

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE

8:30 a.m.

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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

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P R O C E E D I N G S

(8:30 a.m.)

1
2
3 DR. HAMMER: Good morning. I'd like to convene
4 this meeting. This is the Antiviral Drugs Advisory
5 Committee. Today we're here to discuss zanamivir, or
6 Relenza, for the treatment of influenza A and B.

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

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

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

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

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

22 DR. HENDELES: Leslie Hendeles, University of
23 Florida.

24 DR. STOLLER: Jamie Stoller, Cleveland Clinic.

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

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

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

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

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

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

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

13 MS. STOVER: Rhonda Stover, FDA.

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

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

17 DR. VERTER: Joel Verter, George Washington
18 University.

19 DR. WITTES: Janet Wittes, Statistics
20 Collaborative.

21 DR. FLYER: Paul Flyer, FDA.

22 DR. ELASHOFF: Mike Elashoff, FDA.

23 DR. STYRT: Barbara Styrt, FDA.

24 DR. MEYER: Bob Meyer, FDA.

25 DR. BIRNKRANT: Debra Birnkrant, FDA.

1 DR. JOLSON: Heidi Jolson, FDA.

2 DR. MURPHY: Diane Murphy, FDA.

3 DR. HAMMER: Thank you.

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

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

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

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

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

25 In addition, we would like to disclose that Dr.

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

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

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

20 DR. HAMMER: Thank you.

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

23 DR. BIRNKRANT: Thank you very much.

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

1 inhalation for the treatment of influenza.

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

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

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

13 Zanamivir for inhalation fits not only into
14 one, but all of these categories. It is a new chemical
15 entity for the treatment of influenza and also first in its
16 class. Being a neuraminidase inhibitor with in vitro
17 activity against influenza A and B, its mechanism of action
18 differs from the only other marketed drugs for influenza A,
19 that being amantadine, which was approved more than 20
20 years ago, and rimantadine, which was approved in the
21 1990s.

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

1 | infected humans.

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

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

25 | Other issues deserve mention, including the use

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

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

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

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

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

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

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

16 Thank you.

17 DR. HAMMER: Thank you very much.

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

20 DR. RUBIN: Thank you and good morning.

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

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

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

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

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

1 | the general population.

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

14 | Just a few words about influenza in the general
15 | population, and you'll hear more from Dr. Hayden about this
16 | in a few minutes. It's a disease that affects all age
17 | groups. It typically has a sudden onset, and it's often
18 | temporarily debilitating. Influenza and the pneumonia that
19 | parallels it epidemiologically is responsible for up to
20 | 300,000 hospitalizations each year, but even more common
21 | and I think equally important is the absenteeism from work,
22 | from school, and overall the enormous added burden that's
23 | placed on families by this disease. I think it goes
24 | without saying that each year influenza as a whole has a
25 | tremendous economic impact on society.

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

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

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

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

25 Well, since zanamivir was and is the first in

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

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

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

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

1 | zanamivir. In October of 1993, we filed the IND. A year
2 | later, we began the phase II clinical program. In May of
3 | 1997, we initiated the global phase III program, and in
4 | October of last year, submitted the NDA, which was granted
5 | priority review status in December. Of course, this brings
6 | us up to today's meeting.

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

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

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

21 | DR. HAYDEN: Thank you and good morning.

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

1 | past two dozen years.

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

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

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

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

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

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

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

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

14 Influenza is spread primarily by droplets and
15 small particle aerosols.

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

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

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

1 and usually increasingly severe cough.

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

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

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

22 These epidemics also translate into roughly
23 150,000 excess hospitalizations annually, with the broad
24 range indicated here.

25 With respect to economic effects, in 1986

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

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

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

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

1 elderly.

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

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

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

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

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

1 influenza deaths among persons aged less than 65 years.

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

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

22 With respect to prevention, clearly pre-season
23 immunization is the primary means of prevention. And there
24 are annual guidelines published in morbidity and mortality
25 weekly reports.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 Thank you for your attention.

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

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

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

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

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

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

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

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

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

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

1 part of the presentation.

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

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

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

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

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

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

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

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

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

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

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

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

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

9 Now, the primary efficacy endpoint for all of
10 these studies was the time to alleviation of clinically
11 significant symptoms of influenza. This is a particularly
12 demanding but appropriate endpoint in that alleviation was
13 defined as the absence of fever, the absence of
14 feverishness, and a rating of none or mild for the major
15 symptoms listed here of acute influenza infection. These
16 ratings had to be maintained for the 12 hours prior to the
17 first alleviated entry and then for a subsequent 24 hours,
18 that is, across three consecutive diary card entries over a
19 36 hour period.

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

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

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

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

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

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

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

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

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

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

25 | The results of the first phase III study. 455

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

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

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

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

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

1 amount of benefit is very meaningful.

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

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

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

1 Also average maximum daily temperature was
2 statistically significantly less.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 Across the three phase III studies, two of them
11 showed substantial benefit. One did not show a difference.
12 So, we examined more carefully this particular study, and
13 what we saw is that in patients who were enrolled late in
14 the treatment window, more than 36 hours from onset of
15 symptoms, there were very few of them who had what seemed
16 to be an abnormally short duration untreated of influenza,
17 as well as one zanamivir treated patient who, when removed
18 from the analysis, we see that with those enrolled within
19 36 hours of onset of their symptoms, there was a 1 and a
20 half day reduction in their illness.

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

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

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

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

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

1 an 84 percent protective efficacy against febrile influenza
2 illness.

3 Our overall conclusions are that in all phase
4 II studies, three large phase II studies and three phase
5 III studies, zanamivir consistently reduced the time to
6 alleviation with the magnitude of effect ranging from 1 to
7 2.5 days reduction. This reduction was also extended to
8 patients who had either influenza A or B, to the high-risk
9 population, and in addition there was a reduction in
10 complications and antibiotic use across these studies.

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

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

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

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

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

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

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

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

1 the resistance or the potential for that.

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

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

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

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

1 virus, a double mutant.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 | interfere with the cytochrome P450 enzyme system.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

19 | I'll talk briefly also about the prophylaxis
20 | study that Dr. Ossi presented, as this does provide useful
21 | data from a safety perspective as well. This recruited
22 | 1,107 subjects, approximately a 50/50 randomization to
23 | zanamivir and placebo, and they took inhaled drug once a
24 | day for 28 days.

25 | This next slide shows the adverse events from

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

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

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

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

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

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

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

25 | The weight of evidence we feel is that

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

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

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

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

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

1 risk group that I also showed you.

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

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

9 DR. HAMMER: Thank you very much.

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

20 Clarification please?

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

25 DR. HAMMER: I should turn to the agency for

1 | this. Dr. Birnkrant?

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

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

13 | DR. ELLIOTT: Sorry. The statistics on the?

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

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

23 | DR. HAMMER: Dr. Wong?

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

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

7 | DR. ELLIOTT: Yes. We can bring those.

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

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

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

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

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

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

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

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

13 DR. ELLIOTT: Yes.

14 DR. HAMMER: Dr. El-Sadr?

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

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

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

25 I'm sorry. Your supplemental question was?

1 The diary cards.

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

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

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

13 DR. HAMMER: Dr. Kilbourne?

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

17 DR. ELLIOTT: Yes.

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

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

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

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

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

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

14 DR. HAMMER: Dr. Diaz.

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

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

1 | during the same day that the symptoms or the temperature
2 | would occur.

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

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

15 | DR. HAMMER: Please.

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

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

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

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

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

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

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

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

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

4 DR. ELLIOTT: We can certainly do that.

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

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

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

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

21 DR. ELLIOTT: Yes, they were.

22 DR. HAMMER: Dr. Jolson?

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

1 | those patients.

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

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

10 | Thank you.

11 | DR. HAMMER: Dr. Yogev.

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

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

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

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

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

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

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

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

16 | DR. ELLIOTT: Slide 77.

17 | Sorry. Was any?

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

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

22 | DR. YOGEV: On the bottom.

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

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

9 | DR. HAMMER: Dr. Wittes?

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

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

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

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

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

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

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

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

13 DR. HAMMER: Thank you.
14 Please.

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

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

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

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

13 DR. HAMMER: Thank you.

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

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

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

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

3 (Recess.)

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

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

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

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

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

8 Population categories, including persons aged
9 65 or over or having chronic respiratory, metabolic, or
10 immunologic disorders, are considered at increased risk of
11 complications from influenza, and the phase III studies of
12 zanamivir were designed to include subjects in such groups
13 in whom information on effects of influenza treatment would
14 be particularly welcome.

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

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

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

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

25 Finally, as you have heard, this drug has a

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

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

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

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

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

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

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

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

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

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

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

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

25 Finally, symptoms were recorded for 14 days in

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

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

10 Dr. Elashoff will now present some statistical
11 considerations.

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

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

25 As already mentioned, there are three phase III

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 Next are the secondary symptoms, nasal

1 | symptoms, weakness, and loss of appetite.

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

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

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

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

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

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

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

11 So, we started thinking about other ways to
12 capture this information in ways that the primary endpoint
13 did not. The first idea was to take the same criteria that
14 were used to define the primary endpoint, but instead of
15 identifying a particular time of alleviation, as for this
16 patient, simply count the days that they did or did not
17 meet the definition over the 14 day period. So, for
18 example, for this patient, we would count days 0, 1, 2, 3,
19 6, and 7 as not being alleviated since by the primary
20 criteria they really weren't. Then we also did additional
21 analyses factoring in the secondary symptoms, relief
22 medication, and the overall assessment.

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

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

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

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

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

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

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

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

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

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

25 So, another way of assessing benefit is to look

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13 Further, on looking back at the phase II
14 studies, a similar discordance was there. Studies 2005 and
15 2008 had a North American component and a non-North
16 American component, and the analyses in the phase II
17 studies of the non-North American part were generally
18 significant while the North American component was not.

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

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

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

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

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

1 effect on the overall pattern of results that we saw.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 inhalation delivery symptom in the specific setting of
2 influenza treatment.

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

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

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

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

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

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

1 studies.

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

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

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

25 Laboratory abnormalities in the principal

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

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

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

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

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

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

25 Three deaths have been reported in ongoing

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

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

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

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

1 few with diabetes or immune compromise.

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

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

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

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

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

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

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

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

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

25 In the principal phase III treatment trials, it

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 | Plaque reduction assays showed increases in

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 With regard to safety, the principal studies

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

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

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

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

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

18 | DR. HAMMER: Thank you very much.

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

25 | DR. HENDELES: Could you clarify for me a

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

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

18 | DR. HAMMER: Dr. Wong.

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

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

1 Elashoff?

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

13 Does that answer your question?

14 DR. WONG: Yes.

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

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

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

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

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

9 DR. HAMMER: Dr. Hamilton.

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

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

25 I think it's quite interesting to consider

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

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

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

12 | DR. HAMMER: Thank you.

13 | Dr. Masur?

