tolerated, as well as high doses of inhaled drug administered over prolonged periods of time, which all predicted a remarkable safety profile in man. And Dr. Elliott will confirm that in his

part of the presentation.

Moving to the phase I program for first time in human clinical pharmacology studies, over 600 subjects participated in 22 trials, 490 of which received at least one dose of zanamivir. After oral ingestion, low bioavailability was seen. As well, low systemic exposure was found after inhaled administration. Gamma scintigraphy scanning after an inhaled radiolabeled dose of zanamivir showed deposition of drug throughout the lungs and a 10 milligram dose resulted in estimated concentrations 1,400 times the EIC50 of viral neuraminidase in this study.

Zanamivir is rapidly excreted unchanged in the urine, is not metabolized, and this, along with the low systemic exposure and the fact that there is negligible protein binding of circulating drug, results in a low potential for drug-drug interactions.

Again, as predicted by the preclinical toxicology, very high doses of zanamivir administered intravenously over 5 days and 40 milligram doses administered by the inhaled route for 14 days were well tolerated. This supports then the progression to further clinical trials in terms of this data.

It's important to prove the concept of the antiviral effect in man, and the experimental human challenge model allows us to evaluate that principle of

again administration of therapy directly to the site where virus is replicating. In this model, volunteers, sero-susceptible to the test strain of virus, are inoculated intranasally with either influenza A or B virus producing in most cases an upper respiratory infection and to a lesser degree fever. Zanamivir or placebo is administered also intranasally either before or after the challenge, and antiviral activity is evaluated as well as illness measures and safety in this model.

The results were that zanamivir administration topically resulted in significant reduction of viral replication for both influenza A and B viruses, was safe and effective in treatment and prophylaxis in this experimental infection. More frequent administrations up to 6 times a day were no more effective than twice a day administration for treatment or once a day for prophylaxis. This then extends the observations seen in animals and forms then the basis for evaluation of topical administration in further clinical trials, which we will now discuss.

Phase II studies. Over 2,000 patients were evaluated in studies that were conducted throughout the northern and southern hemisphere across several respiratory seasons. The objectives for phase II were tc demonstrate a treatment effect in naturally acquired infection for the

first time and to test again the chosen endpoint prior to phase III and to settle on a dosing regimen. Then the phase III studies, that we'll describe as well here, form the basis for the proposed indication for treatment of influenza.

The device used to deliver study drug, whether it be placebo or zanamivir, is shown here. The disk in the active drug contains 5 milligrams in each blister of zanamivir so that two inhalations would provide 10 milligrams per dose and in a twice a day dosing scheme, one disk then would be a 1 day supply of treatment.

The disk is easily placed in the device, rotated from blister to blister, pierced with the piercing needle allowing drug to be easily administered through the mouthpiece. There are similar devices for approved products on the market that operate as this one does.

In terms of all of these trials that we'll present, they were randomized, double-blind, placebo-controlled, multi-center studies in which patients with the constellation of symptoms compatible with influenza were enrolled at the time influenza was circulating in their respective community. They were followed for up to 28 days, and patients assessed their symptoms from a scale of none to severe and recorded this self-rating twice a day on diary cards throughout the study. They were each provided

with standardized relief medications consisting of acetaminophen and cough suppressant in these trials.

The populations evaluated were the intent-to-treat population, which was all patients who were randomized regardless of their outcome in the study, and then the population of most interest, those that were influenza-positive identified by laboratory confirmatory tests that you see listed here.

Now, the primary efficacy endpoint for all of these studies was the time to alleviation of clinically significant symptoms of influenza. This is a particularly demanding but appropriate endpoint in that alleviation was defined as the absence of fever, the absence of feverishness, and a rating of none or mild for the major symptoms listed here of acute influenza infection. These ratings had to be maintained for the 12 hours prior to the first alleviated entry and then for a subsequent 24 hours, that is, across three consecutive diary card entries over a 36 hour period.

Patients who had no evidence of alleviation because of being lost to follow-up or missing diary cards were assigned essentially as failures, that is, not alleviated at the end of the study.

Now, what we'll do is look at the results across the general population of patients and then also

describe results in those that were infected with influenza A, those infected with influenza B, and then the population subgroup of special interest, the high-risk population.

There were two large phase II studies carried out, one in the northern, one in the southern hemisphere, in which inhaled plus intranasal and inhaled administration alone were evaluated compared to placebo. In the interest of time, I'll just present the results for the northern hemisphere study as the outcomes for the southern hemisphere study were similar. And the second study I'll present evaluated twice and four times a day dosing of the combination of inhaled plus intranasal administration.

In that first study, 417 patients were enrolled within 48 hours of the onset of their symptoms. There was a reduction in the time to alleviation of each of the active treatment arms that received zanamivir, in other words, compared to placebo. These were statistically significant differences for the inhaled treatment arm of influenza-positive patients and as well for both populations that received zanamivir who were febrile at entry. These patients enjoyed a 3 day reduction in the time to resolution of their symptoms.

I should mention as well it was clear that there was no real difference in the outcomes for those that had the combination of inhaled plus intranasal compared to

the inhaled alone. This was again the same outcome from the southern hemisphere study.

In this study, again we see reduction of the time to alleviation for zanamivir treated patients of a day and a half in the influenza-positive population and no real advantage to administering drug four times a day versus twice a day administration.

So, our conclusions from these phase II trials is that treatment with zanamivir results in a more rapid resolution of illness in naturally acquired infection. Increased frequency of dosing, in addition to intranasal administration, did not provide any added benefit, and these studies then formed the basis for carrying forward the dose of 10 milligrams twice a day for 5 days into the phase III studies, which now we'll discuss with you.

To look at the demographics across the three phase III studies that were done, generally these characteristics were balanced across these studies. Possibly there was a two maybe to three times increase, as you might expect, in vaccine uptake in the North American study compared to the other two studies. Otherwise, these characteristics were relatively similar. I should also mention that within each individual study, the treatment arms were balanced in terms of these demographics.

The results of the first phase III study. 455

patients were enrolled in this study within 36 hours of onset of symptoms, randomized to 5 days of therapy, zanamivir 10 milligrams inhaled twice a day or matching placebo. Diary cards were completed by patients through day 14.

The results show a reduction in the time to alleviation of symptoms in each of the populations, a reduction of a day and a half to 2 days, all stastically significant differences. Secondary endpoints also supported that positive result.

In the second phase III study, over 700 patients were enrolled within 2 days of onset of symptoms. A temperature of 37.8 degrees Centigrade was required for entry. Same treatment arms in each of the phase III studies of 10 milligrams twice a day or placebo for 5 days. Diary cards were completed for all patients through day 14 and for those with continuing symptoms, through day 28.

The results of this study show a reduction in the time to alleviation of symptoms for zanamivir treated patients in the intent-to-treat population, as well as the influenza-positive population.

Now, the 1 day difference for the 569 influenza-positive population we feel is certainly a clinically meaningful benefit, as any of you who may have had flu recently can attest. In an acute illness that

amount of benefit is very meaningful.

Now, the result did not reach statistical significance, but in a sensitivity analysis performed on the primary endpoint, there was a statistically significant difference. In this analysis, patients who had no evidence of alleviation due to missing data were censored at their last non-alleviated entry. So, that provided on the primary endpoint a statistically significant difference.

In addition, we looked at a variety of prospectively defined secondary endpoints for this study, and what was found, as you see in the right-hand column, statistically significant differences in favor of zanamivir for this variety of secondary evaluations. For the investigator assessment where investigators evaluated patients at entry and then again at day 6, at the end of treatment, there was a significantly greater proportion of patients who were asymptomatic in this assessment for zanamivir treated patients.

Also in terms of what might be for most the more frightening part of the illness of flu and the hallmark of flu, fever, there was a reduction in the time to alleviation of fever for zanamivir treated patients. For example, within 24 hours of treatment, 22 percent of placebo treated patients had been alleviated, whereas 36 percent of zanamivir treated patients achieved that status.

Also average maximum daily temperature was statistically significantly less.

In terms of cough, which is again one of the more troubling symptoms of influenza, there was a reduction from 4.5 days in the placebo group to 3 days, a difference of a day and a half in the time to alleviation of cough, which was a statistically significant difference.

As well, cough severity was less not only during treatment but with no rebound when we look at the cough through day 14, and this occurred despite the increased use of cough suppressant in the placebo treated patients.

As very good evidence, we feel, of the meaningfulness of the 1 day reduction for zanamivir treated patients, there was a reduction in complications from 22 percent to 15 percent placebo compared to zanamivir, which was a statistically significant reduction.

In viewing these results then, the weight of the evidence clearly demonstrates a positive benefit for zanamivir treated patients in this study.

The third phase III study conducted in 356 patients who were enrolled within 2 days of onset of symptoms. Same treatment arms, same diary card completion through day 28 for patients who were still symptomatic at day 14.

The results of this study show highly statistically significant differences of 2 and a half days for patients who received zanamivir compared to those who received placebo. Secondary endpoints in this study also supported this significant difference as well.

So, to summarize, at this point for the general population of patients, in each study comparing the dose submitted for approval of 10 milligrams twice a day to placebo, the plot here of the difference, placebo duration versus zanamivir duration of illness, shows consistently results to the right side of the 0 line.

In addition, in terms of 95 percent confidence intervals around these differences, none of those bars cross 0. This then constitutes substantial evidence of the existence of a treatment effect for zanamivir, although the treatment effect varies from the point of view of the magnitude of effect. This is not unexpected when you evaluate endpoints in a variety of trials. But actually there is consistency from the point of view that there is a great deal of overlap in these error bars up and down the line.

Two other important measures of benefit from treatment of influenza are the occurrence of complications and the use of antibiotics. In these trials, all three phase III studies, there was a reduction in the proportion

of patients who investigators felt had a complication as a result of influenza and a concomitant reduction in all three trials in antibiotics prescribed to treat those complications. These complications that occurred were primarily upper respiratory, not very serious, some lower respiratory, sinusitis, pharyngitis, otitis, and then bronchitis, exacerbation of asthma, and some lower respiratory tract infections that could be treated for the most part on an outpatient basis in this otherwise healthy population.

Now, this slide shows the broader impact across the 1,167 flu-positive patients where there was statistically significant reductions in the likelihood that a patient would suffer a complication and/or require antibiotic use to treat a complication.

Now we'll look briefly at the subpopulations that were evaluated, those that had influenza A, those that were infected with influenza B, and then high-risk subjects. In terms of the integrated phase III studies, there was a comparable 1 and a half to 2 day benefit from treatment with zanamivir regardless of influenza subtype A or B, as shown in this slide.

High-risk patients were eligible to be enrolled in one large phase II study and all three phase III studies, and here is listed the categories of high-risk

patients that were actually enrolled. Most of them were in the top two bulleted categories: chronic respiratory disease and elderly patients.

In the large phase II study of over 1,200 patients, there was a 2 and three-quarter day reduction in the time to alleviation of influenza illness for the zanamivir treated patients. In the combined phase III analysis, there was a comparable 2 and a half day reduction in this endpoint.

Across the three phase III studies, two of them showed substantial benefit. One did not show a difference. So, we examined more carefully this particular study, and what we saw is that in patients who were enrolled late in the treatment window, more than 36 hours from onset of symptoms, there were very few of them who had what seemed to be an abnormally short duration untreated of influenza, as well as one zanamivir treated patient who, when removed from the analysis, we see that with those enrolled within 36 hours of onset of their symptoms, there was a 1 and a half day reduction in their illness.

In terms of the occurrence of complications and antibiotic use in this population, there was comparable reduction in the likelihood that high-risk subjects would suffer a complication or require antibiotic use. This is aga n very important for this population although, because

patients had relatively stable underlying diseases, these were not serious complications. The value, however, of this is supported by the fact that in the two phase II studies, there were overall less unscheduled health care contacts during the study.

Our conclusions from looking at the high-risk populations are that zanamivir reduced the duration of symptoms by an average of 2 and a half days in the combined phase III studies, also reduced the frequency of complications in antibiotic use.

There was a large phase III study conducted to evaluate prophylaxis of influenza, and although this does not provide evidence for the treatment claim, it does provide support of the antiviral capabilities of zanamivir, as well as long-term safety information. We will take just this slide to quickly show you those results.

In this study, 1,107 primarily college or graduate students were randomized at the time influenza was circulating in their respective college communities, the University of Michigan and the University of Missouri, to receive either zanamivir 10 milligrams once a day or placebo once a day for 28 days. And they were followed for the occurrence of influenza illness during that time. The results are that zanamivir prophylaxis resulted in a 67 percent protective efficacy from symptomatic influenza and

an 84 percent protective efficacy against febrile influenza illness.

Our overall conclusions are that in all phase II studies, three large phase II studies and three phase III studies, zanamivir consistently reduced the time to alleviation with the magnitude of effect ranging from 1 to 2.5 days reduction. This reduction was also extended to patients who had either influenza A or B, to the high-risk population, and in addition there was a reduction in complications and antibiotic use across these studies.

Thank you. Dr. Elliott will complete the presentation with the safety information.

DR. ELLIOTT: Thank you. I'd like to add to that positive efficacy data that you've just seen by reviewing some of the key aspects of zanamivir that's both the comprehensive investigation of virus susceptibility but also very importantly the large database that we've amassed on safety, both clinical and in the preclinical setting.

In collaboration with some of the world's leading experts on influenza, we've undertaken an extensive investigation of virus susceptibility, and the majority of this has now been published. What we find is resistance is not readily generated in vitro; however, can be selected by the passage of virus in the presence of drug. It's important at this stage to note that this resistance is

generally a lot harder to generate than with rimantadine or amantadine, the current two agents available.

Mutants generally fall into two categories. There are hemagglutinin mutants. These have reduced affinity for cellular receptors of influenza virus and do not alone confer resistance in vivo. And the clinical significance of these is thought to be unclear.

Also, we can generate neuraminidase mutants, and these are usually associated with prior hemagglutinin mutants. These have reduced affinity for zanamivir and either reduced stability or catalytic activity. The double mutant is approximately tenfold less susceptible in vivo. That's in the mouse or the ferret model. And we have a lot of data on this, and if there's need for discussion during the day, we can bring all that data forward to the committee.

The general prediction from these data in the preclinical setting is that resistance would be uncommon, but of course we need to go on and study that further.

This slide shows the investigation of virus susceptibility undertaken in our phase II/III clinical program. We collected samples from more than 300 patients treated with zanamivir and by combination of a neuraminidase enzyme assay, plaque reduction, in vivo antiviral assays, and sequencing, we looked in detail at

the resistance or the potential for that.

The analysis included 59 matched pairs of patients who received zanamivir who had samples taken at baseline and either during or at the end of treatment to look at the effect of drug on the generation of resistant virus.

The reason for this 59 being low compared to the 300 that we recruited for samples is really twofold. First of all, the natural course of influenza is for viral shedding to reduce during the course of the illness during the first 3 to 4 days, but also secondly, in the face of highly effective antiviral therapy, there's even more pressure on the virus and it's even harder to get samples. So, the analysis is based around these 59 matched pairs.

Based on these, there's no evidence for the emergence of resistant virus during the clinical program. The EIC50 range by the neuraminidase assay is showing now going from .2 to 12 nanograms per ml.

There has been one published case of a resistant virus. This wasn't in the clinical program. This was a case of a child treated on a compassionate use basis under an emergency IND. And in brief, it was an 18-month-old female patient with influenza B occurring after bone marrow transplant for leukemia, and during late and prolonged zanamivir therapy, she developed a resistant

virus, a double mutant.

The initial treatment was with continuous aerosolized ribavirin for this influenza B for 6 days. The clinical course did progress in spite of this, and she was switched to zanamivir, again nebulized, for a further 15 days.

Really in spite of both those antiviral therapies, the course was one of gradual progression and ultimately zanamivir was stopped after 15 days. And unfortunately, the patient died of respiratory failure 2 days after that.

It is important to note that the respiratory compromise was progressing well before the resistant virus occurred and really in spite of both therapies that were used.

Just to briefly review the sequence changes on the virus isolated during the course of zanamivir, at baseline, day 0, the aspirates from the endotracheal tube showed no mutations. First of all, on day 8 a mutant at the hemagglutinin site was seen, and then finally on that day 15 of therapy, the day therapy was stopped, a double mutant was isolated with mutations both at hemagglutinin and neuraminidase.

It's known that the hemagglutinin virus carrying the 198 mutation certainly has altered HA

specificity, and the virus we isolated on the very last day there was certain less virulent than the ferret model of influenza, required approximately 60 times more virus to grow in the ferret model than was required for the wild type virus. So, this is this case, and this has been published in the Journal of Infectious Diseases towards the end of last year.

Our conclusion on resistance is that clearly we can demonstrate this in vitro generally by multiple passage of virus in the presence of drug. Virus with both mutations is less virulent in the ferret model. In the clinical program we saw no resistant variants, and our expectation is that this would be an infrequent occurrence in a broad-based clinical setting.

However, of course, Glaxo Wellcome, as the panel well knows, has a long experience of monitoring resistance in areas such as HIV and herpes, and we plan to continue this in the influenza area. We've been talking to the WHO and public health bodies around the world over the last 6 to 12 months, and our plan is to have protocols in place and agreed by the summer of this year and before the next the northern hemisphere winter starts, we will initiate a global surveillance program to look at resistance and gather many more samples than we have to date. So, this will be ongoing work in progress.

Touching briefly on our toxicology studies, there has been an extensive program in this area. From a systemic basis, we administered high doses of intravenous drug more than 1,000 times in one species and found no systemic toxicity.

Also, of course, very important for this drug as it's delivered to the respiratory tract directly, we did respiratory toxicology studies and saw no respiratory tract irritancy in studies going up to 52 weeks.

Additionally, the drug is not mutagenic or carcinogenic and neither is it teratogenic.

So, this data gave us some confidence to move forward into the clinical pharmacology and indeed the broad based clinical program.

The safety of zanamivir has been assessed in more than 6,000 subjects and more than 4,000 of these patients and subjects have received drug in the clinical program. We predict a favorable safety profile consistent with what we know about zanamivir. It is highly specific for influenza virus neuraminidase. It does not affect the other neuraminidases in the mammalian or bacterial kingdom. It's delivered topically direct to the respiratory tract. The systemic exposure is low, of the order of 10 to 15 percent, and that drug that's seen systemically is excreted unchanged in the urine. It's not metabolized and does not

interfere with the cytochrome P450 enzyme system.

In our clinical trials, the randomized double-blind, placebo-controlled program, more than 2,000 patients received zanamivir in all dosing regimens and 1,132 were treated with the 10 milligrams twice daily 5 day dose that we're seeking approval for.

This slide just shows a summary of the events, which I'll show in a little bit detail on the next few slides.

Clinical adverse events, first of all, were comparable to placebo across the events that we were monitoring, and no individual adverse event occurred with a frequency of greater than 3 percent.

Dose-limiting adverse events, those events that required patients to stop therapy, were uncommon, occurring at 2 percent in both the zanamivir and the placebo treated group.

And the serious adverse events were rare, occurring at an incidence of 1 percent.

Additionally, we of course looked at hematology and chemistry monitoring, both at baseline, at the end of therapy, and at the end of follow-up. We saw no changes there that suggested any difference between the active drug and the placebo drug. Additionally, in the completed studies, there have been no deaths in patients either

receiving zanamivir or placebo, although at this point I should say that in ongoing studies in the nursing home setting, there have been 3 deaths to date, 1 in the placebo group, 1 in the rimantadine group, and 1 in the zanamivir group. Again, we can review those later on in the meeting if the committee would like to do that.

Looking now at the clinical adverse events from these studies from the 1,132 patients who received the twice daily for 5 days regimen and the high-dose group on the far left-hand side. What you can see from this table is that, as stated, adverse events as an individual event are uncommon, and there really is a great degree of comparability between the placebo and the actively treated groups.

We also, of course, looked at those patients we recruited within the high risk category and this slide shows those patients with chronic respiratory disease, and the majority of these, indeed, had asthma.

A number of things you see on this slide. First of all, the adverse events were again comparable between the active and the placebo treated groups.

Not surprisingly, for a population of asthmatics, the most common events were recorded in the lower respiratory system. You may expect approximately 15 to 20 percent of patients with asthma to exacerbate during

the course of acute influenza, and indeed you see 15 percent asthma exacerbation in the placebo group and 7 percent in the active group.

We also looked at those patients over the age of 65. The middle column shows the 59 patients recruited within the treatment studies. We also added some patients to this 59 on the far left-hand column, including patients from a nursing home study. These patients were in the prophylaxis studies. They didn't have active influenza, but received a 2 week course of twice daily therapy. So, we add them in for some extra experience at a higher exposure. Again, these adverse events from the GI and respiratory system show the consistent pattern that adverse events as an individual event are uncommon, and the pattern of comparability between zanamivir and placebo treated patients is conserved in the elderly.

Discontinuation occurred at 2 percent both in zanamivir and the placebo treated patients. the few events that did result in early discontinuation included sore throat, nausea, GI disturbance, and headache. There were no individual events occurring at an incidence of greater than 1 percent.

Serious adverse events shown on this slide, less than 1 percent for each group, zanamivir and placebo, one event assessed as possibly drug-related in the

zanamivir, a patient with severe headache during therapy and dizziness, but again there was no difference in body system or pattern of these events between treatment groups.

We did look at laboratory values, and this is one summary table from many, and it compares the baseline sample to any blood sample taken after therapy started to a predetermined threshold range. This displays the more common changes that occurred. Two things really to note. The changes were not particularly common, and again the consistent pattern that these changes are comparable between the active and the placebo receiving group. These changes probably more likely reflect underlying variation associated with influenza and indeed normal variation that does occur in lab parameters.

The findings were, of course, entirely consistent with the low systemic exposure of zanamivir and the fact that it's not metabolized and is excreted unchanged in the urine.

I'll talk briefly also about the prophylaxis study that Dr. Ossi presented, as this does provide useful data from a safety perspective as well. This recruited 1,107 subjects, approximately a 50/50 randomization to zanamivir and placebo, and they took inhaled drug once a day for 28 days.

This next slide shows the adverse events from

these subjects. Again what you see is the pattern that adverse events occur at a comparable rate between the zanamivir and placebo treated groups. There are no events that appear to be particularly different.

It's interesting actually, just an observation while looking at this table, no event occurs more commonly in the zanamivir treated group. It either occurs at the same rate or a percentage point or 2 less.

This large safety experience is really very useful, especially the long exposure that occurred here.

Additionally, of course, we did monitor lab parameters, and really changes here were much more infrequent than in those patients with influenza. Only three parameters were elevated above the threshold range.

Now I'd like to move on to some conclusions from the whole presentation.

Influenza is an annual epidemic disease. it comes every year and it has a significant public health and economic impact on society and also, of course, on the individuals who catch influenza.

Treatment with zanamivir resulted in a clinically meaningful benefit by consistently shortening the symptomatic course of influenza by between a day to 2 and a half days.

The weight of evidence we feel is that

zanamivir clearly demonstrates a positive treatment effect across phase II/III treatment studies.

In the high-risk patients that Dr. Ossi presented, there's also a beneficial effect in these subjects, although we recognize that we'll continue to recruit more subjects within the high-risk categories.

Zanamivir did reduce complications and antibiotic use, and the reduction in antibiotic use is heartening. It's a great issue in the United States ID community and public health community over the last 10 years or more, antibiotics being used inappropriately for viral illness, and the increase we're seeing in bacterial resistance associated with this. So, we're heartened to see the reduction in antibiotic use across all of our studies.

In the clinical program, as you saw, there were no resistant variants isolated during the clinical trials, just that one case and a rather atypical case of an immunocompromised child receiving very prolonged therapy late in the course of her illness.

It's very important, of course, for any drug that we bring forward, to look in great detail at the safety, and we did this and we feel very comfortable about the safety profile of zanamivir in the general population and also in various categories of patients within the high-

risk group that I also showed you.

The clinical results demonstrate that inhaled zanamivir is safe and efficacious in the treatment of influenza A and B, and we believe that that supports the indication for the treatment of influenza A and B in adults and adolescents.

With that, I'd like to finish and I believe we have some time for questions.

DR. HAMMER: Thank you very much.

We're going to reserve some time this afternoon for the formal question period. In order to move the morning along, what I'd like to ask the committee is whether there are any immediate clarification questions about the data presented. If anyone would like to have supplementary data presented this afternoon in a targeted fashion -- and I emphasize targeted -- you could please write that down, pass it over to us over here, and we'll pass it on to the sponsor and see that early this afternoon.

Clarification please?

DR. HENDELES: I was under the impression that the FDA policy required that two pivotal studies be conducted in the United States. Is that incorrect or was that waived?

