DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE

Tuesday, March 19, 2002

8:00 a.m.

Holiday Inn
Two Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

Roy M. Gulick, M.D., M.P.H., Chair
Tara P. Turner, Pharm.D., Executive Secretary

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Sharilyn K. Stanley, M.D.
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FDA

Russ Fleischer, PA-C, M.P.H.
Debra B. Birnkrant, M.D.
Thomas Hammerstrom, Ph.D.
Mark Goldberger, M.D.

NON-VOTING MEMBER

Eugene Sun, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. GULICK: Good morning, everybody. I am Tip Gulick, from Cornell University. I am happy to call to order this meeting of the Antiviral Advisory Committee. We would like to start by going around the table and introducing the members of the committee. So please, state your name and your affiliation. Dr. Sun, shall we start with your?

Introductions

DR. SUN: Eugene Sun, Abbott Laboratories.

DR. BRASS: Eric Brass, Harbor-UCLA Medical Center.

DR. RELLER: Barth Reller, Duke University Medical Center.

DR. HENCHAL: I am Erik Henchal, US Army Medical Research Institute for Infectious Diseases, Fort Detrick.

DR. GARDNER: Jacqueline Gardner, University of Washington, in Seattle.

DR. ATMAR: Robert Atmar, Baylor College.

DR. WONG: Brian Wong, VA Connecticut Health Care System and Yale University.

DR. FLETCHER: Courtney Fletcher, from the

School of Pharmacy, University of Colorado Health Sciences Center.

DR. TURNER: Tara Turner, executive secretary for the committee.

DR. SCHAPIRO: Jonathan Schapiro, Stanford.

DR. GORDIN: Fred Gordin, VA Medical Center, Washington, D.C. and George Washington University.

DR. KUMAR: Princy Kumar, Georgetown University, Washington, D.C.

DR. DEGRUTTOLA: Victor DeGruttola, Harvard School of Public Health.

DR. ENGLUND: Janet Englund, University of Chicago.

DR. HAMMERSTROM: Tom Hammerstrom, FDA.

MR. FLEISCHER: Russ Fleischer, FDA.

DR. BIRNKRANT: Debra Birnkrant, FDA.

DR. GULICK: Thanks, everyone. I believe we have Dr. Sharilyn Stanley.

DR. STANLEY: Hello, good morning.

DR. GULICK: Hi. You are coming in loud and clear.

DR. STANLEY: Good. Then, I won't yell.

DR. GULICK: You can yell a little if you

like. Dr. Stanley will be participating by teleconference for this meeting. I would like to turn to Tara Turner to read the conflict of interest.

Conflict of Interest Statement

DR. TURNER: Thank you. The following announcement addresses conflict of interest with regard to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting.

We would like to disclose for the record that Dr. Eugene Sun, from Abbott Laboratories, is participating in this meeting as an industry representative, acting on behalf of regulated industry. As such, he has not been screened for any conflicts of interest.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial

interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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

DR. GULICK: Thanks. We will turn to Dr. Birnkrant for some opening remarks.

Introduction/Opening Remarks

DR. BIRNKRANT: I would like to welcome everyone to today's advisory committee meeting on pleconaril for the treatment of the common cold.

In addition to our Antiviral Advisory Committee members, I would like to acknowledge our guests and other members participating from other FDA advisory committees, including Dr. Reller from the Over-the-Counter Drug Products Advisory Committee, Dr. Gardner, from the New Risk Management Advisory Committee, and Dr. Brass, formerly of the Over-the-Counter Drug Products Advisory Committee. I would also like to thank ViroPharma for their efforts in developing this product.

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The marketing application we bring before you today represents a departure from the indications we usually present before our committee. Generally we present an application for a serious or life-threatening disease, such as HIV or hepatitis C. Today, though, we will be discussing an application for a disease that is acute and self-limited, with an average duration of illness of about 7 to 11 days, but one that repeatedly affects the entire population.

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Why, then, are we bringing this application before you today? At previous advisory committees we have reviewed our processes for bringing applications before the advisory committee and today I will do the same.

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In general, we bring applications before the committee for the reasons you see on this slide: either it is a new chemical entity or first drug in its class; it has a novel mechanism of action and it poses complicated analytic and safety issues. In my brief comments I will explain how pleconaril fits into these categories.

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Pleconaril is a new chemical entity and first drug in its class. Whereas other treatments for the common cold, such as decongestants and nonsteroidal anti-inflammatory agents provide relief of individual symptoms, pleconaril's novel mechanism of action prevents viral attachment to susceptible cells and prevents encoding of rhinoviruses and enteroviruses, thus, impacting multiple cold symptoms through its antiviral effects.

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This application also poses several complicated analytic issues. The two principal studies were double-blind, placebo-controlled studies of pleconaril or placebo for five days. Treatment had to begin within 24 hours of onset of symptoms. Both trials had the same endpoint of time to resolution of rhinorrhea and alleviation of five other symptoms, such as cough and nasal congestion, to absent or mild sustained for approximately 48 hours. Even though both studies were identically designed, the treatment effect varied to about half a day in study 043 and one and a half days in study 044. Further, there was a

treatment differential in smokers versus non-smokers.

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With regard to safety issues, we are bringing this application before you today because pleconaril induces CYP3A4. This was brought to our attention through reports of menstrual irregularities in a six-week prophylaxis study of pleconaril. This was further investigated through a drug interaction study of a single dose of an oral contraceptive and five days of pleconaril, where it was shown that concentrations of ethinyl estradiol were reduced by 35 percent. Safety issues related to CYP3A4 induction relate to the effect of pleconaril on oral contraceptives, possibly resulting in breakthrough bleeding and the potential for unintended pregnancy. In addition, there is concern that there is potential for other drug interactions such as those of protease inhibitors. We will also be discussing safety findings of palpitations and tachycardia and my colleague, Russ Fleischer, will elaborate on these issues.

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In sum, we are asking you to discuss the

safety and efficacy findings presented in the application today. When you discuss efficacy, please consider the following: the totality of the data from Phase II and Phase III trials, considering the treatment effect across the studies as well. Please also consider the results in subgroups and the need to use pleconaril within 24 hours of symptom onset. In your discussions, also please address the empirical use of an antiviral agent without a diagnostic assay.

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With regard to safety, we will ask you to discuss the safety of pleconaril as it relates to CYP3A4 induction with the potential for other drug interactions, as well as drug interactions with oral contraceptives.

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Lastly, given that the effectiveness standard for approval requires substantial evidence from adequate and well-controlled trials, as outlined in the Amendments to the Food, Drug and Cosmetic Act in 1962, what we are asking you today is what level of risk is acceptable in this setting of using pleconaril for the treatment of the common cold.

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With this slide I would like to turn to the agenda for today's presentation. We will start off with a presentation by ViroPharma. This will be followed by the FDA presentation by Russ Fleischer and Dr. Tom Hammerstrom. Then we will take a break. We will return from the break for a discussion of the presentations. This will be followed by lunch and an open public hearing. Following the open public hearing we will continue our discussion and pose the questions to our advisory committee. Thank you very much.

DR. GULICK: Thanks, Dr. Birnkrant. Now will turn to the sponsor, ViroPharma, for their presentation.

Sponsor Presentation

Introduction

DR. MCKINLAY: Good morning.

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My name is Mark McKinlay, head of research and development at ViroPharma. Today represents a significant milestone both in the develop of pleconaril and the field of antiviral chemotherapy. Until now there has not been a drug that treated the viral cause of the cold, reducing multiple

symptoms and reducing the overall duration and severity of the illness.

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Following this brief introduction, Dr. Frederick Hayden will discuss the impact the cold has on patients. I will return to review the preclinical profile and the clinical pharmacology of pleconaril, including the drug interaction data. The rest of the presentation will be given by my colleague, Dr. Ellen Cooper, who will summarize the safety and efficacy of pleconaril for this indication. Dr. Cooper will conclude with an overall assessment of benefit/risk of pleconaril for use in the treatment of the common cold.

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Pleconaril was rationally designed to be a specific inhibition of picornaviruses, the predominant cause of the common cold. Pleconaril has activity across the human picornaviruses including the rhinoviruses and enteroviruses. It is a potent, orally bioavailable compound that inhibits viral replication and reduces symptoms.

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The indication that we are seeing is for the treatment of acute picornaviral upper

respiratory illness, or the common cold, in adults.

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At this time I would like to introduce Dr. Frederick Hayden to discuss the impact that colds have on patients.

Impact of the Common Cold

DR. HAYDEN: Thank you, Dr. McKinlay and good morning, ladies and gentlemen.

To start, I would like to disclose that I have been a paid consultant to ViroPharma since the founding of the company and I have also served as an investigator on the majority of the Phase II and Phase III studies of pleconaril for the viral respiratory indication. My background is in internal medicine and infectious diseases, and my laboratory has engaged in studies of antiviral drugs and vaccines for over two decades.

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During that time there has been considerable progress with regard to the development of interventions for influenza virus. Indeed, we currently have four approved antiviral drugs and the agency is actively reviewing a new attenuated vaccine.

With regard to RSV infection, there is

aerosolized ribavirin and passive immunoprophylaxis, and there are several kindred vaccines that are in active clinical testing right now. In contrast, for picornaviruses and rhinovirus colds specifically there is no approved antiviral drug. The large number of immunotypes make the prospect for a vaccine very unlikely, and our current treatments have significant limitations which, I think, clearly indicate that there is a need for an effective antiviral option.

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The picornavirus family causes the majority of colds. Most of these are due to rhinovirus infection but it is worth bearing in mind that between five and ten percent of colds are due to enteroviruses. In addition, rhinoviruses cause a substantial number of other complications, involving both the upper and lower respiratory tract, many of which are then associated with antimicrobic use. On an average basis, a person in this country will experience about one rhinovirus infection annually. The number of colds experienced in this country has been estimated to be as high as a billion episodes annually.

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We know that the incidence of common cold is clearly age related so that children have the highest attack rates. In younger adults the rates average about two to three episodes per year. Then, in older individuals the rates drop, in part because of increasing immunity but also decreasing exposure. Rhinoviruses are year-round pathogens and they account for about half of colds episodes on an annual basis. In addition, there are seasonal peaks of activity in the spring and the fall months, during which rhinoviruses have been implicated in 80 percent or more of colds episodes.

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Several years ago we undertook a study of approximately 350 adults who had self-diagnosed colds. Over 80 percent of these individuals had a documented rhinovirus infection. These individuals were able to rapidly self-recognize the onset of their illness so that 69 percent were able to make a self-diagnosis within eight hours of the onset of their symptoms.

Sore throat was the most common initial symptom occurring in about 40 percent of these individuals. But, as the illness evolved, other symptoms predominated so that rhinorrhea became the

most bothersome symptom. Indeed, this is one of the rationales for its inclusion in the outcome measure used in the Phase III studies of pleconaril. Fever is uncommon during rhinovirus colds and, indeed, predicts against the presence of a rhinovirus infection. The degree of morbidity associated with these illnesses was substantial so that the average duration of sleep disturbance was four nights and this may, in fact, contribute to some of the daytime performance problems that have been documented in common cold sufferers. The overall duration of symptoms until resolution of the illness was 11 days in this particular cohort. The other studies have found, depending on the particular definition of illness used, durations ranging from 7 to 11 days, but it is worth noting that about a quarter of cold sufferers will have symptoms into the second week of their illness.

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It is worth looking at the pathogenesis of these illnesses in some greater detail because this has important implications with regard to our therapeutic interventions. Clearly, colds start with viral infection of the nasal mucosa. These in turn, then, drive certain host responses in terms

of the elaboration of proinflammatory cytokines and chemokines and also neurogenic reflexes, but then lead to the familiar symptoms associated with colds episodes.

Current treatments are directed against specific host responses, such as vasodilation or mucus secretion, and by doing so they provide them relief of individual or small numbers of symptoms. In contrast, what has been recognized in studies of experimental antiviral drugs, including pleconaril now, in the natural cold setting is that treatment of the viral etiology itself can lead to treatment benefit for the whole range of cold symptoms. Indeed, this is consistent with the hypothesis that ongoing viral replication is important in driving the symptoms associated with colds.

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The morbidity of these illnesses is also reflected in current practice patterns. We know that 75 percent of patients will seek self-treatment so that they will use a high frequency of over-the-counter medications, of which there are over a thousand available in this country currently. The most common ones that are used include cough preparations; combination,

multi-ingredient, cold products; as well as analgesics. Over half of individuals will use sedating type antihistamines as well as decongestants. Of course, the benefits with these over-the-counter remedies are variable, tend to be temporary in nature and focused on individual symptoms. It is important to recognize that they don't reduce the duration of these illnesses, nor have any impact on the likelihood of complications. In addition, of course, a number of these, particularly antihistamines which have sedating effects and oral decongestants, have significant side effects and there is appropriate precautionary wording in the labels for these drugs.

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Colds are also a leading cause of visits to physicians. Indeed, the estimates are anywhere from 25 million to 52 million physician visits in this country annually for colds episodes. About 15 percent of cold sufferers will seek a physician contact. When they do so, they commonly leave the office with a prescription either for a prescriptive remedy with a combination cold product or an antibiotic. About 30-50 percent of individuals will actually receive an antibiotic

prescription, based on recent trials and, of course, we know from the basis of carefully controlled studies that antibiotics neither benefit the symptom profile of colds, their duration or reduce the likelihood of complications associated with these episodes. So, I think this is an important problem in terms of driving the excess use of antibiotics in this country and the potential for emergence of drug-resistant respiratory bacteria.

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To summarize then, colds cause significant morbidity. Patients commonly seek treatment. Our current treatments are targeted to host responses and do not address the cause of colds. Indeed, in some instances these treatments are harmful. Again, this is a problem associated with excess antimicrobic use.

I think this background indicates that there is a need for a safe and effective antiviral option for common cold treatment. Thank you.

A New Option for Treating Colds

DR. MCKINLAY: Thank you, Dr. Hayden.

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Pleconaril was designed to be a specific

inhibitor of picornavirus replication. Pleconaril is shown here, on the left, and a cut-away view of the virus is shown here, on the right. In blue is the outer capsid protein shell of the virus that surrounds the single-stranded RNA core. Picornaviruses attach to their cellular receptor via a deep depression or canyon that surrounds each five-fold axis asymmetry on the virus. Pleconaril interacts in a specific hydrophobic pocket in this capsid. This pocket is highly conserved across the susceptible viruses in terms of its shape, presumably because of the critical role that it plays in determining the overall stability of the virus and its participation in the encoding process. When pleconaril interacts in this site it blocks the encoding or the release of the RNA into the cytoplasm to initiate infection. Pleconaril blocks encoding of all susceptible picornaviruses.

In addition to encoding, for those rhinoviruses, the 90 percent that use ICAM of the cellular receptor, when pleconaril binds in this site it causes a conformational shift in the floor of this canyon, blocking attachment to ICAM. While this pocket is highly conserved across the rhinoviruses and enteroviruses that are susceptible

to pleconaril, subtle changes in shape lead to changes in susceptibility to inhibition.

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The inhibitory concentrations, measured in micrograms per mL, are shown here for the rhinoviruses and enteroviruses. They range in susceptibility from single digit nanograms per mL to approximately 10 percent of viruses, both rhino and entero, that are not susceptible to inhibition at 3.8 mcg/mL, the highest testable concentration in cell culture. Because pleconaril is specific to the picornavirus family, viruses outside the picornaviruses are not inhibited by pleconaril. Inhibitory concentrations are achieved following a single 400 mg dose of pleconaril.

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Plasma concentrations reach a maximum of 2 mcg/mL approximately three hours after dose, and decrease in two distinct phases, a short alpha phase of approximately 2.8 hours and a terminal elimination phase of 180 hours. At eight hours, which approximates the Cmin in a TID dosing regimen, the plasma concentration exceeds that required to inhibit replication to 75 percent of rhinovirus serotypes. Plasma concentrations

increase with increasing dose.

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These increases are dose proportional across the range of 50-1000 mg. We learned early on in the program that the bioavailability of pleconaril is significantly increased when administered with food. In subsequent studies, all Phase II and III studies, patients were advised to take pleconaril following a meal. Despite its high protein binding, pleconaril has a high volume of distribution. Very little of the drug is excreted intact in the urine. Phase I studies have demonstrated no clinically significant effect of renal impairment, age or gender on the pharmacokinetics of pleconaril.

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Pleconaril is metabolized predominantly through reductive processes. Intestinal microflora cleave the oxadiazole ring to the ring open benzenamine derivative. Subsequent metabolism occurs via the conjugation and opening of the isoxazole ring. Since p450 enzymes are not predominantly involved in the metabolism of pleconaril, drugs that induce or inhibit p450's would not be expected to affect pleconaril

pharmacokinetics.

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To investigate the potential for an interaction with drugs that are metabolized by p450, we investigated the effects of pleconaril in vitro and in humans on CYP450 activity. We first evaluated the effects of pleconaril in vitro on purified CYP isozymes and found that pleconaril had no effect on five isozymes and only weakly inhibited three isozymes, 1A2, 2C9 and 2C19. We followed this with probe molecules for 1A2 and 2C9 and found no effect on the pharmacokinetics of S- and R-warfarin, and a small effect on theophylline AUC and t1/2, and I will show you these data shortly.

As Dr. Birnkrant mentioned, in the course of the six-week prophylaxis study conducted last fall, we noted an interaction between oral contraceptive use and pleconaril. To determine the mechanism of this interaction, we very rapidly implemented studies to determine the mechanism of this interaction. The results of these studies showed that pleconaril increased 3A activity, using two probes for 3A, midazolam and the ethinyl estradiol component of the oral contraceptive

Ortho-Novum.

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First, beginning with theophylline interaction, this being the probe molecule for 1A2 inhibition that we saw in vitro, in this study theophylline-naive patients were given a single dose of theophylline followed by pleconaril TID for five days. Another single dose of theophylline was administered, followed by pleconaril again TID for two days. The pharmacokinetics of theophylline were measured before and after exposure to pleconaril. We saw no change on Cmax, a 15 percent increase in the AUC, and less than a 20 percent increase in the t1/2 of theophylline. Other than this interaction with theophylline, we would not expect any interaction with pleconaril with any other drug as a result of inhibition of p450 enzymes.

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The investigation of CYP3A increase in activity was conducted with midazolam and the oral contraceptive Ortho-Novum. First the IV midazolam study, IV midazolam was administered before and after a five-day course of pleconaril. The pharmacokinetics were compared and we noted a 28

percent decrease in the AUC of midazolam and a 16 percent decrease in the t1/2.

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A similar magnitude of effect was seen with the estrogen ethinyl estradiol component of the oral contraceptive Ortho-Novum. In this study subjects were administered a single dose of Ortho-Novum, followed by five days of pleconaril TID. Another single dose of Ortho-Novum was administered followed by two more days of pleconaril TID. The plasma concentration of the estrogen ethinyl estradiol and the progestin norethindrone were compared before and after exposure to pleconaril. We noted no clinically significant increase in the Cmax of ethinyl estradiol, a 34 percent decrease in the ethinyl estradiol AUC and, importantly, no effect on the progestin norethindrone pharmacokinetics were noted in this study. No evidence of CYP induction was seen in the preclinical studies. In fact, preclinical studies showed pleconaril to have an excellent safety profile.

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The safety profile preclinically is shown here. Pleconaril has low acute toxicity at doses

up to 2 g/k. We saw no significant effects in rats or dogs administered pleconaril for one or six months. Pleconaril is not genotoxic, teratogenic, and has no effect on male or female fertility. We also noted no effects on the growth, development or reproductive performance of rats exposed to pleconaril in utero through weaning.

At this time, it is my pleasure to introduce Dr. Ellen Cooper, who will summarize the safety and efficacy of pleconaril in the treatment of the common cold.

Clinical Efficacy and Safety

DR. COOPER: Thank you, Mark.

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Good morning. My name is Ellen Cooper. I am the vice president of clinical and regulatory affairs at ViroPharma. It is my privilege to be here to summarize the clinical data supporting the safety and efficacy of pleconaril for treatment of the common cold.

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The clinical development program for pleconaril for treatment of the common cold began in 1996 with the proof of concept virus challenge study in normal volunteers. The results of this

placebo-controlled study demonstrated that pleconaril lowers virus levels in nasal mucus and reduces the severity and duration of cold symptoms.

Following this study, a Phase II program in adults, with naturally acquired upper respiratory illness, was initiated. The criteria for enrolling patients with a high likelihood of picornavirus colds, the definition of the primary efficacy endpoint and the frequency of self-assessment of cold symptoms evolved over the course of these studies, culminating in the design and conduct of two pivotal Phase III studies. ViroPharma also has an ongoing program investigating the safety and efficacy of pleconaril for the treatment of colds in children, and we recently completed a six-week prophylaxis study in adults.

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From the Phase II treatment studies we gained important insights in three major areas. First, we developed a better understanding of the clinical manifestations of colds that are caused by picornaviruses. These characteristics include significant rhinorrhea in the absence of fever. Second, we found that certain co-factors, including

smoking, allergic rhinitis and the use of concomitant cold symptom relief medications, tend to obscure the ability to evaluate the primary symptom-based endpoint. Third, it was determined that alleviation, rather than complete resolution of all symptoms, is a more appropriate endpoint for evaluating the clinical benefits of the antiviral drug in the earlier, more bothersome phase of illness.

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These insights were incorporated into the design of the two Phase III studies which were conducted during the fall of 2000. The two placebo-controlled Phase III studies enrolled over 1000 patients each at almost 200 centers across the United States and Canada. Both studies used identical entry criteria.

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The target population was otherwise healthy adults. To reduce enrollment of patients with non-infectious causes of upper respiratory symptoms, patients were required to answer "yes" to the question "do you have a cold today?" All patients were required to have moderate or severe rhinorrhea and another upper respiratory symptom.

A systemic symptom was not required. The maximum time from onset of symptoms to first dose of study drug was 24 hours. Patients with fever, active allergic rhinitis or asthma were excluded. Patients were randomized equally to pleconaril 400 mg three times daily or to matching placebo.

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Randomization was stratified by smoking status and prior use of cold symptom relief medication. Because earlier studies indicated that smoking and the use of concomitant cold symptom relief medications confounded the ability to detect a treatment effect, stratification on these variables was considered important to ensure balance between the treatment groups. Concomitant use of cold symptom relief medication during this study was discouraged but acetaminophen and dextromethorphan were provided to all patients for their use if necessary. The primary outcome variable in these studies was based on patient self-assessments of their cold symptoms.

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Patients were provided with study diaries in which they were instructed to record twice daily the severity of each of six cold symptoms as

absent, mild, moderate or severe, and whether or not they felt they still had a cold. In addition, they were asked to record once daily the number of tissues they had used, whether or not their sleep had been disturbed, and whether or not their normal level of activity had been impaired by their cold symptoms. Use of concomitant cold medications was also reported. These were the first pleconaril studies in which virologic testing was performed on all patients.

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Blow-nasal mucus samples were collected at baseline, which was study day one; two days later, which was study day three; and at the end of treatment, which was study day six. RT-PCR testing was performed on all nasal mucus samples. If the baseline sample tested positive, it was cultured. If the baseline culture was positive, post-baseline samples from the same patients were also cultured. All culture-positive samples were tested for susceptibility to pleconaril. Patients who were infected with the picornavirus, as detected by RT-PCR, comprised the primary efficacy population.

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The intent-to-treat infected, or ITT-I

population, consisted of the 63 percent of patients enrolled in study 043 and 67 percent of patients enrolled in study 044 who tested PCR positive, for a total of 65 percent picornavirus infected patients across both studies. The intent-to-treat, or ITT, population consisted of all randomized patients. All of our safety analyses were performed in this population. Pleconaril was not expected to have any benefit in PCR-negative patients who do not have picornavirus colds. Efficacy analyses were performed on all three populations. This presentation focuses on the results of the primary efficacy population.

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Baseline demographics were similar across both treatment groups in both studies. Overall, the patients were relatively young, mostly female, predominantly white, and a little over a quarter were smokers. Demographics in the intent-to-treat population were similar. At baseline disease characteristics in both the intent-to-treat and the intent-to-treat infected populations were evenly matched.

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The median time from onset of cold

symptoms to first dose of study drug was 20 hours in both treatment groups in both studies. Approximately one-third of patients reported using cold symptom relief medication prior to enrollment. The median total symptom severity score in all groups at baseline was 9 out of a theoretical maximum of 18 if all 6 symptoms were assessed as severe. The primary endpoint measured sustained improvement across multiple cold symptoms.

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The primary efficacy endpoint was defined as the time from initiation of study drug to the absence of rhinorrhea and all other cold symptoms to absent or mild for at least four consecutive half-day reporting periods without the use of cold symptom relief medication. Analyses of the primary endpoint in the primary efficacy population in both studies demonstrated the clinical benefits of pleconaril in reducing the duration and severity of picornavirus colds.