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

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

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

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

14 DR. ELASHOFF: I don't have any graphic
15 presentation. I guess just my overall sense of looking at
16 individual patients. It often occurred sort of in the day
17 5 to 7 range that a patient might have come down and then
18 head back up in the range of between 5 and 7 days. It
19 generally wouldn't continue, say, out to day 14, but there
20 would be extra symptomatic days.

21 DR. HAMMER: One interpretation -- I am sorry
22 to interrupt -- that there are extra symptomatic days is
23 one might imply from this that there's a treatment effect
24 that's lost after the medication stopped because this was a
25 5 day treatment course. So, if there looks like there's a

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

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

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

18 | Dr. Bertino?

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

25 | DR. ELASHOFF: Yes. The use of relief

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

13 DR. BERTINO: It does.

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

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

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

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

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

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

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

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

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

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

18 DR. HAMMER: Dr. Stoller?

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

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

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

7 DR. ELASHOFF: That's correct.

8 DR. HAMMER: Please.

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

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

16 DR. HAMMER: Dr. El-Sadr.

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

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

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

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

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

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

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

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

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

4 DR. YOGEV: If we can get that.

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

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

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

18 From publications, the amount of lactose
19 required to generate GI disturbance in those people with
20 lactase deficiency is about 10 to 12 grams. So, with our
21 20 milligrams per blister, we're well short of that.

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

25 DR. HAMMER: Dr. Stanley.

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

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

12 DR. HAMMER: Dr. Wittes.

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

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

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

25 DR. WITTES: Yes.

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

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

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

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

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

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

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

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

16 DR. HAMMER: Not a surprising result, though.
17 Dr. Li?

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

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

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

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

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

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

(1:15 p.m.)

1
2
3 DR. HAMMER: I'd like to convene the afternoon
4 session.

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

10 (No response.)

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

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

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

20 What I'd like you to do is think about the
21 phrase, there's more than one way to look at things. I
22 think this is particularly applicable to influenza, which
23 is a self-limited disease maybe lasting 5 to 7 days, up to
24 10 days. Think about what type of treatment effect you
25 would actually expect in this type of illness as you

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

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

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

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

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

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

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

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

11 Thank you very much.

12 DR. HAMMER: Thank you.

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

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

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

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

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

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

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

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

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

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

25 Firstly, as Dr. Ossi alluded to, we believe

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

19 Thank you.

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

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

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

9 DR. HAMMER: Dr. Hamilton.

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

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

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

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

4 | DR. HAMMER: A question from Dr. Kilbourne.

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

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

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

1 | in these kinds of studies.

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

6 | DR. HAYDEN: Thank you for that suggestion.

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

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

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

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

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

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

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

25 I will now turn over the podium to Richard

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

5 DR. BETHELL: Thanks very much, Marc.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18 If I can have the next slide. This is going
19 back to the phase II and this is actually showing you the
20 numbers where the isolation rate, even using nasal washes
21 which were optimum, shows a fairly low after day 3. So, at
22 day 1, we're getting high levels of isolation, 86, 85
23 percent. Day 2 it's going down 64 percent in the placebo,
24 48 percent in the treated. By day 3, then it's down to 50
25 percent in the placebo and just 26 percent, and then by day

1 | 4 and 5, it's very low.

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

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

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

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

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

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

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

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

12 The third problem with all cell-based assays,
13 we know that the virus can spread from cell to cell in a
14 cell-based assay, and this is what we think we're seeing in
15 the plaque assay. So, sometimes even with isolates at day
16 1, they appeared to not be susceptible to zanamivir and to
17 other neuraminidase inhibitors, but in fact it's probably
18 because the virus is able to spread from cell to cell
19 bypassing the function of the neuraminidase, whereas if you
20 look at them in vivo, they are sensitive.

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

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

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

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

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

1 cell spread.

2 We now have a yield reduction assay which is a
3 24 hour assay, and that appears to be less variable, but it
4 still isn't that consistent but it's more consistent than
5 plaque assay.

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

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

13 DR. TISDALE: Margaret Tisdale.

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

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

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

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

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

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

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

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

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

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

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

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

1 Next slide. We used a randomized, double-
2 blind, placebo-controlled design. Again, as I just went
3 over, one spray per nostril corresponds with a 3.2
4 milligram dose; two sprays per nostril corresponds with a
5 6.4 milligram dose.

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

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

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

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

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

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

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

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

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

25 We took the opportunity to evaluate in

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

6 | 13 adults were recruited. It was a double-
7 | blind, randomized, placebo-controlled, so each volunteer
8 | actually received both zanamivir and placebo. So, they
9 | were their own control. The study was powered to detect a
10 | difference in the ratio of the PC20 between zanamivir and
11 | placebo of fourfold in either direction.

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

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

1 higher the concentration.

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

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

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

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

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

25 A third question that came up right before

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

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

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

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

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

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

1 the written and oral questions we took before lunch.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 We are looking at the nursing home setting and

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

19 Here we have the people under the age of 18,
20 and this would be from the phase III program. 139 subjects
21 in the intent-to-treat population, 106 in the influenza-
22 positive population, and you see the overall benefit over
23 on the right-hand side there, reducing from 5 days down to
24 4 days.

25 I can move very quickly through the other age

1 subsets.

2 DR. BERTINO: Was that significant
3 statistically?

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

8 Let move forwards. This is the 18 to 34-year-
9 old age cut. Again you see the same sort of degree of
10 efficacy. This is the biggest group of patients, almost
11 700, with again about 70 percent flu-positive.

12 This will be the 35 to 50, intent-to-treat of
13 400 or so.

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

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

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

24 DR. HAMMER: Dr. Wittes?

25 DR. WITTES: I have a series of questions and

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

3 | DR. HAMMER: Please.

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

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

15 | DR. KEENE: Oliver Keene, Glaxo Wellcome.
16 | You're asking about why the confidence
17 | intervals were asymmetric.

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

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

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

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

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

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

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

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

1 | influenza --

2 | DR. WITTES: The febrile, yes.

3 | DR. KEENE: In the A3002 and B3002 studies.

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

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

8 | DR. WITTES: Oh, okay.

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

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

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

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

1 phase III studies.

2 DR. WITTES: That's right.

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

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

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

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

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

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

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

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

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

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

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

18 | DR. WITTES: Okay, thanks.

19 | DR. HAMMER: Dr. Kilbourne.

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

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

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

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

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

25 So, to your point really, the analyses stand up

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

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

11 | Does that answer the question?

12 | DR. KILBOURNE: Yes, it does.

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

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

18 | DR. HAMMER: Dr. Yogev.

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

1 DR. ELLIOTT: Can we look at the time to
2 enrollment slide that has the phase II and the phase III
3 studies on it?

4 Hopefully on this slide we'll show that
5 actually we managed to segment our U.S. patients into less
6 than 36 hours or more than 36 hours, remembering that the
7 window for this was 2 days. What we actually found was
8 that the majority of patients did come in -- and this is
9 the flu-positive population -- in less than 36 hours, only
10 a small number after 36 hours. Maybe not surprising, the
11 degree of effect when you treat earlier is more than when
12 you treat later, and that's entirely consistent with the
13 course of influenza.

14 DR. YOGEV: Do you have the same data for the
15 so-called successful studies, the European and Australian?
16 Were they less than 24, the majority?

17 DR. ELLIOTT: The European study we didn't
18 segment by this time frame. Everyone was in within 24
19 hours. What we get anecdotally was that the majority were
20 in the second day and probably in the early part of the
21 second day. So, I suspect it will be similar to the U.S.
22 study, but we don't have the numbers.

23 In the Australian study, time to entry was 36
24 hours, so no one came in after 36 hours. We had more in
25 the 0 to 24 than the 24 to 36, but actually no difference

1 | in effect within that.

2 | So, the data suggest what we had all guessed,
3 | that the greater effect is by treating earlier, but we do
4 | see a positive effect still out to 2 days in the studies.

5 | DR. HAMMER: Thank you very much. I think
6 | we'll close this section.

7 | We're going to move on to the questions to the
8 | committee, but I think before we do that, we'll take a 5 to
9 | 10-minute max stretch break, and then the committee will
10 | deliberate.

11 | (Recess.)

12 | DR. HAMMER: I'd like to reconvene the
13 | afternoon session. We're entering the last part of the
14 | agenda. This is where the committee discusses the
15 | questions that have been put before the committee by the
16 | agency.

17 | The first question is a voting question, and
18 | first let me list for the record the voting panelists.
19 | They are Drs. Diaz, El-Sadr, Masur, Hamilton, Wong, Yogev,
20 | Li, Stoller, Hendeles, Stanley, Bertino, Cox, Wittes,
21 | Verter, Kilbourne, Poland, and me.

22 | The first question is the voting question.
23 | What I'm going to do is first go around the table and give
24 | each member a chance to comment on the question, and then
25 | after everyone has had a chance to comment on the question,

1 I will call for the vote.

2 I will read the question for the record.
3 Number 1, does the information presented by the applicant
4 support the safety and effectiveness of zanamivir for
5 treatment of influenza? If no, what additional studies are
6 needed? If yes, we have several other questions we've been
7 asked to address.

8 I'd like to begin on my left side with our
9 expert consultants. Dr. Poland, would you please take the
10 first question, or would you like Dr. Kilbourne to take the
11 first question?

12 (Laughter.)

13 DR. HAMMER: He's swallowing and we don't want
14 aspiration pneumonia as part of the afternoon's events.

15 (Laughter.)

16 DR. KILBOURNE: You didn't ask me whether I'd
17 like to take the first question.

18 DR. HAMMER: Pardon, but it's the prerogative
19 of the chair. I'm sorry.

20 DR. KILBOURNE: Okay.

21 I feel that we have here something that shows
22 promise and it shows promise particularly at the level of
23 the phase II trials. The theory I think is quite elegant
24 as a targeted, deliberately designed drug that goes right
25 to the active site. So, I wish I could answer in the

1 affirmative about whether it should be approved for use
2 right now. That's not the question exactly, but I think
3 certainly further work has to be done.

4 I think this issue of the site differences is a
5 very important one. It may have something to do with
6 cultural differences. It probably does not have anything
7 to do with viral severity in Europe versus here, and I
8 conferred with Nancy about that in terms of similar strains
9 circulating at that time. So, I think that's out of the
10 equation as being a reasonable possibility. Particularly
11 with the evidence of so few resistant variants emerging, I
12 don't think it's likely that there was a resistant variant
13 circulating here but not over there. So, it seems to me a
14 number of further studies have to be done.

15 I still remain not completely satisfied with
16 the answer about the level of replication of virus in these
17 populations. I think this is an important determinant and
18 particularly might bear on the question that came up about
19 rebound which I think might actually be on the side of
20 zanamivir, as you were indicating. What you'd like to know
21 is whether there's a concomitant increase in virus at the
22 time the headache comes back, and I think unless you get
23 really quantitative virology -- my own understanding is --
24 and I can be corrected on this by those initiating the
25 study -- that the quantitative virology was mainly done

1 | with phase II and not necessarily phase III. That is true
2 | where we're talking about in addition to PCR and really
3 | mainly you're talking about actual isolation of virus. But
4 | I believe that's non-quantitative. I think that that was
5 | simply at a single dilution. So, that tells you the
6 | presence of infective virus or not.