DR. HAMMER: I should turn to the agency for

this. Dr. Birnkrant?

DR. BIRNKRANT: In general, we like to see at least two adequate and well-controlled studies. They don't necessarily have to be conducted in the United States. We accept foreign data as well.

DR. HAMMER: I just have one quick question. On the special populations you presented, those with influenza B, the high-risk group, the incidence of complications and antibiotic use, I realize the numbers were small and many analyses were done, but was any statistical test applied to those? The trends were there, but were those statistically different?

DR. ELLIOTT: Sorry. The statistics on the?

DR. HAMMER: For zanamivir versus placebo -- this is on efficacy, so maybe Dr. Ossi should answer this -- for influenza B, the high-risk group, and the incidence of complications and antibiotic use. And if this is something that would be better deferred till the afternoon, that's fine.

DR. ELLIOTT: It looks as maybe it is. It seems that we've got the numbers there, but maybe for time we could do that this afternoon.

DR. HAMMER: Dr. Wong?

DR. WONG: If you're going to show some more data this afternoon, one thing I'd like to see would be the

distributions or the kind of time-to-event curves for the primary efficacy endpoint in the phase III trials because what we got in the briefing books were medians and p values only, and to me it didn't give a very complete understanding of the magnitude of the effect. So, if you have those data, I'd like to see those.

DR. ELLIOTT: Yes. We can bring those.

DR. STANLEY: I had a question. You showed a lot of your data as the aggregate over all three trials, but in trying to get at why the North American trial was different, was there a difference in how quickly the patients were enrolled after being symptomatic or was there a difference in dropout.

DR. ELLIOTT: Two questions there. The time to enrollment -- the great majority of patients in the U.S. study were in the up to the 36 hour window. There were some in the 36 to 48 hour window, and there was about, I'm going to say, 4 to 5 percent who were outside the 48 hour window. That's correct. 4 to 5 percent outside the 48 hour window.

DR. STANLEY: And how does that compare to the other two studies?

DR. ELLIOTT: It was higher. It was about two times higher than the other studies. We actually have looked at some analyses in removing the effect on those

patients, and you may be not surprised to hear it makes the study look more positive.

DR. HENDELES: I was wondering if you calculated how many patients had to be treated in the aggregate of your phase III studies to save one patient 2.5 days duration.

DR. ELLIOTT: I'm not sure. I'm getting a shaking head from our statistician. We could think on that. It was not analysis we preset, so I don't have that one on the top of my head.

DR. HAMMER: Maybe we can hear about that this afternoon.

DR. ELLIOTT: Yes.

DR. HAMMER: Dr. El-Sadr?

DR. EL-SADR: I'm wondering about also of the patients enrolled in the phase III studies, how many were lot to follow-up and how many had incomplete diary cards?

DR. ELLIOTT: I've got a slide that we could show on that data very quickly. Let me find that very quickly. It's B34.

This slide shows the deviations. On the earlier question, the number of patients who didn't take their first dose within 2 days of symptoms -- this is the U.S. study -- is 4 percent.

I'm sorry. Your supplemental question was?

The diary cards.

Well, the diary card again there is about 4 percent of patients who we didn't get a return on the diary card. So, there is some missing data in there.

DR. EL-SADR: And the 20 percent no post-treatment visit. Right? 3 percent.

DR. ELLIOTT: Post-treatment visit was delayed from day 6 till day 8, so a longer lag in ability to collect that data and do the assessments that were meant to occur right at the end of therapy. And these are just the major deviations. Minor deviations we didn't classify on this list.

DR. HAMMER: Dr. Kilbourne?

DR. KILBOURNE: I hope there will be more discussion about in vitro correlates defining your susceptibility --

DR. ELLIOTT: Yes.

DR. KILBOURNE: -- and settling on perhaps some one model for that.

I have another every trivial question, and that is, does zanamivir have any taste to it?

DR. ELLIOTT: We don't believe that zanamivir does. I guess there are people shaking their heads from our laboratory side. The lactose carrier, I think people from the respiratory group would agree, that some patients

do have a slight sweet taste to the lactose carrier, but zanamivir itself does not.

DR. KILBOURNE: Just one other thing that I hope is discussed this afternoon, and that is whether there's any effect on any other antibody measurements of response other than HI, hemagglutination inhibition. Specifically, were there any measurements of anti-neuraminidase antibody response?

DR. ELLIOTT: I'm not sure that we've done those measurements. Going back to your original question, we have a short slide series that compares the neuraminidase to plaque reduction to animal models and we can certainly go through that this afternoon.

DR. HAMMER: Dr. Diaz.

DR. DIAZ: Just a quick question about the diary cards. Could you just review exactly what patients were instructed to do? In other words, were they instructed to take their temperature a certain number of times per day? Was the diary card just filled out with the previous day's subjective responses? Just a little more detail on that.

DR. ELLIOTT: It was really done on a daily basis. The studies differed between two times and four times reporting. The Australian one did it more frequent. They were generally asked to keep up with it, so do it

during the same day that the symptoms or the temperature would occur.

DR. DIAZ: And in terms of their symptomatology and their feelings of their symptomatology, was that to be recorded overall for that day, in other words, or at the time that they were to take their dose? Was it looked at more than one --

DR. ELLIOTT: I think they generally did when they took the dose. I mean, that was the easier instruction to give, that you do all these study things at once, take your dose, and then record the various things, and likewise the adverse events and things of that order. So, generally, it was done on an ongoing basis even throughout the day.

DR. HAMMER: Please.

DR. EL-SADR: One question. I realize the baby who had the resistant isolate. How many patients have been treated on a compassionate, expanded access basis?

DR. ELLIOTT: The compassionate program -- I don't have a slide summarizing this. There has probably been U.S. and rest of world of the order of 15 or so patients treated in this way. And we've had a variety of experience. The general experience is that most received drug very late. I think the average time for us getting the first phone call is a week or 10 days, and the agency

have been working with us on this in the U.S. cases.

The outcome in quite a few of the cases, 5 of the cases including that one, did die. That's both within the U.S. and around the world. Other cases have actually recovered and cleared virus.

It's clearly not enough of a piece of data to say anything about yet. What we would like to do with these cases is obviously get treatment to them as soon as the virus is detected, but there's always within a non-approved drug, just even awareness that the drug is around sometimes comes in late.

So, experience is certainly limited. There have been fatalities similar to that one you already saw. We haven't found any resistant virus from any of the other cases. We always try and get virus back from all of these cases.

DR. HAMMER: Dr. Verter and then Dr. Bertino.

DR. VERTER: For this afternoon, a couple of things would be helpful. Although over all in these trials that you presented, it looks like a 1 day difference, in the books that we were given and also in the presentation, there are at least five studies, not three, that had inhaled versus placebo, and there were three subgroups that are specified: the time of onset, 30 to 36 hours; whether there was fever or not; or whether they were influenza-

positive or not. It would be very helpful if there could be some overview of the consistency or lack of consistency of effect across those subgroups across the trials.

DR. ELLIOTT: We can certainly do that.

DR. BERTINO: On the administration of the powder, I'd say that I'd guess that most patients have never used that device before. Could you please tell us how patients were trained to use the device? Was there a standard way the patients were trained?

DR. ELLIOTT: Yes. In the clinical studies, obviously we trained our study staff at investigator meetings, the coordinators and the investigators, and there was a booklet that went along with the device. Generally there was a period of instruction with the study nurse or a member of the study staff who would walk them through the device. That's how it was done within the program.

We found compliance to be over 90 percent across all of our studies.

DR. BERTINO: Were patients observed, let's say, for the first dose to --

DR. ELLIOTT: Yes, they were.

DR. HAMMER: Dr. Jolson?

DR. JOLSON: Dr. Elliott, since there were some questions about the compassionate use program, it might be helpful just to clarify the formulation that was used in

those patients.

DR. ELLIOTT: Yes, thank you. That's a very good point.

In all of the compassionate use patients, both within the U.S. and actually outside the U.S., we used our nebulized solution. That is a formulation that's been used on this basis and also a study with the CASG. So, it's a different formulation of zanamivir than we're talking about today.

Thank you.

DR. HAMMER: Dr. Yogev.

DR. YOGEV: On the study that you did multiple dose six times a day versus two, were any studies done to look at how much virus was shed? Was there any difference in the amount of virus shed in the six versus two?

DR. ELLIOTT: It was four times versus two, and we didn't see any differences in the viral shedding or time to below limit of quantification. The viral shedding was only actually done at one of our centers in Rotterdam, so the numbers were about 12 to 15 per group, but within that restraint, there wasn't any difference.

DR. YOGEV: I was looking more for quantitation of the virus.

DR. ELLIOTT: I'm looking at Margaret. The quantitation likewise for 2008, did we see a difference in

the twice daily versus four times daily? No, we didn't see a difference there.

DR. YOGEV: And in the prophylaxis study, was any attempt done to look into resistance of those who got the influenza?

DR. ELLIOTT: You didn't see the full numbers. The attack rate in that season was low. We only had a 6 percent attack rate in the placebo group, 2 percent in the active group. We did attempt to collect virus, but we had, I think, only one or two positive swabs from culture, and we didn't find resistance in those. But those numbers are small.

DR. YOGEV: In those on safety, slide 77, you have 4 pneumonia and the drug versus the placebo. Was any attempt done to --

DR. ELLIOTT: Slide 77.

Sorry. Was any?

DR. YOGEV: Any attempt to identify what was the reason for pneumonia? Is that statistically different?

DR. ELLIOTT: The pneumonia and other adverse events and complications you see --

DR. YOGEV: On the bottom.

DR. ELLIOTT: -- yes, I see it there -- is really a clinical diagnosis. This isn't pneumonia as you'd recognize, x-ray proven with a positive culture. This is a

clinician's diagnosis. We also looked at that data, and what I more tend to do is look at those low respiratory infections as a whole. So, you have pneumonia, LRTI, where there's 1 case versus four cases, and maybe even bronchitis, where there's 4 versus 3 percent. So, we didn't go any further in the specific diagnosis. That is the answer. But I don't think there's a specific point for concern there.

DR. HAMMER: Dr. Wittes?

DR. WITTES: Yes. I have a question about the diary cards in terms of the translations and the back translations. Given the subjective nature of those responses, how did you calibrate one language against another? How do we know what one observes in one country is the same as in another?

DR. ELLIOTT: Comparing the European study to the U.S. study, for instance?

DR. WITTES: Well, I assume the European had many languages. Is that not right?

DR. ELLIOTT: Yes, it did. That's correct.

DR. WITTES: So, I'm actually asking language specific rather than study specific.

DR. ELLIOTT: And I'm still not sure of the question. So, are you saying do we know it's equally effective in France, UK, and the U.S. or?

DR. WITTES: No. I'm asking if somebody has a diary card, does that person interpret the question differently depending on the language? How do you know that the translation was perceived the same way across languages?

DR. ELLIOTT: We don't have a tool that measures the perception. We have a great deal of experience of translating documents, and we do many multi-center, multi-country studies. I think we just have to rest on our experience and assume that the translation is true to the meaning. We haven't measured that specifically.

DR. HAMMER: Thank you.

Please.

DR. STOLLER: My question regards the definition of high-risk populations. You've characterized the elderly, which comprises a minority of the high-risk group, the majority being I think 61 percent in the briefing book of high risk. In the context of a study population whose mean age is 37, what is the specific definition of high risk with regard to chronic respiratory conditions? How is that ascertained? Was it self-reported? Were there any objective measures of chronic respiratory conditions that comprise that definition, et cetera?

DR. ELLIOTT: The majority of those were asthmatics. We didn't use objective measures. It was really the clinical investigator's opinion, and generally it was based on use of medications for asthma. So, we weren't doing FEV assessments, anything of that order. Again, it was more in this clinician's experience with this patient, managing this patient for asthma.

The number of COPDers was very small and that was generally based on the usual definition of that condition.

Chronic cardiac disease was a smaller group, and that was based on a list of conditions again.

DR. HAMMER: Thank you.

I'd like to defer further questions to this afternoon.

Again, I'd repeat if any of the members of the committee want additional data, please write it down, pass it to us, and we'll give it to the sponsor. I would ask the sponsor, in preparing the responses this afternoon, to keep the remarks also targeted and brief so that there's adequate time for discussion.

The last request. During the break and maybe during lunch, some members of the committee might like to see the device itself, and if there's a sample handy to pass around during the break, it would be nice.

On that note, we'll take a 30-minute break now and return at 10:35.

(Recess.)

DR. HAMMER: Again, we're going to continue with the FDA presentation. Dr. Barbara Styrt.

DR. STYRT: Good morning. I'd like to introduce the FDA presentation for zanamivir for inhalation for treatment of influenza.

As you're aware, the applicant has submitted three principal phase III studies in support of a treatment indication. Several phase II treatment studies have also been submitted and have been used for supportive and supplementary analyses during the review process. In addition, the safety review has considered studies from phase I, studies from the ongoing development program for prophylaxis of influenza, and other information such as compassionate use cases.

There are several features of this application which are a little different from the typical application brought to the Antiviral Drug Advisory Committee. It's not common for this division to see treatment studies for an acute disease which resolves completely and permanently without treatment in most cases and in which the major objective of treatment for most patients is the reduction of self-reported symptoms.

This is also a disease which has the potential for very different outcomes in specific risk groups. Although influenza can certainly cause fatal disease in people without underlying risk factors, this is fortunately rare enough to make it difficult to study enough subjects in the average influenza season to demonstrate an effect on this outcome.

Population categories, including persons aged 65 or over or having chronic respiratory, metabolic, or immunologic disorders, are considered at increased risk of complications from influenza, and the phase III studies of zanamivir were designed to include subjects in such groups in whom information on effects of influenza treatment would be particularly welcome.

Influenza also differs from some of the diseases considered by this division in that the diagnosis of influenza-like illness and the initial treatment decision are usually made presumptively from clinical evaluation, but confirmation of infection with influenza virus depends on diagnostic test results which commonly are not available at the time of first contact, so that a proportion of patients treated with a specific antiviral will have diseases other than influenza and would be at risk for any adverse events associated with treatment but not eligible for treatment benefit.

Much of today's discussion of efficacy focuses on subjects who tested positive for influenza because those who did not have influenza could not be expected to show a treatment effect, but intent-to-treat analyses of all randomized subjects are also considered in the review.

The clinical criteria for entry were reasonably predictive of influenza in specific epidemiologic circumstances in which these studies were conducted, so there were not major differences in overall conclusions from intent-to-treat and influenza-positive analyses. However, the predictive value of clinical criteria for the diagnosis of influenza could vary substantially, depending on what type of influenza season and clinical setting is involved, and these other factors would have to be taken into account in the risk-benefit comparison for a specific patient or population.

This application also involves the first proposed use of a dry powder inhalation product for treatment of an acute viral infection. A few drugs using similar lactose-based dry powder inhalation delivery systems have previously been approved in the Division of Pulmonary Drug Products, and we are grateful for the assistance and consultation of our colleagues in that division in the course of this review.

Finally, as you have heard, this drug has a

novel mechanism of action and raises some new questions about appropriate approaches to measurement of activity and surveillance for resistance.

Endpoint measurement by self-recorded assessment has been a subject for discussion in many stages of influenza drug development. There doesn't appear to be any universally accepted right way of measuring responses to influenza therapy.

As you have heard, the principal endpoint in the phase III treatment protocols was time to symptom alleviation based on a combination of temperature and symptom scoring. This slide illustrates a few of the variety of other types of endpoints which have been used in other influenza studies in the past. Some of these and additional analyses were used for supplemental analysis of the data in this NDA to try to explain and explore some of the concerns arising from inspection of the primary analysis.

The focus of the FDA analysis is on the three principal phase III treatment studies, which we will be designating as NAIB3001, the southern hemisphere study performed in the 1997 influenza season; NAIB3002, the European study performed in the 1997-1998 influenza season; and NAIA3002, the North American study also performed in the 1997 to 1998 influenza season. We will be looking at

some of the patterns of differences across these studies that were noted in principal analyses in the NDA submission and at supporting and explanatory data.

Study design of the principal phase III treatment studies had several common features. Subjects were required to have at least two major symptoms of influenza-like illness and had to be judged sufficiently stable overall to expect to complete the study on an outpatient basis without compromise of their medical condition. All three studies used a 5 day treatment course of two inhalations of zanamivir or placebo twice daily, with the first dose administered at the study site at the time of enrollment. The principal assessments of response to therapy were self-reported symptom scores with additional assessments by study personnel at baseline and after completion of therapy.

There were also a number of differences in design between the studies, as illustrated on this slide. The left and right columns in the table are the European and North American studies which had essentially similar protocols, and the center column is the southern hemisphere study which differed in a number of aspects.

The southern hemisphere study required that subjects be symptomatic for no more than 36 hours before the first dose of study medication, while the other two

studies required that the first dose be administered on the first or second calendar day of symptoms.

The southern hemisphere study required subjective feverishness, but did not have an objective temperature cutoff for entry as the other studies did.

Predefined high-risk subgroups recruited into the studies included those aged 65 and over and those with cardiovascular or respiratory disease as defined in the protocol usually by use of chronic medication. Other predefined high-risk subgroups included endocrine and metabolic disease or immune compromised in the southern hemisphere study and renal failure in the other two studies, although as you've noted in the sponsor's presentation, no renal failure patients were actually entered.

The tests used to determine influenza positivity differed in that culture and serology were used in all three studies, but the southern hemisphere study also used direct tests such as immunofluorescence, and the other two studies used an investigational polymerase chain reaction assay. These direct or rapid tests cannot be assumed to correspond to any rapid tests that might be used when a patient in this country at the present time visits a physician's office with influenza-like illness.

Finally, symptoms were recorded for 14 days in

all three studies, but in the European and North American studies, those who were still symptomatic at day 14 were asked to record symptoms out to day 28.

We will be proceeding to talk about some issues in the analysis of efficacy, then to safety analyses and a variety of other issues, including information on specified subgroups and special populations, microbiology issues, manufacturing issues, and issues regarding use of the drug device delivery system and patient instructions.

Dr. Elashoff will now present some statistical considerations.

DR. ELASHOFF: I'm Michael Elashoff, the statistical reviewer for the zanamivir application.

In my talk today, I'm going to first quickly summarize the applicant's phase III study results. The bulk of my presentation will be on the FDA efficacy analyses that addressed the robustness of the treatment effects in each study. As you'll see, those analyses will indicate an inconsistency of results in the North American study compared to the results outside of North America. And I'll show you some further investigation into this discordance by looking at some important subgroup analyses and then summarize the overall efficacy picture as it now stands.

As already mentioned, there are three phase III

studies. The first NAIB3002 is referred to as the European study and abbreviated EU. The second study was in the southern hemisphere, mainly Australia, and I'll refer to it as the SH study, southern hemisphere, and finally NAIA3002 was in North America, predominantly the United States, and I'll call this the NA study for North America.

Overall, about 1,500 subjects were randomized and treated in these studies, and a little over 70 percent of them were considered to have been influenza-positive. For these subjects, we have complete 14 day diary cards for about 92 percent of the patients, with partial diary card information for most of the remainder. So, there was very good follow-up.

Now, there are two analysis populations that we find of interest: first, the intent-to-treat population which includes all randomized and treated subjects; and second, the subset of patients who were determined to be probably influenza-positive, and I say probably since there was really no gold standard for determining influenza status.

There were three tests used in these studies: culture, serology, and PCR, with a rapid test substituted for PCR in the southern hemisphere study. Ideally every patient would get all three tests, and they would all agree. However, the reality was that some patients were

tested with only one test or only two tests, and often there was internal disagreement among the tests.

The influenza-positive population in these studies will be composed of patients who had at least one positive influenza test, and this included, again, about 70 percent of subjects in the phase III studies.

In general, the differences in treatment response for the intent-to-treat analysis were in the same direction as those in influenza-positive patients, but not surprisingly with a smaller magnitude since influenza-negative patients could not be expected to benefit from the antiviral therapy.

These two analysis populations really address somewhat different questions. The influenza-positive analysis gives us an estimate of efficacy in the patients that we want to treat, but since the influenza status is not known at the time the patient is seen, the intent-to-treat gives us an efficacy assessment in the patients that we actually treat. And we look forward later on how to best assess treatment effects in this situation.

The primary endpoint that was agreed to at the protocol stage was the following. Symptoms were measured on a 4 point scale: severe, moderate, mild, none, also 3, 2, 1, 0. And if the patient met the six criteria listed her[illegible] for a 24 hour period, then they would be called

alleviated. As you will see, it was this last element of the definition, symptoms only needing to meet the definition for a 24 hour window to reach this endpoint of alleviation, that turned out to be critical in assessing the robustness of the treatment effects.

Secondary symptoms, such as nasal symptoms and weakness, were also recorded but did not factor into the protocol primary analysis.

The primary analysis was based on times of alleviation with a p value calculated using the Wilcoxon test, and treatment effect, as you saw, was summarized using the median time to alleviation and differences in the median. Some symptoms were generally assessed twice a day. The median time to alleviation had units of one-half a day increments.

Now, this definition and this analysis plan seemed reasonable, although it was recognized that other ways of looking at the data would have to be similar in order to be convincing. At the time, there was no real data to suggest a better way of quantifying efficacy.

So, the trials were run, the NDA came in, and as the company has showed you, the primary analysis found a median difference of 2 and a half days in Europe, 1 and a half days in the southern hemisphere, and 1 day in North America. The first two results, Europe and southern

hemisphere, were statistically significant, while in North America, the results were not. These differences in at least two studies seemed like quite reasonable treatment effects. However, we had two concerns after seeing these results.

First, the largest treatment effect was seen in the smallest study, while the smallest treatment effect was seen in the largest study, and that study was as large as the other two studies put together.

Second, it was the North American study, arguably the most relevant study for us, that was the one with the smallest treatment effect and the nonsignificant p value.

So, it was with those concerns in mind that we started reviewing the efficacy results in more detail. It started to become apparent that for this amalgam of six criteria that composed the primary endpoint, on an individual patient-by-patient level, it did not really do justice through the course of their disease, and I will illustrate this by using the day-by-day symptom diary for one patient in the southern hemisphere study on zanamivir.

First are shown the five primary symptoms on the scale from 3, severe, to 0, none, headache, sore throat, fever, aches, and cough.

Next are the secondary symptoms, nasal

symptoms, weakness, and loss of appetite.

Third, the patient recorded the total number of tablets of acetaminophen and the total doses of cough syrup on each particular day.

And finally, patients were asked each day what's your overall assessment of your influenza symptoms, and this overall score on the same 3, 2, 1, 0 was also recorded.

This patient was considered to have been alleviated in the primary analysis at day 3.5.

Now, one thing we noted is that patients would have a day where the five primary symptoms were mild or none, but then the next day or a following day one or more of those symptoms would be back up again. However, those symptoms wouldn't count since the time to alleviation had already been met. And in fact, about 30 percent of patients in these studies had such a pattern, and in fact, more patients on the zanamivir arm than the placebo arm had such a pattern.

Another finding was that patient's other flu symptoms that the protocol considered secondary, nasal symptoms, weakness, loss of appetite, did not always improve at the same rate as the primary symptoms. Sometimes they improved faster and sometimes, as in this patient, they took longer to resolve.

And relief medication use also considered past alleviation in many circumstances.

Additionally, when patients were asked the question about how do you rate your overall symptoms of influenza, often they rated themselves as overall moderate, even on a day where their individual primary symptoms might have been mild. That really shouldn't be surprising, since if a patient has a mild cough, mild muscle aches, mild headache, mild sore throat, they might not be feeling so mild anymore.

So, we started thinking about other ways to capture this information in ways that the primary endpoint did not. The first idea was to take the same criteria that were used to define the primary endpoint, but instead of identifying a particular time of alleviation, as for this patient, simply count the days that they did or did not meet the definition over the 14 day period. So, for example, for this patient, we would count days 0, 1, 2, 3, 6, and 7 as not being alleviated since by the primary criteria they really weren't. Then we also did additional analyses factoring in the secondary symptoms, relief medication, and the overall assessment.

Here are the results of that first analysis where we used the same criteria to define a particular day of alleviation, but simply counted the days over the 14 day

period instead of identifying a particular time of alleviation and saying symptoms after that didn't matter. So, here you can see on the first row the mean number of days without alleviation for placebo, for zanamivir, and the mean difference.

One thing to note is that you see smaller treatment effects across the board compared to the primary analysis. Now, why are we seeing smaller treatment effects?

First, when you summarize the treatment effects using a median, that can exaggerate small differences since the endpoint is very discrete, alleviation occurring in half-a-day units.