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The median treatment benefit was 0.6 days in study 043 and 1.5 days in study 044. The results of both studies, based on the prespecified primary endpoint, were statistically significant.

The magnitude of the differences at the 25th and 75th percentiles indicates similar variability of outcomes in the two studies.

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The Kaplan-Meier graphs of the primary endpoint show sustained benefit in both studies. In this self-limited viral infection pleconaril caused a more rapid alleviation of illness in both of the studies.

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To explore the apparent differences between the two studies in the size of the treatment benefit as measured by the primary endpoint, post hoc analyses using slight modifications of the primary endpoint were performed.

The required duration of sustained symptom alleviation was modified from the 48 hours in the prespecified endpoint to 24 hours and to 72 hours. The results of these post hoc analyses indicated that the median treatment benefit of pleconaril in reducing the duration of illness was approximately one day in both studies. While the treatment benefit was larger in study 044 than in study 043 using the prespecified endpoint, requiring 48 hours

of sustained symptom alleviation, the analyses using 24 hours of sustained alleviation showed a greater benefit in study 043. When sustained alleviation of 72 hours was used, the size of the treatment benefits in the two studies were almost identical, one day. These results support the consistency of the treatment benefit across both studies.

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Analyses of the primary endpoint in the intent-to-treat population also favored pleconaril. As expected, the magnitude of the treatment benefit in the ITT population was slightly less than in the ITT-I population, with a median benefit of 0.5 days in study 043 and 0.9 days in study 044. The addition of PCR-negative patients diluted the treatment effect observed in the ITT-I population. As anticipated, patients who did not have picornavirus colds received no benefit from pleconaril. The median duration of illness in the PCR-negative patients was approximately 6 days in both treatment groups in both studies.

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The antiviral activity of pleconaril was assessed using virus culture. Of those patients

who were culture positive at baseline, proportions of patients who remained culture positive during or at the end of treatment were calculated. Fewer patients in the pleconaril groups in both studies had positive cultures on study day three, the first post-baseline sampling day. Analyses of virus levels relative to baseline, as measured by the TaqMan PCR assay, indicate the virus levels were less than one percent of baseline on study day six. In study 044 fewer patients treated with pleconaril than placebo remained culture positive on day six. The antiviral efficacy of pleconaril parallels the clinical efficacy across a broad range of symptoms.

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The prespecified secondary clinical endpoints included time to resolution of individual cold symptoms; time to patient-assessed "no cold;" tissue use; the proportion of nights of sleep disturbance and days of impaired activity due to cold symptoms; the number of days of concomitant use of cold symptom relief medication; and the sum of the total symptom severity score.

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Time to resolution of each of the six cold symptoms was shorter in pleconaril patients than in

placebo. [Slide]

Time to resolution of each of the four respiratory and two systemic symptoms demonstrated that pleconaril reduces the duration of multiple cold symptoms. The asterisk indicates significant differences between the treatment groups, which favored pleconaril in all cases. In addition, analyses of the other secondary endpoints consistently favored pleconaril.

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For each of the endpoints shown on the X axis the bars represent the percent change in the pleconaril group compared to the placebo group. The treatment differences for study 043 are shown in white, and in green for study 044. For example, the last bar on the right indicates a 22 percent reduction in the total symptom severity score in patients on pleconaril compared to placebo. The green bar, next to it, indicates the 16 percent reduction in study 044. The asterisks indicate a statistically significant benefit of pleconaril compared to placebo within a study. In all cases the direction of the change favored pleconaril.

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To explore the clinical action of

pleconaril post hoc analyses of changes in symptom severity by day were performed. This analysis focuses on differences in the proportions of patients in the two treatment groups each day who reported any symptom as moderate or severe which was defined as bothersome or interfering with normal activity. The horizontal axis shows the half-day reporting intervals through day six, and the vertical axis shows the percent of patients in each treatment group who reported any symptom as at least bothersome. In both studies significant differences in favor of pleconaril were observed in the proportion of patients who assessed any cold symptom as bothersome, beginning on the second day of treatment.

This approach to analysis is conservative in that it requires all symptoms to be mild or absent for a person to achieve non-bothersome status. Despite this strict definition of improvement, the results support the efficacy of pleconaril in providing early and sustained reduction in the severity of cold symptoms.

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Another post hoc analysis of symptom severity explored the differences between the

treatment groups in the percent change from baseline in the total symptom severity score, which consisted of the sum of all symptoms, scored from zero for absent to three for severe, for each reporting interval. This approach to analyzing the morbidity of picornavirus colds also showed that the decrease in symptom severity was faster in pleconaril patients than in placebo in both studies, beginning on the second day.

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The data from our pivotal studies were analyzed to investigate the consistency of treatment outcome between subgroups, defined by the prospectively determined strata of smoking status and prior use of cold symptom medications, and by age, gender and race.

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The results indicate no evidence of inconsistency of treatment outcome in the subgroups based on prior use of cold symptom relief medication or in the subgroups defined by age, gender and race. However, a significant interaction between treatment and smoking status was found. Therefore, efficacy analyses were performed separately in non-smokers and smokers.

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Analyses of the primary endpoint in the pooled data set of smokers showed no evidence of a treatment benefit of pleconaril, whereas in non-smokers a median benefit of 1.3 days was observed. The 25th and 75th percentiles indicate similar variability in outcome in both subgroups. Analyses of the proportion of patients with positive cultures at baseline and on study days three and six demonstrate the antiviral activity of pleconaril in both smokers and non-smokers.

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Analyses of the pooled data showed that fewer patients in the pleconaril groups remain culture positive in both the non-smoker and smoker strata. Post hoc analyses of the differences in total symptom severity scores indicate that pleconaril reduces symptom burden more rapidly than placebo in both smokers and non-smokers, consistent with its antiviral activity.

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These analyses of differences between the treatment groups in the total symptom severity score as a percent of the baseline score show that symptom severity declined faster in pleconaril than

in placebo patients during the early treatment period, regardless of smoking status. Although a treatment benefit of pleconaril, as measured by the primary endpoint, was not apparent in smokers, pleconaril has antiviral activity in both smokers and non-smokers, supporting the biological activity of pleconaril independent of smoking status.

One hypothesis to explain the differences in the observed benefit in smokers and non-smokers is that the chronic symptoms of smoking may be difficult to distinguish from resolving cold symptoms, obscuring the treatment benefit.

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Virological testing was performed on all patients enrolled in the pivotal studies. All nasal mucus samples that were PCR positive were cultured for the presence of picornaviruses. All culture-positive samples were tested for susceptibility to pleconaril in a cell culture assay.

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Of the 744 patients in the two pivotal studies who had positive viral cultures at baseline, 87 percent had viruses that were susceptible to pleconaril at concentrations less

than or equal to 3.8 mcg/mL, the highest testable concentration, and 13 percent had viruses that were not susceptible. This spectrum of sensitivity is similar to that reported in the literature from other patients with naturally acquired picornavirus colds. The clinical benefit of pleconaril was evaluated separately in patients whose viruses were susceptible and non-susceptible at baseline.

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In patients with drug-susceptible viruses, analyses of the primary efficacy endpoint showed a median treatment benefit of 1.8 days in study 043 and 2.1 days in study 044. In the relatively small proportion of patients with baseline viruses that were not susceptible to pleconaril there was no evidence of a treatment benefit.

To determine the incidence of post-treatment viruses with reduced susceptibility, virus cultures that were positive at baseline and at days three or six were tested for susceptibility to pleconaril.

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Paired isolates from the same patients were compared. Among the 294 placebo patients with positive virus cultures at baseline and at least

one post-baseline positive culture for which susceptibility could be determined, two patients had post-baseline viruses with at least a ten-fold reduction in susceptibility. Among the 263 pleconaril patients, 28 or 10.7 percent had post-baseline viruses with reduced susceptibility. Because drugs with a specific antiviral mechanism of action exert selective pressure on susceptible viruses, co-existing variants with reduced susceptibility have the opportunity to predominate in the virus population. The possible consequences of post-treatment viruses with reduced susceptibility on the clinical benefit of pleconaril was assessed.

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The duration of illness, based on the primary endpoint and on time to patient-assessed "no cold" was analyzed in the 28 patients with post-baseline viruses with reduced susceptibility, and in the larger groups of pleconaril and placebo patients in whom a ten-fold change in susceptibility was not observed. These results indicate that the duration of illness in these patients is no longer than in patients without a change in susceptibility.

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The viruses with reduced susceptibility were characterized in vitro. These viruses were found to be physically less stable than wild type susceptible viruses. Genetic characterization revealed amino acid substitutions at positions 98, 122 and 180 in the hydrophobic pocket into which pleconaril binds. The genotypic and phenotypic profile of these viruses is similar to that observed in lab-derived Coxsackie B3 viruses that were selected in vitro for reduced susceptibility to pleconaril. These viruses were shown to be attenuated for replication and were less virulent in a lethal murine model. The virological profile of pleconaril indicates that post-treatment viruses are unlikely to result in adverse clinical consequences for individual patients, and that viruses with reduced susceptibility appear to be less fit than wild type viruses.

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The pivotal clinical trials demonstrated that pleconaril reduces the median duration of picornavirus colds by about one day. Importantly, the clinical benefits of pleconaril in reducing total symptom severity are evident by the second

day of treatment. As expected from an antiviral drug, pleconaril reduces the severity and duration of multiple cold symptoms in parallel with its antiviral activity.

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The clinical safety of a new drug for the treatment of the common cold is an important part of a benefit/risk assessment. The pleconaril safety database summarized in the NDA consists of nearly 3900 individuals who received pleconaril, most of whom were adults.

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These patients participated in 39 adult and pediatric studies that were completed prior to June, 2001. Safety analyses were performed on the following subsets of patients: adults in any Phase II/III study; adults in the six cold treatment studies; and adults in the three Phase II/III cold treatment studies in which the tablet formulation was used. This presentation focuses on analyses of patients enrolled in the cold tablet studies since the safety profile is very similar in all data sets.

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The patients enrolled in the cold tablet

studies, which includes the two pivotal studies, better represent the proposed dose formulation and target population. In addition to the five- to seven-day treatment database, over 700 adults received six weeks of pleconaril in a recently completed cold prophylaxis study. Adverse events were reported by approximately 55 percent of patients in both treatment groups in the five- to seven-day treatment studies.

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Thirteen patients experienced serious adverse events, six in the placebo group and seven in the pleconaril group. One woman died in an automobile accident 30 days following completion of pleconaril treatment. Headache was the most common adverse event reported, followed by diarrhea and nausea. Frequencies were similar in pleconaril and placebo patients, with a slight excess incidence associated with pleconaril. Nearly all adverse events were classified as mild or moderate.

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Less than five percent of patients reported any severe adverse event. Discontinuations due to adverse events were also low.

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Discontinuations were reported in 2.7 percent of placebo patients and 3.4 percent of pleconaril patients. Headache, diarrhea and nausea were the most common reasons, with less than one percent of patients discontinuing study drug for any of these reasons.

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Analyses of the laboratory safety database revealed no clinically significant changes. Testing performed prior to and at the conclusion of treatment revealed no clinically significant changes in hematology, renal or liver function or in other laboratory safety values.

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To assess the safety of pleconaril administered over a longer period of time, over 1000 healthy adults were enrolled in a cold prophylaxis study that was conducted this past fall. This study had two major objectives. The first was proof of concept of the ability of pleconaril, given once or twice daily, to prevent the development of picornavirus colds. The second was to obtain clinical safety data on exposure to pleconaril of longer than one week. The total dose

administered in the pleconaril BID group in the six-week study was 5.6 times larger than in the proposed treatment dose of 400 mg three times daily for five days. Preliminary analyses of the safety database from the prophylaxis study were performed. However, efficacy and pharmacokinetics data have not yet been analyzed.

The incidence of adverse events in the clinical laboratory safety profile of pleconaril following six weeks of exposure was similar in the five- to seven-day treatment database, underscoring the safety of a five-day treatment regimen. The one exception was a higher frequency of menstrual disorder adverse events in women taking oral contraceptives and pleconaril in the longer study.

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The first reports of breakthrough bleeding in two women taking oral contraceptives resulted in notification of all women enrolled in the study of the apparent increased risk of menstrual disorders, the possibility of decreased oral contraceptive efficacy, and the need for re-consent to continue participation in the study. All women were queried regarding their interval menstrual histories at the biweekly clinic visits.

When the study was analyzed the incidence of menstrual disorder adverse events was found to be higher in the pleconaril groups than in placebo. Most of these adverse events were reported as spotting or early withdrawal bleeding in women taking oral contraceptives. Review of all menstrual disorder adverse events in the five- to seven-day treatment database indicated a higher incidence of 3.5 percent in women taking oral contraceptives and pleconaril, compared to placebo. In both the five- to seven-day treatment studies and in the six-week prophylaxis study none of the menstrual disorder adverse events in women taking oral contraceptives and pleconaril were severe.

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In the five- to seven-day treatment studies none of the menstrual disorder adverse events resulted in discontinuation of study drug. In the six-week prophylaxis study less than one percent of women in each treatment group discontinued study drug as a result of a menstrual irregularity. In the five- to seven-day cold treatment studies the incidence of menstrual disorder adverse events in women taking pleconaril and oral contraceptives was 3.5 percent, almost

identical to that in all Phase II/III treatment studies.

A Phase I study to investigate the mechanism of the increased incidence of menstrual disorders in women taking oral contraceptives indicated that treatment with pleconaril results in a modest induction of CYP3A enzymes, causing increased clearance of ethinyl estradiol. There was no change in the pharmacokinetics of the progestin component norethindrone.

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We carefully reviewed all pregnancies that were reported in the five- to seven-day treatment studies and in the six-week prophylaxis study. Among the 722 women enrolled in the prophylaxis study, seven pregnancies were reported during the 12-week observation period. One woman each in the placebo and low-dose pleconaril groups and five in the BID pleconaril group became pregnant. Two of these pregnancies occurred in women taking oral contraceptives.

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The incidence of pregnancies reported by patients in the five- to seven-day treatment studies was also low. Six pregnancies were

reported among the 3400 women who received pleconaril in the five- to seven-day treatment studies, two-thirds of whom were between the ages of 18 and 40 years. Approximately 300 women in the placebo and 400 women in the pleconaril groups were taking oral contraceptives. Four of the six pregnancies occurred among women who received placebo, one of whom was taking oral contraceptives. Two pregnancies were reported among women who received pleconaril, both of which progressed to delivery of normal infants.

While the incidence of pregnancies was too low to draw definitive conclusions regarding the possible effect of pleconaril in reducing the efficacy of oral contraceptives, there is no indication of increased risk of pregnancy in women taking oral contraceptives in five to seven days of pleconaril.

The safety database of over 4500 adults and children who received pleconaril in our placebo-controlled studies demonstrate that pleconaril is safe and well tolerated for the proposed five-day treatment regimen.

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The most common adverse events were

headache and GI symptoms. The frequency of these adverse events in the pleconaril group was slightly higher than in placebo, and were not related to dose or duration of treatment, indicating that most are background incidence in the population studied.

No clinically significant changes in laboratory safety parameters were observed in either of the five- to seven-day treatment studies or in the six-week prophylaxis study, demonstrating that pleconaril does not adversely affect any major organ system.

Although the incidence of menstrual irregularities was higher in women using oral contraceptives who were also taking pleconaril, the total incidence reported in the five- to seven-day treatment studies was low. Similarly, there was no evidence of an increased incidence of pregnancies in women taking five to seven days of pleconaril, and none were reported in women taking oral contraceptives. Thus, the safety profile of pleconaril supports empiric treatment of patients with colds.

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Because colds affect people with many different conditions, ViroPharma understands the

importance of thoroughly pursuing the safety of pleconaril in a wide variety of settings and medical circumstances. To this end, we are committed to conducting appropriate additional studies to characterize further the safety and efficacy of pleconaril in adults and in children.

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A PK/PD study in chronic theophylline users is under discussion with experts. To further characterize the modest induction of CYP3A enzymes, two additional drug interaction studies are under way. A two-cycle oral contraceptive interaction study will assess the maximum PK and PD effects of pleconaril. Another study, using oral midazolam, will determine the duration of the increased CYP3A activity. A large post-marketing study is planned to track the safety of pleconaril in ongoing use by practicing physicians in an expanded range of patients.

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This Phase IV trial will be designed to confirm the safety and efficacy of pleconaril in patients with underlying respiratory conditions and other medical co-morbidities. In addition, we will conduct a post-marketing study of the potential

impact of pleconaril in reducing antibiotic use in the outpatient setting. We are also committed to continuing our pediatric program and to expand it to include children with asthma.

To explore approaches to further investigate post-treatment viruses with reduced susceptibility, we are in active discussion with a variety of experts. Three possible designs include a family transmission study, a virus challenge model, and a cohort study in immunocompromised patients.

The results of all of these studies will provide treating physicians with additional guidance for the use of pleconaril in a broader range of patients.

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In summary, we have demonstrated that pleconaril is an important first in class antiviral that is safe and efficacious for the treatment of the common cold. We have demonstrated in well-controlled trials that pleconaril reduces the duration of picornavirus colds and causes more rapid symptom alleviation than placebo, beginning on the second day of treatment. Pleconaril shortens multiple cold symptoms simultaneously, and

the antiviral activity in patients with picornavirus colds parallels its clinical benefits. Pleconaril has been shown to be safe and well tolerated at the proposed dose of 400 mg three times daily for five days. The risks associated with the treatment course of pleconaril are few and manageable.

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Patients taking pleconaril and theophylline may experience a slight increase in steady-state plasma concentrations of theophylline. Women using oral contraceptives may experience an increased incidence of menstrual irregularities. Pleconaril has the potential to cause a modest reduction in concentrations of drugs with narrow concentration response relationships that are metabolized predominantly by CYP3A enzymes.

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ViroPharma will provide specific guidance to physicians in managing their patients with colds. First, patients should be convinced that their upper respiratory symptoms are the result of a cold and not to allergic symptoms or to some other non-infectious cause. The clinical presentation should include significant rhinorrhea

without fever. Treatment with pleconaril should be initiated within a day of onset of symptoms. Patients should be instructed to take pleconaril with food three times daily. They should be advised that pleconaril may result in a slightly increased risk of headache or nausea. To be cautious, women taking oral contraceptives should be advised to use an additional form of birth control.

Because pleconaril increases the activity of CYP3A enzymes, patients taking drugs with narrow concentration response relationships, such as cyclosporine and HIV protease inhibitors, may experience a decrease in efficacy of these drugs. The physician should be aware that there are limited data at the present time on the safety and efficacy of pleconaril in the elderly and in patients with significant medical co-morbidities. However, there are no signals in our overall safety database to indicate increased risk.

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The development of the first antiviral drug to treat the predominant cause of the common cold is a landmark achievement in the history of anti-infectives. I remember quite clearly the

review and approval of acyclovir nearly twenty years ago. Acyclovir was the first antiviral drug to treat chronic herpes simplex infections that caused recurrent, painful outbreaks. Fifteen years ago the development and approval of zidovudine, the first anti-retroviral drug for the treatment of AIDS, brought new hope to patients with HIV. Zidovudine was the first in a series of advances to transform AIDS from a fatal disease into a manageable chronic illness.

Now we have the opportunity to reach a new milestone in antiviral drug therapy, the approval of the first antiviral agent to reduce duration and severity of picornavirus colds. Although colds are neither chronic nor serious, they cause substantial acute morbidity and can be highly contagious. The development of each of these first in class antiviral drugs represents important achievements. None were easy and all required new ways of thinking. In each case, not only was a new chemical entity with a new mechanism of action developed, but new standards for the design and interpretation of Phase III clinical trials were determined for diseases that had never been treated.

In conclusion, pleconaril is the first antiviral drug that has been shown to be safe and efficacious in the treatment of the common cold. The demonstrated clinical benefits outweigh the potential risks. Thus, pleconaril represents an important new option for physicians in managing their patients with upper respiratory infections. Thank you for your attention.

DR. GULICK: Thanks, Dr. Cooper, Dr. Hayden and Dr. McKinlay. We are going to hold questions from the committee and we will proceed right with the agency's presentation. Russ Fleischer is going to kick it off.

We have some people joining us on the committee. So why don't we have them introduce themselves and state their affiliation? Dr. Wood, welcome.

DR. WOOD: Thank you. I am with the National Cancer Institute.

DR. GULICK: And Dr. Goldberger?

DR. GOLDBERGER: I am the Acting Director of the Office of Drug Evaluation IV.

DR. GULICK: Thanks. Dr. Stanley, can you hear us? We will take that as a no.

Agency Presentation

Overview of NDA and Issues

MR. FLEISCHER: Good morning, committee, guests and members of the audience.

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I am pleased to be here today to lead the FDA's presentation on the NDA for pleconaril for treatment of acute picornaviral VRI in adults, known as the common cold.

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This morning I will start by giving you an overview of the NDA and some of the issues we identified in the review. Dr. Hammerstrom will present the statistical review of efficacy and then I will return and go into some depth on the safety, and provide an overall summary.

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The clinical development program for pleconaril for the VRI indication consisted of six trials, two pivotal trials, studies 043 and 044, where pleconaril was administered 400 mg three times a day for five days, and four Phase II studies, studies 010, 013, 020 and 032. We are not going to talk about studies 10 and 13 today but we will go into a lot more detail about 20 and 32 as they were two very large Phase II studies.

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I will review the application and identify a number of regulatory and scientific issues. The big ones are listed on this slide and in our presentation we will cover each one of these in some detail.

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The overall study results was the first thing we looked at, and pleconaril has been investigated for treatment of a couple of other viral infections, enteroviral meningitis and hand, foot and mouth disease. In both these cases consistent efficacy was not demonstrated for a variety of reasons. The company moved on to the early VRI studies. In a few of them there was difficulty in establishing efficacy, and we are going to go into those trials a little bit more in detail. We now have the results of the two large Phase III studies, studies 043 and 044, and in these trials pleconaril provided about half a day faster time to resolution in the all randomized patient population, and about a day faster time to resolution of VRI in infected patients.

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In a large Phase II study and both Phase

III pivotal trials pleconaril failed to produce a treatment effect in smokers. The pivotal trials were open to enrollment of patients over the age of 65 but only a very small number of elderly patients actually entered the trials so it was difficult to draw any conclusions about efficacy in that subpopulation. The pivotal trials enrolled otherwise healthy adults and patients with any kind of cardiac or respiratory disease, or any kind of immunosuppression were excluded.

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You have heard about the all randomized patient population and you have heard about the infected population, and both are legitimate populations for assessing efficacy of an anti-infective agent. To look at the infected population one has to have some confidence that you can reliably identify infected patients, demonstrate a treatment effect in those patients, but not harm patients who do not have the infection.

Arguably, all randomized patients is also a valid population as they are more reflective of actual use. We believe that in this case, if pleconaril is approved, it will probably be

prescribed to all-comers based on presenting symptoms, and there are no rapid diagnostic assays available to identify infected patients. Alternatively, pleconaril could be prescribed to an asymptomatic patient with instructions to initiate at the time of self-diagnosis of a cold.

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The human picornaviruses, as you heard, encompass over 170 different serotypes. This is a flow chart of what the applicant did to identify infected patients. At entry into the two pivotal studies a nasal mucus sample was collected, and it was run on a real-time TaqMan RT-PCR assay. If the result was positive, it was sent for viral culture. If it was negative, it was retested on an ELOSA, an experimental ELOSA RT-PCR assay. Again, positive samples were sent for culture and a negative was considered really negative.

So, at baseline 61 percent of the patients went into the two pivotal trials who were considered infected by a positive PCR. Then, 63 percent of this 61 percent actually had a positive culture. So, the total patient population in the pivotal trials that had a positive culture was about 40 percent.

On days three and six additional or repeat virologic testing of nasal mucus was done, but only with the TaqMan assay, and this identified another approximately three percent of infected patients, but these patients had tested negative at baseline. So the overall population of patients infected, as the applicant showed you, was about 64 percent.

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We evaluated the qualitative and quantitative aspects of the RT-PCR assay to see how well they were identifying infected patients. The applicant reported that the TaqMan could detect 90/100 rhinoviruses; 3/53 enteroviruses; and none of the parechoviruses from laboratory isolates. Sensitivity of the assay was reported at 93 percent, and the sensitivity was determined using nasal mucus samples from symptomatic patients enrolled in one of their large Phase II studies. The assay is run for 60 cycles and any sample that crossed the 0.1 fluorescence level was considered positive. Appropriate controls were not included in the design of the assay and there was a lack of reproducible sampling. Therefore, we could not validate the assay's ability to quantify viral nucleic acid.