7 | I also would like to see evidence that the PCR,
8 | if that's going to be used as a determinant or an easy
9 | determinant, that it be shown that it is correlated well
10 | with the presence of infective virus and not also the
11 | presence of inactivated virus. Here the proponents of the
12 | study might help themselves because actually if you are
13 | measuring essentially dead virus, then you might show an
14 | advantage of zanamivir which has not been shown.

15 | So, that's my initial reaction.

16 | DR. HAMMER: Dr. Poland.

17 | DR. POLAND: The chair may or may not want to
18 | do this, but in my own mind I would divide the question and
19 | ask first are there safety concerns.

20 | DR. HAMMER: It really is a two-part question.
21 | You can and should comment on safety and effectiveness.

22 | DR. POLAND: In my own mind, I don't have any
23 | substantive safety concerns at all.

24 | When it gets to effectiveness, I suspect that's
25 | where we're all feeling a bit of a tug here. To use a

1 | baseball analogy, since those of us from Minnesota no
2 | longer use football analogies --

3 | (Laughter.)

4 | DR. POLAND: -- this is maybe a base hit, but
5 | it's not a home run. I think that's probably where many of
6 | us come down on the side of this, saying that there are two
7 | studies that followed a prescribed protocol that show some
8 | degree of efficacy, but there is this problem with a larger
9 | study that failed to show efficacy. So, I really feel
10 | quite divided about this in terms of efficacy. I've not
11 | clearly made up my mind yet.

12 | DR. HAMMER: Thank you.

13 | Dr. Cox.

14 | DR. COX: Thank you.

15 | I think that I don't really have substantial
16 | concerns about the safety of zanamivir. I think that the
17 | studies have shown that the compound is quite safe.

18 | I think that I would agree with Dr. Kilbourne
19 | in saying that the development of this particular compound
20 | is a very elegant approach and very impressive. I think
21 | that when one looks at the positive effect for the
22 | individual, it isn't so striking, particularly in the North
23 | American study, but even in the European study, the
24 | positive effect on the individual isn't as striking as one
25 | would really like.

1 I think that from a public health point of view
2 what would be extremely useful is to understand whether
3 treatment really reduced shedding of virus and therefore
4 the number of additional individuals who were infected by
5 the treated person. So, family studies would be
6 particularly important in looking at this question because
7 if there is a positive benefit for society by treating
8 people who are shedding, that would be very important to
9 determine.

10 DR. HAMMER: Thank you.

11 Dr. Hendeles.

12 DR. HAMILTON: First of all, I think there are
13 no safety concerns that I have. The data for the asthma
14 patients I think are sufficient for me not to have concern
15 about it directly increasing airway reactivity. The PC20
16 for methacholine was very low. It was about .5 milligrams
17 per milliliter which is associated with rather moderate
18 asthma, and in other studies that we've done with drugs
19 like propafenone, an anti-arrhythmic that has very weak
20 beta blocking activity, you can change the airway
21 reactivity to methacholine even though the FEV1 stays
22 constant. So, I think that's a marker of whether a drug
23 has increased risk. My gut level is that's not a problem.

24 I think the Diskhaler is a device that is more
25 difficult or more complex than the metered dose inhaler in

1 | some respects, but I think you have to take into account
2 | that all controlled studies show that all forms of inhaled
3 | devices are problematic for patients to use unless they get
4 | first-hand instruction, and even then with the MDI, the
5 | patients return to a second visit and still aren't using it
6 | correctly. So, I think any inhaled device has its
7 | problems.

8 | My impression of the Diskhaler is that with
9 | adequate instruction -- and I don't think written
10 | instructions will do it. I think if either a doctor shows
11 | the patient how to use it or a pharmacist shows the patient
12 | or family member, then I think for sure they'd be able to
13 | use it successfully over the time period.

14 | The last question relates to efficacy, and
15 | while I appreciate that every attempt was made to identify
16 | the endpoints, my impression of the data, especially from
17 | the North American study, is that there isn't sufficient
18 | efficacy to warrant me recommending this drug for my family
19 | or myself.

20 | I recognize that it did show some efficacy in
21 | the other studies, but I can't help but feeling that the
22 | differences between Europe and the North American study
23 | might have some sociological implications. Certainly it's
24 | not study design, but there must be something sociologic.
25 | There's a signal there telling us that something is

1 different, and that's the population that we're concerned
2 with here today, the U.S. population. I think there's
3 something different. I was hoping to come here today and
4 learn something substantial, like the use of acetaminophen
5 was the difference, but quite frankly looking at how the
6 FDA statistician presented the data, I just don't think it
7 has sufficient effectiveness.

8 DR. HAMMER: Thank you.

9 Dr. Stoller.

10 DR. STOLLER: I share the other members'
11 enthusiasm for the concept of the drug and its design, and
12 I applaud the magnitude of the studies.

13 My reservations regard two issues: the
14 robustness of the data with regard not only to site, but
15 also to the ability to evaluate the outcome measures,
16 admitting that these were pre-agreed at the outset. But
17 the apparent non-robustness, when one cuts and slices it
18 with different primary outcomes -- I think that further
19 perhaps secondary analyses or additional analyses of that,
20 with time-to-event issues -- needs to be considered.

21 My other concern with regard to the data
22 presented has to do with the non-generalizability to the
23 population in which perhaps the concern is greatest. We've
24 heard some cautions about not using the word "rebound" with
25 impunity, and I would urge not using the concept of high

1 risk impunity. I don't regard the populations that have
2 been labeled as high-risk in these studies to be the kinds
3 of high-risk patients that most of us who are practicing
4 clinicians would be interested in seeing efficacy in. So,
5 I'm not indicting any data shown. I'm just recognizing
6 that there's little that would guide me in my practice of
7 primarily elderly patients or patients with chronic lung
8 diseases beyond relatively mild asthma requiring perhaps a
9 beta agonist only.

10 So, my reservations have to do with the
11 difference between efficacy in a constrained population and
12 effectiveness as it might be used, and I reserve judgment
13 about whether that has been demonstrated at this point.

14 DR. HAMMER: Thank you.

15 Dr. Li?

16 DR. LI: I have some thoughts about safety and
17 effectiveness both.

18 I don't have major concerns about safety, and
19 in fact I'm looking forward to seeing the results of the
20 study of using the drug in patients with asthma because
21 influenza and influenza A is a major cause of
22 exacerbations. I think we will get some important safety
23 information there. We do know there are a variety of types
24 of inhalers. Metered dose inhalers or powders can cause a
25 paradoxical bronchospasm. I'm somewhat reassured that

1 | there was not an observed increase in asthma attacks, but I
2 | think as the larger populations with asthma are studied,
3 | we'll learn more about that. I'm actually looking forward
4 | to seeing what those show.

5 | I do actually have a number of patients using
6 | Diskhalers of various sorts. It's really an excellent
7 | delivery device, but it does take instruction. I almost
8 | assume that it's going to take more than one visit. I give
9 | patients my best shot or the nurses do some teaching the
10 | first time around, but we know that it usually takes until
11 | at least the second visit, be it two weeks or a month
12 | later, for any kind of inhaler to really get the proper
13 | use.

14 | So, as it pertains to generalizability, there's
15 | a chance that the drug might work, in fact, less well when
16 | it's out in practice as compared in the study. When we
17 | evaluate these studies for potential approvability, you
18 | never know whether the drug is actually going to work
19 | better in normal practice than it does in the studies or
20 | work perhaps less well. One of my concerns is that this
21 | drug might work even less well in practice than what we've
22 | been able to see in the clinical studies.

23 | So, that just brings me to the last point about
24 | effectiveness. As I look through the background
25 | information, the way the study was designed, at least the

1 North American study, it was powered and powered
2 appropriately to detect a 1 and a half day difference among
3 treatment groups. The study in fact was overpowered
4 because of increased enrollments.

5 As I look through basically the main efficacy
6 variable which is in the intent-to-treat population, with
7 the North American study, there's a one-half day difference
8 between the two groups, which essentially is not
9 significant. So, granted in the influenza-positive group
10 there was a 1 day difference, but in the intent-to-treat
11 population, which again I think reflects better the actual
12 practice situation should this drug be approved, the
13 intent-to-treat group difference was only a half a day.
14 So, I see the North American study as being essentially a
15 negative study.

16 DR. HAMMER: Thank you.

17 Dr. Stanley.

18 DR. STANLEY: Thank you.

19 I really have minimal safety concerns. I share
20 some of the concerns of Dr. Li, that I'd like to see a
21 little more in asthmatics and maybe COPDers, but I think
22 the safety is pretty clear.

23 Effectiveness. It depends on how you define
24 that. The phase II studies would seem to show some
25 antiviral effectiveness when you look at the virology,

1 | although I bow to the concerns of the virologists on the
2 | committee.

3 | But clinical effectiveness, I'm really
4 | unconvinced. The discrepancy in the studies is one
5 | concern, and particularly with the North American study
6 | being the population we care about that showed no
7 | significant effect to me, but also the FDA's analysis on
8 | looking at the activity score. Even in what was called a
9 | successful European trial where there was a 2 and half day
10 | improvement in reaching endpoint, the activity scores
11 | between the placebo and treated patients really weren't
12 | significantly different, which is telling me that as far as
13 | getting people back to work and really making them on the
14 | whole feel better, I don't think we're seeing much of an
15 | effect. If I take that minimal effect and now translate it
16 | to the real world and to real practice, I agree with Dr.
17 | Li, I think we're going to see even less effect because
18 | you're not going to have as many true influenza-positives.

19 | I think the use of the Diskhaler is very
20 | troublesome because you don't have time for a learning
21 | curve. If you don't start treatment early, you're going to
22 | be even less effective and you don't have the learning
23 | curve to take three and four doses before you're doing it
24 | right.

25 | So, I have significant concerns, and I don't

1 | believe they've shown adequate efficacy.

2 | DR. HAMMER: Thank you.

3 | Dr. Hamilton.

4 | DR. HAMILTON: Unless my colleagues to my right
5 | change my mind in the course of their discussion, I intend
6 | to support the licensure application for safety and for
7 | efficacy from this submission. Why am I doing that?

8 | It's not because all the answers are in. They
9 | certainly are not in. However, I think they've met some
10 | critical guidelines. They've lived up to some guidelines
11 | that were established rather early on in the course of
12 | their research, as arguable as they may be.

13 | I'm coming down on the side that at this moment
14 | just in a general descriptive sense, the time to endpoint
15 | that they've outlined doesn't adequately reflect to me what
16 | the issue is. I think there is disease beyond that 3.5 or
17 | 4.5 days. I don't choose to call it rebound. I call it
18 | continuing disease, continuing misery that will not be
19 | accounted for, will not be reversed by this drug regimen.