Second, the primary analysis did not capture symptoms occurring after the so-called alleviation day, and more zanamivir patients compared to placebo patients had a reemergence of their symptoms after the alleviation day.

So, we have a situation where a very similar analysis to the primary analysis, one that uses the same criteria, but analyzes the data slightly differently, finds noticeably different results. The European and southern hemisphere studies are still statistically significant, although with smaller treatment effects, but the North American study is not really even close to clinical or statistical significance anymore. You can note that the 95

percent confidence interval for the treatment effect, the difference plus or minus 2 standard errors, excludes even 1 day of effect. So, this analysis really speaks to the lack of robustness of the primary analysis, especially in North America.

Again, in the intent-to-treat analysis, a similar pattern was seen across the studies, although with smaller treatment effects.

So, as I said, incorporating relief medication use was recognized early on as an important factor, and one of the applicant's secondary analyses looked at time to reaching the primary symptom criteria while not taking relief meds for this 24 hour window. However, that analysis suffered from the same problems as the primary analysis, not taking later symptoms into account, not taking later relief medication use into account, and using the relatively course median difference to summarize treatment effects.

So, just like before, we counted days where patients did or did not meet the symptom definition or use relief medication. We see again what will be a familiar pattern where results range in two studies from a treatment effect of greater than a day and statistically significant to less than half a day and not statistically significant.

So, another way of assessing benefit is to look

at the number of days patients had a temperature greater than the protocol cutoff of 37.8. In this analysis, there was 0 difference in the North American study with a 95 percent confidence interval ranging from minus .4 days to plus .4 days.

Another of our concerns was in reflecting severity, since symptoms that individually may have felt mild may have actually cumulatively felt worse for that particular patient, and the overall score combined the symptoms in the way that the individual patient thought was most important.

So, in this analysis, as before, we simply counted up days where the patient considered themselves to have severe influenza symptoms or moderate influenza symptoms. This analysis showed a 1.2 day difference in the European study, a 0.7 day difference in the southern hemisphere study, and a 0.1 day difference in the North American study. Again, we are not really even close in the North American study to statistical significance or clinical significance.

This overall question was asked of patients at baseline, and of all the other baseline information, from baseline temperature to individual symptom scores to smoking status, influenza type. Their answer to this one question at baseline was most predictive of the patients'

subsequent number of symptomatic days, just overall how would you rate your symptoms. So, this important question ended up over the course of the study to show no difference at all in North America.

Now, if we had done all of these analyses and some of them had come up with a better treatment effect in the primary, some of them had come up with less, we would have concluded that while the primary endpoint may not have been the perfect definition or the perfect summary statistic, at least we could have said the primary analysis was representative of the overall picture, but clearly that was not the case. One can't really claim that these analyses are biased against showing a treatment effect, since a significant effect was seen in all of these analyses in the two smaller studies where you would think it would be harder to demonstrate a benefit.

So, we ran a bunch of different definitions. These just summarize an additional four definitions and the treatment effects. The first is incorporating the secondary symptoms along with the primary, number of days where something was rated as moderate, the number of days where a primary symptom was rated as severe, the number of days where any symptom was rated severe, and the number of days of subnormal activity as rated by the patient. And again and again we see the same thing. In the intent-to-

treat population, once again a similar pattern, just smaller numbers.

So, we started to come to the conclusion that efficacy not only had not been established, in the North American study but the results weren't even really trending, and the disparity between the studies was still present.

Now, to be sure of these conclusions, we explored other ways of getting at efficacy. It was possible, for example, that zanamivir might have been reducing individual symptom scores by, say, a half a point across the board, which might not have been picked up in some of these analyses. So, we looked at mean symptom scores over time for the five primary symptoms.

This shows over the first 14 days the mean symptom score of the five primary symptoms on the placebo arm, and this is the mean symptom score over time on zanamivir. This particular way of looking at data is one that figured prominently in the rimantadine assessment of efficacy and is also one way the Division of Pulmonary looks at symptom scores over time.

Now, in Europe, these curves are noticeably different. However, in general, the vertical separation between the curves is only about .2 units of symptom score over time. And these curves are very flat, as you can

tell, after about day 3. So, one thing that was happening was that there would be a horizontal difference of, say, 1 to 2 days between these curves, but that was only really reflecting a very small difference in the actual mean symptom scores over time, maybe .1, .2 units on this 3 point scale.

In the southern hemisphere, a smaller difference in mean symptom scores over time, and in North America there was no difference in mean symptom scores over time.

So, another thing to note in looking at all three studies is that there was a very similar course of symptoms across the studies, and in general, you see that patients were still reporting some degree of symptoms even after 14 days on the average.

I'm not going to show you the intent-to-treat version of these curves. You can just imagine less of a difference.

These are the means of the overall influenza symptom score over time. Again, this was the question asked on each day, overall how would you rate your symptoms on this 3 point scale? Again, note the small, vertical difference between the curves in Europe of about .2 units on this scale, about .1 unit in the southern hemisphere, and no difference in North America.

So, these curves over time, the mean symptom score, the overall symptom score, give quite a different picture than the analyses based on the time to alleviation measured in days. A difference of, say, 7 days versus 5 days in the European study sounds impressive, like 2 days less of flu, but the reality even in the best study was one of continued gradual improvement. So, at day 5, for example, patients on zanamivir weren't feeling too much different from patients on placebo even though these zanamivir patients might have been considered alleviated while the patients on placebo might not have been considered alleviated.

These are the activity scores over time measured on a 5 point scale, 1 to 5 in Europe and North America, 0 to 4 in the southern hemisphere. In contrast to the symptom scores which decrease over time, the activity scores increase, indicating patients getting up and around. But the essential picture is quite the same: a slow gradual improvement with a very minor difference in scores over time in Europe, less of a difference in the southern hemisphere, and no difference at all in North America.

Now clearly, though, in any set of three studies, there is bound to be some variability, and one of the studies will necessarily be the lowest. But was this spread in results that we saw really consistent with chance

variation about a real treatment effect or was this spread in results inconsistent with chance variation, leading one to maintain two separate statements about treatment efficacy?

Recall that the North American study was almost as large as the other two studies put together, and if you do a power calculation on the analysis of mean days without alleviation using any of the various definitions, it turns out the study had greater than 99 percent power to detect a mean difference of 1 day. So, this was not an underpowered study, and the results were not significant in any of the analyses.

Further, on looking back at the phase II studies, a similar discordance was there. Studies 2005 and 2008 had a North American component and a non-North American component, and the analyses in the phase II studies of the non-North American part were generally significant while the North American component was not.

Lastly, if you do an analysis that combines the data from all three studies, you come up with significant treatment-by-study interactions. In other words, the results from the studies are not statistically compatible. That means we cannot construct an overall treatment average or conclusion and say that that average or conclusion applies to all of the studies. It means we are left with

two different statements about efficacy and there is a high degree of confidence in each one.

So, given the lack of efficacy in the North American study as a whole, there might still have been an identifiable subset of patients who did benefit. In addition, we thought it possible that differential effects in certain subsets of patients might help us understand the difference in study results, although we viewed these analyses mainly as hypothesis generating and not as trying to explain away the North American results.

The first subgroup we looked at was the predefined high-risk group of patients. The applicant's analysis found two studies with a positive treatment effect and one with a small negative treatment effect. When we ran the same battery of additional analyses and exploratory analyses as we did for the overall group, the same pattern kept coming up: two positive studies and one study with either a negative or zero difference for the high-risk patients.

When we looked at the various demographic variables, gender, race, age, smoking status, vaccination status, symptom duration, influenza type, there were no consistent treatment-by-variable interactions for any of these variables. And so, that means that imbalances in these variables were not likely to have a significant

effect on the overall pattern of results that we saw.

We also looked at various measures of baseline disease severity to see if that might have been the explanation, but as you can see, for various measures of baseline disease severity, mean of this overall score, mean symptom score, mean temperature at baseline, the studies appeared very well matched so that baseline disease severity did not seem to be a good candidate for explaining these study differences.

So, the result of this high-risk analysis and these exploratory analyses was that no subgroup could be identified in the North American study that received significant benefit, and the analyses suggested that none of these factors were responsible for the inconsistent study results.

Finally, we looked at the use of relief medication, and this table shows the mean total use of either tablets of acetaminophen or doses of cough syrup over the 14 day period. For example, in the North American study, patients on average took 21 tablets of acetaminophen over 14 days, broken down as 22 tablets in placebo and 21 in zanamivir.

There are two points here. First is that the use of relief medication was slightly lower in the zanamivir group compared to the placebo group, on the order

of 0 to 2 tablets over this 14 day total period, and maybe about 3 to 4 spoonfuls of cough syrup again over this 2 week period.

Another interesting pattern is that use of relief medication was lowest in Europe, was highest in North America, and was somewhere in between in the southern hemisphere.

Now, an analysis to see if that was responsible for the study results is really hard to do because the use of relief medication is very confounded by the actual symptom scores, but this overall pattern was suggestive that the overall pattern of differences was the same as the overall pattern of differences we saw in the study results together.

So, this analysis was suggestive that relief medication use might have been partly responsible for the difference, but in any case you couldn't actually tell North Americans to use less relief medication. So, it is hard to know what to do with this information.

So, we are left with two distinct findings. There were clear and significant treatment effects in Europe and the southern hemisphere, although when you looked at the mean symptom scores over time, the mean activity score over time, you generally see differences only of a fraction of a point. In North America,

differences as large or as small as 1 day of effect were conclusively excluded on the basis of the confidence intervals in this wide variety of analyses. And in any case, when you look at the means over time, there was no difference at all in any of these symptom scores.

So, analysis after analysis, you have results that are not significant in North America even in the primary analysis which essentially put the best face on the information. And we also have to keep in mind that the treatment effects were smaller in the intent-to-treat analysis.

So, these significant between-study differences in treatment effect, combined with a lack of a proven explanation for the difference, do not allow us to calculate an overall treatment effect and apply that to North America. And even if we ignore the lack of significance in North America, the observed treatment effects were on the order of a fraction of a day or a fraction of a single point in symptom scores.

I'd like to turn back to Dr. Styrt.

DR. STYRT: Let me recapitulate a few of the issues that arose from comparing the different studies. The treatment effect across the three phase III treatment studies were inconsistent with the greatest difference between zanamivir and placebo in the European study, more

modest treatment effects in the southern hemisphere study, and treatment effects that appeared marginal, at best, in the North American study on various analyses.

These differences were first noted as a concern during inspection of the principal analyses in the NDA and secondary and exploratory analyses confirmed the concern but did not provide any clear explanation for the differences. When we looked at the remainder of the application for additional information to confirm or refute these differences, the phase II studies, which allowed comparisons between North American and non-North American data, also had results that were overall generally consistent with the phase III studies.

In addition to the problems posed by these differences in reaching an overall evaluation of the effect of zanamivir, systematic differences between the results of the studies as a whole can call into question the value of pooled analyses of subgroups across studies and make it necessary to examine these subgroups also on a within-study basis.

Proceeding to additional clinical issues, we will be looking at adverse event information from the clinical trials, followed by some points about special populations, microbiology, and manufacturing issues, and points regarding use of zanamivir with its lactose-based

inhalation delivery symptom in the specific setting of influenza treatment.

As you have seen in the information provided by the applicant, the overall clinical adverse event profile in the principal treatment trials was similar for subjects on zanamivir and placebo. As is not unusual at this stage of drug development, the safety database is not large enough to exclude the possibility of rare serious adverse events which might only become apparent with more widespread use of the drug. By the nature of the population recruited for these studies, there is little information on safety in very ill patients or those with acutely unstable medical conditions.

Some events such as cough, chest tightness, headache, sore throat, and dry mouth and throat have been reported as possibly drug associated in some of their occurrences in these studies. These occurred with both zanamivir and placebo. However, here we encounter another feature of this application that is a little different in that placebo subjects were receiving an inhaled lactose preparation that is also the vehicle for the active drug product. While this is apparently characteristic of clinical trials with this type of drug and it's difficult to think of a perfect way of quantitating the relationship to inhaled lactose or the lactose/zanamivir combination,

the possibility must be considered that some of these events are due to the study drug and could be experienced with use of inhaled dry powder zanamivir in clinical practice.

It is also difficult to determine the potential for drug relationship of certain individual events. For example, one subject was discontinued from zanamivir in the North American study because he developed severe headache a few days into treatment and was hospitalized briefly with a diagnosis of meningitis. This subject was influenza-negative. The course of events appears most consistent with viral aseptic meningitis from the information provided, but there also is not sufficient information available to distinguish between this diagnosis and the more remote possibility of drug-associated aseptic meningitis.

As another example, one subject was discontinued from placebo in the southern hemisphere study because of "vasovagal collapse," which on review of the report appeared both suggestive of a phlebotomy associated vasovagal episode, but was reported as possibly related to study drug.

One subject stopped because of hives after the first dose of zanamivir in the North American study, and urticaria were reported in a few subjects in the other two

studies.

Many of the reported adverse events overlapped with influenza symptomatology, making interpretations of treatment relationships particularly complex.

The overlap between types of occurrences reported as adverse events or influenza symptoms was also a concern in evaluating potential risks for patients who have influenza-like illness that is not, in fact, caused by influenza virus.

As you may have noted in the background document, for influenza-negative subjects study in the North American study NAIA3002, the median time to the primary alleviation endpoint was 1 day longer on zanamivir than on placebo. This was another point of difference between the NAIA3002 and the other two principal phase III treatment studies which did have longer times to alleviation on placebo than on zanamivir, even in the influenza-negative subgroup. The treatment difference in the North American study was not stable to additional analyses which showed either no treatment difference or a difference in the opposite direction. Thus, there is no clear evidence of harm to influenza-negative subjects, but looking at the protocol-defined primary endpoint, this is another anomaly.

Laboratory abnormalities in the principal

treatment studies were mostly consistent with common events in influenza or influenza-like viral infections and did not show any clear differences between zanamivir and placebo. The scheduling of laboratory tests did not permit any definite conclusions about whether there is any drug effect, positive or negative, on duration of abnormalities.

Additional studies reviewed for safety information included studies performed in healthy volunteers for purposes of prophylaxis, although a completed efficacy package and request for prophylaxis indication has not been received in this NDA or for assessment of vaccine interactions, limited data from prophylaxis studies in nursing home settings, and other data, including phase I studies, and a few instances of compassionate use.

Studies performed in healthy volunteers without influenza-like symptoms at study entry were considered important in trying to sort out the potential confusion between influenza-like symptoms and drug-related adverse events. In the vaccine interaction and community prophylaxis studies, adverse event reports such as cough, nose and throat symptoms, and headache were substantially more frequent than in the treatment studies where these events might have been reported as symptoms of the disease under treatment. Again, these events were reported both

with zanamivir and with the placebo lactose vehicle inhalation, and in most instances they were not treatment limiting. A few similar events were reported in the small number of subjects receiving dry powder inhalation preparations in phase I clinical pharmacology studies.

In one of the pilot studies in the ongoing clinical development program for prophylactic use of zanamivir, nursing home residents were randomized to receive zanamivir or placebo when an influenza A outbreak occurred and zanamivir or no drug when an influenza B outbreak occurred. This slides shows the total proportion of subjects with adverse events reported, which did not differ much between treatment groups. The adverse events reported on zanamivir were similar to those reported in other zanamivir studies. The numbers in this unblinded study are too small for any confident comparisons but serve to illustrate that at this time there are not sufficient data to make clear safety comparisons between zanamivir and previously available anti-influenza drugs in the populations at greater risk for adverse events. It is hoped that an ongoing study will add to this information.

Of course, we always look at deaths, and none has been reported in the controlled treatment trials of the proposed marketed formulation of zanamivir.

Three deaths have been reported in ongoing

studies of prophylaxis in nursing home patients, one in an elderly patient who developed influenza A during the study, and two in patients who appear to have had serious preexisting medical problems.

Five deaths have been reported in compassionate use of zanamivir, which typically involves administration of a different zanamivir formulation, the nebulized formulation, rather than dry powder inhalation, to immunocompromised patients with severe pneumonia who seemed to have been at very risk of imminent death before treatment was instituted.

One death has been reported from an ongoing study of nebulized zanamivir in hospitalized patients with lower respiratory disease. This study again was designed to enroll subjects who are already at very high risk before entry, and in fact, the patient who died appears to have developed a subsequent episode of pneumonia some weeks after finishing study therapy, and any relation to the study or to the influenza illness would be very uncertain.

In addition to the pooled analyses you have seen, we looked at each principal phase III study for the incidence of influenza complications in the predefined high-risk groups which included subjects aged 65 and over, as well as those with preexisting cardiovascular and respiratory disease and in the southern hemisphere study a

few with diabetes or immune compromise.

This slides shows the proportion of influenza-positive subjects designated as high-risk in each phase III study and the proportion of those who were reported as having complications. There are two points to be made about this slide.

One is that looking at each study separately, which we felt was important because of the differences in overall study results and because high-risk groups and case report form check boxes for predefined complications were not uniform across studies, the numbers are too small to permit firm conclusions.

The second is that if any pattern is discernable in these small numbers, once again the North American study is different. It had a higher proportion of complications in influenza-positive, high-risk subjects on zanamivir than on placebo, contrary to the other two studies. Of course, it is not surprising when small groups are examined if results go in different directions in some of these groups, but again the study with the largest enrollment shows the results which differ from the other studies.

What can we actually conclude about prevention of complications in high-risk patients with influenza? It's important to have as much information as possible

about population groups considered to be at high risk for whom the interest in treatment is likely to be particularly high. We wish to commend the applicant for making an effort to recruit such patients into the phase III studies.

Overall, the number and percent of high-risk subjects who actually entered each study was fairly small. The number in any specific category, such as cardiovascular disease, was even smaller, and those at highest risk, for example, anyone considered likely to be hospitalized during the course of their acute illness, would likely not have been enrolled.

The complications predefined in the case report forms ranged from pharyngitis and sinusitis to congestive heart failure and pneumonia. An aggregate analysis of complications with such a range of severity is somewhat difficult to interpret, and the small number of serious complications reported overall, presented in more detail in your background document, may reflect exclusion of the most unstable patients. It appeared that influenza patients in high-risk categories had fewer complications on zanamivir than placebo in the southern hemisphere and European studies and more complications on zanamivir than placebo in the North American study, but we would consider that overall there simply is not enough information to decide whether there is a substantial effect from zanamivir.

Within the categories designated as high-risk, there have been specific concerns about patients with underlying airways disease not only for safety, but also for efficacy because of the possibility that pulmonary distribution of an inhaled drug could be altered if the preexisting pulmonary disease is exacerbated by the acute viral infection.

As you're aware, the applicant has submitted a study in 13 non-infected subjects with relatively mild asthma showing no major effect of inhaled zanamivir on aggregate results of pulmonary function tests. This does not necessarily tell us what would happen in persons who have asthma and superimposed acute infection that might exacerbate airway hyper-reactivity. Moreover, it should be noted that 1 of the 12 subjects who received active drug experienced a decline in FEV1 by about 35 percent, so to about 65 percent of his previous value, shortly after zanamivir on two separate occasions and did not show a similar pattern after placebo inhalation. So, even though there were not effects which appeared clinically meaningful on mean pulmonary function results across the study population, it can't be ruled out that some proportion of people with underlying asthma could experience bronchospasm when receiving zanamivir.

In the principal phase III treatment trials, it

was difficult to judge the underlying severity of respiratory disease in subjects in this category. In response to inquiries about the issue, the applicant provided an analysis using a number of asthma drugs as a proxy for severity, which did suggest diminished zanamivir treatment effect in subjects classed as more severe based on use of at least two asthma drugs, when compared with subjects classed as less severe based on use of only one asthma drug. Results from this analysis are given in more detail in your background document.

There is not much information regarding patients with very severe or acutely decompensated airways disease, and again, we hope that an ongoing study will provide additional information on both safety and efficacy in the context of underlying respiratory disease.

With regard to pediatric use of zanamivir, the principal treatment studies have enrolled subjects aged 12 and over and a limited number of adolescents are included in the overall results. In younger age groups, limited safety and pharmacokinetic information from a single dose study has been submitted.

We don't know how well this specific preparation can be used by young children in the setting of acute influenza, although there has been pediatric use of a similar device and delivery system in chronic maintenance

therapy for asthma. Development of a different formulation might need to be considered if treatment of very young children is envisioned. Again, we hope that ongoing studies will provide additional information concerning the age group from 5 to 12 years.

As you're aware, the neuraminidase inhibitors differ from previously available anti-influenza drugs in having activity against both influenza A and influenza B. The number of subjects with confirmed influenza B in treatment studies has been relatively small, and in the effort to derive as much information about them as possible, we looked at the results reported from a spectrum of phase III and phase II studies.

In this table treatment studies are listed from left to right in descending order of number of subjects with confirmed influenza B and the two bottom rows show median time to alleviation for influenza B subjects on placebo and on zanamivir. The two right-hand columns show the European and North American phase III studies, which had the smallest number of influenza B subjects. The left-most study with the largest number of influenza B subjects is the southern hemisphere phase III study.

The difference between placebo and zanamivir on this endpoint was 1.5 days and not shown on this table, for confirmed influenza A subjects in that same study, the

difference between placebo and zanamivir was slightly longer, 2.0 days.

The study with the next largest number of influenza B subjects in the next column showed no real difference between placebo and zanamivir in that subgroup, although there was a much greater treatment effect for influenza A in that study.

In each of these two studies, additional analyses again suggested slightly lower treatment effects for influenza B than for influenza A, although no statistically significant treatment by flu type interaction was found, and the small numbers severely limit the interpretation of these findings. It was also noted that entry temperature tended to be slightly lower for influenza B than for influenza A, and attempts to look at simultaneous temperature and influenza type breakdowns yielded such small groups that interpretation didn't seem permissible. The remaining studies had progressively smaller amounts of influenza B.

Overall, what can we conclude about relative activity of zanamivir in influenza A and influenza B? Looking back at some of the animal studies, the dose required to reduce viral titer by a log was reported as about twofold higher for influenza B than for influenza A. This referred only to one strain of A and one strain of B,

but a similar ratio was reported in a mouse model and a ferret model.

We have just one human challenge treatment study with influenza B, suggesting a modest decrease in viral shedding and no decrease in symptoms in the small number of subjects receiving zanamivir compared with placebo.

The clinical treatment studies, for the most part, have small amounts of influenza B, and results are compatible with a modest variable effect. The two studies with the largest number of confirmed influenza B subjects give a slight impression of less effect than for influenza A in the same studies, but this is not consistent across other studies and it is unclear whether there could be confounding of any A versus B effect by baseline temperature effect or vice versa. Overall, we would have to suggest there are not enough data to allow a precise comparison of the effects of zanamivir in disease caused by influenza B against effects in disease caused by influenza A.

The potential for emergence of resistant viruses is an important issue in evaluation of any new drug for influenza. For zanamivir, several investigational methods for assessing resistance have been used. These have not given consistent results. Their ability to

predict human clinical events is not fully defined, and there have been suggestions that development of a better cell culture based method might be desirable for optimal surveillance of resistance. Resistance can emerge during in vitro passage of virus in the presence of drug, including emergence of zanamivir-dependent mutants. Resistance can involve mutations in the hemagglutinin gene, the neuraminidase gene, or both, and the applicant's reports have commented that in vivo relationships between the hemagglutinin and neuraminidase mutations are not clear.

As you have heard, one clinical case has been documented of emergence of resistant virus during treatment of an immunocompromised child with influenza B infection, for whom a hemagglutinin mutation was detected in specimens obtained after 8 days after zanamivir exposure and an additional neuraminidase mutation after several more days.

In the clinical treatment trials, paired viral isolates before and during or after zanamivir therapy have been obtained from between 50 and 60 subjects. For most of these, the last on or post-treatment isolate was reported as obtained within 2 days after the baseline culture was obtained and treatment started, that is, the baseline culture was day 1 and the post-culture was day 2 or 3.

Plaque reduction assays showed increases in

inhibitory concentrations in a few of these. In addition, two specimens reportedly showed increases in inhibitory concentrations in the neuraminidase assay which were reported as nonsignificant because of being marginal in one case, only a threefold increase, and non-reproducible in the other.

Among the total paired isolates reported, there are day 1 and day 3 specimens from 12 zanamivir subjects in the principal phase III treatment trials, all from the North American study. No cell culture based/virus replication based assays were provided from these studies. No salient increases in inhibitory concentrations were reported for the neuraminidase assay which was the sole measurement of drug effect reported for these specimens.