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This is an example of the TaqMan readout. The number of cycles, up to 60, is down here. The 0.1 fluorescence level is right here. Any sample that crossed any time during the 60-cycle run was considered positive for picornavirus.

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A modified experimental ELOSA assay was used to re-test TaqMan negative samples. This assay was reported to identify all rhinoviruses and all enteroviruses, and 1/2 parechoviruses with 97 percent sensitivity.

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This slide shows a representative sample of a TaqMan and an ELOSA gel. The M is the molecular standard. The negative is the negative control. This arrow points to where the 68 base paired expected product showed up for these different samples.

This is an ELOSA gel. Again, M is the molecular standard. The minus is the negative control. Here, the arrows are pointing to a 388 base paired expected product.

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The baseline PCR positive samples were

cultured and HeLa cells expressing ICAM at 33 degrees Celsius. Cultures were considered positive or negative based solely on the presence of cytopathic effects, and there was no serotyping of positive cultures conducted.

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As you heard, about 24 percent of patients had resistance to pleconaril, 13 percent at baseline and about 11 percent by the end of treatment. The isolates were not serotyped so there is no data to determine if certain serotypes were more or less likely to be resistant to pleconaril. Molecular analysis of four viruses that lacked baseline susceptibility to pleconaril demonstrated that three had the same mutation at amino acid position 98 of the binding pocket. We also saw that single amino acid substitutions could result in up to 100-fold decrease in susceptibility to pleconaril.

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This is basically a repeat of what the applicant showed you. These are patients who had treatment emergent resistance. There is a very small number, but it does not appear that there was an adverse outcome for those patients.

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When we looked at susceptible versus not susceptible for placebo and pleconaril, you can see that for patients with not susceptible virus to pleconaril at baseline, and again the numbers are small, there was a delay in time to resolution of VRI. Remember, these are in patients and viruses that have never been exposed to pleconaril before so this was out in the community already.

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Pleconaril needs to be administered with food. Exposures are increased 4 to 6.5 fold with a high fact, high caloric meal. We don't have any data on any other meal compositions because no other ones were studied.

In patients with hepatic impairment exposures of pleconaril increased by 40 percent, and this may have been due to subjects not completing their meals or because the meals were lower in fat content.

In the pivotal trials patients were instructed to take pleconaril three times a day with meals, within 15 minutes of the meal or, if they missed a meal, with a snack. We don't know to what extent patients adhered to these

recommendations or if there was any kind of impact on the assessment of efficacy.

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Generally pleconaril was well tolerated. Headaches, nausea, vomiting, abdominal pain and diarrhea were observed. The major things that we became concerned about was the CYP3A4 induction. We believe this is directly tied to the occurrence of menstrual disorders in the treatment trials and in the six-week prophylaxis study. We believe there is an increased risk for unintended pregnancies, and there is a potential interaction with other medications for which no data is available.

There are also a few cases of tachycardia and palpitations that were triggered by a review of the theophylline interaction study. When I come back I will talk about these in a lot more depth during my safety review.

[Slide]

As I said, there were four Phase II trials in the application. The two biggest ones were study 20 and 32. Both were similarly designed. Study 20 looked at two doses of pleconaril compared to placebo; 32 looked at one dose of pleconaril

compared to placebo. Patients were to present with symptoms of VRI of less than 36 hours. The endpoint was slightly different, time to resolution for 48 hours in 20, and for 24 hours in 32.

Here you can see the results. In the all randomized patient population there was no difference between pleconaril and placebo in 20; the same in the infected populations. In 32 there was no difference in the all randomized. There was about a half day in the infected. In these two trials, using the ELOSA assay, the applicant was only able to identify about 40 percent of patients being infected with picornavirus and Dr. Hammerstrom will go into more detail in his presentation.

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Post hoc analyses of these big studies identified a number of problems that adversely affected the demonstration of a treatment effect. The applicant was not able to identify a high rate of infected patients using the ELOSA assay. Even with changing the sampling method from a nasal wash in study 20 to a nasal blow in study 32, still about 40 percent of patients were considered PCR positive.

Uncontrolled and undocumented cold medication use, inclusion of smokers, inclusion of patients with fever, allergic rhinitis, overly stringent endpoints which required all symptoms to be completely resolved, and the recognition that treatment needed to be given probably within the first 24 hours of symptom onset all impacted the assessment of outcomes in these studies.

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Based on what was learned in Phase II, the applicant designed studies 43 and 44. Just to briefly review them, they were double-blind, placebo-controlled and enrolled healthy adults over the age of 18. Patients presented with moderate to severe rhinorrhea, with symptoms less than 24 hours. They had to answer "yes" to the question, "are your symptoms due to a cold?" Patients with allergic rhinitis, fever, underlying pulmonary, cardiac, immunocompromised patients or other serious illnesses were excluded from the trial.

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Randomization was stratified on smoking status and pre-treatment use of cold medication, both of which appeared to influence assessment of efficacy in Phase II. A patient was considered a

smoker if they were actively smoking or had stopped smoking within three months of study entry. Patients were randomized to pleconaril or placebo three times a day for five days. They had a clinic visit on days 3, 16 and 18, and completed diaries for the 18-day study period. Acetaminophen and dextromethorphan were provided but patients were instructed to use them only as necessary.

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All the symptoms were scored on an ordinal severity score of zero for absent to three for severe. Then, the virologic testing method was as I previously described it.

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About 2100 patients entered the two trials. This is the all randomized patient population, about 69, 70 percent female, 36 years of age; about 30 percent were smokers; 30 percent had used pre-treatment cold medication. The median time to first dose of study medication was about 20 hours. The baseline severity score was nine out of a maximum of 18. Again, at baseline the PCR positive status was about 61 and 62 percent in the two arms respectively.

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With that background, I am going to turn it over to Dr. Hammerstrom to present some perspective on pleconaril's efficacy.

Statistical Review of Efficacy

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DR. HAMMERSTROM: In addition to the two pivotal Phase III trials, 43 and 44, the applicant also provided data from one small Phase II trial, number 10, and two larger Phase II trials, 20 and 32. These latter two trials differ in several ways from trials 43 and 44. Concomitant cold medication use was allowed. Subjects were recruited up to 36 hours after symptom onset. PCR positivity was determined only by the ELOSA assay, without the use of TaqMan. There was no record of OTC co-medication use, and the duration of recording of symptoms was not exactly the same in all four trials.

The applicant originally required all symptoms to be absent in trial 20, but we recalculated the endpoints to require the five symptoms other than rhinorrhea to be merely mild or absent. In trial 32 the applicant required one day of resolution. We recalculated to require two days of resolution. We also attempted to make the

endpoints in trials 43 and 44 more comparable by doing the sensitivity analysis in those two trials in which cold medication use was omitted from the computation of the primary endpoint. The results in these two trials were nearly identical to the results of the protocol primary endpoint, which will be given below.

[Slide]

The next two slides show the status of two pivotal trials by arm with respect to the assay and viral culture results at baseline and during the trial. There is one problem with these data. Specifically, no viral culture was taken for subjects who were negative on the PCR assay. So one column of the 2 X 2 table for assay cross-culture is missing.

[Slide]

This is the same thing for trial 44. Overall, the rate of baseline PCR positivity in trials 43 and 44 was 60 percent consistently across all four arms. In addition, about three percent of patients became positive during treatment. In our analysis, because pleconaril is supposed to be antiviral, we decided not to include patients who only became PCR positive while on treatment.

Furthermore, the day three assay has been used as a secondary endpoint, so it should not also be used as a baseline covariate. We have looked at the analysis both ways and neither estimated quartiles of time to resolution nor peak values changed consequentially.

[Slide]

This slide shows the primary endpoint for the two pivotal trials using the PCR positive population. For each arm the table shows the number who were included, that is, were PCR positive at baseline, three quartiles of time to resolution of symptoms and cold medication use and the p values for the comparison of placebo and pleconaril.

For example, in trial 43 the Q1 equals four shows that 25 percent of subjects on pleconaril had complete symptom resolution within four days. The Q2 equals seven shows that 50 percent of subjects on pleconaril had complete symptom resolution within seven days. The Q3 equals 11 shows that 75 percent of pleconaril subjects had complete healing by day 11, and that 25 percent took 11 days or more to heal.

When we calculated this, we rounded off

all the times to the half day so our numbers are not exactly the same as the applicant's. We didn't think subjects could really identify symptom disappearance to the nearest hour. The p values here were computed stratifying on the same variables used to stratify the random assignment, pre-treatment cold medication use, and smoker, non-smoker. One can see a fairly consistent pattern. The pleconaril arm is one to one and a half days ahead of the placebo arm for all three quartiles in both trials, except the median in trial 43. Statistical significance was achieved in both trials.

[Slide]

This slide shows the primary endpoint for the two pivotal trials for the full ITT population. The layout of information is the same as in the previous slide. One should notice that the size of the pleconaril effect is about half a day smaller than it was in the PCR positive population. That is, it is about half a day instead of one day in trial 43, and it is about one day instead of one and a half days in trial 44. Also, the statistical significance has been lost in trial 43.

[Slide]

This slide shows the corresponding results for the two larger Phase II trials, 20 and 32. Trial 10 was much smaller and is not included here. Recall that the endpoint here is slightly different. Over-the-counter cold medication use was not recorded. It is noticeable that in trial 20 pleconaril showed no benefit in the PCR-positive population. All three quartiles are as long or longer on pleconaril than on placebo. In trial 32 there was a benefit of half a day at the median but not at the other quartiles, and a slight benefit also at the third quartile but neither of these was statistical significant.

As I mentioned, we did attempt to check whether this occurred solely because of the absence of cold medication data, and in trials 43 and 44 one gets no consequential differences in the estimates of the size of pleconaril benefit or in the strength of its statistical significance if one omits cold medication use from the computation of the endpoint.

[Slide]

This slide shows the results from the same two trials, 20 and 32, for the full population. It is noticeable that there is a pleconaril benefit

found in trial 20 but not in 32. The finding in trial 20 is somewhat contrary to the results in the two pivotal trials where the PCR-positive supopulation shows a much clearer pleconaril benefit than does the full population.

It is most plausible that the larger concomitant use of cold medications and the longer delay in recruitment after symptom onset accounts for the lack of treatment effect. These trials may contain more information about the expected effects in general use since longer days in recruitment and wider use of anti-symptom drugs will occur in that setting.

[Slide]

This slide shows the loss to follow-up in the two pivotal trials. One thing to notice is the bimodal shape of the distribution of dropouts. Five to 11 people per arm decided not to participate after being randomized. Four to 11 people per arm dropped out on days one to five, most for adverse events. Only one to three patients per arm dropped out in the long interval, from day 6 to 15. Then, about 50 per arm left after day 16 or later without resolution of the symptoms. That includes everyone who reaches day

18.5 in their diary and is still sick.

[Slide]

The next several slides show the results for the PCR-positive population stratified by number of baseline covariates. Results are laid out as before, except that p values are omitted. This is because the trials are not large enough to detect real effects in subsets. In all these slides only the PCR-positive population is used. In the full population pleconaril benefits become slightly smaller.

[Slide]

This and the next slide show stratification by pre-treatment cold medication use, which was one of the two covariates used to stratify the randomization. The non-users are given here. There is an estimated pleconaril benefit of one and a half to two days in trial 44, and one to one and a half days in trial 43.

[Slide]

This slide shows the pre-treatment cold medicine users. Here, the pleconaril benefit is zero to one days in trial 44; one to two and a half days in trial 43. The overall impression is that the benefit is similar across both strata, possibly

slightly smaller but still positive in this stratum.

[Slide]

This and the next slide shows the results of stratifying by smoker and non-smoker. Here we have included one of the two Phase II trials, trial 32, which was one of the two trials for which we had smoker and non-smoker data. Here are the results for non-smokers and one sees an estimated benefit of one to one and a half days in trial 43; one and a half to two days in trial 44; half a day to two days in trial 32.

[Slide]

The results for smokers are given here. One notices that the pleconaril subjects actually take longer to heal than the placebo subjects within this stratum in all three trials. All of the quartiles for all three trials are as long or longer on pleconaril as they are on placebo.

[Slide]

This slide shows the results stratified by gender. Both trials 43 and 44 have been pooled together in order to increase the sample size within each gender and to eliminate the need for two slides. The females are estimated to have a

pleconaril benefit of one and a half to two days. The males have a smaller but still positive benefit of zero to one days.

[Slide]

This slide shows the results for smoker stratified by gender. Again, trials 43 and 44 have been pooled. One sees the same pattern as shown for smokers previously. Both for females and for males pleconaril is estimated to increase the time to symptom resolution. All of the quartiles in both genders are at least as long or longer for pleconaril.

[Slide]

The next four slides give the results for the time to resolution of each of the individual symptoms and for the time to end of cold medication use. Notice that the primary endpoint was achieved when all symptoms, except for rhinorrhea, were no worse than mild. This table, in contrast, requires each individual symptom to be reduced all the way to absent so it contains a little bit different information than the primary endpoint itself.

The p values have been put back in here because the PCR-positive sample is not being subdivided into several too small subsegments. The

sample sizes are not exactly the same because only subjects who have the given symptom baseline are included. Even so, most of these samples are large enough to be able to detect treatment effects of the size detected for the primary endpoint.

From this slide, one can see that rhinorrhea, congestion and malaise showed statistically significant benefit from pleconaril in trial 43. Cough shows sort of a tie here. One quartile is better, one is worse and one is equal.

[Slide]

This shows the other three symptoms from trial 43. One can see that myalgia and sore throat also showed statistically significant pleconaril benefit in trial 43.

[Slide]

This and the next slide cover trial 44. Here, one can see that rhinorrhea alone showed a statistical significant benefit. Although congestion and cough showed non-significant benefits, the quartiles are smaller for pleconaril. There was no benefit for malaise, except possibly in the first quartile.

[Slide]

Finally, one can see that myalgia and cold

medication use also showed pleconaril benefits, although they did not achieve statistical significance. There was no benefit for sore throat. I should also remark that it makes no sense to look at percent reduction in total symptom score. Symptoms are ordered but they are not numeric. Severe may be conveniently coded as a 3 but is not equal to 3 times mild. One could have used the codes 1 to 4 instead of 0 to 3 and gotten quite different results. Furthermore, separate symptoms cannot be combined in this way and be clinically meaningful. A severe sore throat is not equal to mild rhinorrhea plus moderate cough.

[Slide]

This slide shows the comparison of secondary endpoints, days of normal activity compared, nights with sleep impaired, and incidence rate for complications of colds. Of these, only one was statistically significant in one trial. Although the first two showed a small estimated pleconaril benefit in both trials, one-sixth to one-third of a day with less impairment of normal activity; one-third to two-thirds of night's sleep improved.

[Slide]

Here are the efficacy conclusions, pleconaril is statistically significantly superior to placebo in the PCR-positive population. If the assay has a low false-negative rate, then the PCR-positive population includes most infected subjects and the statistical significance there confirms pleconaril benefit.

[Slide]

Pleconaril showed no statistically significant benefit in the PCR population of trials 20 and 32, which had slightly different endpoints and slightly different recruitment criteria. Pleconaril will be used in the whole population for which the estimated benefit in the two pivotal studies was approximately one half day.

[Slide]

Finally, pleconaril has no effect in smokers. This absence of benefit has been confirmed in three separate studies, 43, 44 and 32.

I will now turn the podium back over to Russ, who will continue with the safety analysis.

Safety Review and Summary

MR. FLEISCHER: Thank you, Dr. Hammerstrom.

[Slide]

I would like to turn to a discussion of safety of pleconaril. The VRI safety database that we looked at consists of approximately 4500 patients who received pleconaril or placebo, about 2500 of which received pleconaril. There were no treatment-related deaths or significant lab abnormalities noted during the clinical trials. The adverse events were generally similar, with headaches and gastrointestinal events being the most bothersome and present. They also led to the most discontinuations, but the discontinuation rates were similar between the treatment arms and I will show you that in a minute.

[Slide]

This is a table of the adverse events occurring greater than two percent in the two pivotal trials. Here the placebo and pleconaril arms are pooled. Headache was the most frequent adverse event, and it was slightly more frequent in the pleconaril arm. We really still don't have a great explanation for why headache occurred so frequently in these trials. Gastrointestinal events, diarrhea, nausea, vomiting, abdominal pain were essentially similar but they led to the most discontinuations and the discontinuations fit an

interesting pattern, where patients would complain of gastrointestinal events within one to two days of the onset of dosing. They would stop the medication, either placebo or pleconaril, and their GI adverse events would go away within a day.

This also occurred with similar frequency between P-seropositive and P-seronegative patients. we didn't think it was an effect of a particular virus being present. So, we hypothesized that one explanation might be something in the formulation of pleconaril. Pleconaril and the placebo formulations were exactly the same, with the exception that the pleconaril formulation contained pleconaril. Each capsule contains sodium laurel sulfate, which is an emulsifying detergent, which is used as a tablet wetting and lubricating agent and this is an agent that is known to cause irritating effects to eye, skin, upper respiratory tract and the stomach.

[Slide]

The first significant adverse event I would like to talk about is menstrual disorders. These were seen in mild to moderate severity of early menses, intermenstrual bleeding, menorrhagia and menstrual disorders not otherwise specified.

They were observed at three to three and a half percent in the five- to seven-day treatment studies. But then there was a significant increased frequency noted in the six-week prophylaxis study, as outlined by the applicant. They also increased sequentially or exponentially as duration of exposure to pleconaril increased during the six-week study. Women were re-consented. A barrier method was recommended and menstrual disorders became a targeted question at each clinic visit.

[Slide]

These two table show the frequency of menstrual disorders in the five- to seven-day treatment studies and the six-week prophylaxis study. You can see here that in the pleconaril it is three to three and half percent among oral contraceptive users compared to essentially nothing in the placebo arm and women who were taking pleconaril and were not taking oral contraceptives.

In the prophylaxis study, among oral contraceptive users the rate was 27 percent in the placebo arm, 58 percent in the pleconaril once daily arm and 81 percent in the pleconaril BID arm. Across the non-OC users it was consistent, between

13 and 16 percent. These rates may be overestimation since the menstrual disorders were events that women were specifically asked about during the remainder of the six-week trial.

It was also interesting to note that the prevalence of menstrual disorders was three percent during the first week of the prophylaxis study, which correlates with the three percent in the one-week treatment studies. After that time they increased significantly.

[Slide]

To investigate possible mechanisms, the applicant conducted a five-day intravenous midazolam study and a five-day oral contraceptive interaction study. We believe the results conclusively demonstrate induction of CYP3A4 by pleconaril. It is evidenced by rapid decreases in midazolam and ethinyl estradiol levels by 28 percent and 35 percent respectively. There was no significant change in the norethindrone pharmacokinetics.

Pleconaril has a long terminal half-life. It is approximately 180 hours after a single dose and after multiple dose it is well over 1000 hours. Also, since the oral contraceptive interaction

study was only five days in duration, we do not know if maximum suppression of ethinyl estradiol was achieved, or how long it takes for ethinyl estradiol levels to return to an effective range following cessation of exposure to pleconaril. The applicant does have an ongoing PK/PD interaction study which may or may not help address this issue.

CYP3A4 induction by pleconaril could potentially impact exposure and effectiveness of a number of important drugs, such as immunosuppressants, antiarrhythmics, calcium channel blockers, protease inhibitors and Viagra, but there are no data on pleconaril's effects on these drugs to date.

[Slide]

The obvious concern was that these menstrual disorders in the presence of decreased hormone levels might increase the risk of unintended pregnancies. In the treatment studies approximately 20 percent patients were oral contraceptive users and in the six-week study about half of the women were using them. So there are another about 230 women who were oral contraceptive users between the two studies.

Thirteen pregnancies were reported in this

database. The ones of interest, there were two pregnancies among 156 oral contraceptive users both in the BID arm of the six-week study. One is ongoing and one ended in an abortion. There were five pregnancies reported in placebo users, one of which was an oral contraceptive user and the outcome of this pregnancy is unknown since the patient was lost to follow-up.

[Slide]

The CYP3A4 induction of ethinyl estradiol probably compromises the oral contraceptive effectiveness for at least an entire cycle. We believe that a backup method of contraception will be necessary for a prolonged duration of time. We attempted to characterize the potential public health risk of unintended pregnancies that could result from widespread use of pleconaril.

A 1998 report from the Guttmacher Institute said that about 10.4 million women between 15 and 44 years of age use some kind of pill form of contraception. Unfortunately, there is no data on the type or duration of those pills. We looked at data that has been submitted to the FDA to support the approval of oral contraceptives ever since the 1960's. Based on those data, the

expected oral contraceptive failure rate is approximately one pregnancy per 100 women per year of use. We believe that the two pregnancies in 156 women in six weeks of pleconaril exposure appears higher than what would be expected in the general population of oral contraceptive users. It is important to note that plasma was shown not to be teratogenic, mutagenic of genotoxic in animal studies.

[Slide]

The next thing that kind of popped up on the radar screen is tachycardia and palpitations. In the theophylline probe study, 15 healthy theophylline-naive volunteers were enrolled. During the second co-administration phase of theophylline and pleconaril, three of these 15 patients complained of palpitations and tachycardia. In general, there was an increased frequency of abdominal pain, nausea, dizziness and syncope during the co-administration phase, and although across the entire study population there was a 15 percent increase in the theophylline area under the curve, there were no significant PK changes in the three patients who complained of palpitations.

[Slide]

We looked at the VRI database and identified seven pleconaril treated patients who complained of tachycardia, with or without palpitations. Three reported a pattern of onset within one hour of ingestion, lasting for about an hour. Four patients discontinued study because of these events. One was serious enough that the patient presented himself to an emergency room but no cardiac etiology was identified. No patient underwent a pleconaril rechallenge so we don't know whether these might have recurred. There were two patients in the placebo database. One complained of tachycardia and palpitations on day five, and the other on day two. Both remained on study with resolution of their events. Overall, there was no appreciable change in heart rate or blood pressure noticed in the database. Since none of these clinical patients were on theophylline or had a history of respiratory or cardiac disease, a clear etiology for these events is still not known.

[Slide]

Let me summarize and go through each of the points that I identified in the beginning of my talk. Efficacy in Phase II was essentially not

demonstrated based on a number of design problems, including difficulty in identifying infected patients.

The results of the two pivotal trials demonstrate approximately a half day benefit in the all randomized population, and about a one day benefit in infected patients. Efficacy in smokers was not demonstrated across three clinical trials, and there were no data in patients with co-morbid conditions such as cardiac or respiratory disease. We also don't have very much data in elderly patients.

[Slide]

The methods used by the applicant appear to be able to identify infected patients. However, quantitative measurement of viral nucleic acid by the TaqMan assay could not be determined. Positive cultures were not serotyped so although the results suggested rhinovirus, we have no data to confirm actual virus present in the cultures. Resistance was present in 13 percent of patients prior to any exposure to pleconaril and these patients experienced a much longer time to resolution of their VRI than patients with susceptible virus. Patients with treatment emergent virus did not

appear to be adversely impacted by that, but the numbers in those analyses are very small. Again, single amino acid substitutions were identified that led to greater than 100-fold decrease in susceptibility to pleconaril.

I just want to take this opportunity to thank Dr. Kathleen Whitaker, from the Center for Devices, who assisted in the analysis of all the clinical virology data.

[Slide]

We believe the efficacy should be considered the way the drug may be used. Essentially infected and all randomized patients both represent legitimate populations for assessing efficacy, but we believe pleconaril will be prescribed to symptomatic patients who present with symptoms of VRI and there is no diagnostic assay that will be available to identify who has an infection with picornavirus and who does not.

We also believe that it is possible that patients would obtain a prescription for pleconaril, with the instruction to hold onto it and use it at the time of initial self-diagnosis of a cold. This could impact any kind of risk communication that would be necessary for this

drug.

Pleconaril requires administration with food three times per day, but how much has not been fully characterized. Since pleconaril is highly lipophilic, the fat content might be important. Finally, pleconaril needs to be initiated early in the illness, within 24 hours of symptom onset.

[Slide]

Pleconaril induces CYP3A4, leading to clinically demonstrable and rapid decreases in ethinyl estradiol levels, leading to breakthrough bleeding that appears to have resulted in two unintended pregnancies. The maximal amount and duration of induction are not known. Although treatment of VRI would be for only five days, pleconaril has a long terminal half-life. Thus, we believe the effectiveness of at least an entire oral contraceptive cycle would be impacted and women would be required to use a backup method of birth control but, again, for how long we really don't know yet.

Also, CYP3A4 induction could negatively impact the effectiveness of many other medications and we have no data to know how much, or which drugs at this time.

Palpitations and tachycardia were observed in the theophylline interaction study in some patients in the treatment trials. In general, pleconaril was well tolerated, with headaches and gastrointestinal adverse events being the most bothersome.