20 | Nonetheless, I think in two studies that were
21 | credibly designed and followed prospectively and analyzed
22 | in depth, notwithstanding the points made by several
23 | members of the committee that it was only part of the
24 | story, I believe they've demonstrated sufficient efficacy
25 | to support their application.

1 I look forward to the discussions of my
2 colleagues to my right.

3 DR. HAMMER: Thank you.

4 Dr. Wong.

5 DR. WONG: I want to divide the question.

6 I think on safety I have no major concerns.

7 On effectiveness, I'm actually convinced that
8 this drug has significant in vivo antiviral activity, but
9 I'm not convinced that the applicant has demonstrated
10 clinically relevant benefits of treatment as the treatment
11 was administered in these studies.

12 I think that one possible explanation is that
13 we may not really know how best to use this drug at
14 present. People have mentioned that the means of
15 administration, the dose, the duration of therapy may or
16 may not be optimal.

17 But secondly, I had a great deal of trouble
18 with the way the data were presented in that the bulk of
19 the efficacy data were presented simply as median values
20 and then a p value was cited. When I asked specifically to
21 see some time-to-event curves, we didn't get to see them.
22 So, I think that this form of presentation of the data,
23 which I think is very abbreviated, might have been
24 convincing had all the studies given the same result and a
25 major effect. In the presence of seeing conflicting data,

1 I can't really conclude that clinically relevant efficacy
2 has been demonstrated.

3 DR. HAMMER: Thank you.

4 Dr. Yogev.

5 DR. YOGEV: I join my colleague to the left in
6 being a little bit upset about the presentation. I think
7 things were omitted which might make the difference on what
8 we're seeing.

9 There is no question that in the phase that you
10 showed antiviral therapy, it's there, but interestingly
11 enough, when you compare your own data, the inhalation
12 versus the intranasal inhalation to the placebo, it almost
13 looked the same in the group who is longer without the
14 intranasal. So, inhaled and placebo go within 3 days to
15 less than 1 log.

16 So, I think that the data presentation -- the
17 adolescent being as part of it was 106. Probably around
18 only 50 of them received the drug -- to suggest that it's
19 okay from 12, I have a problem.

20 Also I have a problem with I don't think the
21 European study is the same as the American study, at least
22 from what I was able to get from you. The time of
23 initiation of therapy seemed to be different, and in my
24 opinion it's a major problem with the whole way the study
25 was done because all of us agree the earlier, the better.

1 Your own data suggested the day 3 viral load is coming down
2 even in the placebo group by itself. One wants to see a
3 much stricter initiation of the drug from the time of
4 symptoms. That might be the whole difference between what
5 we see in Europe and in North America.

6 So, I don't talk about the safety at all
7 because I think it's there, and everybody said the same.

8 I for one think if you break your data down,
9 subpopulation, for example, older than 65, you have some
10 efficacy over there, but you don't have enough of a number.
11 So, I would like to agree with Dr. Hamilton that there is
12 something there. I just think these studies were not done
13 correctly to prove it. The major study, if we accept the
14 result, we have to go that it's a negative study.
15 Therefore, at this stage I don't think I would support that
16 we saw any efficacy of treatment in the way we're going to
17 do it in real life.

18 DR. HAMMER: Thank you.

19 Dr. Diaz.

20 DR. DIAZ: I likewise will break down the
21 question.

22 Very simply, I don't have any concerns about
23 the safety of the drug.

24 Actually with that in mind and with the
25 knowledge of the novelty of this drug and the fact that

1 | it is effective or at least in vitro it's effective against
2 | influenza A and B, I would be very anxious and excited to
3 | have a drug of such caliber if clinical efficacy was well
4 | documented because it would certainly allay a lot of issues
5 | that we have in the treatment of influenza currently.

6 | My concerns really fall along the lines of many
7 | of the concerns that have been issued here today by my
8 | colleagues, in particular, the dichotomy of the phase III
9 | studies based on the location that those studies were in,
10 | and in particular, the lack of predictiveness of the
11 | overseas studies to the North American study. I think we
12 | heard the FDA representative comment that we can certainly
13 | accept overseas studies for licensure if they are in some
14 | way predictive. Unfortunately, in this setting, we don't
15 | have that predictiveness and have a very large or at least
16 | a larger study in North America that shows quite the
17 | opposite.

18 | Although the prescribed protocol was followed
19 | and some endpoints were met, I too have concerns about
20 | whether we've satisfied clinical efficacy to a degree that
21 | is necessary. A lot of people today have shown, both from
22 | the sponsor and from the FDA's standpoint, a lot of very
23 | retrospective pouring over the data to try and sort out
24 | just what the problem or the differences were in that North
25 | American study compared to the other two studies. The

1 answer unfortunately wasn't forthcoming. It may be a very
2 simple answer, and if we only had it, it might explain
3 things, but unfortunately we don't have the answer.

4 Retrospectively I think it may have been
5 helpful to have had more information, very specific
6 information, about things such as exact time to enrollment,
7 the way the drug was taken, maybe issues about how many
8 times a day temperatures were taken, and a lot of very,
9 very detailed information that we frequently don't like to
10 obtain because of the barriers that it puts on the person
11 entering into the study. Yet, in this setting it may have
12 been helpful.

13 But likewise, Dr. Cox' comments I also would
14 laud in terms of it will be, hopefully in the future, very
15 important to know about issues surrounding this drug's
16 ability to decrease transmission in particular, and I think
17 some of the family studies may be helpful.

18 But at this point in time I have concerns that
19 we haven't really gotten to the point of full efficacy
20 documentation.

21 DR. HAMMER: Thank you.

22 Dr. Masur?

23 DR. MASUR: Well, I'm impressed at the entire
24 package of the drug discovery program and the drug
25 development, and I'm impressed that the studies were

1 developed in a very logical way, given the fact that this
2 is a very difficult disease to study with a short natural
3 history.

4 I share everyone's surprise that the 3002 study
5 did not confirm the efficacy of the other two studies.
6 It's not clear, based on the phase I and phase II data, as
7 to why that is. The various speculations have already been
8 reviewed. So, I can only mirror what has been said by
9 several of the people before, that this is a very difficult
10 package to use to be convinced that there is in fact
11 meaningful efficacy in North America for whatever reason.
12 I guess that's the dilemma that we're facing as to whether
13 or not enough data can be teased out to convince one that
14 there's effectiveness.

15 DR. HAMMER: Thank you.

16 Dr. El-Sadr.

17 DR. EL-SADR: I'll comment first on safety. I
18 really would like to see more data in asthmatics because I
19 think that's going to be a group that probably a medication
20 like this would be used for.

21 I think another concern I have is development
22 of resistance. I feel that resistance is part of the
23 safety profile or I consider it as a component of safety.
24 I'm not sure that in the population in which this drug was
25 studied that I would have expected that resistance would be

1 | seen. Probably in an immune suppressed population, maybe a
2 | more fragile population, that's the situation where you
3 | have more replication of virus and a longer course, and
4 | maybe that's where we would expect or where we would be
5 | likely to see some resistance developing. So, I'm not
6 | satisfied yet that resistance is not an issue, and I feel
7 | that studies, especially studies in immune suppressed
8 | populations or high-risk populations, should really look
9 | very carefully at the development of resistance. So,
10 | that's still a concern I have before sort of saying that
11 | this is a safe drug.

12 | Now, going to effectiveness or efficacy, I'm
13 | sitting here going through the sponsor's book actually and
14 | looking at the North American study, and whichever endpoint
15 | I look at, whether it be the time to alleviation of
16 | symptoms, whether we're looking at the influenza-positive
17 | group, or whether we're looking at the ones with baseline
18 | temperature again in the North American study, or whether
19 | we're looking at the development of complications or even
20 | one of the other endpoints, time to return to normal
21 | activity, in none of these endpoints -- none of them -- is
22 | there any evidence of a statistically significant
23 | difference between the placebo and the drug.

24 | I have to say that when I'm presented with two
25 | pivotal studies, one has 700 patients and the other one is

1 much smaller, I consider that the study that I would put
2 the most weight on. I think we've been sitting here trying
3 to think why didn't this drug work in North America. I
4 feel we should be asking why did it work in Europe because
5 maybe this is the gold standard.

6 I don't know whether saying there are cultural
7 differences can really help in explaining what goes on here
8 versus in Europe because we're really looking between the
9 arms of the studies. We're trying to look at a difference
10 between the placebo and the control, and it was clear from
11 the data that the sponsor presented and the FDA presented
12 that even though there was more use of these agents to
13 alleviate symptoms, there was no difference in the use
14 between the two arms.

15 So, I feel that the larger study that was
16 conducted in North America did not demonstrate efficacy in
17 any of the endpoints that I mentioned here, and there are
18 more that I didn't mention. Thus, I feel that the package,
19 as it is, does not demonstrate efficacy of this drug.

20 DR. HAMMER: Thank you.

21 Dr. Verter?

22 DR. VERTER: Yes. From what I heard today, I
23 guess I would concur that I don't have any serious problems
24 with the safety question, although I'd like to make note.
25 I believe it was Dr. Styrt that mentioned the possibility

1 of -- I think what she was saying was -- and I believe it
2 -- potentially underestimating the adverse event
3 comparisons because of the delivery system, that it may be
4 actually masking the difference. And if you were just out
5 there giving this drug with a true delivery system for a
6 control, you might see that those were increased a bit, but
7 that's a minor point perhaps.

8 I was a little disappointed -- I will concur
9 with someone down on my left here -- about the
10 presentation. First, when I read the book that was given
11 to us, it seemed to me there were really five studies that
12 could speak to this issue. I know the FDA said three and
13 then I think Glaxo presented one of these phase II studies,
14 but there was another phase II study. It's true that some
15 of those phase II studies had three arms rather than two,
16 but they did have two arms which were relevant to what we
17 were speaking of.

18 It seems to me if you're going to give an
19 overview of a series of trials that speak to an issue, that
20 somehow you should be able to present all of them in a
21 manner either in the book or for the committee where we
22 could evaluate all these in a similar manner. That goes to
23 things like overall intention to treat for the same primary
24 outcome, overall subgroup analyses such as the positive for
25 influenza, the ones who were febrile was another issue, the

1 timing of it, less than or greater than 30 hours or
2 whatever. I think that would have helped perhaps in
3 focusing on what groups there were that there may have been
4 efficacy consistently across the trials. It may or may not
5 have. I don't know since I don't have all the data,
6 although I tried to tease it apart. It may or may not have
7 strengthened some of your arguments.

8 Let me speak to the issue of the difference
9 between the trials. Whereas it's true that two of the
10 studies used the same protocol and all three studies
11 appeared to be well designed, well run, and well conducted,
12 there are some noticeable differences that I saw.