Only a small proportion of the throat swabs obtained in these studies yielded virus on day 3 and almost none from the post-treatment specimens at day 6 in either zanamivir or placebo recipients. The report commented that the throat swabs were less sensitive than the nasal washings used in other studies, so we are not able to draw conclusions about whether any of the culture-negative subjects still harbored viable virus.

There is no information regarding viral susceptibility in situations of reinfection and retreatment that we have seen. Overall, rapid routine emergence of

resistance has not been observed in zanamivir trials to date, but the number of paired specimens assayed is small. We are not altogether comfortable with surveillance based solely on measurement of an enzyme's activity without some measure related to viral replication, and we don't feel confident that there is sufficient information to fully define the risks and potential implications of emergence of resistance during clinical use.

We don't usually even mention chemistry and manufacturing issues at advisory committee meetings partly because of the proprietary nature of manufacturing information, but in this case there could be some potential implications related to clinical issues, so we will just mention that there are some chemistry issues still under discussion and that humidity can affect lactose-based dry powder inhalation preparations with resulting alterations of stability and that stability issues may require more attention in settings where long-term use or storage of this product might be anticipated.

As you have heard, the proposed market formulation of zanamivir uses a device for drug delivery which is similar to delivery systems employed for a couple of asthma drugs already on the market. Ease of use issues have been raised for some patient groups with such devices, and some additional concerns arose regarding use of the

delivery system for this product because the population and the setting for use are likely to be different. Even if the vast majority of patients are able to learn to use the device delivery system, this would be used in the setting of acute infection where failure to effectively deliver the first one or two doses might substantially alter the interval between symptom onset and the beginning of effective treatment, and even a short learning curve could have a substantial impact on treatment effect.

The clinical trials did not reflect actual expected use of this drug device delivery system in that all of the principal treatment studies restricted enrollment to subjects judged able to use the device satisfactorily and the first dose was administered under supervision and instruction from study staff. Even after this screening and instruction, occasional reports appeared in the NDA of subjects returning incompletely punctured medication blisters which would have caused failure to deliver the drug into the airway.

An illustrated patient instruction sheet has been recently submitted. We have no reports of any testing of its final version.

The applicant has also submitted a synopsis of a marketing ease of use study conducted in 32 subjects using several previous versions of the instructions under

development. Although this was recently received and comments are very preliminary, a few points may be worthy of note from this report.

Most subjects were said to be able to load and use the device within 3 to 5 minutes. It was reported that the majority thought the device would be somewhat or very easy to use, but this question was posed in the study questionnaire without specifying whether this referred to the first time or to ongoing use, and some subjects reportedly added a spontaneous comment that the first use would take some time.

Some subjects reportedly had difficulty with disassembling the device to load it, with completely puncturing the medication blisters, or with keeping the device level to avoid spilling the drug.

The study did not recruit anyone under 21 or over 65 years of age. The recruiting instructions specified that subjects may not have strong accents, and no information on level of education or literacy was provided.

The report also commented that being sick with the flu could increase the difficulty of following the instructions and noted that all subjects appeared healthy and alert.

More recently the applicant has provided reports of studies of the similar devices used in

maintenance therapy of asthma, suggesting that patients experienced with other inhalation medications tested in a non-acute setting are able to operate the Diskhaler system correctly on the first try in the majority of cases using written instructions. In the study which provided the greatest detail, about 60 percent used the device correctly on the first try, and this improved to more than 90 percent if they tried three times.

Again, the concern with regard to influenza treatment is not whether most people can learn to use the device delivery system satisfactorily after a little practice, but what proportion of acutely ill, inhaler-naive, unscreened, and uninstructed patients will get it right on the first try and what impact there might be on effectiveness of the treatment course for any who don't.

To summarize, we have several clinical trials which show variable evidence for efficacy of zanamivir in the treatment of influenza. Looking for factors predictive of response, we've touched only very briefly on issues such as baseline temperature, duration of symptoms at study entry, and type of influenza virus, which you have also heard about from the applicant and all of which appeared possibly related to treatment effect in some analyses, but for which we did not find reliably consistent effects across studies.

Overall, the most striking influence on treatment effect was the difference between studies for which we don't have a complete explanation. There was least evidence of any treatment effect in the North American study and this worries us because this was the largest phase III treatment study. It was proposed throughout its development and conduct as one of the central studies in support of the indication. It should have been very well powered to achieve a statistically significant result for a clinically meaningful treatment effect, and multiple additional analyses have not identified predictive factors to single out subgroups in this study with truly convincing treatment effects. It is true that some subsidiary analyses showed greater effects than others, but it's also true that some subsidiary analyses showed negative treatment effects.

The use of relief medication complicates the interpretation of differences between the studies, but can't be assumed to explain them away. And if the use of common, over-the-counter medications can obscure the treatment effect of zanamivir, it is not clear how this would affect how you describe the expected effect of the drug to a prospective patient who is likely also to be using symptomatic relief medications.

With regard to safety, the principal studies

have not demonstrated major concerns for patients without special risks, but we do consider it possible that some events such as headache, cough, and nose and throat symptoms might be associated with the inhalation of either the active drug preparation or its lactose vehicle.

Safety and efficacy information in severely ill or unstable patients is limited.

Resistance has been shown to emerge. It has not been detected commonly, and the available information does not give us a certain idea of what the frequency would be with widespread clinical use.

Some potential problems with use of the drug device delivery system have been noted which could potentially alter effectiveness for certain patients.

Overall, we consider that this application raises a number of interesting issues on which we will welcome input from the advisory committee. Thank you.

DR. HAMMER: Thank you very much.

We can take some time now for clarification questions. There will be some additional time this afternoon if there are further questions for the FDA presenters, but let me ask if any of the committee members need clarification or wish additional information right now. Please.

DR. HENDELES: Could you clarify for me a

discrepancy between the Glaxo binder and the FDA review related to the methacholine PC20 data? In the sponsor's binder, it said there were no significant effects on peak flow or methacholine PC20, but in the FDA review, it said there was a significantly lower PC20, as well as morning peak flow.

DR. STYRT: There was not a significantly lower PC20. There were not clinically significant apparent effects on the average results in any of the pulmonary function tests. The numerical means were lower in the zanamivir than in the placebo inhalations, but not by an amount that would generally be considered to be clinically significant. The only point that came up as potentially clinically significant was this one patient who did have a decline in FEV1 just after the zanamivir inhalation on two occasions, and Dr. Meyer can add to that if I'm garbling anything here.

DR. HAMMER: Dr. Wong.

DR. WONG: The sponsor in analysis of efficacy made a point of censoring incomplete data at many different points, and the FDA analysis does not really address this practice. I would be interested in the FDA's opinion about how that analysis should be interpreted.

DR. STYRT: I think I'll let one of our statistical reviewers address the censoring issue. Dr.

Elashoff?

DR. ELASHOFF: Yes. I think one of the reasons I didn't touch on it was I think the whole notion of a time-to-event analysis where there's one time of alleviation has some real problems with it based on looking at the data. So, I preferred to look at all of the diary cards even after the symptom alleviations, all of the 14 day diary cards. If someone had high symptoms on one day and then was lost to follow-up, I would consider that person to have high symptoms for the rest of the time, although the actual number of patients who had missing diary card information was relatively small.

Does that answer your question?

DR. WONG: Yes.

DR. HAMMER: Dr. Li, did you have a question?

DR. LI: I wanted to ask whether there was any information about the use of nebulized drug and how is that used and, in particular, if that was used in North America.

DR. STYRT: The clinical treatment trials that are under consideration here are entirely trials of the lactose-based dry powder inhalation product which is the product for which an application has been received. There have been occasional uses of a nebulized preparation, I think you have heard it mentioned, for the compassionate use instances, but we don't have any data from any

controlled trials of nebulized drug. The applicant may wish to comment further on that.

DR. ELLIOTT: The collaborative antiviral study group are currently running a study in patients hospitalized with influenza, and that indeed uses the nebulized drug. In addition, on our ongoing study plan, which we may look at this afternoon, we have plans for looking at the nebulized solution.

DR. HAMMER: Dr. Hamilton.

DR. HAMILTON: Dr. Elashoff's presentation brought into sharp focus, for me at least, an issue that has been bothering me throughout the morning, and that is the reliance on this primary endpoint, time to primary endpoint. Flu doesn't just stop in one day, and a difference in one day between the placebo and the active drug treatment is said to be significant in the sense that it reduces global misery somehow and that it translates into a more productive, let's call it, work force.

It seems to me looking at the graphs and tables and figures that you showed, the disease doesn't end at the time of the primary endpoint. It lingers. It goes on and on, and so to imagine that that translates into a more productive citizen I find that to be something of a leap of faith.

I think it's quite interesting to consider

aloud how these different approaches reveal quite different conclusions about the benefits of this drug, and perhaps this will be addressed further.

I would like to ask the sponsors to confirm for me that the endpoints that they selected were, of course, selected prior to the time these studies were performed and they're not the result of some dredging of data that fits their hypothesis.

DR. ELLIOTT: I'll briefly address that. The analyses we presented were the ones predefined, selected during discussions with the agency during development.

DR. HAMMER: Thank you.

Dr. Masur?

DR. MASUR: I was wondering if Dr. Elashoff could elaborate a little bit on his comment that patients on active drug were more likely to break through after a 24 hour period of relief of symptoms. Was that a statistically significant difference, and how was that assessed? If, for instance, you looked at total symptomatic days over a 10 day period, even given the fact that they were asymptomatic for a day, were there any trends -- I shouldn't say trends -- any differences in one direction or the other?

DR. ELASHOFF: Yes. In the North American study in particular and also in the southern hemisphere

study, if you look at when the person first meets this definition of alleviation and then you looked to see later on would they fail to meet that criteria, more zanamivir patients, and statistically significantly more zanamivir patients, had a rebound compared to placebo patients. The reason for that I don't know.

DR. MASUR: I'm sorry. Just to follow up, is there anything that you can show us on that? For instance, it would be interesting to see, if you looked over 10 days, whether patients on the active drug were more likely to be symptomatic even given the fact that they had a day free of symptoms in the middle than patients on placebo. Do you have any graphic presentation of this?

DR. ELASHOFF: I don't have any graphic presentation. I guess just my overall sense of looking at individual patients. It often occurred sort of in the day 5 to 7 range that a patient might have come down and then head back up in the range of between 5 and 7 days. It generally wouldn't continue, say, out to day 14, but there would be extra symptomatic days.

DR. HAMMER: One interpretation -- I am sorry to interrupt -- that there are extra symptomatic days is one might imply from this that there's a treatment effect that's lost after the medication stopped because this was a 5 day treatment course. So, if there looks like there's a

difference around that time, day 4 to 5, and then there's a rebound, one could say, well, there are some side effects or whatever that may contribute to that, but one also might say that there's a treatment effect that's lost. Is that a fair inference, which is probably all that we can say?

DR. ELASHOFF: Well, I guess if the primary focus is on symptoms, no matter how you measure symptoms overall or individual symptoms, whether you have them early or late doesn't seem to make a whole lot of difference. In aggregate, did you reduce the total amount of symptoms? And I think the answer was no.

DR. HAMMER: But just for the committee's sake and for later discussion, one thing we have to derive from these data, which are somewhat at variance in the studies, is whether there's in vivo activity of this drug, and we have to try to sort that out from the overall treatment results and some of the secondary aspects of the studies.

Dr. Bertino?

DR. BERTINO: Maybe Dr. Elashoff can clarify for me relief medication and what you said about it. I think what I heard you say was that the use or non-use of relief medication may have blurred all the scoring systems that were used, but could I ask for a clarification exactly on what you presented to us?

DR. ELASHOFF: Yes. The use of relief

medication is impossible to disentangle from the actual symptoms. If you do an analysis that looks at use of relief medication, use of relief medication would seem to imply more symptoms because they always go together. In other words, symptoms cause you to use relief medication so that they're very tangled up, and there's no statistical analysis that can say we saw these results because of the pattern of relief medication use. So, whether it's a blurring of efficacy or what efficacy actually means if you're going to be taking these things anyway and you don't detect any noticeable benefit on your symptoms -- does that answer your --

DR. BERTINO: It does.

I guess I would throw a question out then in terms of methodology for the studies. Were patients given relief medications and said, if you have this, this, or this, you should take something, or was it just left up to them? Is there a sociologic difference between the Europeans and the North Americans? I can tell you what my bias is in terms of the quick fix syndrome.

DR. STYRT: Actually one thing I can clarify from looking at the sample diary cards, that each diary card sort of said, write down how many times you took these medications. Don't take them unless you really need them, that kind of thing. I don't remember the precise wording,

which varied a little bit in the diary cards, but it was there.

The other thing I did want to mention was in your background document, there are some additional analyses if you use the same primary endpoint but required that people not have any subsequent recurrence of symptoms that don't satisfy the endpoint.

Was there an additional point of clarification that you wished to make?

DR. OSSI: Yes. As far as use of relief medications, the instructions were for patients not to think that they were supposed to take them automatically. It was only if they required them for relief of symptoms during the study.

The other point of clarification I would like to make is that we keep talking about the length of duration of relief of 24 hours. Actually it's 36 hours. Patients had to be relieved or meet the endpoint for 12 hours prior to being "alleviated," and then to satisfy that endpoint, it was another 24 hours. So, it's a total of 36 hours.

The other point is that when you talk about the kind of analysis that Mike presented, it may not be clinically relevant to think of a situation -- I think the one that you showed, the individual patient had alleviation

of fever plus all the other symptoms, and then 3 or 4 days later developed a moderate headache, and you're considering that as a symptom that should be relieved by drug. So, over a 14 day period, you're going to blunt any effect by adding in individual symptoms that happen 10 days after treatment is over as not considered part of the treatment effect.

DR. ELASHOFF: If you look at how the patient rated themselves overall, overall during that entire period they rated themselves as moderate. So, they didn't feel any better on day 4 and 5, and if you look at the secondary symptoms, both weakness and nasal congestion were rated as severe during that period. I agree with you, there was a rebound of the moderate headache, and maybe that in and of itself a day after alleviation might be important. But looking at the whole pattern, I think this patient wouldn't have considered themselves alleviated at day 3 and a half.

DR. HAMMER: Dr. Stoller?

DR. STOLLER: A point of clarification on Dr. Elashoff's comments about the mean symptom scores and the censoring issue. Did I understand you to stay that when a patient dropped out or failed to return the diary cards and had not alleviated at that point, that their mean symptom scores were carried at the max through the remainder of the mean scores in your analyses?

DR. ELASHOFF: They were carried at whatever their last diary card --

DR. STOLLER: Whatever their last diary card. So, if anything, the non-alleviation early in the study would carry their non-alleviated score throughout the tail end of that mean symptom score analysis. Is that correct?

DR. ELASHOFF: That's correct.

DR. HAMMER: Please.

DR. HENDELES: Were there any studies conducted on doses higher than 10 milligrams per day?

DR. STYRT: There were the phase II studies that used more frequent dosing in some instances up to four times a day, but there were not any that had any higher single dose of the inhaled dry powder preparation at the time of one dosing.

DR. HAMMER: Dr. El-Sadr.

DR. EL-SADR: I have a question -- actually two questions. The first question, in some studies that I've been involved with, at the end of a placebo-controlled blinded study you sort of ask the patient before unblinding them, do you think you were on placebo or active drug? Did any of the studies actually do that?

DR. STYRT: We're getting a no answer here, just for the benefit of the transcriber.

DR. EL-SADR: And the second question goes back

to whatever we call the rebound or remaining symptoms, and Dr. Hammer mentioned the idea of -- it seems that the data suggests that the virus really cleared in most cases by the third day. Any evidence that you have from the phase II studies or other studies that there's actually sort of a rebound of virus beyond the treatment point?

DR. ELLIOTT: We can present a few slides on that this afternoon, but the short answer is no. We did take samples at day 6, a day after the end of therapy, specifically to look for rebound, using exactly the same techniques of swabbing or washing, and around about a percent or less. We got a couple of cases here and there in active and placebo, but really compared to what we had seen at baseline and even at day 2 and 3, no virus to be recovered that was at any measurable level.

DR. STYRT: Again, I think the proportion of throat swabs that were positive at day 3 and day 6 is also summarized in your backgrounder. I believe it was something like 4 percent and 2 percent in the study with the highest proportion -- no, I'm sorry. It was 4 percent and 2 percent, 15 percent and 8 percent at day 3, and much, much lower at day 6.

DR. YOGEV: Can you just clarify for me? I can't get it from any place. Are there enough patients between the age of 12 and 18 to suggest that whatever we're

seeing is sufficient to suggest that we start at age 12?

DR. STYRT: You might even have a breakdown slide for this afternoon. Right?

DR. YOGEV: If we can get that.

The other one is I noticed that 85 to a higher percentage were white. Should there be any definition if that drug will do the same in minority groups that we have a question of compliance and so forth? Are there any data to that?

Lastly, just for the FDA, I'm not sure at all that we're using lactose and was lactase deficiency in the population addressed in any way, shape, or form? Because to me it's surprising the high percent of diarrhea in both groups compared to what one would know from influenza as a whole.

DR. ELLIOTT: I can answer, and again we've got some slides we can show this afternoon on lactose.

From publications, the amount of lactose required to generate GI disturbance in those people with lactase deficiency is about 10 to 12 grams. So, with our 20 milligrams per blister, we're well short of that.

I think the GI disturbance is really part of just underlying influenza or the respiratory illness of all patients to the study and no drug effect there.

DR. HAMMER: Dr. Stanley.

DR. STANLEY: Just quickly. Dr. Elashoff, how representative is the individual patient that you showed with his overall assessment curve of the other patients that you've looked at?

DR. ELASHOFF: It's very common. There were at least 30 percent of people who, after the day of alleviation, had some of the primary symptoms. There was another sizeable fraction who had secondary symptoms that lingered on -- another sizeable fraction that had the overall score past. I don't have the exact percentage but it was noticeable.

DR. HAMMER: Dr. Wittes.

DR. WITTES: Yes. Let me ask sort of a follow-up of your question, and this is related also to the use of pain meds. I really appreciate this problem of entangling the headache and so forth with the medications. In some studies of pain, what will happen is the endpoint is symptom or use of med, sort of clumped together.

The question is, did you look to see whether some of these dips had to do with the person is on meds, is feeling better, gets off meds, and then the headache returns? I know it's very hard to look at.

DR. ELASHOFF: So, on an individual patient, trying to correlate exactly what they do.

DR. WITTES: Yes.

DR. ELASHOFF: I'm not even sure exactly how to approach that kind of analysis. I don't know why they took their relief meds. The diary cards are only once every 12 hours, and they record the relief medication use for the entire day. It's hard to know whether their symptoms in that 12 hour period were sort of reflective of how they were at that time.

DR. WITTES: The question pertains to is this a biologic think happening, that there's a real rebound, or is this a response to symptoms.

DR. HAMMER: Dr. Diaz has a question relevant to this.

DR. DIAZ: I was curious if you see the same rebound in the placebo group who also took pain alleviation medication.

DR. ELASHOFF: There was a sizeable fraction of patients on both arms who had -- I don't even know if I'd call it a rebound. I'd say in general symptoms are a gradual improvement over time. You have your good days, you have your bad days. So, in a 10 day course of influenza, you might have 1 or 2 good days mixed in.

There were more patients on the zanamivir compared to placebo who had sort of, I guess I would call it, the bad days occurring after the time of alleviation, but it was fairly common throughout both arms.

DR. HAMMER: We saw a slide of the use of relief medications, and I know analyses have been done excluding relief medications and they showed the same pattern of efficacy across the three studies. But was there an implication in the use of relief medications that it might be a greater confounder in the North American study because there was some slightly greater use in the North American study, or is that not a correct inference?

DR. ELASHOFF: It's hard to know without knowing why individual patients took relief medications. Some presumably took them only when the symptoms were severe and some only when they were mild. I was just sort of noting that the overall pattern with the lowest use in Europe and highest in America seemed suggestive. There's no way to sort of get at that statistically.

DR. HAMMER: Not a surprising result, though.

Dr. Li?

DR. LI: Is there any information about what percentage of the drug in the blister pack actually reaches the lungs or the lower airway, and do we know how much inter-subject variability there is? And then furthermore, is there any reason for us to think that the North American population was either instructed differently or perhaps was in some way less coordinated than their European counterparts?

DR. STYRT: We're told that the instructions were uniform across studies, and you heard mention that there has been a study using gamma scintigraphy in a very small number of subjects. I don't think we have anything that actually tells us in the broader patient population represented in the clinical studies just what the distribution of the drug is in the airway, but there were those studies that were presented earlier.

DR. WONG: So, do we have a numerical percentage of the amount of drug delivered to the lung?

DR. STYRT: That can be added to this afternoon's presentation.

DR. HAMMER: I think we'll call the question period to a halt now. There can be more questions for the FDA in this afternoon's session. This morning session is over. We will reconvene at 1:15. Thank you.

(Whereupon, at 12:08 p.m., the committee was recessed, to reconvene at 1:15 p.m., this same day.

AFTERNOON SESSION

(1:15 p.m.)

DR. HAMMER: I'd like to convene the afternoon session.

The first item on the agenda for the afternoon is the open public hearing. There's no one officially signed up now to speak, who has given us that information in advance. Is there anyone here present who would like to make a statement in the open public hearing?

(No response.)

DR. HAMMER: If not, I'll declare the open public hearing now closed, and we'll move to the next item.

Before we move on to the sponsor responding to some of the panel's questions, I'd like to call on Debra Birnkrant who wants to speak to us.

DR. BIRNKRANT: Thank you. Well, as we continue our discussion and move towards the afternoon deliberations, I just wanted to make a few comments to help us focus this afternoon's discussions.

What I'd like you to do is think about the phrase, there's more than one way to look at things. I think this is particularly applicable to influenza, which is a self-limited disease maybe lasting 5 to 7 days, up to 10 days. Think about what type of treatment effect you would actually expect in this type of illness as you

deliberate this afternoon, keeping in mind that, for the most part, in patients it's a waxing and waning type of presentation over the course of the 5 to 7 to 10 day period.

I think the other thing to keep in mind is that, as Dr. Styrt presented this morning, that there are a number of ways to look at things with regard to endpoints for influenza trials, and various types of endpoints have been tried out not only for zanamivir, but other drugs as well.

I also wanted to bring to your attention that years ago, when the protocols were submitted for these clinical studies, we did agree to certain endpoints with the applicant, Glaxo Wellcome.

I also want to raise the point that, as you can see, both the FDA and the applicant did multiple additional analyses, and as you can also see, exploratory analyses can either be more or less reassuring, depending on how you look at things.

I'd now like to just make a couple more comments about foreign data. In our regulations, there's a description as to when and how we can accept foreign clinical data. One of the major ways in which we accept foreign clinical data is if we can apply it to the U.S. population and to U.S. medical practice. To relate that

comment to the clinical studies, I just wanted to remind you that the European trial and the North American study followed the same study protocols.

In order to use foreign data in a marketing application for the FDA to review and consider worthy, we also have to be able to validate the data, and that would involve an inspection.

Lastly, we have to make sure that these clinical trials were conducted according to U.S. standards, which they were.

Thank you very much.

DR. HAMMER: Thank you.

I'd like now to turn to the sponsor, Dr. Rubin perhaps, to lead off. This is in response to a number of written questions that were submitted and also issues that came up in the morning discussion.

DR. RUBIN: Thank you very much. We certainly appreciate the opportunity to respond to the issues that came up this morning, and a lot of issues did come up. We're going to do our best to provide you with focused, concise answers to those. We've received both verbal and written questions and, as you'll see, have tried to organize them in a logical order.

I just wanted to start by making a couple of comments, first addressing the use of the term "rebound."

This is just a general comment, but I noticed that we and many of you were using the word "rebound" to describe what happened in these studies. It's my view that we need to be very, very cautious about saying that we're seeing rebound of influenza in these studies. I think in fact that's pointed out by the anecdote that you showed us with that patient because we can have a patient that comes in with rather significant symptoms, a constellation of symptoms in a number of categories, fever, headache, myalgia, cough, et cetera. That can be alleviated within 3 days, and if that patient has just a headache, for example, 2 or 3 days later that he or she scores as anything above mild, that would be a rebound. I think that return of one of those symptoms is not uncommon, if you measure patients over a 14 day period, and so we need to be cautious about using the word rebound. As you'll see, the virology did not support any actual rebound of disease either.

As I mentioned before, when we actually constructed these programs, there was certainly no road map to follow. There was no large database that existed to use. I think the amantadine and rimantadine databases were around 400 or 450 patients in total.

So, we agreed, as was just pointed out, with the FDA prospectively on the important primary and secondary endpoints, and all of the analyses that we

presented to you were these prospectively agreed primary and secondary endpoints that were predefined. I think really sort of the hallmark of clinical development for us is doing that.