Finally, I would just like to acknowledge the other members of the review team. We look forward to your questions and your discussions. Dr. Birnkrant will return later and she will give you your specific charge and review the questions that we are seeking your input on. Thank you very much.

DR. GULICK: Thanks, Mr. Fleischer and Dr. Hammerstrom. That completes the presentations this morning. We are going to take a 15-minute break now. We will reconvene at 10:20 for the question period. Thanks.

[Brief recess]

DR. GULICK: Welcome back, everyone. Dr. Stanley, are you still with us?

DR. STANLEY: I am with you.

DR. GULICK: You are a trooper! This is an opportunity for the committee members to ask questions either of the sponsor or the agency.

People are jumping right in. Dr. Gordin, would you like to lead us off?

Questions to the Presenters

DR. GORDIN: I was wondering, Dr. Hayden, if you could talk a little bit about the common cold in terms of who gets it. Looking at the groups that were excluded from studies here, how many people with a common cold do actually have a temperature over 100? How many people with a cold would have had a cardiac or respiratory illness that would have been excluded? Also, if you could talk about how many days of work are really missed by people with a common cold. I am not sure if that was even looked at here as an endpoint or data collected? Did people not go to school or not go to work? Could you talk a little bit more about kind of populations as a whole in the country versus what was studied here?

DR. HAYDEN: Well, I think that the patients enrolled in these two clinical trials were really representative of the young and middle-aged general civilian adult population. As I indicated, the incidence of colds decreases with increasing age. We know that co-morbidities increase with increasing age so the likelihood of colds

developing in those with underlying cardiac or respiratory conditions is diminished in terms of frequency relative to younger individuals, although their likelihood of having complications from those illnesses and more protracted symptoms is increased.

You asked about fever specifically. In the study that we did in 1994, where we enrolled 346 self-diagnosed adult cold sufferers, 82 percent of those were picornavirus positive. The proportion with fever was less than five percent. Rhinoviruses can cause febrile respiratory illness but it is a very small proportion of these illnesses and that helps, in fact, in terms of trying to make a distinction between a rhinovirus cold and, for example, influenza where fever is a predictor of influenza infection and also response to antiviral therapy. So I think there can be some useful clinical criteria that will help identify appropriate target populations.

DR. GORDIN: What about the question of people who do get colds, how many miss work or school? And, was that specifically looked at in these studies? I know impairment was looked at and the FDA, in their presentation, showed I believe

that in five of the six parameters there was no statistical difference, but did anybody specifically look at missed work, missed school, missed activities?

DR. HAYDEN: The clinical trials did incorporate a self-report of the number of days of impaired activity. Unfortunately, that is a very insensitive measure of the effects of an acute respiratory illness on performance. Prior studies of cold sufferers in general have not found reduction in work time as much as altered performance while on the job. In order to capture effects on quality of life or more detailed psychomotor abnormalities, one would need to use specific instruments to examine those things, and those were not incorporated into these studies of otherwise healthy individuals. I think that is reasonable, given that the likelihood of seeing effects on those endpoints in an otherwise healthy group might be lower than in older individuals or those who have some co-morbidities.

DR. GULICK: Dr. Kumar?

DR. KUMAR: My question is to Dr. Cooper. Dr. Cooper, I am certain you recognize that for most practicing clinicians to administer the drug

within 24 hours would be problematic. So, I wanted to ask you a couple of very practical questions on how you did this trial.

My first question to you is how did you manage to get about 2000 patients in just about three months? Did you have somebody sitting at a phone and as soon as they said "I've got rhinorrhea," "come right in?" I would just like to have a flavor of how you managed to get patients within 24 hours into your clinical trials.

DR. COOPER: Well, we identified the sites beforehand, of course, who had investigators to participate in these studies. Then, as the fall season began or just prior to the fall season there were advertisements, radio announcements -- each site did it differently but basically got the word out to the community that there was a trial that was looking to enroll patients with colds within 24 hours of onset. So we were very pleasantly surprised at how easily we were able to enroll these studies.

DR. KUMAR: Can I ask you a follow-up question? Among the patients that called in and came in, what percentage of them were within the 24-hour period of time?

DR. COOPER: It was very high, between 95-98 percent. If you want an exact number, Dr. Villano can give you the specifics.

DR. VILLANO: Stephen Villano, clinical research at ViroPharma. To the specific question about how patients were screened and enrolled within the 24-hour window, I would note that approximately three patients were screened for every one that was enrolled in a clinical study.

DR. KUMAR: That is what I wanted to know.

[Slide]

DR. VILLANO: In fact, the number one reason for not being enrolled in the study was not being within the 24-hour window, which accounted for approximately 60 percent of the people that were not allowed to be entered into the study.

DR. KUMAR: Thank you. That is exactly what I wanted to know. Thank you, Dr. Cooper.

DR. GULICK: Dr. Brass?

DR. BRASS: I would like to ask, hopefully, a quick series of questions about some basic toxicology and pharmacology of the compound. First, do you have any data on whether or not the compound interacts with any of the PPAR class of receptors in the liver or elsewhere? Is that a

"no?" I heard a "no." Okay.

Next, Dr. McKinlay's slide 19 showing metabolism of the compound -- is it easy to get that slide back on? What is the other product of that first metabolic step where the ring is open?

DR. MCKINLAY: What is the other product? I will ask Dr. Rhodes to come up to address that.

DR. RHODES: Gerry Rhodes. I am with drug metabolism and clinical pharmacology at ViroPharma. If I understand your question correctly, you are asking what is the other product formed. Trifluoracetic acid would be the loss.

DR. BRASS: And, does that reach systemic circulation? And, what do you know about the toxicology of it?

DR. RHODES: It does reach systemic circulation. We have found trifluoracetic acid in the urine of patients in a C14 ADME study. I would like to ask Dr. Hincks to comment on the pharmacologic profile of trifluoracetic acid.

DR. HINCKS: Jeff Hincks, preclinical development at ViroPharma. As far as studying specifically trifluoracetic acid, we have not. However, we have seen that in rats as well, and under those auspices we have studied, I guess, the

metabolism profile that we saw with pleconaril in rats and dogs. We saw similar metabolic profiles.

DR. BRASS: But from the literature elsewhere, is trifluoracetic acid a benign compound?

DR. HINCKS: It is fairly well tolerated at high levels, yes.

DR. BRASS: Next, I just want to emphasize that on slide 17 of the initial presentation --

[Slide]

-- I just want to emphasize that trying to estimate a terminal half-life of greater than 100 hours in duration from that data set is impossible, and when we talk about the duration of potential induction or other pharmacologic actions of this compound, do we have a better way to estimate the half-life, other than that particular figure?

DR. RHODES: The graph in the presentation was clearly for presentation purposes. We have characterized the terminal elimination and half-life of pleconaril to much later time points.

[Slide]

This graph shows the plasma concentration time profile following the last dose of a five-day treatment regimen of 400 mg TID. Again, there is a

long terminal half-life, even difficult to estimate here. We sampled out to over 600 hours, so to even estimate it at 1000 is a bit of a stretch. It is difficult to determine accurately but we do fall very rapidly from Cmax concentrations over a 24-hour period to concentrations that are relatively low, about 0.5 mcg/mL, and then there is a long terminal elimination of drug from that point.

DR. BRASS: Is that the data set that the 1000 hours was derived from?

DR. RHODES: Estimated from, yes.

DR. BRASS: So to the degree these numbers matter, 100 is probably, if anything, an underestimate and one shouldn't be tied into that number quantitatively. Do you agree that is fair?

DR. RHODES: Yes, I agree that is fair. There is going to be, you know, quite a bit of play in that number of 1000. The half-life of 180 hours that was quoted was determined after a single dose where, again, you may not be able to fully describe the terminal phase to the same degree.

DR. BRASS: My last question of this series is when you look at drug interaction data, I think it is very important to think about the drug

interaction data as safety data, not kind of efficacy equivalent data. As such, it is the outliers, particularly in small data sets, that often contain the signal about the magnitude of a potential drug interaction in subpopulations that were exposed to the drug. You showed us mean data for the 3A4 interaction induction experiment. I would be interested to see what the maximal range of effects was in terms of AUC reduction, and how that might relate to a prototypic inducer like rifampin, which is accepted to have a substantive interaction with oral contraceptives.

DR. RHODES: If you don't mind, I would like to start with a comparison with rifampin first.

[Slide]

I would just like to review quickly what we do know about pleconaril and then compare it and contrast it to other potent inducers. We have seen an increase in CYP3A activity with IV midazolam confirmed in an interaction study with an oral contraceptive agent. Ethinyl estradiol levels did drop 34 percent, with a half-life decrease of 18 percent. We didn't see any effect on norethindrone pharmacokinetics. In interaction studies we

conducted with theophylline and warfarin which are probe substrates for 1A2 and 2C9, we didn't see any inductive effect there.

[Slide]

The potent inducers of 3A -- again, I am going to use terms like potent, moderate and modest with respect to current categorizations in the literature, and this is data drawn from the literature -- potent 3A inducers, like carbamazepine, phenobarbital and rifampin have a potent effect on midazolam. I think they drop the AUC of oral midazolam by approximately 95 percent. These potent inducers of 3A don't just affect 3A, however. They also affect 2C9 with drug interactions with warfarin, also drug interactions with theophylline mediated through 1A2. So, the activity of those enzymes also increases.

Some of these inducers also increase phase two drug metabolizing enzymes UDP, glucurosyl transferase activity. Some also induce P glycoprotein synthesis. There are other classifications for 3A inducers where this general pleiotropic sort of induction isn't observed. Topiramate would fall into that class; felbamate would, and with the data we currently have with

pleconaril, we believe it would fall in that class as well. But the effect is mainly on CYP3A.

[Slide]

What I have done on this table is really compare and contrast the literature data for characterizations of potent moderate and modest based on literature precedent. You know, two positive sites indicates a change greater than 50 percent on average. One, less than 50 percent, and at least for the in vivo data we currently have with pleconaril, summarized across the top with midazolam, warfarin, theophylline and then the CYP enzymes are mainly involved in their biotransformation.

So again, this potent class of inducers has significant effects on midazolam, 95 percent; about 60 percent decrease in ethinyl estradiol AUC. Effects on warfarin, effects on theophylline. There is a group of 3A inducers that have less of an effect on 3A, ritonoavir, rifabutin, troglitazone, St. John's wart, for instance, where this is approximately 30-40 percent for ethinyl estradiol. This more moderate classification in terms of the broader spectrum of what they also induce is that you do see some other signals for

warfarin and theophylline interactions, and also rifabutin and troglitazone pharmacokinetics. Topiramate, felbamate, these are 30 percent drops in ethinyl estradiol AUC. Again, there is not much data here, at this point, although there is nothing reported for interactions with warfarin and theophylline, and pleconaril seems to fit into this class where we have about a 30 percent change in ethinyl estradiol but no effect on warfarin, theophylline or norethindrone pharmacokinetics.

Now, with respect to data in our individual studies and the confidence intervals around them, the geometric means, there is individual variability in those studies, of course, and we have seen, you know, higher clearances in some subjects. I think the maximum range in the midazolam study -- and Joe can correct me if I am wrong -- is roughly almost a doubling of clearance in some subjects. Others are affected less. I think that is typically what you do see in drug interaction studies. There will be some individuals that will be more affected than others, yes.

DR. GULICK: Dr. Schapiro?

DR. SCHAPIRO: There are two issues that I

would like to ask about. The first is for the resistance in the virology, are there any data on other compounds that work with a similar mechanism of action being developed by the company or other companies, and which mutations are seen if any cross-resistance studies were done with the isolates that were found here?

DR. MCKINLAY: Yes, I will ask Dr. Hayden to come up and discuss that.

DR. HAYDEN: There has been a series of compounds that are so-called capsid binders, different chemical entities but all targeting the same structure in VP1. Some one years ago, the workers at the common cold unit, under the direction of Dr. David Turrell, actually took one of these selected A-resistant variant in vitro and compared the relative infectiousness of that variant to the wild type virus.

[Slide]

This shows you the results of the clinical trial. These individuals were inoculated intranasally with the parenteral susceptible strain and with a variant that was roughly seven-fold or more less susceptible. You can see that the proportion of individuals developing cold symptoms

was relatively low with both viruses, but less than half with the drug resistant compared to the wild type. Viral shedding was seen in 27 percent compared to 67 percent. Seroconversion, another marker of infection, was substantially lower with the drug-resistant variants. The overall infection was documented in 27 percent of those inoculated with the drug-resistant variant compared to 92 percent, over a three-fold reduction. This reduction in infectiousness then is correlated with some of the laboratory studies of such drug-resistant variants where they have shown reduced stability to pH and in some cases heat.

I can't comment directly on the cross-resistance profiles of the pleconaril less susceptible variants compared to these older agents, but perhaps other individuals can.

DR. SCHAPIRO: The question is really regarding other agents, to what degree what mutations were seen.

DR. MCKINLAY: The data in the literature indicates that there is cross-resistance. For example, the chalcone is cross-resistant with pleconaril, etc. The actual mutation in this particular mutation was not characterized in this

study.

DR. SCHAPIRO: One more question. The issue of complications, I saw some data in the background information. The appearance of acute complications in patients treated or not treated. I think it was Table 17 and 50.

DR. MCKINLAY: Right, I will ask Dr. Villano to comment on the complications.

DR. VILLANO: I believe you are referring to the projectable version of the respirator complications in the intent-to-treat populations.

[Slide]

Is this what you are referring to?

DR. SCHAPIRO: Yes.

DR. VILLANO: This slide demonstrates the respiratory complications of otitis media, bronchitis, sinusitis and pneumonitis, as was asked of the investigators to report had they occurred at any time during the course of the study. It is important to point out that in these studies we did not provide specific definitions for these events, but laid out that if they were to occur during this study, specifically tell us if they occurred.

As shown here, the overall incidence of any respiratory complications was relatively low,

which probably reflects the fact that the population was otherwise healthy and generally at low risk for developing these complications.

DR. GULICK: I will come back to you, Dr. Brass. I will give everyone an opportunity to ask questions and then we will have people repeat if they like. Dr. Fletcher?

DR. FLETCHER: Three questions for the sponsor and then one joint one for both the sponsor and the agency. My first is about the pharmacokinetic/pharmacodynamic basis for the dose selection. Dr. Brass has already commented about slide 17 with the profile. In the presentation it was noted that the eight-hour concentration was approximately 0.5 mcg/mL, about the 75 percent inhibitory value. But that is based on total concentrations, and the drug is 99 percent protein bound so the free drug concentration would be considerably less than that 75th value. So, I don't see from those data a pharmacologic basis for the dose that has been selected, the 400 three times daily. So I am wondering what other pharmacologic data you have, correlations with dose and antiviral effect or emergence of resistance, correlations with concentrations and antiviral

effect and emergence of resistance.

DR. MCKINLAY: Let me call Dr. Rhodes to explain the rationale for the dose selection.

DR. RHODES: Our dose was selected based on an appropriate combination of preclinical and clinical Phase I pharmacokinetic data. Data from Phase II trials were not conclusive with respect to antiviral activity with respect to PK/PD and it wasn't traditionally sampled in that way. However, we did have an appropriate combination of data from which to decide on a dose selection. Our dose is 44 mg TID for five days.

[Slide]

The slide that Dr. McKinlay showed you with the classic concentrations at eight hours, what we did, we had preclinical data suggesting that the tissue to plasma ratio, partitioning of drug from plasma to tissue, nasal tissue, was approximately five-fold. So we looked at a range of Phase I data, at the eight-hour time point, the end of a dosing regimen; looked at the plasma concentrations in individual subjects at that point. We took those subjects with the lowest plasma concentrations, dose over the individual variability, and with that projected five-fold

ratio of plasma to nasal tissue concentration, patients with the lowest plasma concentrations at eight hours, applying that factor would project the nasal tissue concentrations at MIC90 for rhinovirus serotypes. So our dose was selected based on those criteria.

DR. FLETCHER: My second question is about food. In the data the FDA presented they indicated that the food effect increases the AUC by about four- to six-fold. To understand that there must have been some study that was done, drug given fasting or drug given with food. I would like to know what that meal looks like. How many eggs, how much bacon?

DR. RHODES: The study that has been referred to was a comparison of fasting subjects to those getting a standard English breakfast. So it would have been eggs, bacon, hash browns, toast and butter -- a rather heroic meal!

[Laughter]

DR. FLETCHER: And that was done in healthy volunteers or in individuals that were in a study that had a cold?

DR. RHODES: That was done in healthy volunteers.

DR. FLETCHER: So in the pivotal studies, 43 and 44, what were the recommendations there for meals?

DR. RHODES: In the Phase III trials patients were asked to take pleconaril with food. The meal was not specified so it was an open dietary regimen.

With respect to protein binding, the drug is highly protein bound, granted. But it is not like many drugs that are highly protein bound with a very low volume of distribution at, say, just extracellular water volume. Pleconaril's volume of distribution is considerable even with the high protein binding.

DR. FLETCHER: Another drug interaction question. In Dr. Cooper's presentation, she indicated, I believe, that these drug interactions were manageable. I am curious how they were manageable. What are the guidelines by which you would manage the oral contraceptive interaction or the theophylline interaction, or the potential interactions with other CYP substrates?

DR. MCKINLAY: I would like Dr. Joe Bertino to address this, as an individual with a lot of experience in this area.

DR. BERTINO: I am Joe Bertino. I am the section chief of clinical pharmacology at Bassett Healthcare, in Cooperstown. We did the midazolam study.

[Slide]

Dr. Fletcher, in terms of your question, I think that in terms of manageable there are some different issues that I would raise. The immunomodulators, cyclosporin, protease inhibitors -- we, clearly, on this slide have a break where I think that these are the interactions that I would be most concerned about.

The oral contraceptive issue, I think there is an expert in the audience here today, Dr. Mishell, that can probably comment on that a lot more. The question really is do you lose contraceptive efficacy? In the rifampin-rifabutin studies in the literature, a very potent inducer of both ethinyl estradiol and norethindrone, in those studies in the literature in two separate groups of women, women never spiked their progesterone so they never ovulated even in the face of a drug interaction, but there is a lot of variability in the population in terms of estrogen/progesterone exposure.

These agents I have put down here, I think drugs like amiodarone that have very long half-lives, 40-50 hours, the only thing that is reported in the literature for that drug is a case report of a woman with TB that got five weeks of rifampin and then had a ventricular arrhythmia on amiodarone.

Calcium channel blockers, again, probably for hypertension I would think this would be less of an issue if patients were being treated for angina. There is a report in the literature of a rifampin-nifedipine interaction with variant angina coming back into the patient as being a concern.

Benzos, you know, once again the effect was about 30 percent with midazolam. Presumably a drug like alprazolam might show a similar effect. It would be hard to know what the overall implications are for those drugs.

Clarithromycin -- opiate analgesics -- we have alfentanyl here, alfentanyl is also a 3A substrate, and there is probably not a real concern with the statins.

So I think that my concern lies in this group of drugs, here, mostly these two in terms of managing, I probably would be reluctant to use the

drug in patients getting cyclosporin and protease inhibitors.

DR. FLETCHER: I suspect we will come back to the drug interaction topic again, but let me get to my last question, which is a joint one for both the sponsor and I would like the agency to comment as well. That is on whether there is a possibility of ethnicity/race difference in effect with this drug. In study 043 you enrolled about 80 percent whites and in 044 about 90 percent. In the intent-to-treat analysis there was a beneficial effect in 44 but not in 43. Then, in one of the sponsor's subgroup analyses, on page 73 of your briefing booklet, you actually did an analysis looking at the effect of the drug in whites and in non-whites. We realize the sample size issue, but for the white population there was a benefit; for the non-white there was not. So, my question first for the sponsor, and I would like to know if the agency looked at that issue as well, you know, is the reason you found an effect in 44 with intent-to-treat and not in 43 because it has a higher population of whites enrolled? So, the bottom line is are there data here telling us that there may be an ethnicity/race differential effect

with this compound?

DR. HAMMERSTROM: We did look at the analysis stratified by race. There was a smaller effect in blacks. In fact, if I remember correctly, there wasn't much of one at all. But it is a very small subset and it is difficult to decide. You could say there is a signal there. In a perfect world where clinical trials could be run free of charge, we would like to say 500 black patients treated with this drug to find out whether that signal is just noise or not. The way it is now, it looks like it could be just noise but we can't prove it is not. I don't remember whether there was a difference in ethnicity percentage between the two trials.

There is an effect in the ITT population even in trial 43. All of the quartiles are shifted downward about half a day. It is not statistically significant. I think the p value was -- what? -- about 0.2. But there have been other drug approvals where we have approved a drug on the basis of one pivotal trial getting a p value comfortably below 0.05 and the other trial getting a p value that is around 0.09 or something like that. It didn't make the nominal p value.

Remember, p values, for all the popularity of the 0.05 cut-off point, do not drop. It doesn't suddenly change from effective to ineffective as you cross that border.

DR. MCKINLAY: Dr. Villano?

DR. VILLANO: The analysis that we performed looking at the efficacy in the primary endpoint based on race was an analysis that we performed in the pooled data set because, as was mentioned, although we did not enroll patients with any restrictions as to race there were, as it turned out, very, very small numbers in the non-white group.

[Slide]

This slide shows these pooled results that were mentioned in the briefing book. In the large group of subjects who were white there clearly is a demonstrable treatment benefit, whereas, we could not make this conclusion in the non-white subgroup. However, to the extent that we could try to analyze whether there were true differences between these groups or not, we did apply a Cox regression model to try to analyze whether there was consistency that could be demonstrated within these groups. Obviously, it is very difficult because of the very

small group. That value was insignificant, suggesting that there was no inconsistency of effect between those groups to the extent that that analysis can help.

However, in addition, to help support the activity of pleconaril in both subgroups we also looked at a supporting endpoint, the viral culture results based on race as well.

[Slide]

That is shown in this slide. Looking at the white and non-white population on the right and left-hand side of the screen, there was an interesting difference between the white and non-white groups in that the non-white population actually, at day three, had a notably lower viral culture positivity rate, although in both groups there was treatment effect seen. So to the extent that we could analyze it, we have not seen notable differences between those groups although, again, our numbers are very small.

DR. GORDIN: To follow-up, I was also concerned, in the same Table, 25, that gender appears to be a major factor as well. Where the numbers are substantially larger, it appears that, again, the effect is seen in women but not in men.

I was wondering if you could show that. I was also, again, interested in the agency's opinion on this, and how much of the gender race is intermixed with smoking as a factor. If you could kind of talk a little bit more about the subgroups.

DR. BRASS: You might as well add age to that too.

DR. VILLANO: First let me show you the analogous slides with regard to gender. Again, I will stress that the protocols were enrolled without restriction as to gender, although based on some of the epidemiology that you might have heard about colds, they are certainly more prevalent in women which probably reflects the enrollment in our studies.

[Slide]

This also shows the viral culture results based on gender, also showing that both women and men had a demonstrable effect in terms of antiviral activity, culture positivity reduction on day three compared to the placebo groups.

[Slide]

With regard to the primary endpoint, we did the exact same type of analysis, looking at the primary endpoint, pooling the studies together to,

again, maximize the numbers. In this instance we see that women had the greater result in terms of reduction compared to placebo. The direction clearly was also in favor of pleconaril in men, although the magnitude of the change was not as large.

We attempted the same Cox regression analysis to see if that could demonstrate significant differences between those groups. We did not find that difference in that particular analysis.

You also mentioned smoking as well. What I would like to do is just give an overall view, again, of our ability to try to discern which of these variables, prestratified variables and demographics might have had influence on the primary outcome measure.

[Slide]

This slide demonstrates, again, our attempt to use a Cox regression model to evaluate each of these variables in turn as to whether or not there was effect on the treatment efficacy of pleconaril. As shown here, looking for any p value that showed significance, the interaction was positive only for smoking status, suggesting that

of all these variables, including demographics, that was the one that clearly had an effect on treatment outcome based on the primary efficacy endpoint.

DR. HAMMERSTROM: Our analysis pretty much confirms the sponsor's analysis. We did have, if you remember, a slide up there crossing gender with smoking and there didn't seem to be a three-way interaction of treatment, gender and smoking. The absence of effect among smokers was about the same. There is a smaller effect in males estimated, but it is still positive. There is not enough N to get a p value and say that it is small at 0.05 even when you pool the two studies together because, remember, only a third of the patients are males.

We didn't look that much at age, but there is not that much variation in age. Most of these people are working age adults. There are not that many elderly and there are no children.

DR. GULICK: Dr. Englund and then Dr. Wong.