13 For example, comparing the European study and
14 the North American study, the placebo group in the European
15 study had a median of 1 and a half days longer in the
16 course of the disease, which would suggest that there's
17 more room to play in reducing the median. It was 7 and a
18 half versus 6. That may or may not play into it.

19 If you look at the zanamivir across the trials,
20 the median time to alleviation is quite similar across the
21 studies. So, a lot of this may be the underlying disease,
22 the etiology of it, the course of it, the environment in
23 which it's being studied.

24 Speaking to that latter issue, the other thing
25 which to me is almost pointing me in a direction is the

1 relationship between the use of acetaminophen and the cough
2 syrup, the percentage use versus the delta median. It's
3 almost a linear relationship. I agree with the FDA
4 presenter, Dr. Elashoff, that this is a very difficult
5 issue. These folks are taking it probably in response to
6 the symptoms. They may be taking it because they think it
7 will alleviate the symptoms, and teasing it apart is
8 probably impossible, although I have some thoughts about
9 things we could play with and maybe give you a hint. But
10 it's possible that the answer to that question is that in
11 North America, you have to tell people to stop taking
12 acetaminophen and cough syrup and maybe you'll see the
13 effect.

14 I think I'll stop there.

15 DR. HAMMER: Thank you.

16 Dr. Wittes?

17 DR. WITTES: Well, I don't have much to add to
18 what everybody has said.

19 As far as safety, I respect my clinical
20 colleagues' judgment about that.

21 As far as efficacy or effectiveness, I think
22 the problem that we're facing -- and it was expressed by
23 Dr. Wong -- is that when one sees marginal results in the
24 study that should have been the pivotal study, the most
25 important study, it's really crucial to present the data in

1 a way that's really clear and really covers all the
2 questions that reasonable people could ask. For me this
3 was one of the problems both in the presentation in the
4 book and in the presentation today and in the responses to
5 questions. So, if you analyze the data and look at it in a
6 way that tries to tease out what was there about the North
7 American study that was different from the others, or as
8 you had said, why are the others different from the North
9 American one, perhaps you could have given us more insight
10 as to what was going on.

11 The other issue that concerns me -- and it was
12 addressed by a few around the table -- is that when this
13 goes into practice, when this goes into the public, it's
14 very unlikely that the very high rate of flu that you had
15 in this study will be replicated. So, therefore, what one
16 would hope to see a larger effect -- that the magnitude of
17 the effect in the group with flu in the study one would
18 hope would have been larger so that there would be in the
19 intent-to-treat population in the real world, there would
20 actually be some effectiveness.

21 DR. HAMMER: Thank you.

22 Dr. Bertino?

23 DR. BERTINO: In terms of the safety issues, I
24 think that I could be convinced that this is a safe agent
25 in relatively healthy individuals, but I think that the

1 people with asthma, COPD, comorbid conditions, where
2 influenza may have a very large impact, those are the
3 people where we really need to see safety data in.

4 This really spills that into the efficacy
5 question. A couple of things come to mind. First of all,
6 I want to raise a question that Dr. Hendeles raised this
7 morning back to the FDA and maybe they could answer it at
8 the end of my comment, which is the two foreign studies
9 that show efficacy of a drug, is that enough to approve a
10 drug? So, I'll just leave that out there for a minute.

11 What I'm thinking is that out in the real
12 world, it's a Friday night, somebody is not feeling too
13 well, how are they going to get this drug? Or you have a
14 nursing home population where all of a sudden you have an
15 influenza outbreak and you've got 185 residents, most of
16 whom who cannot or will not cooperate with inhaling an
17 agent like this.

18 So, I think that in the populations in those
19 two foreign studies, efficacy in my mind was shown. I
20 think in the age breakdown data that we saw this afternoon,
21 I'm more convinced that efficacy in ages 50 and greater was
22 shown. To me a half a day difference in symptomatology or
23 feeling lousy or something like that, even if it was
24 statistically significant, I'm not sure that it's
25 clinically significant for most people.

1 So, that's my comments on it.

2 DR. HAMMER: Thank you.

3 Does the agency want to respond?

4 DR. BIRNKRANT: I'll begin the agency response,
5 in case others want to follow.

6 In general, we look at the totality of the
7 data. We've used that phrase many times. We have three
8 phase III trials, and we have two phase II trials, and we
9 have other supporting data. So, we look at the entire
10 package. So, that comprises not only phase I, II, and III
11 trials, but it also comprises, if you break it down a
12 different way, foreign studies and domestic studies. So,
13 we look at the whole package. We don't necessarily put
14 more weight on foreign versus domestic, domestic versus
15 foreign. We look at the total picture as we evaluate the
16 marketing application.

17 DR. HAMMER: I think that response answers it.
18 Dr. Jolson, do you have anything to add?

19 DR. JOLSON: Just another point that I'd make
20 --- and I think everyone's points are really well taken --
21 is that some of the issues that have been raised are
22 labeling issues in terms of how to use it, who should use
23 it, how to diagnose influenza, things that are really
24 separate from an efficacy determination. That gets a
25 little bit into the intent-to-treat versus the influenza-

1 positive treatment effect. That gets to the issue of how
2 to counsel a patient or how to decide on which patients
3 might be likely to benefit from it.

4 The question to you all would be is there data
5 that would help guide those choices, then assuming that the
6 label would capture some of those issues.

7 DR. HAMMER: Thank you.

8 I'll be the last one to comment on the first
9 question.

10 I'll take a step back. Personally I think we
11 have to really think about the disease under study. This
12 is a self-limited disease for the most part in healthy
13 individuals, although we're, as clinicians, most concerned
14 about the immunocompromised and high-risk populations that
15 have been described. But if you think about it from a
16 clinical trials perspective, a self-limited illness in a
17 mostly healthy population, we have to think about how
18 difficult those studies are to perform, what differences
19 you're really looking for that will be statistically
20 significant and clinically significant in a disease, for
21 the most part, that people get better from in 4 to 5 days,
22 even though some symptoms may linger, and also where
23 endpoints that one is discussing, except for temperature,
24 are soft. Coming from the HIV experience, which this
25 committee has had a lot of past history with, we know the

1 difficulty in interpreting soft and clinical types of
2 endpoints, and these are among the softest and most
3 objective, but what else is there when they in fact define
4 the disease?

5 In thinking about the data package that we've
6 seen, I respectfully disagree a little bit with some of my
7 colleagues. I think the package that was put together for
8 us to review was complete from basic science through the
9 clinical trials, and this morning's presentation I think
10 mirrored the backgrounder that we were given, and there was
11 a very good attempt to answer our questions in a very
12 slide-driven presentation this afternoon, which is a
13 testimony to technology. I imagine some of those slides
14 were made during the lunch hour.

15 I think from the experience on this committee,
16 it's not uncommon to see differences in the FDA analysis,
17 or at least new angles from the FDA analysis, that heighten
18 our questions and sharpen our focus. It's also the
19 function of the panelists to sharpen the focus and ask
20 questions that haven't been directly answered in the
21 initial presentation.

22 What I see on the safety side is really not an
23 issue. I think everyone thinks about whether the lactose
24 carrier will have some negative effects, but there's really
25 nothing one can tease out from how these studies were done

1 to say that. Again, I agree that there were no safety
2 issues presented.

3 On the efficacy side, I don't think personally
4 we can discount -- we have three pivotal trials that we've
5 been presented with and again two other phase II trials and
6 other supporting data. To toss out two of three trials
7 that show significant effects and are well done trials I
8 find difficulty with. Even though they were smaller and
9 less well powered than the major study, I think we've been
10 given some guidance that geography alone should not guide
11 our decision about which studies to think about. We should
12 take each one on its merits.

13 I personally also think -- and this may be
14 coming from the HIV perspective -- international studies
15 and doing more international cooperative studies is a plus.

16 Thinking about the North American study,
17 obviously we all would have liked to have seen a more
18 clear-cut result, but I look at it from where the two
19 presentations have consensus here as far as the sponsor and
20 the FDA. If you look at the intent-to-treat population
21 that was influenza-positive, it wasn't significant, but a
22 .078 p value to a nonstatistician at least is a trend when
23 we've got statistical significance in the other studies. I
24 may be incurring the wrath of some around here, but at
25 least to me that's supportive when you've done two other

1 studies that show significance.

2 I'm also impressed by the point estimate graph.
3 It was slide A55. At least the point estimates were
4 trending all on the same side of 0.

5 So, at least to me I think two studies show
6 efficacy. One does not. Is that strong enough to negate
7 those two studies? I think I've expressed that for me it's
8 not the case.

9 I think we also have to recognize that
10 oftentimes -- it's probably true more frequently than not
11 -- that the first agent in a class is not the ultimate
12 drug, and that there's importance, if one can see it from a
13 safety side and an efficacy side, to approve a drug both
14 for the population at risk and to promote further studies
15 both by this sponsor and by other sponsors.

16 The issue about where this drug will be used as
17 far as the general population that does or does not have
18 influenza, approval of such a drug will drive the
19 diagnostics such that rapid diagnostics for influenza in
20 physician's offices will become I think something we'll see
21 fairly soon.

22 So, those are my comments on safety and
23 efficacy.

24 Before we move to the formal vote, are there
25 any other comments on question 1 by the panel?

1 (No response.)

2 DR. HAMMER: Okay. If not, then it's time --
3 Dr. Jolson?

4 DR. JOLSON: Just a last issue, just to touch
5 on the issue that you raise, Scott, about self-limited,
6 acute illness that everyone is going to get better in a
7 couple days, the difficulties of the clinical trial design.
8 Would it be of any benefit just to spend a few minutes to
9 discuss the evidence that supported the approval and some
10 of the pitfalls of the two approved influenza agents, if
11 that would provide any additional context? That's one
12 issue that hasn't been discussed today.

13 DR. HAMMER: I would ask my colleagues whether
14 they would like to hear that and discuss that. I think
15 most of us are aware that the differences that were seen in
16 other studies of influenza, amantadine and more recently
17 with rimantadine, the differences, although significant,
18 were small. The patient numbers were small compared to the
19 package we're seeing today. Those drugs have limited use
20 in practice for the treatment of influenza, greater use for
21 prophylaxis, but still they are approved for this
22 indication with differences that are fairly small. And I
23 think we see those differences in experimental challenge
24 studies of anti-influenza agents, as well as in the
25 efficacy trials we've seen.

1 I don't know if others want to comment. I
2 think probably the best person in the room to talk about
3 this is not me but it's Dr. Hayden, if he wishes to
4 comment.

5 DR. HAYDEN: I would comment that there is a
6 long history of variation in terms of the study results
7 when amantadine and rimantadine have been tested for both
8 prophylaxis and efficacy. Some of this relates to
9 differences in strain and severity of illness, but more
10 often it's timing issues in terms of, for treatment,
11 clearly the earlier, the better, and I think we're probably
12 seeing that same sort of pattern here with the results of
13 the inhaled zanamivir trials.