While we certainly appreciate the FDA's enthusiasm for doing exploratory analyses from this now very large database that we've accumulated -- and in fact, we share that enthusiasm -- I think we also need to be cautious about drawing definitive conclusions about this drug and its efficacy from those exploratory analyses. I do think that they will be very helpful for us as we look toward the future perhaps in designing new trials and trials with other drugs in this class.

We do, I think it's clear from a discussion and presentation of the agreed primary analyses, clearly and unequivocally have two studies that are statistically and clinically meaningful and significant. Those data were presented by us and also by the FDA.

There is obviously some concern, as I mentioned in my introductory comments, about the U.S. study and some disparities, and let me just take you through top level reasoning why we believe this study is positive and why we believe there may have been some differences. Perhaps some of our other speakers will go into this in more detail.

Firstly, as Dr. Ossi alluded to, we believe

that a 1 day benefit in this disease is a clinically meaningful benefit, and we did in fact agree to that up front. All of the key analyses, the predefined key analyses that Dr. Ossi described, showed significant effects and many clinically meaningful effects, but the effects clearly were somewhat less than we saw in the European and the southern hemisphere studies and that is clear.

What are some of the reasons for the lower magnitude of the effect? Well, I think probably the most important is that we do expect to see some range of effects when we do multiple large trials. That does happen and it's not completely unexpected.

Importantly, we did see significantly increased usage of relief medications in the U.S. trial. If you compare that to the European trial, which are quite comparable in design, there was a two to three-fold increase in relief medications, both protocol-specified relief medications and protocol non-specified relief medications. So, clearly that existed and may have blunted the response. If we look, in fact, at the placebo response between the European and the U.S. studies, we see that there's a day and a half difference. It's a shorter duration of illness in the U.S. study, whereas the zanamivir response is the same in both. So, we may,

indeed, have blunted the comparator arm, making meaningful differences more difficult to show.

As we saw in terms of protocol violators, more patients entered after 48 hours in the U.S. study compared to the European study.

I think while none of these we would want to hang our hat on as offering a definitive explanation for the differences, I think taken in concert, they certainly offer some explanation for why these differences exist. But again, we do believe that this study shows a meaningful benefit and is certainly supportive of the weight of the evidence with the other two positive studies.

So, I'll stop there. I'm now going to turn the podium over first to Dr. Fred Hayden who is an investigator, as you know, in our program and he'll give you some of his perspectives from the phase I and phase II trials.

DR. HAYDEN: I wanted to take the opportunity just to make a few comments in response to some of the questions that were raised based on my experience as an investigator in the phase I and phase II trials, although I've not been involved in the phase III trials with zanamivir.

I also share a concern about the use of the term "rebound" because it raises, I think, some important

clinical issues, the first of which would be, of course, in flu there is some increased risk for subsequent bacterial and other complications. So, if someone in fact has a rebound in symptoms, as a physician I wonder whether they're in fact experiencing a complication. This might be associated not only with symptoms, but also a return of fever. That was not seen in the phase II trial, the 2005 trial, which is included your briefing documents.

Furthermore, in that study there was a trend toward reduced complications overall in the zanamivir groups compared to placebo. As you've seen, this kind of pattern is true in the other phase III trials.

A second possible explanation for a rebound has already been alluded by Scott Hammer, and that might be an insufficient duration of therapy. One might anticipate that this would be associated with recrudescence of symptoms, of course. In fact, the symptom curves which were presented don't show a rebound in symptoms -- they show a continuing downward curve -- or return of fever, which to my knowledge was not observed in the absence of complications, or a rebound in viral replication.

The one slide I wanted to show you is from again this 2005 trial where three centers, John Traynor at Rochester, Fred Ioke in Manitoba, and our center, accumulated nasal washings on enrollment in the study and

then on days 2, 4, 6, and 8 after initiation of the protocol. The placebo curve is shown in the light blue. These individuals peaked at just over 5 logs of infectious virus on the second study day in their nasal washings and then returned to baseline negativity by day 6.

With inhaled zanamivir, a similar pattern in general, and this is the expected result because again inhaled zanamivir provides very little drug in the nasal passages and would not be expected to elicit a virologic response. In contrast with the combination of inhaled and intranasal, there was a much more rapid decrement in recoverable virus. All of these individuals were negative by day 4. Importantly, after the cessation of the 5 day treatment period, there was no evidence of a virologic rebound.

So, I think that indeed I agree that there is sometimes a waxing and waning in influenza studies, but the natural history is one in most individuals of gradual spontaneous recovery.

Another part of this from my perspective that's important is how does this translate in terms of functional effects. Indeed, in the 2005 study and some of the others, these individuals wer, in fact, able to get on their feet more quickly and get back to their usual activities.

Just a few more comments. Then I'll stop.

We did look at other subset analyses in that trial. This was conducted during the 1994-1995 season, and because there weren't a sufficient number of subjects enrolled, we combined data from studies in North America and Europe. Before doing so, we made certain that in fact these groups were comparable in terms of their demographic characteristics and indeed in terms of their clinical outcomes. To my knowledge, based on the prospectively defined endpoint, there were no differences in terms of drug efficacy between North America and Europe.

There was a significant amount of influenza B circulation during that particular season, mostly in Europe and to a lesser extent North America, and again, there were positive effects seen in influenza B infected individuals. Indeed, six of the seven studies that were presented showed positive effects against influenza B, and this is consistent with the effects of this drug at the enzyme level and also in animal trials.

You've not been told about a challenge study in which we looked at its activity for prophylaxis against influenza B and again saw a positive signal there.

Be cautious about interpreting the influenza B challenge model data. It involves an enormous inoculum of virus, 10 to the 7th infectious units typically. It's not associated with usual illness, a mild upper respiratory

infection with no fever and very little cough. The only really useful information that comes out of it is the virologic endpoint.

Finally in this particular study, we did find in subset analyses that early treatment was clearly important, so that the earlier the drug was initiated, the greater the effect. In fact, that half of the patients that were enrolled after 30 hours, we found nearly no evidence of a treatment benefit, and I wonder whether in some case in the North American study where individuals might have been coming in later to initiate therapy, that could explain some of the reasons for a less dramatic clinical benefit.

So, in summary, although I was not involved in the phase III trials, I think the data that I've seen are, in general, consistent with those that we observed in the phase II and indicate that this drug has a clinically meaningful effect.

Thank you.

DR. HAMMER: We'll allow one question from Dr. Masur, maybe two.

DR. MASUR: Fred, on that one slide about percent of patients with a positive nasal wash, I assume that was a qualitative culture that was all or none? Do you have any quantitative virology?

DR. HAYDEN: I'm sorry. That was quantitative virology. I should have explained it more thoroughly. The vertical axis here was the log of infectious virus per milliliter of nasal wash. The frequency of having viral positivity did not differ significantly between the three groups, but there was an antiviral effect reflected in reductions in titers in those who got intranasal drug. Of course, again this was sampling at the nasal level.

DR. HAMMER: Dr. Hamilton.

DR. HAMILTON: Possibly the only benefit of having influenza is that you generate some level of immunity that protects you in part from subsequent attacks in subsequent years, assuming the types, strains are the same.

Is there any evidence that treatment blunts that immunologic response and renders you susceptible more than others at later dates?

DR. HAYDEN: In this particular trial, we did look at geometric mean antibody titers after therapy and the change, acute to convalescent, and found really no evidence of reduction in serum hemagglutination inhibition antibody levels. We did not examine other antibody types, but in general, that should be a fairly good predictor of protection against subsequent infection so that the frequency of serologic rise and the magnitude of that rise

were not influenced by antiviral therapy. That's consistent with earlier studies in adults where amantadine and rimantadine have been used.

DR. HAMMER: A question from Dr. Kilbourne.

DR. KILBOURNE: Fred, you showed in this particular slide you just showed what seemed to be significant differences between the impact of adding on the nasal medication to the inhaled medication, something you do not stress in later studies. Indeed, you went on to use the inhalation alone.

Is there any possible pharmacologic effect here in measurement of virus? In other words, do you have pharmacologically active zanamivir present in that nasal wash that might be acting in the in vitro assay?

DR. HAYDEN: I think that's a very important issue to resolve in terms of examining viral endpoints. In fact, we've done some preliminary studies to show that with nasal washes in which had added drug and virus artificially you could, indeed, see artifactual inhibition. But remember that this drug influences late events in viral replication, of course. The initial binding in the first phases of replication proceed uninhibited. One can overcome this inhibition entirely by simply washing the drug out after the absorption period. The bottom line is that it's possible to get, I think, clear quantitative data

in these kinds of studies.

DR. KILBOURNE: May I suggest an easier way to do it is simply to use a plaquing system with an overlay, including your wash material. In other words, keep it present during the assay, if it is present.

DR. HAYDEN: Thank you for that suggestion.

DR. HAMMER: I've given some request to the sponsor to really try to limit their comments this afternoon. So, I think in deference to that, we'd like them to finish their comments, and then if there are critical questions that have not been answered, the panel can ask them. Thank you.

DR. RUBIN: Thanks. I'm just going to make two more brief comments to address issues that have been raised and then turn it over to some of our other presenters.

First, around the comparability between the studies outside of the U.S. and the U.S., or North American, study, in particular focusing on the European study, the protocol was virtually identical. The demographics were the same for the two populations. The strains of infecting influenza were the same in terms of proportion overall. Our measurements of compliance indicated that there were no differences in compliance with the device between the European and the U.S., or North American, study, and they were both administered in the

ambulatory care setting. So, our view is that these are really quite comparable, and that the patient population is quite representative of the U.S. population.

I also just wanted to make a couple of very quick comments about the Diskhaler because we certainly recognize that this is a very new delivery system for delivery of a drug for infectious diseases, although it's clearly used in other settings.

We recognize the importance of education here, education of patients and education of physicians. We will, of course, have a package insert with text instructions for use included with all of the zanamivir packaging. We'll have a color illustrated instructional leaflet with every carton of Relenza. In addition, we'll be providing placebo inhaler kits to physicians and to pharmacists so they can learn how to use it and, of course, instruct patients or family members of patients how to use it.

These are just some of the examples of the proactive approach that we're taking. We've been working closely with the agency on this. We will continue to work with them and certainly are open to other suggestions. But we recognize the importance and we're taking steps to address that.

I will now turn over the podium to Richard

Bethell who will run through some of the virology issues. Just so you know the order, we're going to go through the virology issues, the clin/pharm issues, and then clinical efficacy issues if there are more to address.

DR. BETHELL: Thanks very much, Marc.

I'd like to address two of the issues that came up this morning, the first related to the comparative activity of zanamivir against influenza A and influenza B viruses, and the second related to a question concerning possible changes in antigenicity associated with viruses that have been selected to have reduced sensitivity to zanamivir.

So, my first slide is just by way of introduction to show the experimentally determined binding of zanamivir to the active sites of influenza A neuraminidase. The drug is shown here in green, bound to the influenza A neuraminidase, and in yellow bound to the influenza B neuraminidase. You can see the remarkable conservation both in the conformation of the drug and its interaction with active site residues within the neuraminidase active site.

This just summarizes the comparative activity of the drug in both the neuraminidase assays or the enzyme inhibition assay in which we've taken the principal strains that we've used in each of our preclinical assays,

comparing first in the enzyme assay, in the plaque reduction assay in vitro, and then in our two animal models of infection involving reductions in virus titers in the lungs of mice and reductions in viral titers in the nasal washes of ferrets.

In the case of the two animal models, these are the doses in milligrams per kilogram required to effect a 1 log reduction in virus when given twice a day. Again, one can see the very much greater activity of the drug in comparison with current antiviral agents against influenza.

So, I'll now move on and address the question of the antigenicity. A question was posed about whether we had monitored the antigenicity of the zanamivir resistant viruses that we had selected during our preclinical program.

So, this slide shows one of the hemagglutinin molecules, the crystal structure determined by Don Wiley and his colleagues with the HA1 shown in green and the HA2 shown in yellow. Superimposed on that are shown the principal antigenic regions of the hemagglutinin, shown both in dark blue and light blue.

The light blue areas are residues in which we have found alterations in zanamivir resistant viruses that have been selected in our in vitro studies. As you can see, a small number of these, 4 out of 12, do occur within

the A and the B antigenic regions of the influenza virus hemagglutinin. However, we've not observed any alterations in the C, D, or E antigenic regions of the hemagglutinin.

The majority of the mutations that we've observed, shown in red, do not fall within the antigenic regions of the influenza virus hemagglutinin.

We've done a lot of sequencing of hemagglutinin of viruses isolated during our clinical trials, and among these we have found two mutations in hemagglutinin among viruses that were cultured up either during or after treatment. These two are shown in red. As you can see, they do not fall within the principal antigenic regions of the influenza hemagglutinin, and the mutations that were noted were naturally occurring mutations; that is, in other different strains of the same subtype, these particular residues had already been known.

We believe that among immunocompetent patients that zanamivir is very unlikely to select for mutations that affect antigenicity. For a start, there is no question of any change in the hemagglutinin subtype. We therefore believe there's no possibility of antigenic shift.

As Michael Elliott explained in this morning's presentation, neuraminidase inhibitor resistance, the results from changes in the hemagglutinin, is confirmed by

reductions in sialic acid binding affinity, and in vitro studies have shown that reduced sialic acid binding activity results in reduction in the binding and absorption of viruses containing these mutations, arguing that these viruses would be expected to be less pathogenic.

Furthermore, the overlap between the sialic acid binding site and the A and B antigenic regions of the hemagglutinin means that circulating antibodies may limit the selection of mutants that have a growth advantage in the presence of neuraminidase inhibitors.

To date we have tested a number of the viruses containing hemagglutinin mutations in our animal models, and none have been shown to be resistant to zanamivir in vivo.

Furthermore, as I've shown you, there have been no neuraminidase mutations in antigenic regions during the clinical trials of zanamivir. However, in the one mutant virus that was isolated from the immunocompromised patient that Michael Elliott talked about this morning, the virus which contained the mutant in the hemagglutinin was found to have increased HAI titer to one reference serum and a decreased HAI titer to another one.

Finally, we briefly noted this morning our plans to monitor the susceptibility of influenza viruses following approval, and monitoring of the antigenic

properties of these viruses will be key component of these activities.

I'll finish there unless there are follow-up questions to the presentation that I've just made.

DR. HAMMER: I think we should let you complete your presentation which is in response to our questions and then we'll ask more questions later.

Can I ask the speakers to please speak directly into the microphone? Some of the members are having difficulty hearing you.

DR. TISDALE: I will quickly address some of the questions that were addressed to the clinical virology sections, and if I can have E66 again, which is the slide that Fred Hayden showed you.

I just wanted to explain to you why so many of our isolates were from early time points and also why we got so few isolates in the phase III.

In the phase II studies, in the U.S., we took samples every other day and in Europe we took daily samples from core centers, expert centers. In Europe it was Professor Osterhaus at Rotterdam.

Really what I wanted to show you here, particularly as Fred pointed out, when you give the drug by inhalation alone, which is the chosen route, then nasal washings aren't the suitable sample to look at because

we're not seeing an effect on virus titers. So, we needed for phase III to take throat swabs.

If I can have the next slide. This shows you the results from 2008 in Europe. Again, this was the study where we compared b.i.d. and t.i.d. This shows you the b.i.d. results. The q.i.d., four times a day, were just to the right of this. So, in fact, the b.i.d. on viral titers did look fractionally better. There was no significant difference.

But what I want to really show you here is that in the treatment group, the virus titers go below the limit of detection very rapidly and even the placebo are going down below the limit of detection around day 4, day 5.

If I can have the next slide. This just shows you the phase III, again 41 percent, 60 percent isolation rates here, going down to 8 percent, 15 percent at day 3, and very low at day 6.

If I can have the next slide. This is going back to the phase II and this is actually showing you the numbers where the isolation rate, even using nasal washes which were optimum, shows a fairly low after day 3. So, at day 1, we're getting high levels of isolation, 86, 85 percent. Day 2 it's going down 64 percent in the placebo, 48 percent in the treated. By day 3, then it's down to 50 percent in the placebo and just 26 percent, and then by day

4 and 5, it's very low.

So, really, for susceptibility monitoring, we wanted to get the suitable site and also we needed to get isolates that had the maximum exposure to the drug, and for this we chose day 3 because day 4 there's very few. Then we also looked at day 6.

So, these are the reasons really. We were limited by the self-limiting nature of the disease, plus the percent we could isolate, and that's why we had so few. In fact, from all the studies we did have 16 isolates that were at day 4 and 1 isolate from day 5 and 1 isolate from day 6. So, we did look at more than just the day 2 and 3 isolates.

If I can now move on to just discuss some of the problems we've had with the susceptibility monitoring, looking at the plaque assay, and that's going on to E71.

From our clinical studies and also from the preclinical studies, from looking at matched isolates, we would prefer to use the plaque assay because it isn't virus input dependent, and that was the method of choice. But there are several reasons why this isn't an ideal method for looking at neuraminidase inhibitors in particular, but also for looking at clinical isolates.

What we found with the fresh clinical isolates, the plaques were very diffuse, very variable. In the 2008

trial, they were extremely difficult to read. So, this makes really comparisons for susceptibility monitoring very difficult.

With neuraminidase inhibitors also we see that they reduce the plaque size rather than the plaque number frequently, and this again makes the results very subjective when you're looking at large numbers of isolates.

So, for this reason we wanted to get away from plaque assay. We've used it for the first two trials, but we find it too variable.

The third problem with all cell-based assays, we know that the virus can spread from cell to cell in a cell-based assay, and this is what we think we're seeing in the plaque assay. So, sometimes even with isolates at day 1, they appeared to not be susceptible to zanamivir and to other neuraminidase inhibitors, but in fact it's probably because the virus is able to spread from cell to cell bypassing the function of the neuraminidase, whereas if you look at them in vivo, they are sensitive.

I'll just go on and show you a little more data. Is this okay?

Other reasons why we felt the plaque assay was not the best assay. We saw a poor correlation between plaque reduction on in vivo susceptibility, and I'll show

you some of that data. There was no apparent correlation when we looked at the zanamivir susceptibility in the 2008 trial of the day 1 samples between plaque reduction and the duration of virus shedding. Again, I can very briefly show you that.

From Rob Webster's data in the immunocompromised patient, he reported that there was a problem with the MDCK cell line using plaque assay for reporting resistance. In this assay, rather than seeing resistance where we don't think it occurred, it was the opposite. They were missing the resistance in the MDCK cell line, and we believe this is because of the mixture of receptors, alpha-2,3 and alpha-2,6, in the MDCK cells, and that the virus had reduced binding to the alpha-2,6 but not to the alpha-2,3. So, there are several reasons why we believe that plaque reduction assays in particular are not ideal.

We've also spent some time trying to improve on the methods trying to use alternative cell-base methods using virus yield reductions where we've quantified virus using ELISA assays. We've done a 3 day assay where we've found that again to be very variable. Fred Hayden also looked at the same assay and he found it very variable. The problem with these sort of assays, again they are virus input dependent and they also have the problem of cell-to-

cell spread.

We now have a yield reduction assay which is a 24 hour assay, and that appears to be less variable, but it still isn't that consistent but it's more consistent than plaque assay.

If I can have the next slide. This is just showing you the variability, but I've been told I've got to finish. This shows you that the neuraminidase assay really agrees with the in vivo data, and that's why we prefer the neuraminidase assay.

DR. HAMMER: Would you please identify yourself for the transcriptionist? She didn't catch your name.

DR. TISDALE: Margaret Tisdale.

DR. ELLIOTT: There were a number of clinical questions that came up during the morning. I'll try and address these in what I hope is a reasonable order.

First of all, some of the more clinical data on influenza B, although Rich Bethell has already covered the virological aspects and that's really the in vitro bullet you see at the top there.

Also in animal models in the ferret and mouse we see equivalent activity both in treatment and prophylaxis for influenza B compared to influenza A.

In the human challenge model work performed by Dr. Hayden and John Traynor, we also see activity that's

comparable against influenza A and B, and we'll show that data very briefly. My colleague, Betty Hussey, will show that.

Also in the clinical studies, the next couple of slides, 216 patients with influenza B across 3 years of programs, we really see comparable efficacy across the subtypes of A and B. Actually specifically relevant for this panel asking for a full-sized efficacy study in influenza B might be looking for a full-sized study for a nucleoside analog, say, for HIV-1 and HIV-2. We draw the comparison to be of that order.

Just looking at the data now, these are three of the studies amongst the studies which were presented this morning by Dr. Styrt, and you see some variation but generally positive effect for influenza B, which is shown in the pale blue bars, compared to influenza A. You see one study where there's apparently less effect, one study where there's apparently more, and this study where it's really about the same, about half a day of difference. Those were the studies which recruited well in influenza B. As Dr. Hayden pointed out in his epidemiology, influenza B does not come every season. It's about every third or fourth season, so I think we're actually quite lucky to be presenting an application with such an amount of influenza B.

If you look at the phase III program on the next slide, this is putting all these three studies together, so the influenza A and B from the phase III program, that Australian, European, and the U.S. study. Again, you see the comparability of the data. I'm not thinking of claiming any difference here. Both influenza subtypes, patients with those subtypes gain an equivalent benefit of a day and a half for influenza A and 2 days for influenza B, and again, a good number of patients in the phase II series there on each treated group.

So, from a clinical perspective and the data we had seen to date, there's really a consistent story. The molecule was designed to fit those matched influenza A and B sites in vitro, in vivo, in the animal models, in the human challenge model, and the final arbiter really, in the clinic as well we see equivalent activity.

I'll now pass briefly to Betty Hussey who will review the challenge data because this is really what let us get into the full-scale clinical programs.

DR. HUSSEY: I was just told to be very quick.

I need slide F56. Briefly I'm just going to walk you through the challenge study that was done to look at influenza B. The objective of the study was to evaluate the effects, and we looked at very low doses in the study, one spray per nostril and two sprays per nostril.

Next slide. We used a randomized, double-blind, placebo-controlled design. Again, as I just went over, one spray per nostril corresponds with a 3.2 milligram dose; two sprays per nostril corresponds with a 6.4 milligram dose.

Next slide. These were healthy adult male and female volunteers. They were serologically susceptible to the strain of virus. You will note this was a 10 to the 7 inoculum, as Dr. Hayden has already mentioned. When we did the influenza A studies, we looked at a 10 to the 5th inoculum.

The volunteers were isolated for a period of about a week and monitoring consisted of daily nasal washes, oral temperatures four times a day, symptom assessments that they filled out twice a day, and then routine safety assessments.

I'll skip over this one because the same data is on the next slide.

This breaks down the different dosing arms. Looking at zanamivir dosing arms, one spray b.i.d. where the treatment was actually initiated 32 hours after the inoculum for influenza B. Looking at the influenza A studies, zanamivir was administered six times daily as a drop formulation and that was initiated both at one treatment arm with 26 hours and one treatment arm 50 hours

after the inoculum, and then a twice daily regimen as well initiated at 26 hours.

If you look over at the viral titer area under the curve, you can see that in all cases the zanamivir arms were reduced compared to the placebo. However, in the influenza B placebo arm, only 50 percent of the subjects that were inoculated actually went on to shed virus, in other words, anyone that had a positive culture at any time. This area under the curve actually reflects the area after the initiation of treatment.

So, you can see that even with the low infection rate in the placebo group, there's a twofold reduction in the viral titer area under the curve. This is not as impressive as the influenza A, but if you note the differences between the two placebo arms, that may explain that to some degree.

I'll move on to the next question which had to do with methacholine challenge, and I'll just briefly walk through what was done in this study.

F78. Methacholine is a cholinergic agonist. It acts directly on smooth muscle to stimulate bronchoconstriction. It's nebulized, and the PC20 is defined as a provocative concentration of methacholine that's associated with a 20 percent drop in the FEV1.

We took the opportunity to evaluate in

asthmatics. I would like to point out that this study was actually done prior to initiating phase II studies, so it was really our first assessment just to look at the safety to assure ourselves before we opened it up to patients with asthma.

13 adults were recruited. It was a double-blind, randomized, placebo-controlled, so each volunteer actually received both zanamivir and placebo. So, they were their own control. The study was powered to detect a difference in the ratio of the PC20 between zanamivir and placebo of fourfold in either direction.

As I said before, each individual was exposed to either the lactose placebo or zanamivir for two distinct periods. Each volunteer was supposed to receive 54 doses total, twice daily on the first day, four times for the rest of the period. The PC20, the methacholine challenge, was done on day 1 and day 14. So, the intent was to actually assess the effect of placebo, to assess the effect of zanamivir, and then to enable us to make a comparison between the lactose and the zanamivir.