DR. ENGLUND: Yes, I wanted to discuss a little bit more about the diagnosis, specifically the PCR diagnosis you used. Although it was not for the primary endpoint, in fact, slide after

slide you have shown us is showing culture as an indicative endpoint. In fact, culture was only attempted when PCR was done. I am not an expert in rhinovirus PCR but, in fact, based on what I do know about some of the TaqMan systems, you have chosen a lower threshold of 0.1, I believe, and doing it for 60 cycles, whereas most of, at least the flu things, have been 45 cycles. So perhaps could someone discuss the methodology and why this was done, and if there was even a subset analysis if there are any culture positive with PCR.

DR. MCKINLAY: Right, we can show you the clinical data by subset by culture positives. But, first, let me have Dr. Collett come up and talk about the assays.

DR. COLLETT: Marc Collett, virology, ViroPharma. The TaqMan assay that you are specifically referring to, we used a 60-cycle assay run. All the performance data were generated using that cycling run. We have demonstrated that the results from both the performance evaluations and supplementary testing, which may not have been provided in your book, indicate that the TaqMan assay maintains its high level of sensitivity and specificity throughout the cycles.

[Slide]

Shown on this slide is a breakdown by cycle, and confirmation by cycles of TaqMan positive samples, grouped here at less than 20 cycles, 30 cycles, 40 cycles, 50 and 60 cycles, showing the number of TaqMan positive samples in this collection of clinical specimens tested from the three studies. The confirmation rate by the independent RT-PCR assay, which uses different primers and is a different methodology, the assay agreement is quite high. The assay agreement is high across all levels of CT values or threshold crossing values. So it appears that the specificity is maintained at the higher cycles.

DR. ENGLUND: But you have no culture data. In fact, there are study samples which might include patients receiving therapy or not receiving therapy. Correct?

DR. COLLETT: Yes, these are baseline samples.

DR. ENGLUND: Oh, this is baseline?

DR. COLLETT: Yes.

DR. GULICK: Dr. Atmar?

DR. ATMAR: In the description of the assays in the application the ELOSA was said to be

more broadly reactive an assay. There really aren't any data describing what the relative levels of detection of the two assays are in terms of amount of viral genome. Do you have information about that for us, and what is your explanation for the apparent lower number of positives in the ELOSA column compared to the TaqMan column?

DR. COLLETT: Are you referring to these particular data, here?

DR. ATMAR: I am referring to these data in terms of comparison of the TaqMan to the ELOSA and then just a question about what the relative level of detection is in terms of the number of genomic copies per sample need to be present.

DR. COLLETT: Let me first start with the spectrum of detection by the two assays because that differs slightly. As we get that slide up, for the TaqMan assay the primers were derived based on an analysis of rhinovirus sequences. So the TaqMan assay turns out to be more rhinovirus specific than more broadly cross-reactive to picornavirus encompassing both rhinoviruses and enteroviruses.

[Slide]

Shown here, the TaqMan assay identified 89

percent of the 101 prototypic serotypes but very few enteroviruses, whereas the ELOSA, using the different primer set, was able to detect all the prototypic viruses, both the rhinoviruses and the enteroviruses.

Going back to the assay agreement between the two assays, there is some disagreement, as shown in the previous slide, that could relate to differences in the viruses that were being detected, as well as differences in the efficiency of the two assays since they are using different primer sets and, actually, different assay technologies.

DR. ATMAR: But my question is how much viral genome per mL or per sample needs to be present? You use 1B I guess --

DR. COLLETT: We use the 1B as a standard but we have also looked at five prototypic serotypes and looked at the lower limit of detection, which I believe is what you are asking.

[Slide]

This slide is showing it for the TaqMan assay in two units, either the traditional or more customary PFU, which these viruses are all quantified by. We see that the lower limits of

detection are less than PFU. If we then calculate based on estimations of absolute RNA quantities, we get, as you can see, a variation of genome detection sensitivities across the five serotypes. This doesn't appear to be unexpected. We would expect this type of diversity due to their genetic diversity as well.

DR. ENGLUND: But just one more follow-up though, but that assay is done using viruses grown in tissue culture, or something like that.

DR. COLLETT: That is correct.

DR. ENGLUND: My other concern about all this is you are using frozen mucus collected in Saran wrap or other methods, and do you have any data? There is actually good data about the inactivation with the thick mucus of other viruses and I just haven't seen any data on rhinoviruses.

DR. COLLETT: Excuse me, other viruses?

DR. ENGLUND: Other viruses when TaqMan procedures are used, that it will actually limit the detection by PCR. So I am concerned because we are getting an endpoint -- not an endpoint, excuse me, but we are analyzing our data and we are all thinking critically based on the culture results which are determined by PCR, for which I see no

good standardization or even increased data on the methodologies.

DR. COLLETT: The data collection paradigm was that individuals were evaluated for PCR positivity and then those individuals were subsequently cultured. Based on performance evaluations prior to the pivotal studies, we did an assay agreement analysis, a three-way comparison of all the assays to determine what number of virus culture positives we might get outside of the TaqMan detection sphere, and that turned out to be quite low. This was an evaluation of 855 baseline samples from the 032 study. There, we found 0.6 percent of the sample were virus culture positive but scored negative by both RT-PCR assays. So we would have missed some patients in the pivotal trials because we didn't do virus culture on all samples, but we estimate that would be a very low number, approximating about six to eight individuals.

DR. ENGLUND: But in that early study, how were those samples collected? Were those washes as opposed to mucus blows?

DR. COLLETT: It was blown mucus collection, very similar to what was done in the

pivotal studies.

DR. ENGLUND: I thought the pivotal studies were done two different ways. No? They were done both with nose blows?

DR. MCKINLAY: Right, it was blown mucus in study 32 and a swab was taken --

DR. ENGLUND: Yes.

DR. MCKINLAY: -- of the sample, whereas in 43 and 44 the whole sample was taken.

DR. GULICK: Did we get to all your questions, Dr. Englund? I thought you had one more.

DR. ENGLUND: I did, but now I have forgotten it. You can go on.

DR. GULICK: Thanks. Dr. Wong and then Dr. DeGruttola.

DR. WONG: I want to return to the safety profile of the drug. I think I have a reasonably good flavor for the efficacy, but I was concerned, when I read the book and then also during the presentation, about the possibility that this drug really may cause excess unintended pregnancies in women taking oral contraceptives. When I looked at the data that would really bear on that question I couldn't really make an assessment for myself

because some of the denominators, for example, were missing in some of the groups. I was wondering if you could reassure me that that is not the case. I mean, show us the data that bears directly on that point.

DR. MCKINLAY: First I will ask Dr. Villano and then we have an expert in our midst, Dr. Mishell, who can comment on this as well.

DR. VILLANO: Specifically, I would like to review again the data that we presented with regard to the pregnancies that occurred in both the five- to seven-day treatment studies and then distinctly in the six-week prophylaxis study.

[Slide]

This slide summarizes the pregnancies that occurred in all five- to seven-day treatment studies that were conducted with pleconaril. Among placebo patients there were 1500 women, 303 of whom were using oral contraceptives. There were four pregnancies reported in this group, one of which occurred in an oral contraceptive user. Among the patients receiving pleconaril the number was greater, 415 women were using oral contraceptives during any of these studies and there were two pregnancies, neither of which occurred in women who

were using oral contraceptives.

As presented earlier this morning, we don't have outcome on this particular woman. We tried several times. The patient refused follow-up despite several contacts.

[Slide]

In distinction, the incidence in the six-week prophylaxis study obviously encompasses a longer treatment period and follow-up period. This slide shows these results. On the top, we see the placebo patients. I can reiterate the numbers here. We have approximately 100 women on oral contraceptives in each of the first two groups. I am sorry, they are not on the slide, but approximately 100 women on placebo; approximately 100 on 400 mg once a day; and approximately 60 on 400 mg BID. The pregnancy rate is shown here. We had one in the placebo group, one in the 400 mg Q day group and five in the 400 mg BID group, and this is where we had two pregnancies that occurred in women who were receiving oral contraceptives. One had an elected abortion; one is still ongoing, outcome to be determined in several months.

Specifically with regard to any implications as to pleconaril's effect on the

efficacy of oral contraceptives, we find that our data are actually fairly limited with regard to numbers to make conclusions. But I would like to invite Dr. Mishell to come up and comment on these results.

DR. MISHELL: Thank you. Good morning, everyone. My name is Dan Mishell. I am the professor and chairman of the Department of Obstetrics and Gynecology at the Keck School of Medicine, University of Southern California.

I would just like to start off by telling you my qualifications for commenting on this. I have been involved with contraception as my main area of interest since I entered academic medicine in 1963. I have been a consultant to the Population Council in New York and am a consulting senior scientist to them. That is the organization that developed the copper T intrauterine devices, as well as the Norplant implantable contraceptives. I have also been a consultant to the World Health Organization on their contraceptive development program in the 1970's. I edit the medical journal Contraception, which is a monthly journal, and since its inception in 1970 I have been the editor in chief. It is a peer reviewed journal dealing

exclusively with contraception. I have also chaired the NIH symposium on contraception that was held here, in Bethesda, last summer, and I have written chapters on contraception for numerous medical texts, including Cecil's textbook of medicine.

I would like to just tell you about oral contraceptives. They are composed of two steroids, progestin which is the steroid in the oral contraceptives that is mainly responsible for their contraceptive effect. What progestin does is inhibit the mid-cycle LH surge which is a stimulus release of the egg from the follicle so ovulation doesn't occur. The progestins have been used by themselves as very effective contraceptives. There is an injectable agent which is a progestin, which has no estrogen and is extremely effective in preventing pregnancy.

The implants that I just mentioned are also composed of just progestins. There is no estrogen, and they also have an extremely high effectiveness rate. Both of these types of progestin only contraceptives have failure rates less than half of one percent per year.

The progestins also prevent pregnancy by

secondary mechanisms, keeping the cervical mucus such that the sperm doesn't ascend to the upper genital tract to fertilize the egg, and also alters the endometrium, suppressing the growth of the glands which make the glycogen which supports the growth metabolism of the blastocysts while in the endometrial cavity so it really prevents implantation if fertilization happens to occur.

The other steroid in oral contraceptives is estrogen. In most combination oral contraceptives there is an estrogen and it is called ethinyl estradiol. It is a synthetic steroid. There are a couple of pills that are progestin only pills but they are not used very frequently but they are fairly effectiveness, low dose progestins. This estrogen in the oral contraceptives, its main action is to maintain the endometrium and prevent intermenstrual bleeding and to prevent bleeding except after the pills are stopped and then the woman has withdrawal bleeding for several days. The estrogen also has a contraceptive mechanism that inhibits follicular growth by suppressing FSH, but its main effect is maintaining the endometrium.

This agent, pleconaril, stimulates the

enzyme that helps metabolize the estrogen, ethinyl estradiol. That is why the area under the curve of ethinyl estradiol is reduced. There is increased metabolism of the estrogen. But it has really no effect on the progestin in the study. That is to be expected because of the mechanism of action of the enzyme and how the estrogen and progestin are metabolized differently.

[Slide]

Let me just sort of summarize what I have said. The main action of the steroids in the oral contraceptives, progestin, is to inhibit ovulation. That is the way it works, it inhibits the LH surge and thickens the mucus. So progestins alone are contraceptives and this agent does not interfere with the metabolism of the progestins. So, I would expect it to not have any effect on contraceptive efficacy. The numbers we saw, as far as pregnancies, are pretty reassuring. In the 400 women who used the oral contraceptives and were taking pleconaril for five to seven days there were no pregnancies. That is really quite reassuring to me.

In the six weeks there were two pregnancies. The numbers are really small, and

typical use of oral contraceptives, in contrast to the studies that were submitted for the approval to the FDA in which the pregnancy rate was around one preclinical, in typical use in the first year the failure rate of combination oral contraceptives is around five percent. Those are studies that were done by Jim Trusseller, published in Contraceptive Technology, based upon national surveys of family growth.

The estrogen's main mechanism is to decrease the breakthrough bleeding or intermenstrual bleeding. It also inhibits follicular growth. So by decreasing the levels of estrogen, one will have an increased incidence of intermenstrual bleeding, which is what has been found in the studies of short-term and long-term use.

[Slide]

Just to remind you of the interaction study in which an oral contraceptive was given alone, in the yellow line, and then after six days of pleconaril another single tablet of oral contraceptives, and this is the estrogen showing significantly reduced levels in the circulation. Then pleconaril was given again at one and two days

thereafter and showed that there was still a decrease in estrogen levels, decreased area under the curve. Therefore, one would expect an increase in breakthrough bleeding which was observed in the clinical studies

[Slide]

If we look at the progestin, I think this is what is reassuring to me because this is what prevents pregnancy. You can see that these two curves are superimposable. It is the same study. This is progestin levels, and the yellow and blue lines are superimposable even after two more days of pleconaril, after giving it on the six day. So I am really reassured about this data and the pharmacokinetics. This agent will be associated with an increased incidence of intermenstrual bleeding, which is more what we call a nuisance side effect. It is really not a health side effect. Women don't like to have unscheduled bleeding, but as the dose of estrogen has declined in oral contraceptives formulations there has been an increase in the incidence of intermenstrual bleeding. With the low estrogen dose pills that we have today, the lowest that is approved in the United States and marketed is 20 mcg of estrogen

and about ten percent of the women have breakthrough bleeding or spotting. As I said, it is an annoyance but it doesn't cause anemia, doesn't need blood transfusion. As shown in the studies, no woman discontinued use in the five- to seven-day study because of abnormal menses.

There is a drug marketed in Europe with 15 mcg of ethinyl estradiol, 25 percent less than we have here. It is not marketed in the United States, and one of the reasons is because it has a lot of breakthrough bleeding. But I have to say that it is still effective as a contraceptive because it has sufficient progestin to prevent pregnancy. So that is my interpretation of the data. I appreciate the opportunity to address it. If you have further questions, I will be happy to answer them.

DR. GULICK: Could we also ask the agency to respond to the same question?

DR. BIRNKRANT: Sure, I will begin with that response. I think one thing we have to keep in mind is that in the six-week clinical trial of prophylaxis women were re-consented to use a backup barrier method during the clinical trial. So, it is not just that we are seeing a handful of

pregnancies. We may have seen actually more had they not been re-consented to use barrier methods as a backup.

The other thing I wanted to mention is we don't really know how long this induction lasts. We only have this drug interaction study of five days. We don't really know how much longer it goes, and how long it takes to recover. The applicant will be conducting further studies to help shed additional light in that area.

In addition, I just wanted to comment that the pregnancies that we saw were only in the six-week trial period, and it is my understanding that typically for oral contraceptive development these trials are approximately a year long, with low levels of contraceptive failure rates and here we are seeing failure rates after only six weeks.

MR. FLEISCHER: I would like to chime in. The other thing is that in the five- to seven-day treatment trials there was no targeted questioning of menstrual disorders and we may actually have under-reporting because, if the woman had some breakthrough bleeding she may not have thought it was anything because it was just part of her cycle. We don't know. In the six-week study they were

specifically asked so we may actually have an overestimation.

The other thing that is interesting in the six-week study is that there appears to be a dose response. If you look at the once daily pleconaril and compare that to the twice daily and compare that to pleconaril, it is increasing exponentially as the dose of pleconaril increases.

The other thing in the five- to seven-day treatment trials is that there was no long-term follow-up so we don't know what happened maybe a month later with women who may or may not have gotten pregnant.

Then, in the pharmacokinetic studies the slope remains decreasing at 48 hours when the measurements were made. As Dr. Birnkrant said, we don't know when that plateaus and we don't know when they come back.

So, we agree that we don't have hard data to know what the risk is, but we believe there is a potential risk that has to be dealt with somehow in the labeling and communicated to patients in a way that they would not freak out.

DR. GULICK: People had a couple of follow-up comments. Dr. Wood and Dr. Kumar?

DR. WOOD: One of the questions I had was concerning potential repeat exposure to pleconaril after you had an initial exposure. Since the half-life is so long, the question then becomes is there any idea, in terms of whether or not there would be a continued reduced effectiveness of contraception, if a woman were to be re-exposed. Let's just say she took a five- to seven-day course as she would if she had a cold, and then maybe developed cold symptoms five weeks later or six weeks later where conceivably the drug might still be around from her initial dosing. Could you comment on that at all? Are any studies planned?

The other issue is in the studies planned by the pharmaceutical sponsor of interactions with oral contraceptive pills, there is only a BID dose that is going to be studied, not a TID dose. It didn't seem like there was a TID dose of pleconaril, which is the therapeutic dose in the 043 and the 044 studies.

DR. MISHELL: Could I just respond to the agency's comment before that question is answered? Yes, I agree that warnings need to be put in the labeling about the chances of increased bleeding, similar to what occurs with other drugs such as the

anticonvulsants which sort of do the same thing. But as far as the numbers of pregnancies, you are dealing with two pregnancies in oral contraceptive users. I mean, the N is so small you can't really make any conclusions about that. As I said, in typical use of oral contraceptives the failure rate is five per hundred women in the first year of use. So, in six weeks, which is a quarter of that, it would be a little bit more than one. You know, the numbers are so small we can't really interpret it.

DR. GULICK: Dr. Birnkrant?

DR. BIRNKRANT: Our consultant from the agency, Dr. Leslie Furlong, will respond.

DR. FURLONG: With due respect to Dr. Mishell, I don't think you can actually use the typical use rates in this setting. Dr. Trusseller's typical use rates are based on retrospective survey data where women were asked for the preceding four years, month by month, what they were using as a birth control method. We are talking about a clinical trial here, and we thought an appropriate comparator would be contraceptive efficacy clinical trials in which we see actually, on average, 0.7 pregnancies per 100 women per year in all our currently approved products.

The five-day studies, I don't believe, were designed to detect pregnancies. The six-week studies were modified. There was a protocol modification once the breakthrough bleeding data came along, and they were looked at from the standpoint of pregnancy detection. In those studies we see no pregnancies in the placebo group in patients who were on oral contraceptives. We see none on the low dose pleconaril group on oral contraceptives, and we see two in 156 women who were using pleconaril and oral contraceptives.

We agree that the numbers are too small to state anything with statistical significance, however, it is interesting that we see none in placebo, zero also in the low dose pleconaril and two as the dosage increases. In addition, we, at the agency, are not as sure about which of the two components of the combination birth control pills is responsible for efficacy. We believe it is an interaction. I don't believe that the progestin only pills are simply watered down versions of combination oral contraceptives for many reasons. One obvious reason is that the progestin only pills are taken on a daily basis. There is no seven-day window of non-use. The combination oral

contraceptives must continue to be effective through a seven-day window in which women are not taking the pill. So there is a very large difference there.

In addition, we know that ethinyl estradiol induces sex hormone binding globulin, which is a protein to which man of the progestins are highly bound. We don't reach steady state levels of norethindrone in some of our pills until they have been taken for two weeks. So, a single dose midazolam study is not adequate to address even norethindrone concentrations in an average pill user.

So for those reasons we think there is still concern about the two pregnancies that were detected in the six-week trials, and we think that the drug should be labeled that way.

DR. GULICK: Mr. Fleischer?

MR. FLEISCHER: You mentioned that you agreed that information should be contained in the labeling about this interaction, should it be approved. What would you recommend putting in there? A mention in the adverse events section, a precaution, a contraindication, a warning or a black box?

DR. MISHELL: Well, I would use something similar to what is in the anticonvulsant drugs. I believe it is in the warning section and also in the patient package insert, as well as the physician's insert. I guess it depends on whether you want to put a warning in against unwanted pregnancies based upon two pregnancies or not. I still think that the data are very reassuring in the initial study, the way the drug is being given and also the pharmacokinetics of the progestin. It is not something that is going to cause a great number of pregnancies, I don't think, if it actually does enhance the pregnancy rate, and I don't think there is evidence that it does from the data that we have right now.

DR. GULICK: First Dr. Kumar and then Dr. Wood. We got a little sidetracked.

DR. KUMAR: First I want to make a comment and then ask a question. I want to move a little bit away from pregnancy to intermenstrual bleeding. You alluded to the fact that intermenstrual bleeding is more an annoying problem than something that is clinically worrisome. I think that is in the context of which drug is given for what indication. For an anti-epileptic that is given

for a serious condition, then I would agree with you, sir, that it is more annoying and that the benefits far outweigh the risk. But for something like a common cold about which we are talking, the intermenstrual bleeding, in those circumstances you are giving up one set of annoying complaints for another set of annoying complaints. So, I do wish to point out a woman's perspective on that.

DR. MISHELL: I totally agree with you, but I think most of the intermenstrual bleeding or spotting doesn't require sanitary protection. I think it has to be put in the labeling, as the agency said, that this does occur.

DR. KUMAR: You certainly have more expertise than I ever had but I just wanted to point out my view.

The second thing, and this is to Mr. Fleischer, I just wanted to make sure I understood from the briefing document and from the slide that you showed on menstrual disorders, is there more intermenstrual bleeding in patients who took pleconaril but did not take oral contraceptives? That is the way I understood it.

MR. FLEISCHER: No.

DR. KUMAR: Even patients who did not take

oral contraceptives, was there increased intermenstrual bleeding?

MR. FLEISCHER: In the six-week study?

DR. KUMAR: In the prophylaxis study, yes.

MR. FLEISCHER: Remember, they became targeted adverse events. So it is possible that women, when they started to ask about them, they answered more positively. It ran about 13-16 percent across the pleconaril and placebo arms. That was very consistent across the three arms in non the non OC users.

DR. MISHELL: But in women taking oral contraceptives in the placebo arm there was no increased intermenstrual bleeding than in women taking pleconaril. The incidence was the same. In the women taking pleconaril and on placebo the incidence was the same, identical.

DR. KUMAR: In the prophylaxis study, in women not taking oral contraceptives was there an increased intermenstrual bleeding in the pleconaril arm?

DR. MISHELL: You probably ought to look at the data.

DR. VILLANO: There were several questions of a related nature. Let me just address the

latter and we may want to come back to the former. I am going to show a slide that depicts all menstrual disorder events in both the five- to seven-day and the six-week prophylaxis studies. I would like to divide the women into those who were receiving any estrogen or progestin component of any kind. We further subcategorized those women into those who were receiving an oral contraceptive and those who were receiving any other estrogen or progestin compounds, such as hormone replacement or Depo-Provera and those who were receiving no estrogen or progestin of any kind, to show you the difference between those groups.

[Slide]

To your specific question, I will focus on the right-hand of the slide with the longer-term follow-up in the sex-week prophylaxis study. Among all women in the six-week prophylaxis study the three groups are shown here. The incidence of any menstrual disorder ranged between 21 and 32 percent. The differences clearly lie in the oral contraceptive use group, with a difference of between two and three times greater incidence in those receiving pleconaril.

Of note, of those receiving any other

estrogen or progestin, there were actually no episodes of menstrual disorders in those who received pleconaril; three in those receiving placebo. Among those women who were receiving no estrogen or progestin of any kind, the rates are shown here, between 18 and 21 percent, with no significant difference. I think that was the question.

DR. KUMAR: Thank you.

DR. GULICK: Dr. DeGruttola?

DR. DEGRUTTOLA: I just had a technical question on the subgroup analyses of how the estimate or how the testing of the consistency of results across subgroups was done. Was that a test of interaction between the subgroup and question like sex or the effect and question like sex and treatment?

DR. MCKINLAY: I will ask Dr. Hudson to come up.

DR. HUDSON: Good morning. Spencer Hudson, biostatistics ViroPharma. I would like slide 1812.

[Slide]

These are the results of a series of Cox regression models that were used to look for

inconsistency between the effect of treatment and the individual subgroups. All these were done on the pooled data so we maximized the power of these tests. The first one we did was simply looking at the consistency between treatment effect in the two studies. You can see here that that is not significant.

DR. DEGRUTTOLA: Could I ask what you mean by consistency? Was there an interaction term, a study by treatment interaction term?

DR. HUDSON: Exactly, yes. Then we went down to the two prespecified strata of smoking status and cold medication, and then we followed up with the three demographic variables, age, race and gender. Of all those tests, only the smoking status came out as being significant.

DR. DEGRUTTOLA: I just want to comment I think that is the appropriate way to look at it. I get a little concerned when people look at subgroup analyses and say for certain groups it looks significant, a p value less than 0.05, and for other groups it looks not significant because the p value is greater than 0.05. I just want to point out that even if the predictor in question has no effect, like gender for example, just by chance you

are going to see that situation arising. So I think that those results are interpretable.

Then, I have one question for the agency. There was a comment of an exponential increase by dose, I believe, in the prophylaxis study for the risk of bleeding, I think it was. I just wanted to comment, if that was referring to the slide that was on immediately previous to this.

MR. FLEISCHER: I used exponential without an exponent. It was a big increase between what we saw in the placebo compared to pleconaril once day, to pleconaril twice a day.

DR. DEGRUTTOLA: Is that referring to the Tables 46 and 47?

MR. FLEISCHER: What page was that?