14 But I think it's important to bear in mind that
15 in fact those drugs are associated with similar kinds, if
16 one looks historically, of effects on symptom resolution
17 and on functional improvement, as described in the
18 documents provided to you regarding zanamivir. It is I
19 think important to bear in mind that seeing some trials
20 where there's not statistical evidence of difference has
21 been the expected finding during flu trials historically.

22 DR. HAMMER: Thank you.

23 If there are no other comments or questions.

24 DR. MURPHY: One last thing because it came up
25 a couple of times, Scott, which is about the future ways

1 | that this may be used in practice, since there could be
2 | quite a number of variations upon that theme, if you will.
3 | That really should not be in your consideration. Your
4 | consideration is when the drug was used the way it was
5 | prescribed to be used, did it or did it not show efficacy.
6 | So, I just wanted to reemphasize that.

7 | DR. HAMMER: Thank you.

8 | DR. LI: Just a very quick question, point of
9 | information to the agency, for the non-American studies,
10 | are there site visits conducted and are they done in the
11 | same manner with the same results?

12 | DR. BIRNKRANT: We have a Division of
13 | Scientific Investigations with investigators who go out to
14 | predetermined sites based on consultation with the Review
15 | Division. So, we do have investigators in Australia and we
16 | will investigate the U.S. study sites as well.

17 | DR. MURPHY: I just want to expand upon that
18 | because it has come up a number of times and I think it's a
19 | very important point that the committee has to be
20 | comfortable with, and that is at one time the FDA was not
21 | as enthusiastic about some foreign studies. Over the last
22 | decade, we have spent a tremendous amount of time globally
23 | in harmonization of studies. It is going to become
24 | increasingly, I think, apparent, if not already apparent
25 | certainly in HIV, malaria, TB, that we will see studies

1 from foreign countries. The whole effort that has been
2 going on has been that there's standardization, there are
3 guidances on protocols, on manufacturing, on inspections,
4 on reporting, on data collection.

5 What we're trying to tell you is that we are
6 comfortable that the foreign studies were conducted,
7 implemented, data collected, and evaluated in an acceptable
8 manner, and at the same standards as if though they were
9 performed in the U.S.

10 DR. LI: Do you think it would have made a
11 difference in our discussion if we had been talking about
12 the pivotal studies as study A, study B, and study C,
13 rather than the southern hemisphere, the European, and the
14 American studies?

15 DR. MURPHY: Possibly.

16 DR. HAMMER: I think the agency has answered
17 the question. I think geography is not the issue. The
18 issue is each study, how it stands on its own merits, and
19 then comparing the studies as to their relative merits and
20 strengths. At least speaking as the Chair, I would suggest
21 that the geographic location of the studies not be a
22 consideration.

23 I don't think these two studies would be before
24 us, the non-U.S. studies. They wouldn't be in the package.
25 They wouldn't be presented here if the agency felt that we

1 shouldn't consider them comparably performed to the North
2 American study.

3 Dr. Verter.

4 DR. VERTER: Just a quick one. In my comments,
5 in fact I was conceding that the studies were conducted
6 well, but I can't separate the geography because of the
7 differences that I see.

8 DR. HAMMER: I'm only talking with respect to
9 quality of the study and quality of the data. There may be
10 explanations for why there are differences, but I don't
11 think we should be assuming in any regard that these
12 studies were less well done, the data less well put in the
13 case report form, or there were any site monitoring issues
14 that make us suspect of the performance of the studies.
15 Now, the differences may be because of other factors, but
16 honestly, I don't think we would be seeing these studies
17 today if the agency felt they weren't ready for prime time
18 and to be here in front of us as pivotal trials.

19 DR. VERTER: I agree with that.

20 DR. MURPHY: Or we would point out to you where
21 the issues were.

22 DR. HAMMER: Dr. Stanley?

23 DR. STANLEY: Just one last point to build on
24 something that Dr. Verter said earlier. As far as the
25 successful European study, I think it's really key to look

1 at the role of the anti-inflammatories because the reason
2 you got to a 2 and a half day savings is not because the
3 treated people go there quicker, but it's because the
4 placebo people stayed symptomatic longer. With using half
5 the dose of acetaminophen compared to the other two trials,
6 I think there's a very clear indication that what you're
7 doing is you're replacing the use of acetaminophen. You
8 can achieve close to the same goal if they just use more
9 acetaminophen, which is why I go back to the role of this
10 drug in viral shedding and, from the public health aspect,
11 its effect in being able to stem an epidemic within a
12 family or within a location as opposed to treating an
13 individual to make them feel clinically better.

14 DR. HAMMER: A point well taken.

15 Dr. Stoller?

16 DR. STOLLER: I have a question which bears on
17 kind of FDA input, and that is, the principle of fairness
18 would obviously dictate that if the primary outcome
19 measures were pre-negotiated as these time points for
20 resolution of symptoms, then that bears on one assessment
21 of our deliberation as to whether that endpoint has been
22 satisfied. If, on the other hand, I think we've heard
23 around the table that there's some reservation about the
24 clinical relevance of that outcome measure, albeit it pre-
25 negotiated, and in fact the comments that we've heard from

1 | the FDA have a lot to do with examining the primary outcome
2 | measure in other perhaps more clinically relevant ways.
3 | So, the question is, from a committee deliberation point of
4 | view, how do we react to that?

5 | I suppose if I were asked seven years ago
6 | whether I would have acknowledged the outcome measure as
7 | articulated, we might have heard a similar discussion at
8 | that time to what we're seeing now. And in fairness to the
9 | discussions, I think it's relevant to hear comment on that
10 | because the equivocation, at least in my own view, regards
11 | the perhaps clinical non-relevance and, as I think some
12 | other members have commented, the inability to flush out
13 | the real clinical evolution of disease based on that
14 | outcome measure. So, some discussion of that might be
15 | helpful to my thoughts.

16 | DR. JOLSON: I think it's an issue that we
17 | struggle with as well, not just with this application. I
18 | think it was also something that was recognized at the time
19 | that the protocols were submitted, that drugs for treatment
20 | of influenza for the reasons that Dr. Hammer mentioned are
21 | extraordinarily difficult to develop, and it is
22 | extraordinarily difficult to capture a treatment effect
23 | when these are all healthy adults and they're going to get
24 | better before you can blink your eye. We realized at the
25 | time that any endpoint that we used was somewhat arbitrary.

1 | These were the endpoints that were used after some initial
2 | clinical development and were agreed upon, and they were
3 | the best guess at the time.

4 | In general, when we've agreed to an endpoint,
5 | in the absence of other information, and an endpoint is
6 | met, usually that implies that something favorable will
7 | happen to the application. That's not always the case. If
8 | it turns out in hindsight that the endpoint doesn't stand
9 | up to scrutiny, then it has to be reexamined.

10 | I think here in the FDA presentation, what
11 | we've tried to do is not to say that the initial choice of
12 | endpoint was wrong. I think we're just saying to you that,
13 | as Dr. Birnkrant was mentioning, there are many ways to
14 | look at the data, and we could probably spend the rest of
15 | the afternoon with different exploratory analyses that
16 | would provide different levels of reassurance and other
17 | analyses that would just raise anxiety more.

18 | We're still left, though, with at some point we
19 | did make a cut, and it's very hard to say that it was a
20 | poor choice or a good choice. And one thing that we would
21 | hope the committee would think about is, well, if not this
22 | endpoint, then what's a better way of looking at it because
23 | even counting days of symptoms through 14 days may not be
24 | reasonable either since most of the severe symptoms, the
25 | really debilitating symptoms, are very early on and the

1 other things are more a nuisance. It doesn't seem right to
2 weigh all those days the same way.

3 So, I think our analysis is just one stab of
4 looking at it. I don't think it's a perfect way of looking
5 at it, and I don't think it betrays the whole picture. It
6 just was an attempt to show just different ways of
7 reflecting the data.

8 So, I hope that answers your question.

9 DR. MURPHY: I think I might phrase is slightly
10 differently, which is that I don't think we've changed our
11 opinion of that adequate endpoint at this time. I think we
12 felt it's our responsibility to present as many different
13 ways of looking at it, but I think from a clinical
14 endpoint, we would still say in these studies that these
15 would be basically the endpoints because again, as Dr.
16 Jolson said, we felt we picked the more severe points. The
17 fact that you have a headache on day 7 if your temperature
18 is down and the other parameters that were the endpoints
19 were there, that's what we agreed to and I think we still
20 stick to that.

21 DR. HAMMER: One more comment. Dr. Elashoff?

22 DR. ELASHOFF: Yes. I guess I would disagree
23 with that. In looking at the data over the past two
24 months, it's really apparent that the primary endpoint does
25 not capture what's happening on a patient-by-patient basis.

1 Individual symptoms might come and go, but the overall
2 measures -- they were asked an overall question, how are
3 your symptoms -- in the North American study, there was no
4 difference. They were asked an overall activity. How much
5 activity do you have? Again, no difference.

6 So, there wasn't a lot of information to guide
7 what might be a good endpoint. This was certainly a
8 reasonable one. On reflection, looking at all the data, it
9 was a poor choice. I'm not saying I know what the best
10 choice is, but all of the ways that I looked at it that I'm
11 comfortable with, there was really no effect in North
12 America and that was as large as the other two studies.

13 DR. MURPHY: I think that what you understand
14 is that we have and we encourage differences of opinion.
15 Okay? That is a statistician speaking. You have heard
16 from the clinicians. You have a combination of clinicians
17 and statisticians around the table. That's why you're
18 here, to deliberate and give us your opinion also. So,
19 we're trying to tell you that we do have a variety of ways
20 of looking at the data. The statisticians look at it one
21 way and the clinicians are looking at it in another.
22 That's why we need your advice also.

23 DR. HAMMER: Thank you. We do need to move on
24 to our vote. I think only questions that clarify issues of
25 regulatory phenomena that help us make a ruling or a vote

1 | should be asked right now because we have much more work to
2 | do possibly.

3 | I think what this discussion highlights is the
4 | reason why this is before the committee in the first place.

5 | We are now ready for the vote. The first
6 | question is the voting question. I'll repeat it again.
7 | Does the information presented by the applicant support the
8 | safety and effectiveness of zanamivir for treatment of
9 | influenza? I listed before the voting members which I
10 | think is everyone or everyone here. If you are voting in
11 | the affirmative, that is, you think the data do support
12 | safety and effectiveness of zanamivir, please raise your
13 | hand. This is the affirmative vote.

14 | DR. YOGEV: Can you separate the two?

15 | DR. HAMMER: No, we cannot separate the two.
16 | We can as a secondary vote, but as a primary vote, this is
17 | the question we're being asked.

18 | Again, just to make sure everyone is clear,
19 | we're voting on safety and effectiveness, the first
20 | question, voting in favor of.

21 | (A show of hands.)

22 | DR. HAMMER: Those who think safety and
23 | effectiveness have not been demonstrated, again as a global
24 | question.

25 | (A show of hands.)