This is the geometric means looking at both pre-study, as well as day 1 and day 14 after receiving the lactose, and you can see that the pre-study and the day 1 are fairly consistent. It does go up slightly on day 14. Keep in mind the higher the score, the less sensitive. The

higher the concentration.

Again these are means. For zanamivir, the numbers stay pretty consistent from pre-study, day 1, and day 14.

If you look at the ratio, it's fairly consistent on day 1 and day 14, with the zanamivir numbers being slightly lower.

So, in conclusion, inhalation of the placebo, lactose, had no significant effect. Zanamivir had no significant effect, and our conclusion was that this did not significantly increase or decrease airway reactivity compared with the placebo.

Now, there was one subject mentioned that had decreases in FEV1, and I'd just like to take just a second to summarize that patient's course during the study. At pre-study, this individual had a very low PC20 of a .05. In fact, we even questioned whether he should have been enrolled in the study. He was a 40-year old male. If you would note, wheezing was reported as an adverse event consistently throughout the two treatment periods, and actually during the placebo period, adverse events of cold, headaches, flu, and chest tightness were also reported.

Then I'll just leave you with the FEV1 graphic representation of what happened on day 1 and day 14.

A third question that came up right before

lunch was on pulmonary deposition. If you'll go to F12.

Gamma scintigraphy is a non-invasive imaging technique, which we took the advantage of to try to characterize the deposition of inhaled zanamivir into the respiratory tract. 12 adult volunteers received a 10 milligram dose blended in the lactose powder, and this was labeled with technetium. Images were then taken at the views you see here at the approximate times to be able to approximate the distribution into the various airways.

This is a graphic representation of the image. Anything colored basically represents where drug would have been distributed to. The more dense areas, the green, yellow that you see up there, that's the oral pharynx, and at the bottom that's the stomach. So, you can see the distribution is pretty thorough throughout the lung.

Overall, the median deposition was 12 percent and that ranged from 4 to 21. If you look at the specific regions, 0.5 milligrams or 5 percent of the administered dose was in the central lung region, whereas about 4 percent made it into the intermediate and the peripheral lung regions, respectively.

I'm not sure who I'm turning it over to.

DR. ELLIOTT: I'll try and be quick as well because I know we're running up on time. I'd like to go through four or five of the issues that have been raised in

the written and oral questions we took before lunch.

First of all, looking at this difference -- and of course, we looked in great detail at this -- between North America and the European studies that we've conducted to date. This slide is a little bit busy for numbers. There are three studies or pairs of studies here. The 2005 was the first large phase II study, which had sites both in the U.S. and Europe, slightly more recruitment in the U.S. The 2008 study likewise had two parts. It was a well recruited study and again slightly in the U.S. than Europe, and the two 3002 studies conducted in the same flu seasons, both sides of the water.

Really the column to focus on here on the far right-hand side is the difference in days, the positive effect for zanamivir. The first study, really the same .75 in U.S. and a day in Europe of positive benefit. The 2008 study, a day of benefit in both of these studies; and the U.S., as you've seen at length this morning, the A3002 study, a day of benefit; and the European study with a 2 and a half day benefit.

So, we conclude that although there is variability here between North America and Europe for some of the reasons we've talked about, that there's also a fair degree of consistency there. This is part of conducting studies across a number of respiratory seasons, actually

with increasing number of study sites to ensure that we get enrollment in the varieties of flu seasons that we see. So, that's just my one slide on that.

There has been questions about sensitivity analyses. Slide D24. These are the principal sensitivity analyses that we used. One was looking really at just a variation on the primary endpoint, getting to that point of alleviation but then also no use of concomitant relief medications. That was an endpoint the agency and we agreed to and interacted a lot at the end of phase II meetings to install in our phase III program.

The other one also is a censoring analysis of missing data for those patients with no evidence of alleviation, and again that was an analysis that came from discussions with the agency. Actually at the pre-NDA phase, it was an extra analysis we did for our phase III program.

I'll just show these very quickly. The first study is the Australian study, B3001, and maybe not surprisingly in a very positive study, if you stretch the data some, you still get positive outcomes: 2 days of positive benefit, a day and a half of positive benefit, significant to the statistical tests as predetermined.

Looking now at the U.S. study, here we have the alleviation with no use of relief medications. It didn't

quite reach statistical significance here and a three-quarter day benefit. If you look at that endpoint with censoring applied to it, you have a day and a half of benefit, which is significant, and also here at the bottom this is the overall sensitivity analysis for the primary endpoint of the flu-positive patients: a day of benefit still. But you can see that this reflects the curves for symptom alleviation is stretching out some. So, now you see a statistically significant p for that endpoint.

And finally, the European study, B3002, again the most significant of the studies all on the primary endpoint. Maybe there's no surprise, but likewise when you stretch the data some, you get significant p values with 2 and a half to 3 days on those sensitivity analyses.

And questions now about a uniform population. Let's go to A55 to start with.

DR. HAMMER: Could I ask if you could try to finish up in the next 3 to 5 minutes because we are running over?

DR. ELLIOTT: Okay. I'm just trying to think. Let's do this quickly then.

This is the slide presented in the main presentation, and these are uniformly defined populations. These are influenza-positive patients with the same endpoint predetermined, the 95 percent confidence intervals

applied to these. This doesn't state febrile in the top, although the vast majority of these patients and these patients were febrile.

If you go to slide B111, you see the analysis with febrile patients. That only really changes marginally the first study and the Australian study also moved slightly further away from the 0 time point and become more positive.

B76. Two or three people asked about compliance within these studies. This was assessed by the study staff by questioning the patients by looking at the diary cards and also looking at puncturing of blisters, putting these facts together to make an assessment of compliance. And actually return of the disks and the blisters was very good, although of course in any study some patients didn't return these, but the other two assessments were used to make this. As you can see, compliance was over the 90 percent rate across all of the studies, including the prophylaxis studies where people were taking drug for a month.

Let's talk about the ongoing studies. There were quite a few questions about what studies we have ongoing, what are we going to investigate. I'll talk about these very quickly as time is short.

We are looking at the nursing hc..e setting and

prophylaxis. This is a prevention study to try and prevent outbreaks in the nursing home. We have studies both in the U.S. and in Lithuania in Europe to address this. The U.S. study is comparing to rimantadine in outbreak control. The Lithuanian study is comparing to placebo. These studies are ongoing. We expect them to finish this season. The primary endpoint will look at attack rate in those patients in both groups.

We also are looking in the family setting for prophylaxis studies, and Dr. Hayden is an investigator in this study, again recruiting families preseason when they have an index case that looks like influenza, either treating the whole family with zanamivir as a preventative basis or treating them with placebo, and again looking at differential attack rates.

Of course, we're looking at asthma/COPD. We have a full-size 500 patient study underway to really tease out some of the differences and the positive effects we expect to see in this population. That's a treatment study, so come in with the symptoms of influenza, 5 days of therapy.

Of course, we're looking at children. We have a study looking at children from age 5 and above because all of our evidence from our respiratory colleagues suggest that children from about the age of 4 to 5 can use a

Diskhaler quite readily. So, we're doing a pediatric, again a treatment study, 5 days of therapy. The primary endpoints are somewhat similar to the adult treatment studies.

We have planned studies to start in the near future, in the next 6 to 12 months. We're looking at treatment of the elderly, obviously an important population. We'd like to expand that experience.

Other studies to look at the assessment of viral shedding, maybe collecting much more in the way of samples in the first few days.

We're looking at pediatrics under the age of 5, probably using the nebulized formulation.

And also, we're investigating appropriate studies to do in the HIV immunocompromised setting.

Underlying all of this program will be, of course, collection of samples for surveillance for resistance in addition to a more broad-based program with wider use of the drug.

There are a couple more things here, but I suspect time-wise I could probably stop there. And I'm seeing a nod, unless there's anything that needs to be answered.

DR. HAMMER: There may be a couple of other questions. Thank you very much for this organized response

to the questions done on such a quick, rapid basis.

I'd like to give a few minutes to the panel to ask additional questions that have not been sufficiently answered either this morning or with this response to the written questions. Dr. Bertino.

DR. BERTINO: Could you please tell us how many adolescents, 12 to 18, were in the studies, and also was there a difference in response and toxicity in that group versus the middle range and the elderly?

DR. ELLIOTT: Can we look at the efficacy by age, Patty? We're coming up.

I'll not try and remember the numbers. There were certainly more than 100 in the 12 to 18 category. Efficacy you'll see in a second or so.

Safety was actually the same from the youngest through the ages up to the elderly, the same pattern of general adverse events that you saw was repeated in each of the various different age cuts.

Here we have the people under the age of 18, and this would be from the phase III program. 139 subjects in the intent-to-treat population, 106 in the influenza-positive population, and you see the overall benefit over on the right-hand side there, reducing from 5 days down to 4 days.

I can move very quickly through the other age

subsets.

DR. BERTINO: Was that significant statistically?

DR. ELLIOTT: We didn't apply statistics to these subset analyses. There's always a temptation and I won't even try and guess it whether it was or not. We didn't apply multiple statistical analyses.

Let move forwards. This is the 18 to 34-year-old age cut. Again you see the same sort of degree of efficacy. This is the biggest group of patients, almost 700, with again about 70 percent flu-positive.

This will be the 35 to 50, intent-to-treat of 400 or so.

This is taking us up to 65-year-olds. Actually you see here there's an apparent difference, increasing, and actually a reasonable number of patients, more than 200 in the intent-to-treat.

And the over 65s. These are put down greater than 1.5 because you see the placebo is down as greater than 12.5. Again, a positive benefit in the elderly.

So, that's a quick run-through. As I said, the safety really does show no difference in these age categories.

DR. HAMMER: Dr. Wittes?

DR. WITTES: I have a series of questions and

some of them are really follow-ups to what I had written down. Can I run through them?

DR. HAMMER: Please.

DR. WITTES: I've been trying to sort of disentangle and understand some of the numbers, and I've been having a hard time. So, for example, one of the questions I had asked was the method used to calculate the confidence limits for the difference in days because they're asymmetric. I assume that's because they're from medians. But what surprises me is that the direction of the asymmetry is different in them. So, I just wanted to make sure I understood.

DR. ELLIOTT: Okay. Oliver, why don't you come up? You can put A55 up.

DR. KEENE: Oliver Keene, Glaxo Wellcome.

You're asking about why the confidence intervals were asymmetric.

DR. WITTES: Why they're asymmetric and specifically why they're asymmetric in opposite ways.

DR. KEENE: It's true if you use the parametric procedure to derive confidence intervals, you'll get symmetric confidence intervals, and that's most often used in clinical trials. These ones were actually derived non-parametrically using bootstrap methods, and therefore, if you use a non-parametric approach to getting confidence

intervals, it's entirely possible to get asymmetric intervals. Sometimes these will go in one direction, and sometimes these will go in the other direction.

DR. WITTES: When they're going in opposite ways, it's suggesting that the skewness in the two distributions are really quite different. The relevance here, it seems to me, is that we're talking about trying to estimate the effect in a population. So, one wants to know not only that point estimate, but one wants to get a good sense of the range or at least the center of the range. So, it surprised me to see the different nature of the asymmetries.

DR. KEENE: Okay. You're asking about the nature of the asymmetries. The other thing to remember is we measured time to alleviation in half-days. So, clearly it will tend to jump somewhat because you go from 1 and a half days to 2 days. So, you do get a jump. It's being measured in half-a-day intervals.

DR. WITTES: Let me ask two more questions because I know that time is of the essence.

In slide 44, what was striking and was stressed in the morning was the effect in the febrile IP group. That makes sense. What I asked whether we could see is, for the 3002 studies, the same group.

DR. KEENE: So, you're asking about the febrile

influenza --

DR. WITTES: The febrile, yes.

DR. KEENE: In the A3002 and B3002 studies.

DR. WITTES: That's right. Are you seeing the same kind of result there?

DR. KEENE: With those particular studies, it was actually an entry criteria to begin with.

DR. WITTES: Oh, okay.

DR. KEENE: But we did actually take out the few patients who were afebrile at entry and thus such in the briefing document. We don't have a slide for that, but it's in the briefing document. The actual effect size is similar because there were so few of those patients. The effect size is the same and the p value is very similar, both for A3002 and for B3002.

DR. WITTES: Okay, thanks. I missed that.

Then finally, some of the tables, as I understood the analyses, had aggregated over all the studies, and I couldn't tell whether the differences and the p values and so forth that you were presenting were simply all the data sort of lumped together and taking an analysis or whether the analysis reflected the studies as strata.

DR. KEENE: Yes. You're asking about whether we did a stratified analysis when we put together the three

phase III studies.

DR. WITTES: That's right.

DR. KEENE: In terms of the time to alleviation, yes, that was again a non-parametric analysis, Wilcoxon test, but it was actually stratified by each of the studies separately.

DR. WITTES: Was that the approach you took in general?

DR. KEENE: Yes. When there was a p value for the time to alleviation, yes, that was a stratified analysis.

DR. WITTES: And if there's just a difference in days, is that a stratified or a non-stratified?

DR. KEENE: No. It's a non-stratified. So, the actual summary statistics reflects putting all the data together. When there was a p value, it was a stratified analysis.

DR. WITTES: Okay. I'll ask one more. The sensitivity analysis. When I asked for sensitivity analysis, I meant a kind of a range. There are, depending on how you calculate it, it seems like 4 to 10 percent of people who didn't finish the follow-up, and they didn't finish over various times. It seems to me we have two analyses, one which is the analysis in the study and the other which is the analysis that assumes censoring. But

did you do a range of assumptions about what might have happened to those people who didn't finish the 14 days, or is that the only two analyses?

DR. KEENE: Yes. There are 28 days in the A3002/B3002 study, so it's somewhat longer in those.

Yes, I think my feeling was that that was the sort of range of possibilities. On the one hand, if people are not alleviated, you put them -- people have a missing time for non-alleviation. You put them as not alleviated by the end of the study. The other extreme is to censor them that they're non-alleviated at entry. So, that kind of gives you a range.

DR. WITTES: But that doesn't look at the entire range of assumptions. That's a quite restricted range.

DR. KEENE: Well, those are the two analyses that we performed.

DR. WITTES: Okay, thanks.

DR. HAMMER: Dr. Kilbourne.

DR. KILBOURNE: When we're looking at an antiviral drug, I think it's reasonable to expect an exhibition of antiviral effects. I am a little disturbed by the reliance so extensively on PCR as rather an untried method quantitatively in assessing positivity or negativity with reference to influenza. Could you tell us a little

bit more about that in terms of whether there's any attempt to quantify that and also to recognize that that's measuring not only infective virus but non-infective virus that remains on the site?

DR. ELLIOTT: Of course. I'll make a general comment while we find the slide.

We used PCR as a technique in the last two studies, the U.S. and the European study. Across all of the studies, we used culture and serologies as the baseline, if you will. What we found was that the flu positivity, if you just take culture and HI, was of the order of 68 to 78 percent across all the studies. What we did in the U.S. study, we added an extra about 8 percent to that by using PCR. So, the core of the flu-positive patients, the vast majority, was by culture and HI. We added a small percentage by PCR.

Actually, what we found was by removing that 8 or so percent who were PCR positive, the statistics just went the right side of the 5 percent level, and so it's actually the culture and HI flu-positive population, ignoring PCR, that showed a day of benefit which was statistically significant. So, it seemed the PCR didn't add either a particularly positive or negative effect to that.

So, to your point really, the analyses stand up

on culture and HI. We have PCR adding on a few patients but not really changing the analysis substantially either way.

We still would support our PCR. It was done by Maria Zambon at PHLS. We're entirely comfortable with the technique. We accept it's a newer technique and not generally available certainly in the regular setting, but we don't have any issues with the technique. But still we can pull the studies out and say by culture and HI, and the results still stand there.

Does that answer the question?

DR. KILBOURNE: Yes, it does.

DR. HAMMER: But let me just qualify. You really didn't use PCR as a quantitative measure over time. You just used it as a diagnostic in these studies.

DR. ELLIOTT: It was a plus/minus. Yes, absolutely.

DR. HAMMER: Dr. Yogev.

DR. YOGEV: I was asking before, data for when the patient enrolled in time of symptoms, how many having symptoms for 12 hours, how many for 24. A couple of presenters suggested there was later enrollment in the North American study versus the European. I just wonder if we can get if that was statistically significant because maybe that's where the issue might be.

DR. ELLIOTT: Can we look at the time to enrollment slide that has the phase II and the phase III studies on it?

Hopefully on this slide we'll show that actually we managed to segment our U.S. patients into less than 36 hours or more than 36 hours, remembering that the window for this was 2 days. What we actually found was that the majority of patients did come in -- and this is the flu-positive population -- in less than 36 hours, only a small number after 36 hours. Maybe not surprising, the degree of effect when you treat earlier is more than when you treat later, and that's entirely consistent with the course of influenza.

DR. YOGEV: Do you have the same data for the so-called successful studies, the European and Australian? Were they less than 24, the majority?

DR. ELLIOTT: The European study we didn't segment by this time frame. Everyone was in within 24 hours. What we get anecdotally was that the majority were in the second day and probably in the early part of the second day. So, I suspect it will be similar to the U.S. study, but we don't have the numbers.

In the Australian study, time to entry was 36 hours, so no one came in after 36 hours. We had more in the 0 to 24 than the 24 to 36, but actually no difference

in effect within that.

So, the data suggest what we had all guessed, that the greater effect is by treating earlier, but we do see a positive effect still out to 2 days in the studies.

DR. HAMMER: Thank you very much. I think we'll close this section.

We're going to move on to the questions to the committee, but I think before we do that, we'll take a 5 to 10-minute max stretch break, and then the committee will deliberate.

(Recess.)

DR. HAMMER: I'd like to reconvene the afternoon session. We're entering the last part of the agenda. This is where the committee discusses the questions that have been put before the committee by the agency.

The first question is a voting question, and first let me list for the record the voting panelists. They are Drs. Diaz, El-Sadr, Masur, Hamilton, Wong, Yogev, Li, Stoller, Hendeles, Stanley, Bertino, Cox, Wittes, Verter, Kilbourne, Poland, and me.

The first question is the voting question. What I'm going to do is first go around the table and give each member a chance to comment on the question, and then after everyone has had a chance to comment on the question,

I will call for the vote.

I will read the question for the record. Number 1, does the information presented by the applicant support the safety and effectiveness of zanamivir for treatment of influenza? If no, what additional studies are needed? If yes, we have several other questions we've been asked to address.

I'd like to begin on my left side with our expert consultants. Dr. Poland, would you please take the first question, or would you like Dr. Kilbourne to take the first question?

(Laughter.)

DR. HAMMER: He's swallowing and we don't want aspiration pneumonia as part of the afternoon's events.

(Laughter.)

DR. KILBOURNE: You didn't ask me whether I'd like to take the first question.

DR. HAMMER: Pardon, but it's the prerogative of the chair. I'm sorry.

DR. KILBOURNE: Okay.

I feel that we have here something that shows promise and it shows promise particularly at the level of the phase II trials. The theory I think is quite elegant as a targeted, deliberately designed drug that goes right to the active site. So, I wish I could answer in the

affirmative about whether it should be approved for use right now. That's not the question exactly, but I think certainly further work has to be done.

I think this issue of the site differences is a very important one. It may have something to do with cultural differences. It probably does not have anything to do with viral severity in Europe versus here, and I conferred with Nancy about that in terms of similar strains circulating at that time. So, I think that's out of the equation as being a reasonable possibility. Particularly with the evidence of so few resistant variants emerging, I don't think it's likely that there was a resistant variant circulating here but not over there. So, it seems to me a number of further studies have to be done.

I still remain not completely satisfied with the answer about the level of replication of virus in these populations. I think this is an important determinant and particularly might bear on the question that came up about rebound which I think might actually be on the side of zanamivir, as you were indicating. What you'd like to know is whether there's a concomitant increase in virus at the time the headache comes back, and I think unless you get really quantitative virology -- my own understanding is -- and I can be corrected on this by those initiating the study -- that the quantitative virology was mainly done

with phase II and not necessarily phase III. That is true where we're talking about in addition to PCR and really mainly you're talking about actual isolation of virus. But I believe that's non-quantitative. I think that that was simply at a single dilution. So, that tells you the presence of infective virus or not.

I also would like to see evidence that the PCR, if that's going to be used as a determinant or an easy determinant, that it be shown that it is correlated well with the presence of infective virus and not also the presence of inactivated virus. Here the proponents of the study might help themselves because actually if you are measuring essentially dead virus, then you might show an advantage of zanamivir which has not been shown.

So, that's my initial reaction.

DR. HAMMER: Dr. Poland.

DR. POLAND: The chair may or may not want to do this, but in my own mind I would divide the question and ask first are there safety concerns.

DR. HAMMER: It really is a two-part question. You can and should comment on safety and effectiveness.

DR. POLAND: In my own mind, I don't have any substantive safety concerns at all.

When it gets to effectiveness, I suspect that's where we're all feeling a bit of a tug here. To use a

baseball analogy, since those of us from Minnesota no longer use football analogies --

(Laughter.)

DR. POLAND: -- this is maybe a base hit, but it's not a home run. I think that's probably where many of us come down on the side of this, saying that there are two studies that followed a prescribed protocol that show some degree of efficacy, but there is this problem with a larger study that failed to show efficacy. So, I really feel quite divided about this in terms of efficacy. I've not clearly made up my mind yet.

DR. HAMMER: Thank you.

Dr. Cox.

DR. COX: Thank you.

I think that I don't really have substantial concerns about the safety of zanamivir. I think that the studies have shown that the compound is quite safe.

I think that I would agree with Dr. Kilbourne in saying that the development of this particular compound is a very elegant approach and very impressive. I think that when one looks at the positive effect for the individual, it isn't so striking, particularly in the North American study, but even in the European study, the positive effect on the individual isn't as striking as one would really like.

I think that from a public health point of view what would be extremely useful is to understand whether treatment really reduced shedding of virus and therefore the number of additional individuals who were infected by the treated person. So, family studies would be particularly important in looking at this question because if there is a positive benefit for society by treating people who are shedding, that would be very important to determine.

DR. HAMMER: Thank you.

Dr. Hendeles.

DR. HAMILTON: First of all, I think there are no safety concerns that I have. The data for the asthma patients I think are sufficient for me not to have concern about it directly increasing airway reactivity. The PC20 for methacholine was very low. It was about .5 milligrams per milliliter which is associated with rather moderate asthma, and in other studies that we've done with drugs like propafenone, an anti-arrhythmic that has very weak beta blocking activity, you can change the airway reactivity to methacholine even though the FEV1 stays constant. So, I think that's a marker of whether a drug has increased risk. My gut level is that's not a problem.

I think the Diskhaler is a device that is more difficult or more complex than the metered dose inhaler in

some respects, but I think you have to take into account that all controlled studies show that all forms of inhaled devices are problematic for patients to use unless they get first-hand instruction, and even then with the MDI, the patients return to a second visit and still aren't using it correctly. So, I think any inhaled device has its problems.

My impression of the Diskhaler is that with adequate instruction -- and I don't think written instructions will do it. I think if either a doctor shows the patient how to use it or a pharmacist shows the patient or family member, then I think for sure they'd be able to use it successfully over the time period.

The last question relates to efficacy, and while I appreciate that every attempt was made to identify the endpoints, my impression of the data, especially from the North American study, is that there isn't sufficient efficacy to warrant me recommending this drug for my family or myself.

I recognize that it did show some efficacy in the other studies, but I can't help but feeling that the differences between Europe and the North American study might have some sociological implications. Certainly it's not study design, but there must be something sociologic. There's a signal there telling us that something is

different, and that's the population that we're concerned with here today, the U.S. population. I think there's something different. I was hoping to come here today and learn something substantial, like the use of acetaminophen was the difference, but quite frankly looking at how the FDA statistician presented the data, I just don't think it has sufficient effectiveness.

DR. HAMMER: Thank you.

Dr. Stoller.

DR. STOLLER: I share the other members' enthusiasm for the concept of the drug and its design, and I applaud the magnitude of the studies.

My reservations regard two issues: the robustness of the data with regard not only to site, but also to the ability to evaluate the outcome measures, admitting that these were pre-agreed at the outset. But the apparent non-robustness, when one cuts and slices it with different primary outcomes -- I think that further perhaps secondary analyses or additional analyses of that, with time-to-event issues -- needs to be considered.