DR. DEGRUTTOLA: It is page 98 in the book and Dr. Hammerstrom just told me the lower slide on page 17.

MR. FLEISCHER: Do you have it? Are you happy?

DR. DEGRUTTOLA: Yes. I assume the increase you were referring to was in OC users, menstrual disorders going from 27 percent to 58, to 81 percent.

MR. FLEISCHER: Yes.

DR. DEGRUTTOLA: Thank you.

DR. MCKINLAY: Dr. Wood, I apologize. We didn't answer one of your questions.

DR. WOOD: My concern was about individuals who may get repeated doses of pleconaril, with the long half-life, who are taking oral contraceptives.

DR. MCKINLAY: I will ask Dr. Rhodes to come up. Dr. Cooper? Ellen had a comment first.

DR. COOPER: First of all, regarding both the increased incidence of spotting and breakthrough bleeding in women on oral contraceptives and pleconaril, and also the concern about decreased contraceptive efficacy, again, it is important to differentiate between five-day treatment and the six-week study.

In terms of Dr. Wood's question about repeated dosing, let's say a month later a woman takes five days of pleconaril and then a month later gets another cold and takes another course of treatment, the half-life, the long half-life is the terminal half-life. As Dr. Rhodes showed, for the initial half-life the levels really fall off quite quickly. So, there really are very low levels. They are there but they are very low for prolonged

periods of time. So, we really wouldn't expect any substantially different effect with the second course a couple of weeks or a month later.

I would just like to say that we certainly, at ViroPharma, agree that the numbers are small in terms of the pregnancies both in the five- to seven-day and in the six-week. We do have two pregnancies in women taking oral contraceptives and pleconaril in the six-week study. But I think that we can't draw conclusions one way or another, absolute conclusions one way or another from this data.

We certainly agree that there is a need to look at the duration of the increased induction of the enzymes, and we are in the process of doing that. We also certainly expect to include in the labeling advice to physicians and to patients to use a backup form of birth control.

DR. WOOD: So how long would you recommend that they use that backup form of birth control if they had a single course of pleconaril?

DR. COOPER: For a minimum, for the remainder of the cycle. Whether we would recommend it for an additional month would depend on the outcome of the study in terms of looking at the

duration of the induction of the CYP3A enzymes.

DR. GULICK: Dr. Reller, then Dr. Sun.

DR. RELLER: This will be for Dr. Cooper, Dr. Hayden or anyone they choose. The primary endpoint in smokers versus non-smokers, could you explain again why it seems that the smokers who get pleconaril have prolonged symptoms that are at about the same magnitude of the people who are non-smokers had a decrease in symptoms? What is the pathophysiology of that relative to placebo?

DR. MCKINLAY: Dr. Villano?

DR. VILLANO: In terms of the results we have seen in smokers versus non-smokers, what we started with in our analyses was looking at the results showing that we do, in fact, have antiviral efficacy in both subgroups, as demonstrated during the primary presentation. However, we did analyses to try to understand why that antiviral activity did not translate into efficacy in the primary endpoint which required that all symptoms be at least mild and, in fact, rhinorrhea resolved to absent.

In reviewing this, we considered the natural history that is known about smokers and non-smokers in terms of their symptoms of the cold.

Smokers are known to have colds associated with greater mucus production and are also known, at baseline, to have more chronic symptoms, such as rhinitis and cough. We hypothesized that the primary endpoint in particular that was utilized in these studies, which required all symptoms to be mild and at least the rhinorrhea to be resolved completely, may not be the best endpoint to analyze the efficacy that may be seen in smokers. We showed earlier that the symptoms score is reduced early in the course of illness. That is a post hoc analysis and, again, we did not demonstrate efficacy in the primary endpoint.

In terms of your specific question regarding the differences between the pleconaril and the placebo groups, basically we are cautious about conclusions in this subgroup in that there were only 28 percent of patients who were, in fact, smokers. While we can conclude that we don't see any efficacy in the primary endpoint, we cannot further differentiate that magnitude of change between the two groups.

DR. GULICK: Follow-up?

DR. RELLER: Another thing that was paradoxical, at least for my assessment, is slide

16 that was shown by the agency that looked at time to primary endpoint, comparing those whose isolates were susceptible or resistant to pleconaril. I don't know if it is possible to put that up.

DR. MCKINLAY: We actually have the same slide that they do.

DR. RELLER: It is slide 16, on page 6 of the handout from the agency.

[Slide]

DR. MCKINLAY: This is a little different format but it is the same thing.

DR. RELLER: So the question is in the susceptible isolates, those patients given pleconaril had decreased duration of symptoms, whereas in the non-susceptible isolates there was actually an increased duration of symptoms. Why might that be?

DR. VILLANO: We can specifically look at this group of 13 percent overall of subjects who had baseline isolates that were non-susceptible to pleconaril. Not only were, obviously, these groups relatively small, in which case the primary endpoint value is somewhat sensitive because of the small numbers to the median, but also we found small imbalances in the percentage of patients who

were smokers, an excess of patients on pleconaril versus placebo, and also slightly higher baseline total symptom scores in those in the pleconaril group compared to the placebo group. Again, probably the largest influence on this is the relatively anomalous low duration of illness as determined in the placebo group which is probably sensitivity to the relatively low numbers of subjects in those categories.

DR. RELLER: If one looked at the susceptible strains, one would be trying to infer that if you got an agent that is active it works. But is it just small numbers? Just luck of the draw that those patients with resistant strains who received pleconaril actually had more symptoms, greater persistence of symptoms? How do you get there?

DR. ENGLUND: Did you identify what those viruses were? I mean, we have kind of a lack of knowledge if they were even rhinoviruses versus enteroviruses. At least those specimens, do we know what those were?

DR. MCKINLAY: Well, we tested a cross-section and actually sequenced the viruses. Of the subset we tested, 99 percent were

rhinoviruses.

DR. ENGLUND: Of these resistant ones?

DR. MCKINLAY: Well, no, they were a subset of what we tested. Marc Collett, could you come up?

DR. COLLETT: In the combined studies there were 95 patients who were infected with viruses that were not susceptible. We are in the process of looking through those and we have recent data on the sequencing of amplicons derived from those viruses. We have sequenced, I believe, about 44 of them so far and they are all rhinoviruses.

DR. GULICK: Dr. Schapiro, follow-up?

DR. SCHAPIRO: Along those lines, it did seem quite impressive that there was about a four-day increase. Russ, you mentioned earlier that the vehicle there is an irritant. I think you mentioned also to the respiratory tract. Was there any consideration that if the virus is not sensitive there is some background irritation? I think you said there is a concentration of the drug in the epithelium. Why are we seeing in some cases an additional effect?

MR. FLEISCHER: We didn't really look at the vehicle.

DR. GULICK: Dr. Sun and then Dr. Atmar.

DR. SUN: I have two questions. The first is actually continuing this thread. What struck me is that you seem to have two sets of resistant viruses, those that are present at baseline and those that are post-baseline, and it sounds like you are doing some genotypic analysis. But from your preliminary data, do you identify differences in the mutation patterns in those two sets? Because it is striking that the clinical course of the baseline resistant viruses appears to be longer than either the sensitive virus treated with pleconaril or placebo, whereas, as you referred to in your presentation, the post-baseline resistant viruses may have perhaps trended towards a shorter course. You evoked at that time an argument about reduced fitness. So there is a little bit of a disconnect here which could potentially be sorted out by some genotypic analysis. I think it is an important question because you have a fairly high rate of treatment emergent resistance. So, with successive seasons of use you might induce actually a population prevalence of resistant virus. So, it is important to know the biologic characteristics of that virus. Then I have a second question.

DR. MCKINLAY: Dr. Collett?

DR. COLLETT: Indeed, I am happy to have the opportunity to clarify the viruses that we were observing that have reduced drug susceptibility to pleconaril. Indeed, there are two types of viruses that we have been referring to. Those are viruses that are observed at baseline that are not susceptible and these are naturally occurring viruses that turn out to be just not susceptible. They are picornavirus viruses or rhinoviruses. Then there are the viruses that are identified in patients that are treated with pleconaril that appear post-baseline in individuals that are infected at baseline with sensitive viruses.

[Slide]

In referring to that group of viruses, as was indicated earlier, we identified 28 individuals in the combined studies that had viruses that exhibited greater than ten-fold change in drug susceptibility relative to their baseline samples. It is important to note that these viruses actually preexist in the baseline samples at a low frequency. We know this because workers have done this in working with these types of inhibitors in the literature, and we have done this with

pleconaril and we have actually done it with patients in the pivotal trials. If we look at susceptible virus populations at baseline, we can find these types of viruses that have reduced drug susceptibility.

[Slide]

If we go on to slide 1760 and continue looking at the samples from the 28 patients, we find that 21 of the 28 are still susceptible to pleconaril, with a median IC50 value of 270 ngm/mL. So these would expected to be inhibitable at readily achievable plasma concentrations. There are seven that are no longer inhibited by pleconaril at the highest testable level in the cell culture assay. We have gone on to characterize these viruses and we are still working in this area, but it is important to note, which has been shown earlier, that these patients had no unusual clinical outcome.

[Slide]

If we go on to slide 1440, we have gone on to characterize these viruses both molecularly and physically. We have so far sequenced 22 viruses with reduced drug susceptibility post-baseline, sequenced across the drug binding pocket, and we

find a very interesting, very clear story. There are two amino acid positions that appear to be changed relative to the baseline sequence in these patients, and that is at position 98 and 122 and we find two other viruses at position 180. The location of these mutations are all in the drug binding pocket.

[Slide]

I show in this rendition or depiction of the drug binding pocket the position and location of these mutations, and how they impinge on pleconaril. Isoleucine 98 is at the top of the drug binding pocket into which pleconaril is integrated, and interacts with the isoxasole ring of the compound. Isoleucine 122 is below, at the bottom of the pocket, also interacting with phenoxy ring. Serine 180 actually causes a change in the position of the two adjacent amino acids, causing a distortion of the pocket. By substituting larger, bulkier amino acids at these positions, such methionine, it impinges in the pocket, thus, preventing or decreasing the affinity of the drug for the binding pocket, thus, explaining the means by which these viruses are now less susceptible to pleconaril.

If we look at the physical characteristics of the viruses with these mutation in the drug binding pocket, we find that in 29 of the 30 cases that we have evaluated so far from samples from the pivotal studies, in those cases the viruses are more labile to acid exposure.

[Slide]

Here we show an example of the baseline virus isolated from a patient and its infectivity inactivation as a consequence of exposure to decreasing pH, and in two isolates a 122 mutation and a position 98 mutation. You see the instability of the virus under these conditions.

These observations are totally consistent with all preclinical data in studying viruses that we have selected in cell culture that are of reduced drug susceptibility to pleconaril. It seems that they all have mutations in the drug binding pocket and in large part at that position, 98.

[Slide]

In patients that we have observed with these viruses, again, there seems to be no unusual clinical outcome. The amino acid changes are all in the drug binding pocket. The viruses are all

unstable, either from clinical studies or the preclinical work that we have done. So it appears that the development of reduced drug susceptibility as a consequence of pleconaril treatment results in a virus that is less stable and likely to be less competitive in nature.

When we look at these viruses in an animal model, some of the in vitro viruses, in particular the Coxsackie virus that have these mutations in the drug binding pocket, we find that those viruses are attenuated for replication in the animal model, as well as attenuated for virulence in that model. So, it appears that viruses acquire the reduced drug susceptibility are definitely enfeebled, as we can tell with data to date. So, we feel that the treatment emergent viruses don't pose any threat to individuals.

DR. GULICK: A follow-up from Dr. Schapiro.

DR. SCHAPIRO: I would disagree with that comment. I think there is a concern. If these are viruses which are seen in wild type and these are viruses which have specific mutations, I don't think we can assume that they are not going to be pathogenic. I think that from other models in

viruses and bacteria we have seen mutated resistance, and I think we have had bad experiences assuming that these viruses would not be pathogenic. That is the model we have consistently seen when we have hoped that these would be crippled pathogens. It is also not surprising that for the first treatment you would still have the same outcome if this was an emerging resistance which happened after a couple of days of treatment.

So, I would like the company to address a concern that I have, that this is a high rate of generation of mutations which in viruses that have these mutations or that are resistant we do not see an effect. I think that the fact that there is possible cross-resistance to other compounds that work with a similar mechanism of action, and here we are giving it for a minor indication -- if these are viruses which are now resistant and ultimately we do develop more potent compounds against serious infection by the picornavirus, I think this is an issue which is very concerning to me. I would like that to be addressed. I mean, wouldn't there be a potential that by treating a relatively mild disease -- we repeatedly see one million infections a year in the States -- after a few years we

generate a mutant population against not only this compound might not work but other compounds, and if we have serious infections down the road we won't be able to treat them. That is a concern I would like to hear addressed.

DR. GULICK: Let me hold that. Let's resist the temptation to jump into discussion and just finish up off the question and answer session this morning. That will be one of the topics that I think we will address after lunch, if that is okay.

DR. SUN: Can I just clarify what your response was? You showed us primarily data on the post-baseline resistant virus. Are you still working on characterizing the 26, or I think actually you have 50 isolates, from the two studies?

DR. COLLETT: Yes, we are. As I mentioned earlier, there are 95 patients in which we isolated those viruses that were not susceptible at baseline. We are working our way through that. As you can imagine, these viruses are all different and finding the appropriate probes to do the appropriate sequencing is a challenge. We have gone through about 45 so far. We haven't completed

work on the sequencing across the drug binding pocket so right now we don't know the molecular basis for their non-susceptibility but those studies are ongoing.

Again, not to de-emphasize this issue, we believe it is very important and we are very committed to studies that are under consideration which, perhaps during the discussion session, we can go through and elaborate on those.

DR. GULICK: Dr. Reller, did you have a follow-up comment?

DR. RELLER: Not a comment, a question. I realize the numbers are probably small but related to Dr. Schapiro's inquiry, a question from the epidemiological standpoint, did you happen to enroll in this study any family members or subsequent patients in the household, or dormitory or fraternity, sorority, etc. that may have been a second or third exposure?

DR. MCKINLAY: I don't think we have any information on that. That wasn't specifically excluded.

DR. RELLER: It wasn't excluded but it might be worth going back and looking. I mean, there may be only a few such patients or a small

number but it may provide some interesting information, given the incredible amount of sequencing and molecular work that has been done on the basic biology of these viruses.

DR. GULICK: We have time for a few more questions. Dr. Sun, did we get to your second question?

DR. SUN: No. Can I ask it now? This may be a question that you may not have data on, so if you don't maybe you could just speculate, but I was wondering how you think treating the common cold with pleconaril might affect the development of serotype specific immunity. Specifically, I think you did show some data suggesting that viral titers and viral burden is decreased in patients receiving the drug. To the extent that neutralizing antibody is important in acquired immunity, and this may be something Prof. Hayden might like to address, what do you see as the effect of the development of neutralizing antibody, which is particularly relevant given your introductory comments about the decreasing incidence of the cold with increasing age, and might that reflect the building of a repertoire of neutralizing antibody earlier in life to a variety of common cold serotypes?

DR. HAYDEN: To my knowledge, there aren't specific data to address the question of the effect of pleconaril treatment on the development of serotype specific neutralizing antibody. There are data from earlier capsid binding type agents in the experimental model, showing that there is no effect on the frequency or height of antibody response when those proof of principle studies were tested.

Also, I think if one would look at the precedent with regard to influenza infections, treatment of acute respiratory illness is not associated with a diminution in the HAI antibody response in terms of frequency or height of that response. So, when used for treatment in an acute illness where there is already substantial antigenic exposer there is likely going to be an adverse effect on the humoral immune response.

The other side of this, of course, is that there are so many immunotypes, over 100 recognized immunotypes for rhinovirus, that an effect, even if it were there which I doubt would occur, would mean that it would probably be lost in the broad number of potential viruses that these individuals could be exposed to in the future.

DR. GULICK: Dr. Atmar and then Dr.

Gardner.

DR. ATMAR: I have a follow-up question related to the smoking cohort. You learned from your Phase II studies that your endpoints were not appropriate so you modified those for the entire population in Phase III. My question is have you looked at the data for the smoking cohort to see if there was a particular symptom that was responsible for the apparent lack of effect? There was an allusion to baseline increased rhinitis. Was it persistent rhinitis, or was it moderate cough, or is there some hint?

DR. MCKINLAY: Dr. Villano?

DR. VILLANO: We did evaluate the population based on smoking status and tried to determine if there was one or a group of symptoms specifically that was leading to the attainment of primary endpoint. As a reminder, the primary endpoint is defined as the time point at which all rhinorrhea is completely resolved, other symptoms having achieved a level of mild or absent. In all of our analyses of any subpopulation the criterion for complete resolution of rhinorrhea has in all cases been what we call the driver of achieving the primary endpoint. That is the case in smokers and

non-smokers as well.

[Slide]

However, on this slide, for your interest, we have another depiction of the characteristics that contributed in various degrees to achieving the primary endpoint. Just to describe this slide for you, based on smokers and non-smokers in each treatment group, this slide shows the percentage of patients who had a given symptom in the time period immediately before reaching the primary endpoint. That is, what was still there just before they reached the primary endpoint.

As you can see, the presence of rhinorrhea, although somewhat less prominent in smokers than in non-smokers, is by far the biggest contributor to achieving the primary endpoint. The notable difference among smokers is in the presence of cough. Cough was somewhat more prevalent just before reaching the primary endpoint in smokers than in non-smokers.

Again, we actually analyzed the primary endpoint even excluding cough. If we just took that symptom out of the equation altogether, the results are virtually the same because that resolution of rhinorrhea is still so important to

our specific primary endpoint.

DR. GULICK: Dr. Gardner then Dr. Henchal.

DR. GARDNER: I have two questions. Dr. Gordin asked about who gets the common cold. I didn't hear anything about smokers. Can you tell us whether smokers are considered to be more susceptible to infection with rhinoviruses?

Secondly, in considering risk management alternatives, I wonder if it is fair to ask the company whether the marketing plan for pleconaril includes direct to consumer advertising.

DR. MCKINLAY: On the first question, Fred, do you have an answer, or Dr. Black?

DR. BLACK: I am sorry, I don't know whether smokers are at increased frequent risk of having colds because of their smoking status. Certainly, when they do develop illness, as you have heard, they tend to have more protracted symptoms and have more morbidity associated with those illnesses, but I am just not certain, from the epidemiologic data that I am familiar with, whether there is any alteration in the frequency. Again, in the older smoking cohort the individuals with co-morbidities, where there might be underlying chronic airways disease, the frequency

of these illnesses does diminish but it relates heavily, of course, to exposure in the household setting.

DR MCKINLAY: Then the question about direct to consumer advertising, I will ask Dr. Wickler to comment.

DR. WICKLER: Matt Wickler, ViroPharma medical affairs. Although we have not yet finalized the pleconaril communications plan, it will focus almost exclusively on educating healthcare providers. So we do not currently have any large efforts under way or plans to do any DTC promotions.

DR. GULICK: Dr. Henchal?

DR. HENCHAL: Yes, my question is for Dr. Collett with regard to the RT-PCR assays that were used for these studies. When the endpoint limit of detection results were shown, it appeared to me that there may be two to three orders of magnitude difference in the ability of your assay to detect different serotypes. I wondered if there is a possibility that this would introduce unfortunate bias in your studies, especially your clinical virology studies.

DR. COLLETT: The viruses we are trying to

detect, the rhinoviruses and picornavirus, are a large group of genetically diverse viruses. We would expect that any assay would have a range of detection sensitivities. Certainly cell culture, which is the traditional or historical standard, is very variable in its ability to detect these viruses and we found similar variation with both of the RT-PCR assays which, again, use different primers and are distinct. The range of detection sensitivities with the viruses that we have looked at closely, and that represents five serotypes, you are correct, it does range over three orders of magnitude in detection sensitivity on a genome basis. On a PFU basis they are within ten-fold of one another.

With respect to your question about introducing a bias, I don't know that we have any information that would bear on that.

DR. HENCHAL: It appears that you are doing some sequence analysis of isolates. Does it appear that the viruses that you are sequencing fall in any particular serotype groups?

DR. COLLETT: We did not serotype viruses in this study. Serotyping is useful for determining the serotypic or immunotypic diversity

of the viruses that you encounter. We did look at the drug susceptibility across all the viruses that indicated a wide range of drug susceptibilities, which actually mimics that of the drug susceptibility profile for the 101 serotypes, the prototypic serotypes.

You mentioned that we are in the process of sequencing, and I alluded to it several times, a number of these viruses. We have sequenced the amplicons of 146 of these viruses and we see quite a wide range of genetic diversity and we are continuing those studies to further characterize the viruses, but it doesn't look like there is any bias introduced. It is quite a diverse range of gene sequences that we are observing.

DR. GULICK: Dr. Stanley, you are out of sight but not out of mind. Do you have questions?

DR. STANLEY: Thank you. Actually, most of mine have been answered. I did have concerns about the resistant viruses. I guess we will talk more about that this afternoon. So I think my fellow committee members have covered most of my issues.

DR. GULICK: Okay. I think all the committee members have had a chance to ask

questions. I have a couple myself. Could the sponsor please review specifically what the exclusion criteria in terms of concomitant illness and concomitant medications?

DR. MCKINLAY: Dr. Villano?

DR. VILLANO: I will just run through the specific exclusion criteria as they were set forth in both protocols and, again, both 43 and 44 were identically designed studies. All these criteria apply to both studies.

[Slide]

I will just run through them. The exclusion criteria exactly as set forth in the studies, we excluded any known pregnant or nursing females; persistent cough or rhinitis. We excluded temperature over 100 F; a cold that was suspected to be caused by any other virus; allergic rhinitis requiring medical treatment within two weeks before the study start; and asthma requiring treatment within two months before the study start; any prior participation in a pleconaril treatment trial and participation in any other research study within the previous 30 days.

[Slide]

As far as any other medical conditions

that the investigator or sponsor may have been aware of; any evidence of significant hepatic, renal or GI disease that could interfere with absorption; any other underlying medical history that was deemed significant requiring treatment with systemic, nasal or inhaled corticosteroids; any symptomatic respiratory disease or acute or chronic medical condition that could have confounded the evaluation of the cold symptom score because of those symptoms; any known immunodeficiency, HIV status; recent history of alcoholism or use of illicit drugs; and any other psychiatric disorders that could have compromised compliance with the study. I believe that is it.

DR. GULICK: And concomitant medications that were excluded up front?

DR. VILLANO: The only criterion was that cold symptom relief medications, as a general class, were discouraged. They were not specifically ruled out altogether. We provided patients with both acetaminophen and dextromethorphan specifically with the idea that those particular medications would be least likely to interfere with the most prominent nasopharyngeal symptoms that we were studying in the course of the

studies. In fact, that provision was very successful in that of all the patients who used any cold medication during the study, only one to two percent used any other medication other than the acetaminophen or dextromethorphan.

DR. GULICK: That was my second question actually, what percentage of patients ended up using the medications that you provided in each group?

[Slide]

DR. VILLANO: This slide reviews the cold medications that were used during the study. We pooled together the results in those patients who were picornavirus infected, and 58 percent of those in the placebo group used any cold medication during the study, 52 percent in the pleconaril group. As shown here, the most prominent medications used were, in fact, those provided. Acetaminophen use in 45 percent of those on placebo, 39 percent of those on pleconaril, and dextromethorphan, 39 percent of those on placebo and 29 percent of those on pleconaril. The median duration of use of any cold symptom relief medication during the study was one day.

DR. GULICK: My last question is for the

agency. Is there a method for quantitating the risk of unwanted pregnancy that is accepted?

MR. FLEISCHER: I will let Dr. Furlong answer. The answer is yes.

DR. FURLONG: The data that the company has collected from these trials doesn't allow you to quantitate with statistical certainty, if that is what you are asking. Do we have methods for calculating pregnancy rates? Yes, we do but they are for large contraceptive trials involving a thousand women at least starting out and continuing for a year. So, we are talking about different data sets.

DR. GULICK: So everyone has had the opportunity to ask questions. Dr. Brass, I am going to come back to you. I just want to let everybody know that we have to wrap up but you have patiently waited.

DR. BRASS: Thank you. I will just ask two very quick questions. The first has to do with this very unusual finding of palpitations in the theophylline group. Your data says it is clearly not a PK interaction. I was wondering if you looked for PD interactions with any other chronotropic drugs to see whether or not this was a

recurrent theme of drug interactions in terms of drug with intrinsic chronotropic activity.

My second question has to do with the QT interval prolongation that was observed in two patients and not well detailed, just so that we can be reassured.

DR. MCKINLAY: Dr. Villano?

DR. VILLANO: With regard to your first question with respect to the events of palpitations and tachycardia, I am going to focus on the theophylline interaction study that you mentioned. These are the data that we have exclusively.