1 DR. HAMMER: We have 4 affirmative votes and 13
2 negative votes.

3 The corollary question. We had several to
4 consider if the vote was yes. We only have one if the vote
5 was no, although if the agency wishes us to consider
6 additional items here, we'll be happy to do it. If no,
7 what additional studies are needed?

8 I think once again I'll start with our expert
9 consultants and panelists. Dr. Poland.

10 DR. POLAND: Sorry to go back a little bit, but
11 we were only presented with two choices. Yes means
12 something and no means something.

13 DR. HAMMER: Yes. Let me just clarify. What
14 this committee does is make a recommendation to the agency
15 only.

16 DR. POLAND: Right, I understand. I guess the
17 recommendation that I would kind of like to see go forward
18 is the answer is unclear. We have an A study and a B study
19 that suggests one answer, and a C study that's as large as
20 A and B that suggests an opposite answer. So, to me the
21 answer is not yes or no, but unclear and hence further
22 studies are necessary.

23 I guess we've already heard that one family
24 study is either ongoing or about to begin. I think any
25 kind of parameters that could be built in quantitating

1 estimates of viral transmission would be very useful,
2 indeed.

3 I think the other issue would be to try to do
4 that at a lower age group than I think 12 was proposed
5 because it is school children who are the transmitters and
6 the spreaders of this disease, unlike other diseases, and I
7 could see a real value in attacking the problem at that
8 level. So, childhood studies would be important.

9 I think studies of the elderly, high-risk, and
10 immunocompromised are also important, though I don't think
11 necessarily absolutely necessary for licensure.

12 I also think that what may be -- and let me
13 call it confounding or contaminating the studies may very
14 well be the actual time from the beginning of symptoms to
15 the initiation of treatment. I think it would be very
16 helpful to have some very clear-cut, as tight as you can
17 make them, studies looking at early, intermediate, and late
18 initiation of treatment.

19 Finally -- and this reflects my own ignorance
20 about the delivery mechanisms of this -- I wonder whether
21 there couldn't be some studies using this more as a metered
22 dose inhaler type thing rather than the thing that we saw
23 here today.

24 DR. HAMMER: Thank you.

25 Dr. Kilbourne?

1 DR. KILBOURNE: Well, I have the same
2 reservation about the same entry point being assured in all
3 studies in terms of the timing. I think that is critical.
4 It's a disease where most of virus replication has occurred
5 probably before symptoms even begin, and there is a very
6 narrow window. The more sharply that could be defined, the
7 more definitive answer you're going to get.

8 I said earlier I do feel that studies would
9 benefit enormously by getting good, quantitative virology
10 as one goes along. That's a horrible task. It's very
11 labor intensive, but I think it's well worthwhile. That
12 was done with amantadine studies, rimantadine studies, and
13 I think it's not too much to ask of it here.

14 DR. HAMMER: Thank you.

15 Dr. Cox?

16 DR. COX: My comments will echo those of my
17 colleagues who have just spoken. I voted no with real
18 reluctance because there's clearly a great need for
19 additional antiviral compounds for influenza, and watching
20 the development of this particular compound has been
21 extremely exciting. But I think that we do need to see
22 additional information presented to us with virologic
23 endpoints, as my colleagues have mentioned, and to look for
24 reductions in transmission.

25 Also, I think there needs to be some

1 clarification of issues of resistance and whether resistant
2 strains really are antigenically different and whether
3 emergence of resistance in response to use of this drug for
4 treatment could drive antigenic variation. I think that's
5 a very interesting area and one that needs to be explored
6 more fully.

7 DR. HAMMER: Thank you.

8 Dr. Hendeles?

9 DR. HENDELES: I have two suggestions to add.
10 One is that a study needs to be repeated with a larger
11 dosing, a dose response study that includes a dose high
12 enough to see whether what was seen in the North American
13 study was seen because of too low a dose or not. It's
14 possible that they just didn't give a high enough dose or
15 something about the timing of the regimen, et cetera that
16 did not distinguish sufficiently.

17 The second point I want to make is that Dr.
18 Elashoff presented a way of looking at the data that was
19 very meaningful to me. It's on page 8 and 9 of his handout
20 where he looks at the time course of symptoms and
21 activities, and it looks very clear to me there that there
22 weren't big differences between the three different
23 studies, that that time course of symptoms, the difference
24 between placebo and active drug, was similar for all three
25 studies. So, I would suggest looking at the data in that

1 way, and one might want to pick a secondary endpoint as to
2 what it is at 5 days or whatever. But I think this is much
3 more meaningful than the endpoints that were picked and
4 agreed upon by FDA.

5 DR. HAMMER: Thank you.

6 Dr. Stoller.

7 DR. STOLLER: I echo Dr. Cox' comment. I too
8 voted no with some reluctance because I share Dr. Hammer's
9 perspective about the benefits of having a drug for a
10 problem that, although perhaps clinically self-limited,
11 certainly has a burden of illness that's significant, and
12 also for the corollary benefits of having a drug driving
13 diagnostic testing which I believe is much needed in
14 ascertaining influenza.

15 That said, my reservations regard looking at
16 the dynamics of the data and the full picture of the data,
17 as I think we've heard, recognizing time-to-event curves
18 and the distribution of data, would be more helpful in my
19 own assessment.

20 I also quite agree with the comments that have
21 been made that the studies perhaps should be block
22 randomized rather than post hoc analyses of time to first
23 therapy. What we've seen in the secondary analyses is an
24 attempt to tease out the 36 hour time frame as to when
25 therapy was initiated and massaging, if you will, the

1 efficacy in the North American data regarding the benefit
2 in early therapy. But I think that if that point is to
3 truly have credence, that one needs to design that into a
4 stratified, up-front randomization and look at those early
5 treated patients, those intermediately treated patients
6 from first symptom onset to therapy, and those later
7 treated patients as an up-front decision in block
8 randomization.

9 My other comment regards the need, from my
10 point of view, of recognizing the fact that we should
11 absent issues of effectiveness from deliberations of
12 efficacy, which I fully acknowledge. I, nonetheless, think
13 that the impact of such a drug from a population point of
14 view is greatest in those patients in which it's needed the
15 most, and I would be far more clinically impressed with
16 studies, as I understand are now underway, with regard to
17 patients with COPD and immunocompromised, recognizing the
18 tremendous burden of evaluating that population, but also
19 recognizing the outcome measures in that group may be
20 easier to ascertain than the somewhat more nebulous
21 symptomatic outcome measures. So, there may be room for
22 examining focus studies in COPD populations in a larger
23 proportion of truly high-risk individuals that would be
24 more persuasive to me. Even if the magnitude of the
25 clinical benefits were perhaps smaller, the types of

1 | clinical outcome events would be certainly more pronounced.

2 | So, those would be my specific suggestions.

3 | DR. HAMMER: Thank you.

4 | Dr. Li.

5 | DR. LI: First I want to say that I thought the
6 | sponsor's presentation in fact was excellent, and I didn't
7 | have any problem with the way the information was
8 | presented.

9 | In terms of future studies, rather than using a
10 | baseball analogy, maybe I'll use a hunting analogy. I
11 | think these studies were very ambitious and they represent
12 | a shotgun approach. What I might suggest is a more focused
13 | rifle shot approach. That I think is similar to what Dr.
14 | Stoller was saying, as an example.

15 | I think that this drug does have antiviral
16 | activity and there may well be a way to use it and a
17 | population to use it in that's effective. It just didn't
18 | turn out in my view to be demonstrated in the information
19 | that was presented.

20 | Again, as an example, one might try
21 | deliberately to have earlier use of the drug in the course
22 | of the illness, aimed for, say, 24 hours from the onset of
23 | symptoms. It's a little difficult to do. You might have
24 | to have participants learn to use the inhaler, have the
25 | medications available at home. They may have to self-

1 initiate. There may be other challenges, but at least
2 starting earlier as part of the study would be one
3 possibility.

4 I think another population would be the older
5 age group. Maybe patients over 50, if they use the product
6 within 24 hours of symptoms, may show very significant
7 efficacy and maybe enough to have the product approved and
8 available for doctors to use. I think we all would be
9 excited about that if that were the case.

10 I think someone also mentioned the younger age
11 group. I would agree with that also.

12 You could change entry criteria to have maybe a
13 higher body temperature for entry into the study, rather
14 than the lower one.

15 Two other quick points to mention. I still
16 think the intent-to-treat is the proper group to examine,
17 and it was actually quite interesting to see the influenza-
18 positive population results displayed to me. But in fact,
19 the way the drug is going to be used really I think will be
20 based on clinical criteria, at least for the time being.

21 The last point is in the allergy and asthma
22 business, when we look at drug applications or even drug
23 studies, we're very used to looking at symptom scores,
24 supplemental medication scores, global assessment scores,
25 and I think that the way that the agency presented the

1 | information, which was similar to that approach, was
2 | helpful.

3 | DR. HAMMER: Thank you.

4 | Dr. Stanley?

5 | DR. STANLEY: Well, Dr. Li is reading my mind.
6 | I just want to reiterate that I'm very skeptical that this
7 | drug is going to be useful in the general population in
8 | alleviating symptoms. So, I would urge the company to look
9 | at the populations most affected: the young, the elderly,
10 | the true high-risk, the immunocompromised where resistance
11 | may be better evaluated.

12 | I also think that this endpoint is not really
13 | reflective of what's happening in the individuals and would
14 | urge virologic endpoints and total symptom scores, as Dr.
15 | Li said. I think those will end up being much more helpful
16 | than this endpoint.

17 | DR. HAMMER: Thank you.

18 | Dr. Hamilton.

19 | DR. HAMILTON: I'm relatively new to this
20 | committee and I'm struck by a couple of our prior
21 | experiences in which we approved or disapproved various
22 | agents that were proposed for HIV, in which situations, on
23 | the basis of surrogate markers collected over periods as
24 | short as 16 weeks, drugs were provisionally approved. It's
25 | somewhat dismaying to me because I really am much more

1 | interested in the clinical impact of these drugs for
2 | whatever they might be. In this case the sponsors did
3 | their best to identify what those clinical events might be.

4 | Now, I don't think that the population in which
5 | it was demonstrated on this occasion is the one where it's
6 | going to have the greatest impact. I too am in favor of
7 | testing this drug in those at higher risk, special
8 | populations of various kinds, and I would like to encourage
9 | them to focus on clinical endpoints because that's what's
10 | meaningful to the patient. The patient doesn't care about
11 | what their viral load is or what their nasal viral load is.

12 | DR. HAMMER: Thank you.

13 | Dr. Wong.

14 | DR. WONG: Well, I'll be very brief. I also
15 | was very reluctant in voting no because I believe that the
16 | data we saw today shows that this is a very promising
17 | antiviral. I think that just a little bit more prospective
18 | analysis with some of the targeting that we heard about
19 | earlier will nail the case.

20 | DR. HAMMER: Thank you.

21 | Dr. Diaz.