My other concern with regard to the data presented has to do with the non-generalizability to the population in which perhaps the concern is greatest. We've heard some cautions about not using the word "rebound" with impunity, and I would urge not using the concept of high

risk impunity. I don't regard the populations that have been labeled as high-risk in these studies to be the kinds of high-risk patients that most of us who are practicing clinicians would be interested in seeing efficacy in. So, I'm not indicting any data shown. I'm just recognizing that there's little that would guide me in my practice of primarily elderly patients or patients with chronic lung diseases beyond relatively mild asthma requiring perhaps a beta agonist only.

So, my reservations have to do with the difference between efficacy in a constrained population and effectiveness as it might be used, and I reserve judgment about whether that has been demonstrated at this point.

DR. HAMMER: Thank you.

Dr. Li?

DR. LI: I have some thoughts about safety and effectiveness both.

I don't have major concerns about safety, and in fact I'm looking forward to seeing the results of the study of using the drug in patients with asthma because influenza and influenza A is a major cause of exacerbations. I think we will get some important safety information there. We do know there are a variety of types of inhalers. Metered dose inhalers or powders can cause a paradoxical bronchospasm. I'm somewhat reassured that

there was not an observed increase in asthma attacks, but I think as the larger populations with asthma are studied, we'll learn more about that. I'm actually looking forward to seeing what those show.

I do actually have a number of patients using Diskhalers of various sorts. It's really an excellent delivery device, but it does take instruction. I almost assume that it's going to take more than one visit. I give patients my best shot or the nurses do some teaching the first time around, but we know that it usually takes until at least the second visit, be it two weeks or a month later, for any kind of inhaler to really get the proper use.

So, as it pertains to generalizability, there's a chance that the drug might work, in fact, less well when it's out in practice as compared in the study. When we evaluate these studies for potential approvability, you never know whether the drug is actually going to work better in normal practice than it does in the studies or work perhaps less well. One of my concerns is that this drug might work even less well in practice than what we've been able to see in the clinical studies.

So, that just brings me to the last point about effectiveness. As I look through the background information, the way the study was designed, at least the

North American study, it was powered and powered appropriately to detect a 1 and a half day difference among treatment groups. The study in fact was overpowered because of increased enrollments.

As I look through basically the main efficacy variable which is in the intent-to-treat population, with the North American study, there's a one-half day difference between the two groups, which essentially is not significant. So, granted in the influenza-positive group there was a 1 day difference, but in the intent-to-treat population, which again I think reflects better the actual practice situation should this drug be approved, the intent-to-treat group difference was only a half a day. So, I see the North American study as being essentially a negative study.

DR. HAMMER: Thank you.

Dr. Stanley.

DR. STANLEY: Thank you.

I really have minimal safety concerns. I share some of the concerns of Dr. Li, that I'd like to see a little more in asthmatics and maybe COPDers, but I think the safety is pretty clear.

Effectiveness. It depends on how you define that. The phase II studies would seem to show some antiviral effectiveness when you look at the virology,

although I bow to the concerns of the virologists on the committee.

But clinical effectiveness, I'm really unconvinced. The discrepancy in the studies is one concern, and particularly with the North American study being the population we care about that showed no significant effect to me, but also the FDA's analysis on looking at the activity score. Even in what was called a successful European trial where there was a 2 and half day improvement in reaching endpoint, the activity scores between the placebo and treated patients really weren't significantly different, which is telling me that as far as getting people back to work and really making them on the whole feel better, I don't think we're seeing much of an effect. If I take that minimal effect and now translate it to the real world and to real practice, I agree with Dr. Li, I think we're going to see even less effect because you're not going to have as many true influenza-positives.

I think the use of the Diskhaler is very troublesome because you don't have time for a learning curve. If you don't start treatment early, you're going to be even less effective and you don't have the learning curve to take three and four doses before you're doing it right.

So, I have significant concerns, and I don't

believe they've shown adequate efficacy.

DR. HAMMER: Thank you.

Dr. Hamilton.

DR. HAMILTON: Unless my colleagues to my right change my mind in the course of their discussion, I intend to support the licensure application for safety and for efficacy from this submission. Why am I doing that?

It's not because all the answers are in. They certainly are not in. However, I think they've met some critical guidelines. They've lived up to some guidelines that were established rather early on in the course of their research, as arguable as they may be.

I'm coming down on the side that at this moment just in a general descriptive sense, the time to endpoint that they've outlined doesn't adequately reflect to me what the issue is. I think there is disease beyond that 3.5 or 4.5 days. I don't choose to call it rebound. I call it continuing disease, continuing misery that will not be accounted for, will not be reversed by this drug regimen.

Nonetheless, I think in two studies that were credibly designed and followed prospectively and analyzed in depth, notwithstanding the points made by several members of the committee that it was only part of the story, I believe they've demonstrated sufficient efficacy to support their application.

I look forward to the discussions of my colleagues to my right.

DR. HAMMER: Thank you.

Dr. Wong.

DR. WONG: I want to divide the question.

I think on safety I have no major concerns.

On effectiveness, I'm actually convinced that this drug has significant in vivo antiviral activity, but I'm not convinced that the applicant has demonstrated clinically relevant benefits of treatment as the treatment was administered in these studies.

I think that one possible explanation is that we may not really know how best to use this drug at present. People have mentioned that the means of administration, the dose, the duration of therapy may or may not be optimal.

But secondly, I had a great deal of trouble with the way the data were presented in that the bulk of the efficacy data were presented simply as median values and then a p value was cited. When I asked specifically to see some time-to-event curves, we didn't get to see them. So, I think that this form of presentation of the data, which I think is very abbreviated, might have been convincing had all the studies given the same result and a major effect. In the presence of seeing conflicting data,

I can't really conclude that clinically relevant efficacy has been demonstrated.

DR. HAMMER: Thank you.

Dr. Yogev.

DR. YOGEV: I join my colleague to the left in being a little bit upset about the presentation. I think things were omitted which might make the difference on what we're seeing.

There is no question that in the phase that you showed antiviral therapy, it's there, but interestingly enough, when you compare your own data, the inhalation versus the intranasal inhalation to the placebo, it almost looked the same in the group who is longer without the intranasal. So, inhaled and placebo go within 3 days to less than 1 log.

So, I think that the data presentation -- the adolescent being as part of it was 106. Probably around only 50 of them received the drug -- to suggest that it's okay from 12, I have a problem.

Also I have a problem with I don't think the European study is the same as the American study, at least from what I was able to get from you. The time of initiation of therapy seemed to be different, and in my opinion it's a major problem with the whole way the study was done because all of us agree the earlier, the better.

Your own data suggested the day 3 viral load is coming down even in the placebo group by itself. One wants to see a much stricter initiation of the drug from the time of symptoms. That might be the whole difference between what we see in Europe and in North America.

So, I don't talk about the safety at all because I think it's there, and everybody said the same.

I for one think if you break your data down, subpopulation, for example, older than 65, you have some efficacy over there, but you don't have enough of a number. So, I would like to agree with Dr. Hamilton that there is something there. I just think these studies were not done correctly to prove it. The major study, if we accept the result, we have to go that it's a negative study. Therefore, at this stage I don't think I would support that we saw any efficacy of treatment in the way we're going to do it in real life.

DR. HAMMER: Thank you.

Dr. Diaz.

DR. DIAZ: I likewise will break down the question.

Very simply, I don't have any concerns about the safety of the drug.

Actually with that in mind and with the knowledge of the novelness of this drug and the fact that

it is effective or at least in vitro it's effective against influenza A and B, I would be very anxious and excited to have a drug of such caliber if clinical efficacy was well documented because it would certainly allay a lot of issues that we have in the treatment of influenza currently.

My concerns really fall along the lines of many of the concerns that have been issued here today by my colleagues, in particular, the dichotomy of the phase III studies based on the location that those studies were in, and in particular, the lack of predictiveness of the overseas studies to the North American study. I think we heard the FDA representative comment that we can certainly accept overseas studies for licensure if they are in some way predictive. Unfortunately, in this setting, we don't have that predictiveness and have a very large or at least a larger study in North America that shows quite the opposite.

Although the prescribed protocol was followed and some endpoints were met, I too have concerns about whether we've satisfied clinical efficacy to a degree that is necessary. A lot of people today have shown, both from the sponsor and from the FDA's standpoint, a lot of very retrospective pouring over the data to try and sort out just what the problem or the differences were in that North American study compared to the other two studies. The

answer unfortunately wasn't forthcoming. It may be a very simple answer, and if we only had it, it might explain things, but unfortunately we don't have the answer.

Retrospectively I think it may have been helpful to have had more information, very specific information, about things such as exact time to enrollment, the way the drug was taken, maybe issues about how many times a day temperatures were taken, and a lot of very, very detailed information that we frequently don't like to obtain because of the barriers that it puts on the person entering into the study. Yet, in this setting it may have been helpful.

But likewise, Dr. Cox' comments I also would laud in terms of it will be, hopefully in the future, very important to know about issues surrounding this drug's ability to decrease transmission in particular, and I think some of the family studies may be helpful.

But at this point in time I have concerns that we haven't really gotten to the point of full efficacy documentation.

DR. HAMMER: Thank you.

Dr. Masur?

DR. MASUR: Well, I'm impressed at the entire package of the drug discovery program and the drug development, and I'm impressed that the studies were

developed in a very logical way, given the fact that this is a very difficult disease to study with a short natural history.

I share everyone's surprise that the 3002 study did not confirm the efficacy of the other two studies. It's not clear, based on the phase I and phase II data, as to why that is. The various speculations have already been reviewed. So, I can only mirror what has been said by several of the people before, that this is a very difficult package to use to be convinced that there is in fact meaningful efficacy in North America for whatever reason. I guess that's the dilemma that we're facing as to whether or not enough data can be teased out to convince one that there's effectiveness.

DR. HAMMER: Thank you.

Dr. El-Sadr.

DR. EL-SADR: I'll comment first on safety. I really would like to see more data in asthmatics because I think that's going to be a group that probably a medication like this would be used for.

I think another concern I have is development of resistance. I feel that resistance is part of the safety profile or I consider it as a component of safety. I'm not sure that in the population in which this drug was studied that I would have expected that resistance would be

seen. Probably in an immune suppressed population, maybe a more fragile population, that's the situation where you have more replication of virus and a longer course, and maybe that's where we would expect or where we would be likely to see some resistance developing. So, I'm not satisfied yet that resistance is not an issue, and I feel that studies, especially studies in immune suppressed populations or high-risk populations, should really look very carefully at the development of resistance. So, that's still a concern I have before sort of saying that this is a safe drug.

Now, going to effectiveness or efficacy, I'm sitting here going through the sponsor's book actually and looking at the North American study, and whichever endpoint I look at, whether it be the time to alleviation of symptoms, whether we're looking at the influenza-positive group, or whether we're looking at the ones with baseline temperature again in the North American study, or whether we're looking at the development of complications or even one of the other endpoints, time to return to normal activity, in none of these endpoints -- none of them -- is there any evidence of a statistically significant difference between the placebo and the drug.

I have to say that when I'm presented with two pivotal studies, one has 700 patients and the other one is

much smaller, I consider that the study that I would put the most weight on. I think we've been sitting here trying to think why didn't this drug work in North America. I feel we should be asking why did it work in Europe because maybe this is the gold standard.

I don't know whether saying there are cultural differences can really help in explaining what goes on here versus in Europe because we're really looking between the arms of the studies. We're trying to look at a difference between the placebo and the control, and it was clear from the data that the sponsor presented and the FDA presented that even though there was more use of these agents to alleviate symptoms, there was no difference in the use between the two arms.

So, I feel that the larger study that was conducted in North America did not demonstrate efficacy in any of the endpoints that I mentioned here, and there are more that I didn't mention. Thus, I feel that the package, as it is, does not demonstrate efficacy of this drug.

DR. HAMMER: Thank you.

Dr. Verter?

DR. VERTER: Yes. From what I heard today, I guess I would concur that I don't have any serious problems with the safety question, although I'd like to make note. I believe it was Dr. Styrt that mentioned the possibility

of -- I think what she was saying was -- and I believe it -- potentially underestimating the adverse event comparisons because of the delivery system, that it may be actually masking the difference. And if you were just out there giving this drug with a true delivery system for a control, you might see that those were increased a bit, but that's a minor point perhaps.

I was a little disappointed -- I will concur with someone down on my left here -- about the presentation. First, when I read the book that was given to us, it seemed to me there were really five studies that could speak to this issue. I know the FDA said three and then I think Glaxo presented one of these phase II studies, but there was another phase II study. It's true that some of those phase II studies had three arms rather than two, but they did have two arms which were relevant to what we were speaking of.

It seems to me if you're going to give an overview of a series of trials that speak to an issue, that somehow you should be able to present all of them in a manner either in the book or for the committee where we could evaluate all these in a similar manner. That goes to things like overall intention to treat for the same primary outcome, overall subgroup analyses such as the positive for influenza, the ones who were febrile was another issue, the

timing of it, less than or greater than 30 hours or whatever. I think that would have helped perhaps in focusing on what groups there were that there may have been efficacy consistently across the trials. It may or may not have. I don't know since I don't have all the data, although I tried to tease it apart. It may or may not have strengthened some of your arguments.

Let me speak to the issue of the difference between the trials. Whereas it's true that two of the studies used the same protocol and all three studies appeared to be well designed, well run, and well conducted, there are some noticeable differences that I saw.

For example, comparing the European study and the North American study, the placebo group in the European study had a median of 1 and a half days longer in the course of the disease, which would suggest that there's more room to play in reducing the median. It was 7 and a half versus 6. That may or may not play into it.

If you look at the zanamivir across the trials, the median time to alleviation is quite similar across the studies. So, a lot of this may be the underlying disease, the etiology of it, the course of it, the environment in which it's being studied.

Speaking to that latter issue, the other thing which to me is almost pointing me in a direction is the

relationship between the use of acetaminophen and the cough syrup, the percentage use versus the delta median. It's almost a linear relationship. I agree with the FDA presenter, Dr. Elashoff, that this is a very difficult issue. These folks are taking it probably in response to the symptoms. They may be taking it because they think it will alleviate the symptoms, and teasing it apart is probably impossible, although I have some thoughts about things we could play with and maybe give you a hint. But it's possible that the answer to that question is that in North America, you have to tell people to stop taking acetaminophen and cough syrup and maybe you'll see the effect.

I think I'll stop there.

DR. HAMMER: Thank you.

Dr. Wittes?

DR. WITTES: Well, I don't have much to add to what everybody has said.

As far as safety, I respect my clinical colleagues' judgment about that.

As far as efficacy or effectiveness, I think the problem that we're facing -- and it was expressed by Dr. Wong -- is that when one sees marginal results in the study that should have been the pivotal study, the most important study, it's really crucial to present the data in

a way that's really clear and really covers all the questions that reasonable people could ask. For me this was one of the problems both in the presentation in the book and in the presentation today and in the responses to questions. So, if you analyze the data and look at it in a way that tries to tease out what was there about the North American study that was different from the others, or as you had said, why are the others different from the North American one, perhaps you could have given us more insight as to what was going on.

The other issue that concerns me -- and it was addressed by a few around the table -- is that when this goes into practice, when this goes into the public, it's very unlikely that the very high rate of flu that you had in this study will be replicated. So, therefore, what one would hope to see a larger effect -- that the magnitude of the effect in the group with flu in the study one would hope would have been larger so that there would be in the intent-to-treat population in the real world, there would actually be some effectiveness.

DR. HAMMER: Thank you.

Dr. Bertino?

DR. BERTINO: In terms of the safety issues, I think that I could be convinced that this is a safe agent in relatively healthy individuals, but I think that the

people with asthma, COPD, comorbid conditions, where influenza may have a very large impact, those are the people where we really need to see safety data in.

This really spills that into the efficacy question. A couple of things come to mind. First of all, I want to raise a question that Dr. Hendeles raised this morning back to the FDA and maybe they could answer it at the end of my comment, which is the two foreign studies that show efficacy of a drug, is that enough to approve a drug? So, I'll just leave that out there for a minute.

What I'm thinking is that out in the real world, it's a Friday night, somebody is not feeling too well, how are they going to get this drug? Or you have a nursing home population where all of a sudden you have an influenza outbreak and you've got 185 residents, most of whom who cannot or will not cooperate with inhaling an agent like this.

So, I think that in the populations in those two foreign studies, efficacy in my mind was shown. I think in the age breakdown data that we saw this afternoon, I'm more convinced that efficacy in ages 50 and greater was shown. To me a half a day difference in symptomatology or feeling lousy or something like that, even if it was statistically significant, I'm not sure that it's clinically significant for most people.

So, that's my comments on it.

DR. HAMMER: Thank you.

Does the agency want to respond?

DR. BIRNKRANT: I'll begin the agency response, in case others want to follow.

In general, we look at the totality of the data. We've used that phrase many times. We have three phase III trials, and we have two phase II trials, and we have other supporting data. So, we look at the entire package. So, that comprises not only phase I, II, and III trials, but it also comprises, if you break it down a different way, foreign studies and domestic studies. So, we look at the whole package. We don't necessarily put more weight on foreign versus domestic, domestic versus foreign. We look at the total picture as we evaluate the marketing application.

DR. HAMMER: I think that response answers it. Dr. Jolson, do you have anything to add?

DR. JOLSON: Just another point that I'd make --- and I think everyone's points are really well taken -- is that some of the issues that have been raised are labeling issues in terms of how to use it, who should use it, how to diagnose influenza, things that are really separate from an efficacy determination. That gets a little bit into the intent-to-treat versus the influenza-

positive treatment effect. That gets to the issue of how to counsel a patient or how to decide on which patients might be likely to benefit from it.

The question to you all would be is there data that would help guide those choices, then assuming that the label would capture some of those issues.

DR. HAMMER: Thank you.

I'll be the last one to comment on the first question.

I'll take a step back. Personally I think we have to really think about the disease under study. This is a self-limited disease for the most part in healthy individuals, although we're, as clinicians, most concerned about the immunocompromised and high-risk populations that have been described. But if you think about it from a clinical trials perspective, a self-limited illness in a mostly healthy population, we have to think about how difficult those studies are to perform, what differences you're really looking for that will be statistically significant and clinically significant in a disease, for the most part, that people get better from in 4 to 5 days, even though some symptoms may linger, and also where endpoints that one is discussing, except for temperature, are soft. Coming from the HIV experience, which this committee has had a lot of past history with, we know the

difficulty in interpreting soft and clinical types of endpoints, and these are among the softest and most objective, but what else is there when they in fact define the disease?

In thinking about the data package that we've seen, I respectfully disagree a little bit with some of my colleagues. I think the package that was put together for us to review was complete from basic science through the clinical trials, and this morning's presentation I think mirrored the backgrounder that we were given, and there was a very good attempt to answer our questions in a very slide-driven presentation this afternoon, which is a testimony to technology. I imagine some of those slides were made during the lunch hour.

I think from the experience on this committee, it's not uncommon to see differences in the FDA analysis, or at least new angles from the FDA analysis, that heighten our questions and sharpen our focus. It's also the function of the panelists to sharpen the focus and ask questions that haven't been directly answered in the initial presentation.

What I see on the safety side is really not an issue. I think everyone thinks about whether the lactose carrier will have some negative effects, but there's really nothing one can tease out from how these studies were done

to say that. Again, I agree that there were no safety issues presented.

On the efficacy side, I don't think personally we can discount -- we have three pivotal trials that we've been presented with and again two other phase II trials and other supporting data. To toss out two of three trials that show significant effects and are well done trials I find difficulty with. Even though they were smaller and less well powered than the major study, I think we've been given some guidance that geography alone should not guide our decision about which studies to think about. We should take each one on its merits.

I personally also think -- and this may be coming from the HIV perspective -- international studies and doing more international cooperative studies is a plus.

Thinking about the North American study, obviously we all would have liked to have seen a more clear-cut result, but I look at it from where the two presentations have consensus here as far as the sponsor and the FDA. If you look at the intent-to-treat population that was influenza-positive, it wasn't significant, but a .078 p value to a nonstatistician at least is a trend when we've got statistical significance in the other studies. I may be incurring the wrath of some around here, but at least to me that's supportive when you've done two other

studies that show significance.

I'm also impressed by the point estimate graph. It was slide A55. At least the point estimates were trending all on the same side of 0.

So, at least to me I think two studies show efficacy. One does not. Is that strong enough to negate those two studies? I think I've expressed that for me it's not the case.

I think we also have to recognize that oftentimes -- it's probably true more frequently than not -- that the first agent in a class is not the ultimate drug, and that there's importance, if one can see it from a safety side and an efficacy side, to approve a drug both for the population at risk and to promote further studies both by this sponsor and by other sponsors.

The issue about where this drug will be used as far as the general population that does or does not have influenza, approval of such a drug will drive the diagnostics such that rapid diagnostics for influenza in physician's offices will become I think something we'll see fairly soon.

So, those are my comments on safety and efficacy.

Before we move to the formal vote, are there any other comments on question 1 by the panel?

(No response.)

DR. HAMMER: Okay. If not, then it's time -- Dr. Jolson?

DR. JOLSON: Just a last issue, just to touch on the issue that you raise, Scott, about self-limited, acute illness that everyone is going to get better in a couple days, the difficulties of the clinical trial design. Would it be of any benefit just to spend a few minutes to discuss the evidence that supported the approval and some of the pitfalls of the two approved influenza agents, if that would provide any additional context? That's one issue that hasn't been discussed today.

DR. HAMMER: I would ask my colleagues whether they would like to hear that and discuss that. I think most of us are aware that the differences that were seen in other studies of influenza, amantadine and more recently with rimantadine, the differences, although significant, were small. The patient numbers were small compared to the package we're seeing today. Those drugs have limited use in practice for the treatment of influenza, greater use for prophylaxis, but still they are approved for this indication with differences that are fairly small. And I think we see those differences in experimental challenge studies of anti-influenza agents, as well as in the efficacy trials we've seen.

I don't know if others want to comment. I think probably the best person in the room to talk about this is not me but it's Dr. Hayden, if he wishes to comment.

DR. HAYDEN: I would comment that there is a long history of variation in terms of the study results when amantadine and rimantadine have been tested for both prophylaxis and efficacy. Some of this relates to differences in strain and severity of illness, but more often it's timing issues in terms of, for treatment, clearly the earlier, the better, and I think we're probably seeing that same sort of pattern here with the results of the inhaled zanamivir trials.

But I think it's important to bear in mind that in fact those drugs are associated with similar kinds, if one looks historically, of effects on symptom resolution and on functional improvement, as described in the documents provided to you regarding zanamivir. It is I think important to bear in mind that seeing some trials where there's not statistical evidence of difference has been the expected finding during flu trials historically.

DR. HAMMER: Thank you.

If there are no other comments or questions.

DR. MURPHY: One last thing because it came up a couple of times, Scott, which is about the future ways

that this may be used in practice, since there could be quite a number of variations upon that theme, if you will. That really should not be in your consideration. Your consideration is when the drug was used the way it was prescribed to be used, did it or did it not show efficacy. So, I just wanted to reemphasize that.

DR. HAMMER: Thank you.

DR. LI: Just a very quick question, point of information to the agency, for the non-American studies, are there site visits conducted and are they done in the same manner with the same results?

DR. BIRNKRANT: We have a Division of Scientific Investigations with investigators who go out to predetermined sites based on consultation with the Review Division. So, we do have investigators in Australia and we will investigate the U.S. study sites as well.

DR. MURPHY: I just want to expand upon that because it has come up a number of times and I think it's a very important point that the committee has to be comfortable with, and that is at one time the FDA was not as enthusiastic about some foreign studies. Over the last decade, we have spent a tremendous amount of time globally in harmonization of studies. It is going to become increasingly, I think, apparent, if not already apparent certainly in HIV, malaria, TB, that we will see studies

from foreign countries. The whole effort that has been going on has been that there's standardization, there are guidances on protocols, on manufacturing, on inspections, on reporting, on data collection.

What we're trying to tell you is that we are comfortable that the foreign studies were conducted, implemented, data collected, and evaluated in an acceptable manner, and at the same standards as if though they were performed in the U.S.

DR. LI: Do you think it would have made a difference in our discussion if we had been talking about the pivotal studies as study A, study B, and study C, rather than the southern hemisphere, the European, and the American studies?

DR. MURPHY: Possibly.

DR. HAMMER: I think the agency has answered the question. I think geography is not the issue. The issue is each study, how it stands on its own merits, and then comparing the studies as to their relative merits and strengths. At least speaking as the Chair, I would suggest that the geographic location of the studies not be a consideration.

I don't think these two studies would be before us, the non-U.S. studies. They wouldn't be in the package. They wouldn't be presented here if the agency felt that we

shouldn't consider them comparably performed to the North American study.