DR. BRASS: You don't have to go through the whole thing again. I specifically wanted to know whether or not you have thought about potential other interaction. We don't have to rehash all the data.

DR. VILLANO: Fair enough. The second question that you asked with regard to data from EKG collection, we have actually recently even expanded the database of EKG data from what was provided in the briefing book. Actually, I would like to invite Dr. Morganroth to come up and present this information to you.

DR. MORGANROTH: Thank you very much. My

name is Joel Morganroth. I am a cardiologist from Philadelphia, clinical professor at the University of Pennsylvania, and also the key scientist at Ewey Search Technology. I have dedicated a lot of my current years in consulting to pharmaceutical companies, particularly about the cardiac safety issues of non-cardiac drugs and, in particular, the QT interval in terms of how to manage it and how to analyze the data.

[Slide]

The information that is provided by the sponsor in terms of electrocardiographic data comes from a total of 127 subjects in the following six protocols that you have been discussing today.

[Slide]

If you look specifically at the heart rate data, you see a very small change in heart rate on pleconaril given either singly for seven days, BID, or for five to seven days TID. Essentially no significant effects on PR, QRS and the QT interval, of course, should not be looked at individually because we have to look at the potential effect of heart rate correction.

[Slide]

The studies looking at the 65 subjects,

when pooled from the single dose studies, compared to the 56 subjects when given for five to seven days, shows that there is actually a mean decrease in the QTc interval when looked at in this particular data set. The single maximum increase of 47 milliseconds in both sets is better looked at on the next slide.

[Slide]

The use of the CPMP and draft Canadian guidance on ECGs suggests that, from our original data looking at the placebo likelihood of spontaneous variability, the most specific criterion is a 60 millisecond change from baseline, and no subject reached that criterion. You can see, if you look at the 30-60 millisecond group, which is somewhat overly sensitive and not terribly specific, you see that, although there are very small numbers of patients on placebo in these trials, there is no evidence of even a sensitive effect.

I probably could stop there. If you actually go on to look at other slides with gender and age, you also see no evidence of an effect. I will just comment for one second about this issue of tachycardia and palpitations, since I am up here

since it hasn't really been discussed before. I think that, as a cardiologist looking at cardiac safety issues, if you want to determine the effect of a drug on the heart the first question, of course, is what is the preclinical data. There is no signal in this database, as you know. The next question would be is there an effect on blood pressure or heart rate in the thousands of patients that are studied and, as you have been told by both the sponsor and the agency, there is no effect on blood pressure or heart rate. The third issue is do you see an effect on the echocardiogram? The data has shown that it doesn't appear to demonstrate any evidence.

Then, when you go in and you look at the specific cases, it is very apparent that there isn't a single case that has any objective information, other than that the patients had sinus tachycardia for a short duration and the few that had, in fact, any evidence of cardiac finding that might correlate with palpitations, the majority of the cases had no effect on heart rate that had palpitations and no likely pathophysiologic basis, many being many days after pleconaril and some being within 11 minutes of pleconaril's ingestion.

So if you look at any objective findings, there are none. So I think these very non-specific low rate symptoms are something that I personally didn't find worrisome at all. Thank you.

DR. GULICK: We need to finish up, but are there any last burning questions for the sponsor or the agency from the panel members?

DR. WOOD: I just have one question for the agency regarding antiviral effects of other drugs. One of the things that I was impressed by, even though there was a statistically significant difference in the treatment group compared to the placebo, was that 50 percent of the patients were still culture positive. I just wondered how that compared historically to other antiviral agents in terms of culture positivity for therapeutic intervention.

MR. FLEISCHER: How about if we address that after lunch when we put our heads together?

DR. GULICK: Sounds like a good place to stop, doesn't it? It is 12:30 and we will take 55 minutes for lunch. We will reconvene at 1:25.

[Whereupon, at 12:30 p.m., the proceedings were adjourned, to reconvene at 1:30 p.m.]

AFTERNOON PROCEEDINGS

DR. GULICK: Welcome back from lunch. Dr. Stanley, are you with us?

DR. STANLEY: I am with you.

DR. GULICK: Let's see, Dr. Wood ended the last session with a question. Mr. Fleischer?

MR. FLEISCHER: Without getting into too much detail, I talked to the reviewer for the Tamiflu studies. Approximately 80 percent of patients or 80-plus percent of patients who were responders had a negative qualitative culture on day three of treatment.

DR. GULICK: That was for influenza.

DR. WONG: How about the placebo in that study?

MR. FLEISCHER: I don't have that. I am looking for the reviewer; she was here just a minute ago. She may be able to tell us.

DR. GULICK: Dr. Hayden?

DR. HAYDEN: The data from the influenza may not be entirely applicable to the rhinovirus situation. It is noteworthy though that the duration of viral shedding in the influenza trials is not significantly reduced compared to placebo, although titers were reduced. In rhinovirus colds

the best quantitative data come from studies in experimentally infected volunteers where it is possible to do multiple samples over time. Viral titers are highest at the peak of symptoms, generally two days after virus exposure, and then rapidly decline thereafter. We do know that in both the experimental colds as well as those studied naturally about 50 percent of adults would be virus positive, either without treatment or in a placebo treatment setting, at a week, and replication can be detectable if one really looks hard for it into the second week. The main point is that this is a self-limited virologic and clinical illness so that virus is eliminated by specific host immune responses at two to three weeks.

DR. WONG: Thanks.

MR. FLEISCHER: I have the answer. We know that there are differences between flu and rhinovirus VRI but we don't have any other data in rhinovirus drugs. So the answer to Dr. Wong's question is that the placebo rate is about the same.

DR. GULICK: Are there any other questions from the committee that came up over lunch that

need clarification? If not, Dr. Birnkrant will review the charge to the committee. Oh, I am sorry, it turns out we are to go into the open public hearing portion of the meeting. No one has signed up in advance to speak at the open public hearing. Are there any members of the audience who would like to make a statement at the open public hearing?

[No response]

This concludes the open public hearing and we are back to Dr. Birnkrant.

[Laughter]

Charge to the Committee

DR. BIRNKRANT: Just to emphasize the point that we have not made a regulatory decision yet, and we are actually looking to this advisory committee and our guests to help shape our regulatory decision.

[Slide]

With that, what we are really looking for is a thorough discussion of the points that will appear on the following slides with regard to efficacy and safety.

[Slide]

To be able to determine the risk/benefit

of pleconaril for treatment of the common cold, with regard to a discussion of efficacy what we are asking you to consider is the totality of the data from the Phase II and II clinical trials, given that within these clinical trials are examples of perhaps how this drug will be used if it is approved.

In addition, we would like you to consider issues related to the timing of administration, the need to administer with food, the results in smokers, etc.

[Slide]

When you discuss safety, we would like you to focus on pleconaril's effects on CYP3A and the potential for the drug interactions that we discussed today and others, as well as the overall tolerability profile.

[Slide]

In the third point what we are really asking is do the safety and efficacy profiles of pleconaril support its approval for the treatment of VRI in adults. With that, I will turn it back over to Dr. Gulick and we can address the other questions once we approach question three. Thank you.

DR. GULICK: Thanks. Could we have question one back up on the screen? Committee members, let's address the bullet points one at a time as we begin to discuss efficacy. There may be other parts of efficacy that we also wish to bring up. Who would like to jump in? Dr. Brass? We are focusing initially on the efficacy results from the Phase III studies.

DR. BRASS: Could I request your indulgence and talk a little bit more globally about the efficacy?

DR. GULICK: Sure.

DR. BRASS: Because I think it might speed things along if we look at this in totality.

DR. GULICK: All right.

DR. BRASS: My personal reaction as I reviewed this data is that it took a while for the sponsor to figure out how to design a clinical trial that would sufficiently enrich the patient cohort in a responder type of way, and then in a carefully conducted trial could identify that there was relief of symptoms.

What I have some concerns about is how generalizable the conclusion of efficacy is, assuming that I accept that one-day decrease in

symptoms is clinically meaningful. Assume that I accept that, I still have problems with the generalizability. For example, this was done in a time of year that, even for the symptomatic inclusion which were carefully screened for, enriched the number of viral positive isolates. I don't think the intent by the sponsors is to limit its availability to the three months of the year on the calendar when the study was conducted.

As well, there are very small numbers in a variety of subsets of the population which, as everybody has said, is uninterpretable because of the small numbers but raise questions about, again, the generalizability of even the symptomatic relief, most dramatically in smokers versus non-smokers, but the issue of race and gender was talked about. In fact, with respect to race, Hispanic populations were grossly under-represented and the elderly were substantially under-represented. To some degree that reflects the demographics and epidemiology of the illness, but in terms of allowing one to conclude that the efficacy is generalizable, there is some concern.

Perhaps my greatest concern is how well this relates to extrapolation to the use of this

drug. In the OTC world, the FDA requires something called an actual use trial, where the use of the drug in the setting where consumers/patients will actually access the drug and use it without supervision, is assessed to see whether or not the label indications, warnings, patient selection criteria, etc. are, in fact, utilized in the general population.

Implicit in that use of the actual use study was the assumption always that in the Rx setting it is not necessary because you can tell the doctors what to do and they do it right. I think in recent years we have become increasingly cynical about physicians' ability to heed directions and, in particular, non-direct warnings on the label of drugs to maximize their efficacy and minimize their toxicity. When one talks about the variety of decisions that need to be made to select the patient for whom selection for prescription of this drug exactly mirrors the patient population in the clinical trials, I think that I have great concern about the generalizability and the ability of a physician to replicate that patient cohort in order to reproduce the efficacy as was demonstrated in the clinical

trials.

DR. GULICK: Dr. Gordin?

DR. GORDIN: Similarly, my main concern was really the cohort. To me, it was kind of a proof of concept that in a very narrow group it has some, to me, marginal benefit. It is concerning that half the patients cannot benefit that we would be giving this to in terms of the efficacy because they don't have an infection caused by this virus, and we, as clinicians, cannot determine which half that is.

I am also quite concerned about all the groups that were excluded, as just pointed out. But, then, what does the word efficacy mean? Again, I guess it is in the eye of the beholder. I would have liked to have seen some effectiveness shown in some of the real parameters related to lost time from school, lost time from work. But, in fact, the so-called impairment parameters were the same between placebo and the drug.

Over-the-counter drugs that are already available may or may not have been, therefore, as efficacious as this drug had they been studied in a similar way against this drug or against a placebo. As was pointed out by the company, those drugs were

excluded because, in fact, they deal with symptoms. And, what we are looking at here is just that, the symptoms of having a cold, being reduced by approximately one day because the complications of having a cold, such as otitis media, bronchitis etc., were, in fact, no different between the two groups, approximately seven percent in each group. So to me, it is questionable how efficacious it would really be.

DR. GULICK: Dr. Wong?

DR. WONG: I guess I will go back to the issue of the Phase III studies. In my mind, there is really very little doubt that the data show that there was a treatment effect. We didn't really get to see in detail the data from the Phase II studies but I guess both the FDA reviewers and the sponsor told us that they were unable to demonstrate a treatment effect.

In my mind, it comes down to seeing data on a drug now in which there is clear-cut evidence of a treatment effect, but wishing that that treatment effect had been more robust and more profound than it was because it is, indeed, quite modest. What we have is a reduction in symptoms of somewhere between half a day and a day when the

natural history of this disease is that it gets better in everybody. So, my answer to the efficacy question is, yes, it is efficacious. The effect is very small. Whether I vote for approvability or not I think is going to depend mostly on the safety discussion.

DR. KUMAR: Just taking the question of efficacy, in my mind, in the Phase III studies the sponsors did show small but definite efficacy in this group. Very much like what Dr. Gordin referred to, this small but modest efficacy depends upon the patient population. In somebody who just wants to save half a day from not going to work, that may not be very significant but for somebody embarking on a vacation trip, that may be very relevant to them. So in my mind, it has shown a small but definite efficacy in Phase III studies.

DR. GULICK: Dr. Englund?

DR. ENGLUND: I think it is very important to think of efficacy in terms of an antiviral agent for a respiratory virus and we have to realign our thinking to thinking of respiratory viruses which are very different from the other viruses. This is a very different virus than influenza. It is very difficult to design a study and I think the company

is to be congratulated for working and fine-tuning a study which did end up being a homogeneous population to try and get an endpoint. I think it is very important that we need some more studies. But I think that to demonstrate efficacy you have to actually fine-tune the population and focus and target the study so that you can demonstrate it.

They have shown, I believe, clinical efficacy. I wish they had been able to show some more virologic efficacy, and I think perhaps they could have if we had been able to do more studies, and I would recommend that for the future. I think, as clinicians, actually many of us have the ability to do some PCR but they haven't even given us an idea of what is culture positive and what is PCR positive for those of us who do have the ability to do that, which is not, of course, the referring physician. There is a population for which this would be beneficial, but I think they have shown us clinical efficacy which was their primary endpoint.

DR. GULICK: Dr. Schapiro?

DR. SCHAPIRO: I would agree. I think the question really is if these are appropriate studies, if we can consider these approval studies

for the common cold. I think the company did a very good job in showing us the data in a very careful and descriptive way. I am also convinced that in this study there was real benefit. I would agree also that this study does not in any way mean that you can use it for the common cold because, as it will be used for the common cold, I don't think there will be efficacy and I think that is the real question.

DR. GULICK: Feel free to keep speaking about it, but we have begun to address the first two and Dr. Schapiro is moving us towards the third bullet, what is the manner in which pleconaril will likely be used in clinical practice. Some of the issues surrounding that are symptomatic patients, use of diagnostic tools, and then asymptomatic patients. Dr. Englund?

DR. ENGLUND: I just want to say that, of course, one would target the pediatric patients who are having the most infections and potentially might be able to benefit the most, yet, we haven't seen data for that. I know there are things ongoing, but if you look at the epidemiology, it is the children that are suffering a lot from these infections, the asthmatics etc.

DR. GULICK: Dr. Reller?

DR. RELLER: If this drug were approved on a prescription basis, not an over-the-counter preparation, a patient would need to be sick long enough to seek medical attention. I doubt if most people would go to a doctor within 24 hours. So the efficacy data that we have is, again, emphasizing that this study is perhaps not reflective of real-world practice.

Food. People maintain a good appetite or not maintain a good appetite when they feel lousy. We know that 25 percent of the patients studied, at least, were smokers for whom we do not have efficacy. The most objective measure of efficacy was in those patients who had a confirmed infection. Quite apart from the ambiguities of how solid that confirmation was, but let's just assume 50 percent had a confirmed picornavirus infection. In real-world practice, when one includes all of the patients who, for legitimate reasons, were excluded from this trial, then we have a dilution of effect that becomes very striking. Although the numbers of patients studied was substantial, we are talking about several thousand, at most, for a billion event occurrence.

So, I see an incredibly small sample size on which these judgments are being rendered relative to the patient population or event, including the repeated events in the younger people, and then we drift over into the safety issues. We also know, at least from the study sample, that about 20 percent of the patients studied among the women were taking oral contraceptives, and I will save the other comments until we get to the safety discussions.

DR. GULICK: Dr. Kumar?

DR. KUMAR: I want to come back to the issue of having to take the medication within 24 hours of symptoms, and I want to give my clinical perspective on that. In this first charge that was given to us by the agency, that is the one that I find most troublesome.

I can guarantee you that there is no way that a patient can take this medication within 24 hours, unless the patient goes well in advance of the particular season and says give me a prescription; I just want to keep it in my medicine closet. That is the only practical way to get this drug within 24 hours. In any other circumstances, calling the doctor, having the doctor or the nurse

return your call, then calling it into the pharmacy, having the pharmacy prepare it, you then go and pick up the drug -- there is absolutely no way that the drug can be taken within 24 hours. And, I think we need to keep that in mind when we look at safety issues. It is giving it to a number of patients that are going to be keeping it in their medicine cabinets, waiting to take it at the onset of symptoms. That is very different from handing it to a patient right then and there and reviewing the adverse events with the patient.

DR. GULICK: Dr. Henchal?

DR. HENCHAL: I agree with that conclusion, and I wondered if there were really at risk populations that would warrant this preparation where the physician would actually prescribe the drug and let the patient make their own determination when to take it. I can't identify that population.

DR. KUMAR: But we don't have the data for the at risk population.

DR. BRASS: In fact, they were specifically excluded. If you talk about patients with asthma, which is an obvious at risk cohort, they were explicitly -- and I understand why

because you don't want to confuse the symptoms, but in terms of whether or not there would be symptomatic relief or their endpoint relief, all those populations you are most interested in were excluded.

DR. GULICK: Dr. Wood?

DR. WOOD: Just one point, getting back to the issue of efficacy, I wanted to go back to the FDA's efficacy conclusion slide. I think the important statement is regarding the assay to determine infectivity, it is a conditional statement that we have not answered and that has not been answered, to my knowledge, by the data presented. That is, if the assay has low false-negative rates, then the PCR positive population includes most infected subjects and the statistical significance confirms the effect of the drug. However, if the assay has a high false-negative rate, then we would not be able to confirm the same level of confirmation based on the statistical results. To my knowledge, we have not been able to verify what the true false-negative rate is.

DR. GULICK: Dr. Atmar?

DR. ATMAR: Any RT-PCR assay for

picornaviruses is going to be investigational, and the data presented by the sponsor, looking at two different PCR assay using different methodology would suggest that there is a high rate of concordance. The issue that came up this morning in terms of looking at culture positivity as a primary endpoint rather than RT-PCR, there are numerous studies that show that RT-PCR assays are two-fold, three-fold or more sensitive than are culture assays and it really depends upon the ability of labs to do culture. There are people studying this disease in underlying respiratory illness, like asthma and COPD, who don't even bother to do cultures anymore because the additional yield is so low, they have to do RT-PCR anyway.

So, as a person who does use this assay or uses or own home-brew assay for picornaviruses, I am reasonably convinced that, based on the data presented and without getting into all the particulars of exactly how the assay is set up, they have shown that they have a reasonably sensitive assay that corresponds with what we understand about the epidemiology of rhinoviruses or picornaviruses during the fall season.

Regarding efficacy, I agree with what everybody else has said or most people have said, that there was efficacy demonstrated in the trials and, in fact, for a self-limited illness half a day to a day to a day and a half is, though modest, an important or clinically significant benefit, as a person, again, who studies respiratory virus infection. As some of us were talking over lunch, it is very difficult to measure the clinical benefit in an objective fashion, though anecdotally, in doing these kinds of studies, even though blinded, one can reasonably say this person got drug; this person didn't in the flu experience; I don't have any experience with picornavirus. So, actually being able to show a benefit of half a day to a day in a relatively homogeneous population I think shows efficacy.

Is it generalizable? Well, we don't have the data to say that but, in fact, because of the increased variability in symptom duration, the population size needed to be studied would grow, if not exponentially, at least arithmetically. I mean there would be much larger numbers and it would be much harder to prove the efficacy in those groups. That is not to say that those studies shouldn't be

done, but it is not to denigrate the sponsor for not having done those studies already. So there is clinical efficacy at least in the population that they studied.

Then the question as to how it would be used, the same sorts of questions were raised about some of the influenza antivirals, and the comments were made that the drugs can't be prescribed within 36 hours or two days, and that is something to be overcome. But, in fact, as we get more antiviral agents for respiratory disease, this is going to be true of whatever antiviral we are talking about. So, to say that it can't be done or hasn't been done -- we haven't had the agents to do it, or the physicians haven't had the need to be able to respond expeditiously. I think initially it will be difficult but that is not to say that it can't be done and strategies can't be developed.

I think it is efficacious and it then comes back down to the question of the safety of the drug because up to half the people who have a common cold will not have a picornavirus illness. So, there is no short-term likelihood that we are going to get an assay that will give us a rapid diagnosis of a picornavirus infection. So, up to

half the people who have a common cold almost won't derive any benefit because they will have some other viral etiology. So, I think we will have to address those issues when we get to safety.

DR. GULICK: We are going to turn to safety next. Dr. Brass and then Dr. Schapiro.

DR. BRASS: If I could just continue on the efficacy, I was confused by a point that was just made, two points actually. First of all, if it would take considerably larger numbers of patients to demonstrate efficacy in these other populations, are you implying that the magnitude of the efficacy would be smaller in those other populations and that is why it would take more patients? I just don't understand why it would be hard to have this efficacy extrapolated. Then I have one other point after that.

DR. ATMAR: In answer to that, my postulate would be that the variability that one would see in these other populations would be great enough that in a less homogeneous population -- I mean, one's power is affected by the variability in the population, and as the variability increases the number of patients that need to be studied to show that effect go up. I don't remember the

statistics well enough off the top of my head, but if you had a two-fold increase in variability you would need something like four times the number, and one of the statisticians could correct me if I am wrong.

DR. BRASS: That is assuming it is symmetric variability, but it seems to me that what you are really talking about is low responder rate, not more variability in the actual efficacy endpoint.

The second point I was going to make is that the 50 percent number for patients who are exposed to this drug, who might potentially benefit, I think is optimistic. First of all, it assumes that only patients with viral upper respiratory infections as opposed to symptoms that seem like they might be upper respiratory infections actually take the drug, and that patients can differentiate an allergic rhinitis from an oncoming cold within those first critical hours.

So, I think the 50 percent estimate is optimistic and assuming that, again, 10 percent of the strains are not susceptible strains and whether or not that is a factor as well. So I think the 50

percent benefit is an upside estimate, not a realistic estimate.

DR. ATMAR: Well, I will decrease the 50 percent to 45 percent, yielding you the 10 percent resistant isolated not responding. But if you look at the epidemiologic studies that have been done in a number of different populations, not just young healthy adults, consistently about 50 percent of what people identify by different definitions in different studies, 50 percent are shown to be associated with a rhinovirus infection or picornavirus infection.

DR. BRASS: Is that based on the first 12 hours of symptoms or the complete course of their symptoms?

DR. ATMAR: Again, the studies are set up in different ways but, for example, the study that Dr. Hayden I think alluded to earlier, that was done at the University of Virginia, where people self-presented during the fall season, admittedly, with what they self-identified with a common cold, and 80-plus percent of those patients were shown to have a rhinovirus infection. I don't remember the details of the study and whether they didn't include patients who had a history of allergic

rhinitis.

But, you are right, it is a difficult clinical problem and it is even more difficult in patients who have chronic respiratory illness because their baseline is higher. So it makes it harder to study and it makes it harder to identify when an illness is present.

DR. GULICK: Dr. Schapiro?

DR. SCHAPIRO: Do you want us to move into toxicity?

DR. GULICK: Just a moment, Dr. Stanley?

DR. STANLEY: I just want to echo what a lot of people said, which is clearly there is efficacy shown, if I can call half a day to a day decrease in symptoms efficacious in this very select population, but to try to generalize it and to understand the way the drug is going to be used, I think there is a big potential for misuse. We talk about inappropriate use of antibiotics and we are going to get into inappropriate use of antivirals. I don't see anywhere specifically in our questions the whole issue of resistance and what was seen in this fairly limited exposure to this drug to a population. We were getting to it earlier this morning but I don't think we can

assume that a virus developing resistance is something that is ever a good thing. So, I just throw that back out as a factor to put in when you are considering approving this drug for widespread use.

DR. GULICK: Dr. Schapiro?

DR. SCHAPIRO: I would start also by saying that I agree strongly with Dr. Kumar. The only way of mimicking these results is to give the patient this drug at the beginning of the season to have in the medicine cabinet. There is no way today, even in a very luxurious practice, to have the patient in from the beginning of symptoms. That is the only way. I do think when we consider toxicity and resistance we should realize that is the only way we could mimic these results.

I think also when we start making a decision on an individual patient, the risk/benefit decision of who you will give to for their cabinet, we do consider from this study those that have really the best results were white, young, non-smoking females. Those are the ones where we have seen the most efficacy.

Regarding toxicity, and I think that is what Dr. Stanley was referring to, there are two

issues of adverse events or safety. One is I think the global resistance. I think that is a safety issue. Then, there is a personal safety issue. Can we talk about the resistance now?

DR. GULICK: Sure.

DR. SCHAPIRO: Or do you want to wait?

DR. GULICK: Let's try to completely develop the efficacy question. I agree with you to consider resistance as part of the safety, which is our second question. We have considered most of the issues up here. The one we haven't really touched on a lot is the administration with food. Dr. Fletcher, you have food there!

DR. FLETCHER: Yes, the cookie got me in trouble! When I think about the label, you know, the purpose of it is to communicate to prescribers and to consumers how to use the drug in a safe and effective manner. You know, the committee has been discussing that very issue, how would we write a label to use this drug in an efficacious manner? What are the groups that really benefit from it? To me, that is where the food part comes in. It seems what we know in healthy volunteers is if you take it with that standard English breakfast you get a four- to six-fold increase in your area under

the curve. That is not how the drug seemed to be used in the Phase III 043 and 044 studies. There seemed to be a recommendation with food. So, how do you translate that into information that then can be communicated to the prescriber and to the consumer? What do you do with food? From at least a pharmacologic basis, if it affects the area under the curve that much it has to, in some way, affect efficacy but I am lost to know how to translate that into an informative statement.