22 | DR. DIAZ: I think all of my suggestions have
23 | either been echoed by someone else. I think the idea of
24 | block randomization is a good idea, and in particular,
25 | looking at the elderly population and some of the high-risk

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1 population, one is going to have to take into consideration
2 that in those groups, there will be a much higher
3 percentage of individuals who have been vaccinated in that
4 flu season and to keep that in mind in terms of randomizing
5 and getting virologic data on those individuals in
6 particular as to whether their isolate strain matches the
7 vaccine will come into play in analysis in those
8 individuals.

9 I too would comment that perhaps looking at
10 some of these higher risk populations or the elderly or the
11 very young will hopefully nail this very quickly in terms
12 of giving us better endpoints for satisfying efficacy in
13 the panel.

14 DR. HAMMER: Thank you.

15 Dr. Masur.

16 DR. MASUR: Well, I'm impressed that the
17 studies have already been planned or ongoing in children
18 and asthmatics and the elderly and immunosuppressed. So, I
19 would hope that those will continue to be pushed
20 aggressively because, as I guess everybody is emphasizing,
21 this drug logically should have activity, and the real
22 issue is how to use it to its best advantage, both in terms
23 of the way it's delivered, the timing with which it's given
24 in relation to the illness, and in which populations. So,
25 I'm glad that these studies are planned and underway, and

1 | hopefully we'll see the results shortly.

2 | DR. HAMMER: Thank you.

3 | Dr. El-Sadr?

4 | (No response.)

5 | DR. HAMMER: Dr. Verter?

6 | DR. VERTER: I had two suggestions. One, I
7 | have a feeling that both Dr. Elashoff and the statisticians
8 | at Glaxo could probably get a lot of insight into the data
9 | by now dredging it a little bit more, unless you've already
10 | done that, and specifically trying to give yourself some
11 | insights as to what the differences were across the three
12 | studies that may have contributed to this, such as the
13 | timing, the use of the concomitant drugs.

14 | The other is kind of a far-out thought, if you
15 | have the resources, since in the U.S. you're unlikely to be
16 | able to address the control, acetaminophen and cough syrup,
17 | is to maybe consider a factorial trial.

18 | DR. HAMMER: Thank you.

19 | Dr. Wittes?

20 | DR. WITTES: Yes, I'd like to say two things.

21 | First, I too voted reluctantly, and I want to
22 | say that I am uncomfortable changing the primary endpoint.
23 | I feel that we need to evaluate the studies on the basis of
24 | the endpoint that you did prespecify, otherwise I think it
25 | becomes really a moving target. Although we might prefer

1 something else in general, I think it's hard to imagine
2 drug development where you don't know what the game plan
3 is.

4 My own problem really was the way the data was
5 presented. I felt there were unanswered questions for me,
6 too much missing from the description of what you actually
7 did. The sensitivity analysis seemed to be limited only to
8 the North American study. We need to see sensitivity
9 analysis in the other studies as well.

10 So, again, I want to echo what some other
11 people are saying. I think you've got a lot of the stuff
12 there, but you need to analyze it and present it more
13 completely.

14 DR. HAMMER: Thank you.

15 Dr. Bertino.

16 DR. BERTINO: Well, I'm glad Dr. Verter used
17 the term "data dredging" because I was going to use that
18 before, but I'm surrounded by statisticians and I was
19 scared to death to do that.

20 (Laughter.)

21 DR. BERTINO: I think just two comments.

22 While influenza is often a self-limiting
23 disease either by cure or death, if you take a look at the
24 thrombolysis model where we know that if you have chest
25 pain within a certain time period, you use TPA or

1 | retaplastase, and after that you can use streptokinase, and
2 | after that you don't use anything, it would be interesting
3 | to go back and look at the data and say, based on onset of
4 | symptoms and onset of treatment, when should we use this
5 | drug. When is it not going to be effective? Because I
6 | don't think insurance carriers are going to pay for it on a
7 | routine basis anyway. So, I think that that would be of
8 | interest to know.

9 | Then I think probably this drug is going to
10 | have a bigger role -- and I'd be interested to hear what
11 | Dr. Hayden had to say -- in prophylaxis rather than in
12 | treatment because my concern about treatment is that by the
13 | time treatment gets initiated, it may be too late because
14 | of availability of drug, because of inability to administer
15 | this interesting but unusual dosage form of drug. I think
16 | that for a lot of people, if you're going to use it for
17 | treatment, you're going to need something other than a dry
18 | powder. You're going to need a nebulized solution that you
19 | can give them.

20 | DR. HAMMER: I don't have really any other
21 | suggestions. I think the studies that were outlined that
22 | are ongoing or planned by the sponsor cover many of the
23 | bases. What my colleagues have mentioned cover the rest.

24 | I just have one virologic suggestion and it is
25 | a corollary to what Dr. Kilbourne had mentioned earlier.

1 | Although aggressive attempts to culture and quantitate
2 | replication-competent virus need to continue and be
3 | intensified, I think given what we know about the virology
4 | here, developing a quantitative PCR may be helpful to help
5 | monitor this, even though it doesn't tell you whether it's
6 | replication-competent or not, but also I think it's a way
7 | to get a better handle on potential resistance emerging by
8 | using PCR to go after the neuraminidase and hemagglutinin
9 | genes days into therapy. Even when you can't retrieve
10 | virus that's culturable, you maybe able to PCR out those
11 | genes and look at the mutational patterns that you might or
12 | might not see, and I think that kind of virology data done
13 | intensively in a relatively small number of patients may be
14 | quite interesting.

15 | But I think all the other general suggestions
16 | for which populations and what types of studies should be
17 | done -- I just have one safety issue, and that is we have a
18 | 28 day exposure in prophylaxis. We have these 5 day
19 | exposures in treatment. One thing that may happen and we
20 | should be developing some safety data is reexposure to this
21 | because there may be people who get prescribed this two or
22 | three or four times during a season or even the next
23 | season, and if there are potential sensitizing issues that
24 | we don't know about, that's an important thing to develop.
25 | So, I think some safety information on reexposure would be

1 helpful.

2 Let me turn to Dr. Birnkrant and ask her if
3 there are more issues you want us to discuss.

4 DR. BIRNKRANT: I was hoping we can move to
5 question 7 at this point.

6 DR. HAMMER: Okay. I didn't do that because of
7 the instructions on the top of the page, but that's why I
8 asked.

9 This is I think a corollary to some of the
10 suggestions that have been made, but question 7 is really a
11 statement. Please discuss your recommendations for design
12 of future studies of influenza treatment, I think putting
13 some of us on the spot to try to give specific advice.

14 So, I think I'll start on my right this time.
15 And I don't know. Dr. Bertino, do you have any suggestions
16 for the future studies of influenza treatment?

17 DR. BERTINO: Yes. I think a study versus
18 rimantadine for both prophylaxis and treatment.

19 DR. HAMMER: Dr. Wittes?

20 DR. WITTES: I pass.

21 DR. HAMMER: Dr. Verter.

22 DR. VERTER: I made the comment earlier.

23 DR. HAMMER: Dr. El-Sadr?

24 DR. EL-SADR: I think we made the comments. I
25 think there's really nothing wrong with these studies. I

1 think they were well designed and well conducted. I think
2 we've learned an awful lot from the analysis of the results
3 of these studies to try to tailor maybe to different
4 populations, as well as also trying to come up with maybe
5 potentially another type of primary outcome that reflects
6 more of the global symptoms that the patients have. But I
7 think the data that we've looked at today and you've been
8 looking at I think would be very helpful in trying to
9 define outcomes, which I think is the tough part in these
10 types of studies.

11 DR. HAMMER: Dr. Masur?

12 DR. MASUR: I have nothing more.

13 DR. HAMMER: Dr. Diaz?

14 (No response.)

15 DR. HAMMER: Dr. Stanley?

16 (No response.)

17 DR. HAMMER: Dr. Stoller?

18 DR. STOLLER: I'll simply reiterate my
19 comments. It sounds to me, and I'm gratified to hear, as
20 Dr. Masur said, that many of the studies that would be
21 germane to my thinking are actually underway. I would
22 again reiterate what Dr. Wittes said that when those data
23 are shown with regard to the agreed upon primary outcome,
24 that they show the shape of the events as they develop
25 related to the agreed upon primary outcome. I'm not

1 | advocating for altering the outcome as seeing the fullest
2 | dimension of the measures that have been agreed upon.

3 | DR. HAMMER: Thank you.

4 | Dr. Cox?

5 | DR. COX: Yes. I'm very optimistic considering
6 | the studies that are underway, and I would echo a comment
7 | from one of my colleagues that a comparison with
8 | rimantadine would be very useful.

9 | DR. HAMMER: Thank you.

10 | Dr. Kilbourne.

11 | DR. KILBOURNE: I have nothing really to add
12 | except that perhaps following bacterial colonization might
13 | be interesting as a site of necrotizing virus which paves
14 | the way for bacterial colonization, some evidence even with
15 | a live virus attenuated vaccines that this occurs. This is
16 | certainly very indirect, but I think it might give you
17 | information.

18 | DR. HAMMER: Thank you.

19 | I don't have much to add. One thing I might
20 | suggest because it took up so much time in the discussion
21 | here as far as interpretation and what's the proper
22 | endpoint, given the fact that by the nature of this
23 | disease, soft endpoints are going to be part of a global
24 | definition if you did look at an intent-to-treat population
25 | and then the subpopulation of influenza-positive,

1 developing perhaps -- I don't know if this is a cop-out --
2 but two co-primary objectives might be helpful, one that's
3 a crosscut and one that's a broader picture over a
4 respectable period of time, although I think the point made
5 earlier that trying to do symptoms daily over 14 days and
6 coming up with a summary score may be just as problematic
7 as choosing a median time. But I think one of the issues
8 we had today reflects two sides of the interpretation here,
9 and developing a primary endpoint or primary objectives
10 that allow you flexibility within the statistical validity
11 of the study might be quite helpful to avoid some of the
12 difficulties that were evident in the discussion.

13 I also think that the lack of commentary that
14 you've heard is not just people going to the airport, but
15 that the panel is as beguiled by what to do with this
16 disease as the agency and the sponsors in trying to develop
17 good studies and then see them through over years.

18 Also, I keep doing this, but an analogy to HIV.
19 You start a study, you plan a study, then you're three
20 years down the line with the results, and you're always
21 smarter at that end than you were at the beginning. That
22 phenomenon of clinical trials is not going to change.

23 Is there anything further that you would like
24 us to do?

25 DR. BIRNKRANT: I don't think so. Thank you

1 very much.

2 DR. HAMMER: On that note, I'd like to thank my
3 colleagues on the committee, the guest consultants, the
4 members of the agency, the people in the audience who came
5 as interested parties, and particularly the sponsor, Glaxo
6 Wellcome, for their presentation today. Thank you.

7 We're closed.

8 (Whereupon, at 4:05 p.m., the committee was
9 adjourned.)

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