Dr. Verter.

DR. VERTER: Just a quick one. In my comments, in fact I was conceding that the studies were conducted well, but I can't separate the geography because of the differences that I see.

DR. HAMMER: I'm only talking with respect to quality of the study and quality of the data. There may be explanations for why there are differences, but I don't think we should be assuming in any regard that these studies were less well done, the data less well put in the case report form, or there were any site monitoring issues that make us suspect of the performance of the studies. Now, the differences may be because of other factors, but honestly, I don't think we would be seeing these studies today if the agency felt they weren't ready for prime time and to be here in front of us as pivotal trials.

DR. VERTER: I agree with that.

DR. MURPHY: Or we would point out to you where the issues were.

DR. HAMMER: Dr. Stanley?

DR. STANLEY: Just one last point to build on something that Dr. Verter said earlier. As far as the successful European study, I think it's really key to look

at the role of the anti-inflammatories because the reason you got to a 2 and a half day savings is not because the treated people go there quicker, but it's because the placebo people stayed symptomatic longer. With using half the dose of acetaminophen compared to the other two trials, I think there's a very clear indication that what you're doing is you're replacing the use of acetaminophen. You can achieve close to the same goal if they just use more acetaminophen, which is why I go back to the role of this drug in viral shedding and, from the public health aspect, its effect in being able to stem an epidemic within a family or within a location as opposed to treating an individual to make them feel clinically better.

DR. HAMMER: A point well taken.

Dr. Stoller?

DR. STOLLER: I have a question which bears on kind of FDA input, and that is, the principle of fairness would obviously dictate that if the primary outcome measures were pre-negotiated as these time points for resolution of symptoms, then that bears on one assessment of our deliberation as to whether that endpoint has been satisfied. If, on the other hand, I think we've heard around the table that there's some reservation about the clinical relevance of that outcome measure, albeit it pre-negotiated, and in fact the comments that we've heard from

the FDA have a lot to do with examining the primary outcome measure in other perhaps more clinically relevant ways. So, the question is, from a committee deliberation point of view, how do we react to that?

I suppose if I were asked seven years ago whether I would have acknowledged the outcome measure as articulated, we might have heard a similar discussion at that time to what we're seeing now. And in fairness to the discussions, I think it's relevant to hear comment on that because the equivocation, at least in my own view, regards the perhaps clinical non-relevance and, as I think some other members have commented, the inability to flush out the real clinical evolution of disease based on that outcome measure. So, some discussion of that might be helpful to my thoughts.

DR. JOLSON: I think it's an issue that we struggle with as well, not just with this application. I think it was also something that was recognized at the time that the protocols were submitted, that drugs for treatment of influenza for the reasons that Dr. Hammer mentioned are extraordinarily difficult to develop, and it is extraordinarily difficult to capture a treatment effect when these are all healthy adults and they're going to get better before you can blink your eye. We realized at the time that any endpoint that we used was somewhat arbitrary.

These were the endpoints that were used after some initial clinical development and were agreed upon, and they were the best guess at the time.

In general, when we've agreed to an endpoint, in the absence of other information, and an endpoint is met, usually that implies that something favorable will happen to the application. That's not always the case. If it turns out in hindsight that the endpoint doesn't stand up to scrutiny, then it has to be reexamined.

I think here in the FDA presentation, what we've tried to do is not to say that the initial choice of endpoint was wrong. I think we're just saying to you that, as Dr. Birnkrant was mentioning, there are many ways to look at the data, and we could probably spend the rest of the afternoon with different exploratory analyses that would provide different levels of reassurance and other analyses that would just raise anxiety more.

We're still left, though, with at some point we did make a cut, and it's very hard to say that it was a poor choice or a good choice. And one thing that we would hope the committee would think about is, well, if not this endpoint, then what's a better way of looking at it because even counting days of symptoms through 14 days may not be reasonable either since most of the severe symptoms, the really debilitating symptoms, are very early on and the

other things are more a nuisance. It doesn't seem right to weigh all those days the same way.

So, I think our analysis is just one stab of looking at it. I don't think it's a perfect way of looking at it, and I don't think it betrays the whole picture. It just was an attempt to show just different ways of reflecting the data.

So, I hope that answers your question.

DR. MURPHY: I think I might phrase is slightly differently, which is that I don't think we've changed our opinion of that adequate endpoint at this time. I think we felt it's our responsibility to present as many different ways of looking at it, but I think from a clinical endpoint, we would still say in these studies that these would be basically the endpoints because again, as Dr. Jolson said, we felt we picked the more severe points. The fact that you have a headache on day 7 if your temperature is down and the other parameters that were the endpoints were there, that's what we agreed to and I think we still stick to that.

DR. HAMMER: One more comment. Dr. Elashoff?

DR. ELASHOFF: Yes. I guess I would disagree with that. In looking at the data over the past two months, it's really apparent that the primary endpoint does not capture what's happening on a patient-by-patient basis.

Individual symptoms might come and go, but the overall measures -- they were asked an overall question, how are your symptoms -- in the North American study, there was no difference. They were asked an overall activity. How much activity do you have? Again, no difference.

So, there wasn't a lot of information to guide what might be a good endpoint. This was certainly a reasonable one. On reflection, looking at all the data, it was a poor choice. I'm not saying I know what the best choice is, but all of the ways that I looked at it that I'm comfortable with, there was really no effect in North America and that was as large as the other two studies.

DR. MURPHY: I think that what you understand is that we have and we encourage differences of opinion. Okay? That is a statistician speaking. You have heard from the clinicians. You have a combination of clinicians and statisticians around the table. That's why you're here, to deliberate and give us your opinion also. So, we're trying to tell you that we do have a variety of ways of looking at the data. The statisticians look at it one way and the clinicians are looking at it in another. That's why we need your advice also.

DR. HAMMER: Thank you. We do need to move on to our vote. I think only questions that clarify issues of regulatory phenomena that help us make a ruling or a vote

should be asked right now because we have much more work to do possibly.

I think what this discussion highlights is the reason why this is before the committee in the first place.

We are now ready for the vote. The first question is the voting question. I'll repeat it again. Does the information presented by the applicant support the safety and effectiveness of zanamivir for treatment of influenza? I listed before the voting members which I think is everyone or everyone here. If you are voting in the affirmative, that is, you think the data do support safety and effectiveness of zanamivir, please raise your hand. This is the affirmative vote.

DR. YOGEV: Can you separate the two?

DR. HAMMER: No, we cannot separate the two. We can as a secondary vote, but as a primary vote, this is the question we're being asked.

Again, just to make sure everyone is clear, we're voting on safety and effectiveness, the first question, voting in favor of.

(A show of hands.)

DR. HAMMER: Those who think safety and effectiveness have not been demonstrated, again as a global question.

(A show of hands.)

DR. HAMMER: We have 4 affirmative votes and 13 negative votes.

The corollary question. We had several to consider if the vote was yes. We only have one if the vote was no, although if the agency wishes us to consider additional items here, we'll be happy to do it. If no, what additional studies are needed?

I think once again I'll start with our expert consultants and panelists. Dr. Poland.

DR. POLAND: Sorry to go back a little bit, but we were only presented with two choices. Yes means something and no means something.

DR. HAMMER: Yes. Let me just clarify. What this committee does is make a recommendation to the agency only.

DR. POLAND: Right, I understand. I guess the recommendation that I would kind of like to see go forward is the answer is unclear. We have an A study and a B study that suggests one answer, and a C study that's as large as A and B that suggests an opposite answer. So, to me the answer is not yes or no, but unclear and hence further studies are necessary.

I guess we've already heard that one family study is either ongoing or about to begin. I think any kind of parameters that could be built in quantitating

estimates of viral transmission would be very useful, indeed.

I think the other issue would be to try to do that at a lower age group than I think 12 was proposed because it is school children who are the transmitters and the spreaders of this disease, unlike other diseases, and I could see a real value in attacking the problem at that level. So, childhood studies would be important.

I think studies of the elderly, high-risk, and immunocompromised are also important, though I don't think necessarily absolutely necessary for licensure.

I also think that what may be -- and let me call it confounding or contaminating the studies may very well be the actual time from the beginning of symptoms to the initiation of treatment. I think it would be very helpful to have some very clear-cut, as tight as you can make them, studies looking at early, intermediate, and late initiation of treatment.

Finally -- and this reflects my own ignorance about the delivery mechanisms of this -- I wonder whether there couldn't be some studies using this more as a metered dose inhaler type thing rather than the thing that we saw here today.

DR. HAMMER: Thank you.

Dr. Kilbourne?

DR. KILBOURNE: Well, I have the same reservation about the same entry point being assured in all studies in terms of the timing. I think that is critical. It's a disease where most of virus replication has occurred probably before symptoms even begin, and there is a very narrow window. The more sharply that could be defined, the more definitive answer you're going to get.

I said earlier I do feel that studies would benefit enormously by getting good, quantitative virology as one goes along. That's a horrible task. It's very labor intensive, but I think it's well worthwhile. That was done with amantadine studies, rimantadine studies, and I think it's not too much to ask of it here.

DR. HAMMER: Thank you.

Dr. Cox?

DR. COX: My comments will echo those of my colleagues who have just spoken. I voted no with real reluctance because there's clearly a great need for additional antiviral compounds for influenza, and watching the development of this particular compound has been extremely exciting. But I think that we do need to see additional information presented to us with virologic endpoints, as my colleagues have mentioned, and to look for reductions in transmission.

Also, I think there needs to be some

clarification of issues of resistance and whether resistant strains really are antigenically different and whether emergence of resistance in response to use of this drug for treatment could drive antigenic variation. I think that's a very interesting area and one that needs to be explored more fully.

DR. HAMMER: Thank you.

Dr. Hendeles?

DR. HENDELES: I have two suggestions to add. One is that a study needs to be repeated with a larger dosing, a dose response study that includes a dose high enough to see whether what was seen in the North American study was seen because of too low a dose or not. It's possible that they just didn't give a high enough dose or something about the timing of the regimen, et cetera that did not distinguish sufficiently.

The second point I want to make is that Dr. Elashoff presented a way of looking at the data that was very meaningful to me. It's on page 8 and 9 of his handout where he looks at the time course of symptoms and activities, and it looks very clear to me there that there weren't big differences between the three different studies, that that time course of symptoms, the difference between placebo and active drug, was similar for all three studies. So, I would suggest looking at the data in that

way, and one might want to pick a secondary endpoint as to what it is at 5 days or whatever. But I think this is much more meaningful than the endpoints that were picked and agreed upon by FDA.

DR. HAMMER: Thank you.

Dr. Stoller.

DR. STOLLER: I echo Dr. Cox' comment. I too voted no with some reluctance because I share Dr. Hammer's perspective about the benefits of having a drug for a problem that, although perhaps clinically self-limited, certainly has a burden of illness that's significant, and also for the corollary benefits of having a drug driving diagnostic testing which I believe is much needed in ascertaining influenza.

That said, my reservations regard looking at the dynamics of the data and the full picture of the data, as I think we've heard, recognizing time-to-event curves and the distribution of data, would be more helpful in my own assessment.

I also quite agree with the comments that have been made that the studies perhaps should be block randomized rather than post hoc analyses of time to first therapy. What we've seen in the secondary analyses is an attempt to tease out the 36 hour time frame as to when therapy was initiated and massaging, if you will, the

efficacy in the North American data regarding the benefit in early therapy. But I think that if that point is to truly have credence, that one needs to design that into a stratified, up-front randomization and look at those early treated patients, those intermediately treated patients from first symptom onset to therapy, and those later treated patients as an up-front decision in block randomization.

My other comment regards the need, from my point of view, of recognizing the fact that we should absent issues of effectiveness from deliberations of efficacy, which I fully acknowledge. I, nonetheless, think that the impact of such a drug from a population point of view is greatest in those patients in which it's needed the most, and I would be far more clinically impressed with studies, as I understand are now underway, with regard to patients with COPD and immunocompromised, recognizing the tremendous burden of evaluating that population, but also recognizing the outcome measures in that group may be easier to ascertain than the somewhat more nebulous symptomatic outcome measures. So, there may be room for examining focus studies in COPD populations in a larger proportion of truly high-risk individuals that would be more persuasive to me. Even if the magnitude of the clinical benefits were perhaps smaller, the types of

clinical outcome events would be certainly more pronounced.

So, those would be my specific suggestions.

DR. HAMMER: Thank you.

Dr. Li.

DR. LI: First I want to say that I thought the sponsor's presentation in fact was excellent, and I didn't have any problem with the way the information was presented.

In terms of future studies, rather than using a baseball analogy, maybe I'll use a hunting analogy. I think these studies were very ambitious and they represent a shotgun approach. What I might suggest is a more focused rifle shot approach. That I think is similar to what Dr. Stoller was saying, as an example.

I think that this drug does have antiviral activity and there may well be a way to use it and a population to use it in that's effective. It just didn't turn out in my view to be demonstrated in the information that was presented.

Again, as an example, one might try deliberately to have earlier use of the drug in the course of the illness, aimed for, say, 24 hours from the onset of symptoms. It's a little difficult to do. You might have to have participants learn to use the inhaler, have the medications available at home. They may have to self-

initiate. There may be other challenges, but at least starting earlier as part of the study would be one possibility.

I think another population would be the older age group. Maybe patients over 50, if they use the product within 24 hours of symptoms, may show very significant efficacy and maybe enough to have the product approved and available for doctors to use. I think we all would be excited about that if that were the case.

I think someone also mentioned the younger age group. I would agree with that also.

You could change entry criteria to have maybe a higher body temperature for entry into the study, rather than the lower one.

Two other quick points to mention. I still think the intent-to-treat is the proper group to examine, and it was actually quite interesting to see the influenza-positive population results displayed to me. But in fact, the way the drug is going to be used really I think will be based on clinical criteria, at least for the time being.

The last point is in the allergy and asthma business, when we look at drug applications or even drug studies, we're very used to looking at symptom scores, supplemental medication scores, global assessment scores, and I think that the way that the agency presented the

information, which was similar to that approach, was helpful.

DR. HAMMER: Thank you.

Dr. Stanley?

DR. STANLEY: Well, Dr. Li is reading my mind. I just want to reiterate that I'm very skeptical that this drug is going to be useful in the general population in alleviating symptoms. So, I would urge the company to look at the populations most affected: the young, the elderly, the true high-risk, the immunocompromised where resistance may be better evaluated.

I also think that this endpoint is not really reflective of what's happening in the individuals and would urge virologic endpoints and total symptom scores, as Dr. Li said. I think those will end up being much more helpful than this endpoint.

DR. HAMMER: Thank you.

Dr. Hamilton.

DR. HAMILTON: I'm relatively new to this committee and I'm struck by a couple of our prior experiences in which we approved or disapproved various agents that were proposed for HIV, in which situations, on the basis of surrogate markers collected over periods as short as 16 weeks, drugs were provisionally approved. It's somewhat dismaying to me because I really am much more

interested in the clinical impact of these drugs for whatever they might be. In this case the sponsors did their best to identify what those clinical events might be.

Now, I don't think that the population in which it was demonstrated on this occasion is the one where it's going to have the greatest impact. I too am in favor of testing this drug in those at higher risk, special populations of various kinds, and I would like to encourage them to focus on clinical endpoints because that's what's meaningful to the patient. The patient doesn't care about what their viral load is or what their nasal viral load is.

DR. HAMMER: Thank you.

Dr. Wong.

DR. WONG: Well, I'll be very brief. I also was very reluctant in voting no because I believe that the data we saw today shows that this is a very promising antiviral. I think that just a little bit more prospective analysis with some of the targeting that we heard about earlier will nail the case.

DR. HAMMER: Thank you.

Dr. Diaz.

DR. DIAZ: I think all of my suggestions have either been echoed by someone else. I think the idea of block randomization is a good idea, and in particular, looking at the elderly population and some of the high-risk

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population, one is going to have to take into consideration that in those groups, there will be a much higher percentage of individuals who have been vaccinated in that flu season and to keep that in mind in terms of randomizing and getting virologic data on those individuals in particular as to whether their isolate strain matches the vaccine will come into play in analysis in those individuals.

I too would comment that perhaps looking at some of these higher risk populations or the elderly or the very young will hopefully nail this very quickly in terms of giving us better endpoints for satisfying efficacy in the panel.

DR. HAMMER: Thank you.

Dr. Masur.

DR. MASUR: Well, I'm impressed that the studies have already been planned or ongoing in children and asthmatics and the elderly and immunosuppressed. So, I would hope that those will continue to be pushed aggressively because, as I guess everybody is emphasizing, this drug logically should have activity, and the real issue is how to use it to its best advantage, both in terms of the way it's delivered, the timing with which it's given in relation to the illness, and in which populations. So, I'm glad that these studies are planned and underway, and

hopefully we'll see the results shortly.

DR. HAMMER: Thank you.

Dr. El-Sadr?

(No response.)

DR. HAMMER: Dr. Verter?

DR. VERTER: I had two suggestions. One, I have a feeling that both Dr. Elashoff and the statisticians at Glaxo could probably get a lot of insight into the data by now dredging it a little bit more, unless you've already done that, and specifically trying to give yourself some insights as to what the differences were across the three studies that may have contributed to this, such as the timing, the use of the concomitant drugs.

The other is kind of a far-out thought, if you have the resources, since in the U.S. you're unlikely to be able to address the control, acetaminophen and cough syrup, is to maybe consider a factorial trial.

DR. HAMMER: Thank you.

Dr. Wittes?

DR. WITTES: Yes, I'd like to say two things.

First, I too voted reluctantly, and I want to say that I am uncomfortable changing the primary endpoint. I feel that we need to evaluate the studies on the basis of the endpoint that you did prespecify, otherwise I think it becomes really a moving target. Although we might prefer

something else in general, I think it's hard to imagine drug development where you don't know what the game plan is.

My own problem really was the way the data was presented. I felt there were unanswered questions for me, too much missing from the description of what you actually did. The sensitivity analysis seemed to be limited only to the North American study. We need to see sensitivity analysis in the other studies as well.

So, again, I want to echo what some other people are saying. I think you've got a lot of the stuff there, but you need to analyze it and present it more completely.

DR. HAMMER: Thank you.

Dr. Bertino.

DR. BERTINO: Well, I'm glad Dr. Verter used the term "data dredging" because I was going to use that before, but I'm surrounded by statisticians and I was scared to death to do that.

(Laughter.)

DR. BERTINO: I think just two comments.

While influenza is often a self-limiting disease either by cure or death, if you take a look at the thrombolysis model where we know that if you have chest pain within a certain time period, you use TPA or

retaplase, and after that you can use streptokinase, and after that you don't use anything, it would be interesting to go back and look at the data and say, based on onset of symptoms and onset of treatment, when should we use this drug. When is it not going to be effective? Because I don't think insurance carriers are going to pay for it on a routine basis anyway. So, I think that that would be of interest to know.

Then I think probably this drug is going to have a bigger role -- and I'd be interested to hear what Dr. Hayden had to say -- in prophylaxis rather than in treatment because my concern about treatment is that by the time treatment gets initiated, it may be too late because of availability of drug, because of inability to administer this interesting but unusual dosage form of drug. I think that for a lot of people, if you're going to use it for treatment, you're going to need something other than a dry powder. You're going to need a nebulized solution that you can give them.

DR. HAMMER: I don't have really any other suggestions. I think the studies that were outlined that are ongoing or planned by the sponsor cover many of the bases. What my colleagues have mentioned cover the rest.

I just have one virologic suggestion and it is a corollary to what Dr. Kilbourne had mentioned earlier.

Although aggressive attempts to culture and quantitate replication-competent virus need to continue and be intensified, I think given what we know about the virology here, developing a quantitative PCR may be helpful to help monitor this, even though it doesn't tell you whether it's replication-competent or not, but also I think it's a way to get a better handle on potential resistance emerging by using PCR to go after the neuraminidase and hemagglutinin genes days into therapy. Even when you can't retrieve virus that's culturable, you maybe able to PCR out those genes and look at the mutational patterns that you might or might not see, and I think that kind of virology data done intensively in a relatively small number of patients may be quite interesting.

But I think all the other general suggestions for which populations and what types of studies should be done -- I just have one safety issue, and that is we have a 28 day exposure in prophylaxis. We have these 5 day exposures in treatment. One thing that may happen and we should be developing some safety data is reexposure to this because there may be people who get prescribed this two or three or four times during a season or even the next season, and if there are potential sensitizing issues that we don't know about, that's an important thing to develop. So, I think some safety information on reexposure would be

helpful.

Let me turn to Dr. Birnkrant and ask her if there are more issues you want us to discuss.

DR. BIRNKRANT: I was hoping we can move to question 7 at this point.

DR. HAMMER: Okay. I didn't do that because of the instructions on the top of the page, but that's why I asked.

This is I think a corollary to some of the suggestions that have been made, but question 7 is really a statement. Please discuss your recommendations for design of future studies of influenza treatment, I think putting some of us on the spot to try to give specific advice.

So, I think I'll start on my right this time. And I don't know. Dr. Bertino, do you have any suggestions for the future studies of influenza treatment?

DR. BERTINO: Yes. I think a study versus rimantadine for both prophylaxis and treatment.

DR. HAMMER: Dr. Wittes?

DR. WITTES: I pass.

DR. HAMMER: Dr. Verter.

DR. VERTER: I made the comment earlier.

DR. HAMMER: Dr. El-Sadr?

DR. EL-SADR: I think we made the comments. I think there's really nothing wrong with these studies. I

think they were well designed and well conducted. I think we've learned an awful lot from the analysis of the results of these studies to try to tailor maybe to different populations, as well as also trying to come up with maybe potentially another type of primary outcome that reflects more of the global symptoms that the patients have. But I think the data that we've looked at today and you've been looking at I think would be very helpful in trying to define outcomes, which I think is the tough part in these types of studies.

DR. HAMMER: Dr. Masur?

DR. MASUR: I have nothing more.

DR. HAMMER: Dr. Diaz?

(No response.)

DR. HAMMER: Dr. Stanley?

(No response.)

DR. HAMMER: Dr. Stoller?

DR. STOLLER: I'll simply reiterate my comments. It sounds to me, and I'm gratified to hear, as Dr. Masur said, that many of the studies that would be germane to my thinking are actually underway. I would again reiterate what Dr. Wittes said that when those data are shown with regard to the agreed upon primary outcome, that they show the shape of the events as they develop related to the agreed upon primary outcome. I'm not

advocating for altering the outcome as seeing the fullest dimension of the measures that have been agreed upon.

DR. HAMMER: Thank you.

Dr. Cox?

DR. COX: Yes. I'm very optimistic considering the studies that are underway, and I would echo a comment from one of my colleagues that a comparison with rimantadine would be very useful.

DR. HAMMER: Thank you.

Dr. Kilbourne.

DR. KILBOURNE: I have nothing really to add except that perhaps following bacterial colonization might be interesting as a site of necrotizing virus which paves the way for bacterial colonization, some evidence even with a live virus attenuated vaccines that this occurs. This is certainly very indirect, but I think it might give you information.

DR. HAMMER: Thank you.

I don't have much to add. One thing I might suggest because it took up so much time in the discussion here as far as interpretation and what's the proper endpoint, given the fact that by the nature of this disease, soft endpoints are going to be part of a global definition if you did look at an intent-to-treat population and then the subpopulation of influenza-positive,

developing perhaps -- I don't know if this is a cop-out -- but two co-primary objectives might be helpful, one that's a crosscut and one that's a broader picture over a respectable period of time, although I think the point made earlier that trying to do symptoms daily over 14 days and coming up with a summary score may be just as problematic as choosing a median time. But I think one of the issues we had today reflects two sides of the interpretation here, and developing a primary endpoint or primary objectives that allow you flexibility within the statistical validity of the study might be quite helpful to avoid some of the difficulties that were evident in the discussion.

I also think that the lack of commentary that you've heard is not just people going to the airport, but that the panel is as beguiled by what to do with this disease as the agency and the sponsors in trying to develop good studies and them see them through over years.

Also, I keep doing this, but an analogy to HIV. You start a study, you plan a study, then you're three years down the line with the results, and you're always smarter at that end than you were at the beginning. That phenomenon of clinical trials is not going to change.

Is there anything further that you would like us to do?

DR. BIRNKRANT: I don't think so. Thank you

very much.

DR. HAMMER: On that note, I'd like to thank my colleagues on the committee, the guest consultants, the members of the agency, the people in the audience who came as interested parties, and particularly the sponsor, Glaxo Wellcome, for their presentation today. Thank you.

We're closed.

(Whereupon, at 4:05 p.m., the committee was adjourned.)

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