DR. GULICK: Yes, Dr. Gardner?

DR. GARDNER: Well, most of my concern and what I would like to talk about will have to do with safety, but relative to Dr. Fletcher's statement, part of that is that if the most reasonable way to have it available to people who need it when they need it within 24 hours is to prescribe it in advance, which is what is the recommendation for emergency contraceptives, as you know, which have to be taken within 72 hours, then you immediately move away from the ability to communicate in standard labeling ways, at best, to a more analogous situation to an over-the-counter medication, but you also are increasing the likelihood that people for whom it was not

prescribed, who live in the household, will be using it when they feel symptoms coming on. They may or may not have the information about the best way to take it for maximum efficacy and then, obviously, that translates to anything we are going to discuss about safety as well.

DR. GULICK: Any other last comments about efficacy? Let me try to summarize. The committee, in large part, agreed that, yes, clinical efficacy has been documented in the Phase III studies here. People noted this was really a modest effect, on the order of a day of reduced symptoms and that this is a self-limited disease.

The endpoints, people agreed, were difficult to measure. Dr. Englund commended the sponsor on developing an endpoint that was measurable. It is really focused on symptoms and reduction of symptoms. Other committee members regretted that more emphasis wasn't placed on functional measures, such as return to work or return to school. And, there weren't really differences demonstrated in complications of the acute infection.

People were concerned about the limited virological results and there was some discussion

about the applicability of the assays.

The biggest concern on the part of the committee was the generalizability of the results that we saw. Although these were large studies of thousands of patients, it was noted that many of the patients were young, white, healthy women and to generalize this to the world at large was of concern to many of the committee members.

It was also pointed out that, obviously, people who are truly infected with picornavirus are the ones who benefit from this versus others who have self-identified cold symptoms and are infected with other viruses.

People had concerns about specific subsets. There was no definite benefit demonstrated in smokers; benefits in men less than in women. Then there were major concerns in terms of groups that were not assessed, such as non-whites in large numbers; relatively little data in the elderly; those taking concomitant medications or those with complicating conditions. So, that limits the generalizability from the data that we saw.

The last point that people focused on was the actual use of this drug. Again, some

limitations and potential for misuse were noted, and the concern about actually giving the drug within 24 hours and what that would require in terms of the healthcare system; the assumption we would quickly move to a system where this is prescribed in advance and having patients have it on hand; the point that the PCR assay is not something used in clinical practice to try to figure out which patients are truly infected.

Then, towards the end of the conversation, concerns about the food effects and, as brought up in the question and answer period, the likelihood that in the real world people would repeatedly administer the drug. I think that is what we covered.

So let's move to the second point, which is to discuss safety of pleconaril.

DR. BIRNKRANT: We inadvertently left off the issue about resistance. If you could discuss that as well we would appreciate that.

DR. GULICK: Yes, I think it fits nicely into the safety discussion actually. Who would like to start? Dr. Brass, very reliable.

DR. BRASS: I have four areas of exploration in the safety question. The first is

the drug interactions, which I think are obviously potentially clinically significant, and the issue of the oral contraceptives is obviously highlighted because of the patient population studied thus far.

It was very interesting to me to hear the lack of consensus about the role of the estrogen dose in the efficacy of oral contraceptive preparations. I think this point was made, in terms of efficacy of oral contraceptives what the drug interaction is going is making it a lower dose estrogen preparation effectively. If there is any reason to suspect that a lower dose of estrogen is less efficacious than a higher dose estrogen combination preparation, that is of serious concern. I think we have to remember how this drug is going to be made available. We are talking about women who have made a conscious decision that they did not want to become pregnant and that the use of an oral contraceptive was the optimal way they wanted to avoid the pregnancy. Therefore, it seems that any increased risk of an inadvertent pregnancy is almost unacceptable in the context of this symptomatic indication. So, I think that becomes a very important issue.

The second was the cardiovascular. I

noted that the sponsor's consultant indicated there was very little objective data to support that concern. I don't know if the agency would agree with that characterization but, if so, it obviously becomes a non-point. But if there are objective data to support the concern, which we haven't looked at in a lot of detail, then I think further exploration of that would become necessary.

The third is the area of resistance, and there are people here much more qualified than I to comment on it but I will emphasize that, from my perspective, the fact that there is a background rate of resistance that makes those genotypes not susceptible, and we don't know what those genotypes are based on, and experience with other "less virulent" mutations that were identified early on in antimicrobial therapy in general, I think the full scope of the resistance problem can't be addressed yet based on the information we have right now and it is, therefore, of concern.

The final point is, again, that the generalizability, as we talked about in terms of efficacy, also plays right into the safety concerns. We don't have a lot of data about the use of this drug in patients with co-morbid

conditions and a variety of concomitant medications. So, the potential for unrecognized safety concerns in a generalized population, and how patients are actually going to use it apropos of the oral contraceptive concerns, all remain unaddressed when I think about the safety issues.

DR. GULICK: Dr. Henchal?

DR. HENCHAL: Yes, I have the same concerns, especially since the studies didn't seem to have representative proportions of elderly. This might be a target population for the drug in order to prevent upper respiratory infections in that population. It might be easy to dismiss cardiac effects in a healthy population but when you start talking about an elderly population with other health problems, that should raise a lot of concern about the use of this drug.

DR. GULICK: Dr. Reller?

DR. RELLER: The very patients who might most benefit from this drug, based on the evidence we have here, both in terms of the frequency of the entity -- as you get older it gets less frequent -- are the very ones that I think I have serious questions about balancing the risk versus the benefit.

The major objective marker for diminution of symptoms most frequently measured was rhinorrhea. So, are we going to trade a day's decrease in a runny nose for a frequent event of breakthrough bleeding and numbers are too small to know the real risk but the potential risk for diminished efficacy of oral contraceptives when one extrapolates based on question one, these results to a potentially very much larger number of patients where even the potential efficacy would be greatly diluted.

DR. GULICK: Yes, Dr. Gardner?

DR. GARDNER: I am thinking about risk/benefit ratio really considering the substantial group of people who are not expected to derive benefit from this drug but would, nonetheless, be assuming what could be substantial but currently unknown or perhaps even postulated risks. I think we have to take all of those folks into account and that is a very large group of people, as we have talked about today.

Even among those who are expected to derive benefit, the benefit may be small in comparison to substantial risk, particularly with respect, as Dr. Reller said, to oral

contraceptives. Although Dr. Mishell certainly has fabulous credentials to discuss this, I am, nonetheless, unwilling to dismiss the role of ethinyl estradiol and contraceptive efficacy quite to the extent he did. Therefore, even if we were to believe that it had no role in efficacy, nonetheless, I think that women who have been using oral contraceptives for sometime, intentionally attempting to prevent pregnancy without intermenstrual bleeding, would be very concerned if they suddenly began to have it when they took this drug.

In particular, we talked about labeling as being a risk management tool and study after study, including some done by the FDA itself, have shown labeling to be an ineffective method of controlling risk either from the standpoint of directing prescriber behavior or from changing or directing consumer behavior. Probably the most notable serious example of this is in all of the labeling and warning activities that have surrounded Acutane and many years later we still continue to have pregnancies on Acutane.

So, for these reasons and the one that we discussed in terms of efficacy when this drug were

to find its actual use pattern, were it to turn out to be that prescribing in advance of need is the most effective way to deliver it and have it on the shelf for the sign of first symptoms, I think it changes radically our ability to communicate and discuss risks with the people who are actually going to be taking the drug. Certainly labeling won't do it. If the person is taking the drug off the shelf to use it at the sign of first symptoms did not even hear the prescriber's discussion of it at the time it was prescribed, then I think we are in serious compromise of any ability to communicate either risks or the efficacious way to take this product.

DR. GULICK: Dr. Fletcher then Dr. Wong.

DR. FLETCHER: Just to add to that point, I think this is where the drug interaction potential comes back again because how long will that intervening period be between when the prescription is written and when the drug is actually taken? And, what other medications might that patient have started in that period of time? So, even though the physician may know about them, you have the separation of time now that someone could have started on a calcium channel blocker and

when they started the calcium channel blocker, of course, they weren't taking pleconaril and then, you know, here comes a cold; take it. So, we have, in the way that this drug is likely to be used, a different set of drug-drug interaction considerations that will present themselves in a way they don't normally arise.

DR. GULICK: Dr. Wong?

DR. WONG: I guess I just want to say that I agree with the general tenor. I have not seen adequate information, from my point of view, to conclude that this drug is safe as we anticipate it will be used.

Over the past few years we have looked at a lot of different sorts of drugs on this committee, and most of them have been drugs that are directed against life-threatening illnesses. For the most part, we have taken that very much into consideration when we have been looking at safety data, and I think that is an appropriate thing to do here. We are not looking at a drug that is directed against a life-threatening illness. The treatment effect here, although there is a clear consensus that it exists, I think there is also clear consensus that it is not that large.

That has to be taken into consideration. I would like to see a lot more information and a much larger denominator to address the question does this drug decrease the efficacy of oral contraceptive drugs, and I would like to see a much more thorough evaluation of the effect of antiviral drug resistance over time, and also in breadth.

DR. GULICK: Dr. Schapiro?

DR. SCHAPIRO: I would also agree that for the safety I think the major issue is the possible drug interaction, as Courtney mentioned. I would also agree with what Courtney said, that we are going to give this to a patient up front and there would be concern that we have not fully understood this induction. I think that has a lot of potential for danger. Again, as Dr. Kumar said, even if we accept the fact that pregnancy is not increased, the bleeding is a significant issue if what we are saving the person is symptomatic relief. It is an antiviral but the efficacy we have been shown has dealt only with symptoms. We have not been shown any benefit in that we are actually reducing any complications or any other issues.

If we can move into the resistance, I

don't think we have to go into it endlessly but I would repeat what I said before lunch. First of all, it is a large endeavor to do all these studies and I think, as the sponsor mentioned, there is intention to do these. Since we have the luxury here of dealing with a non-life-threatening disease, then we require more information than we would if this were a drug for something which is about to kill our patients. We have learned a lot about antivirals, and we have learned that resistance is a major issue and we have made mistakes. I think some of the presentations here mentioned that when AZT was introduced, I think we did that probably the wrong way and, luckily, by the time we introduced NRTIs we learned something about it, otherwise they would be of no value had we used them differently.

I do think there is concern that we see a ten percent resistance after a five-day course. I don't think it is surprising that those patients did not do worse. I don't think that tells us anything that will happen ultimately. The baseline samples that were resistant did, in fact, not do as well or, in fact, appeared to maybe even do worse. Therefore, it is concerning that a drug which would

be given so much could rapidly produce widespread resistance and this would render it ineffective.

The other concern is that there are other agents being developed that target the same area. We don't know if this will or will not produce a degree of cross-resistance. It may or it may not but we have absolutely no way of knowing today, and we have to keep in mind that this may result in cross-resistance to infections that are life-threatening. Viruses of this family in certain instances do produce diseases which are life-threatening and if we were to produce a population-resistant virus, that could be problematic. There are a lot if's here. It could be that will not be the situation, but I do think for this indication we should have answers to these questions.

DR. GULICK: Dr. Atmar?

DR. ATMAR: In terms of the issue raised about lack of an effect on complications, I would point out that the expected complication rate of things like otitis media or sinusitis, bacterial sinusitis are relatively low, one to two percent for each of those for, I guess, in these studies a cumulative total of about five to seven percent,

and these studies were not powered to look at that endpoint and you really need to study many more patients to be able to show an effect there. I mean, it was disappointing that there was no apparent trend but, because the numbers were small, that is not particularly surprising.

In terms of the resistance issues, I would point out that respiratory virus infections like influenza and picornaviruses are acute self-limited infections and are different from HIV which is a chronic infection. So, some of the same issues that deal with resistance for HIV don't apply to the respiratory viruses. While I think it is a concern, we can be somewhat relieved that with antiviral drugs, even though amantadine and rimantidine haven't been used extensively, resistance to these agents in naturally occurring isolates has not increased over time. One could argue that it is because we don't have a lot of clinical use of the drugs but, nonetheless, it hasn't been observed.

With rhinoviruses, from city to city we have different serotypes in terms of epidemiology in a single season, and they vary from year to year within a season. So, I don't think, though

obviously we don't have the data, it is likely to be a problem that will have an accumulation of resistance within the rhinoviruses over time. With enteroviruses I guess it is harder to know whether that would be a problem. We don't have the data and, short of looking at transmission studies which for rhinoviruses are terribly difficult to do, there is still a lot of discussion in the literature as to what the most important mode of transmission is, whether it is aerosol, and it is still open to discussion. So, I am not as worried about the resistance issues. It is something certainly to be aware of and to continue to look at.

I feel less qualified to address the other safety issues raised in terms of the estrogen dose. I guess a question for the committee to consider is for the short course. We had zero out of 400-plus women in the efficacy trials who were receiving oral contraceptives that became pregnant, and two out of 58 or 60, or whatever, in the prophylaxis study, which was a six-week study. If we are just looking at the five- to seven-day course, the question is what does that denominator have to be, zero out of what number? I don't know what the

answer is. I would like it to be a huge number but from a practical standpoint what kind of direction could one give to answer that? That hasn't really been addressed. Everybody wants a bigger number but what should the number be?

DR. GULICK: Dr. Brass, Dr. Englund and Dr. Kumar.

DR. BRASS: I agree that getting zero out of a big number is a losing battle and that is why I made the point about if I knew, for example, what the relative efficacy was of a combined formulation that had half the estrogen versus the full dose and I was convinced from that data that a half dose of estrogen was associated with no loss of efficacy and the clinical data were consistent with that, that would be very reassuring to me as opposed to studying 50,000 patients to convince myself it was zero.

DR. GULICK: Dr. Englund?

DR. ENGLUND: I just wanted to speak to the resistance issue because I have been interested in that particularly in the hospital setting. I do think that rhinoviruses are totally different from the other respiratory viruses that I have worked with. I have been very concerned about the spread

of resistant influenza virus, and have published on that, and I am not happy with the use of rimantidine in the hospital setting, at least in my hospital setting where there are immunocompromised patients. Rhinovirus is not spread by aerosol. The resistant variants, and I don't know if it is the exact same mutation but the ones that we have with similar mutations don't spread that rapidly, and that is because they are a little bit attenuated because they don't attach so well, because their attachment mechanism is affected.

I am very concerned about the safety and I think the resistance issue could be studied more, needs to be studied more and, to hark back to me being a pediatrician, it needs to be studied in a pediatric setting because those are the kids who are spreading the virus a lot more readily and rapidly than adults are.

DR. GULICK: Dr. Kumar?

DR. KUMAR: I want to come back to the safety issue. At all times it is very apparent that not just the agency and the committee members here but that sponsors work very, very hard to bring safe drugs forward. But in an illness that is self-limited, as the common cold clearly is, the

bar is much higher where safety issues are concerned.

I want to give you a very simple example. In treatment of syphilis, much, much earlier, I still remember being taught and I was told this line, that a moment with Venus, the goddess of love, will give you a lifetime with Mercury.

[Laughter]

I want to go back to this issue and just to think from my perspective, to tell patients -- women on oral contraceptives make that personal choice that that is their method of contraception and to say you have a common cold; I will prescribe this drug. You may get half a day to one day symptom free but you are going to take a whole month of using additional barrier methods of contraception. I think that is practically going to be very relevant.

I want to preface that to say that I would be accepting of that if I knew that I could counsel them right there and then when I write the prescription and give it to them, I can sit them down and say these are the issues. But many people around the table have said that we don't think that is the way it is going to be prescribed.

Prescriptions are going to be given months ahead of time, two or three months, and we really don't have the face-to-face interactions to go through side effects and review, at that moment of time, on what drugs they are. Those really are my concerns as a clinician.

DR. GULICK: Dr. Atmar?

DR. ATMAR: Again, I would say that in terms of the way the drug is going to be used -- I mean, we are all speculating as to what seems to be practical and it doesn't seem likely, certainly in an HMO setting, that one could even see a physician within 24 hours. To assert that prescriptions will be written ahead of time and given to patients, I mean we don't know that.

The sponsor certainly, when asked the question, said that they were going to target their education towards the primary care physician and not towards the public. I guess I am a little bit bothered by making a decision based on speculation as to how the drug will be used.

DR. GULICK: Dr. Gordin?

DR. GORDIN: Well, the flip side of that -- and I agree, it may not be that people will have this prescribed ahead of time in their pharmacy

cabinets, but the opposite, that patients come in on day two or three of their common cold and get given this drug, because of pressures, beyond the 24 hours. Even in the sponsor's own data they presented, I believe it was about 60 percent of people who were screened out because they showed up too late for the study. It was maybe even higher than that. So, I think it is equally likely that instead of having it sitting around ahead of time, people will come in, in a sense, too late at least in terms of what we understand about the efficacy but will be given the drug and, again, experience potential toxicity and potentially no efficacy.

DR. GULICK: Other comments about safety? Dr. Stanley?

DR. STANLEY: I just want to reiterate what somebody else said. I don't think the risk/benefit ratio is there for such a common disease that is not life-threatening, and all these questions that are answerable but have not been answered yet about toxicity, the pregnancy complications and the interactions with other drugs. Those are answerable questions.

DR. GULICK: Let me summarize what I think we said about safety. The committee really

considered safety in terms of four things, the context in which we considered safety, the first being that only about 50 percent of people would actually be infected with picornavirus; the second, again, the generalizability question, that the trials were really done in healthy patients and, arguably, these drugs might be targeted towards the elderly or people with concomitant disease or medications; the point that outside the first 24 hours people might also take the drug.

The other context we considered it in was how the drug would actually be used. There were some differences of opinion but a growing consensus that this would be prescribed in advance and that that decreases the opportunity to review safety information with the patients, at least in the real world.

The fourth and probably biggest consideration of safety is that, of course, the common cold is an acute self-limited illness and that we raise the bar for this disease over some of the other diseases that the committee has considered over the past years.

The two major areas that people focused on in our discussions were drug interactions and

resistance. Again, around the table people felt that we have incomplete information about both of these.

There were some concerns about the decreased estrogen levels, about the breakthrough bleeding, about the potential for unintended pregnancy although there was a difference of opinion on that, and the requirement for additional barrier protection.

In the area where there is really little data to go on, other than some suggestions, there was concern about cardiovascular toxicity and symptoms associated with theophylline use.

Then, the point that many people made is that we simply do not have a lot of information on other concomitant drugs that people would be likely to be taking.

With regard to resistance, a much more controversial discussion really, people pointing out that rhinoviruses are not like other respiratory viruses and certainly not like viruses of chronic diseases. Yet, there was some concern about the ten percent background rate of resistance documented on this study. There were differences of opinion about the potential for widespread

resistance in the community given widespread use of this drug, others pointing out that there are different serotypes in geography with rhinovirus illness.

Other concerns raised previously were about treatment emergent resistance, 13 percent documented in the studies here. Questions that we really don't have any information on are the cross-resistance between this drug and other drugs in development for this and other viral diseases and, again, no information about transmission studies and whether resistant virus is transmissible among family members or other close settings.

Let's consider question three. We are going to take a formal vote on this question. All members of the committee are eligible to vote, with the exception of Dr. Sun. Dr. Brass?

DR. BRASS: Can I make one comment and ask one question?

DR. GULICK: Okay.

DR. BRASS: My comment has to do with the concern about the meaning of the efficacy. I would just point out that consumers are currently spending an exorbitant amount of money buying

products for symptomatic relief and complementary medicines of unclear efficacy that they think work. So, the value of symptomatic relief to the consumer in the real world is actually quite substantial, and I don't minimize the benefit of cutting the symptomatic period by a day and a half.

Similarly, when we talk about safety, there are no risk-free drugs, including those currently available OTC for symptomatic indications. They all have risks. We are able to define those risks and make an assessment of the risk/benefit ratio. So, a zero risk profile is not what is being asked for either in this discussion even for the symptomatic indication.

My question, therefore, is when we answer this question do you want us to answer it in the context of hypothetically if I imagine that there are patients who get benefit and have no risk or little risk associated so that in any patient cohort the answer to this question is yes, do I vote yes? Or, do I have to vote yes only if I think as I extrapolate the data to how it is going to be used and a conceivable label to everybody, do I need to vote yes?

DR. GULICK: Would the agency like to

respond? Dr. Birnkrant?

DR. BIRNKRANT: We do recognize that this is a complex question, and we are looking more for a big picture type of answer. That is, once the drug is approved, then is there adequate benefit to support the risk that we have discussed today?

DR. BRASS: Given that we can only quantify that in a subset of the population based on the data that is presented to us, do we want to base the answer on the subset? If I believe what I just said, does that mean I automatically vote no?

DR. BIRNKRANT: I don't really want to lead you one way or the other.

DR. BRASS: No, I am not asking you to. I have to understand the context. I think you know what I mean. You made this question black and white so my vote has to be black and white so I just have to understand whom I am covering here.

DR. BIRNKRANT: It is focused on approvability, meaning that once the product is approved it will be in the general population, and it is more a question extrapolated to that population.

DR. GULICK: Just to add, the law says substantial evidence of safety and efficacy. That

is what we are focusing on. Everyone has to take their own risk/benefit into account. Mark?

DR. GOLDBERGER: Just to follow-up on what Debbie said. I think what we would like is your take, obviously -- when I say yours, for each of the individuals who will be voting -- on the discussion that was just held with regards to safety and efficacy integrated into your own experience, and that certainly can include how the drug perhaps is intended to be used and how you think it actually will be used. One of the reasons that we have advisory committees is to bring together a group of people who have a wide range of expertise, ranging from purely scientific to practical aspects, etc. and we would like all those factors taken into account in terms of how you decide that you would like to vote.

DR. GULICK: Is that clearer? Let's pose the question then, do the safety and efficacy profiles of pleconaril support its approval for treatment of VRI in adults? I am going to go around the table and ask people to vote yes or no. We skip Dr. Sun so Dr. Brass, you get to start.

DR. BRASS: No.

DR. GULICK: Dr. Reller?

DR. RELLER: No.
DR. GULICK: Dr. Henchal?
DR. HENCHAL: No.
DR. GULICK: Dr. Gardner?
DR. GARDNER: No.
DR. GULICK: Dr. Atmar?
DR. ATMAR: No.
DR. GULICK: Dr. Wong?
DR. WONG: No.
DR. GULICK: Dr. Fletcher?
DR. FLETCHER: No.
DR. GULICK: Dr. Schapiro?
DR. SCHAPIRO: No.
DR. GULICK: Dr. Stanley?
DR. STANLEY: No.
DR. GULICK: Dr. Wood?
DR. WOOD: No.
DR. GULICK: Dr. Gordin?
DR. GORDIN: No.
DR. GULICK: Dr. Kumar?
DR. KUMAR: No.
DR. GULICK: Dr. DeGruttola?
DR. DEGRUTTOLA: No.
DR. GULICK: Dr. Englund?
DR. ENGLUND: No.

DR. GULICK: And the chair votes no. So, no votes for "yes" and 15 votes for "no." I suggest we take a break now. We are going to come back and consider the rest of the questions but I would like to take a ten-minute break. It is 2:40. Let's reconvene at 2:50.

[Brief recess]

DR. GULICK: We will resume. We have several more questions to consider before the end of the day. Dr. Birnkrant, do you want to introduce these to us?

DR. BIRNKRANT: Basically, we focused quite a bit on issues related to oral contraceptive use and resistance. We were wondering if we could perhaps delve into other areas where there would be a need for additional studies, as well as again commenting on the areas of resistance and drug interactions.

DR. GULICK: Specifically, what additional data would the committee like to see? Some things have already been mentioned. Dr. Gordin?

DR. GORDIN: Just to say the obvious, I am sure all of us thought would we want to take this ourselves but I do think having much broader patient pools studied, and not excluding all the

individuals who were excluded by age, and also by concomitant medications, diseases, etc., etc. Clearly, at least for me, that was an important factor in thinking about would this drug really work if generally used. So, I would think that would be an important factor in further studies.

DR. GULICK: Other suggestions about studies? Dr. Englund?

DR. ENGLUND: I really think we need to study the asthmatics and children, which might even be the same, asthmatic children.

DR. GULICK: Dr. Henchal?

DR. HENCHAL: Actually, I was going to agree with that but not just more studies but studies that have a much broader base to represent Hispanics, African-Americans, the elderly, children. All that maybe has to be expanded.

DR. GULICK: Dr. Wong and then Dr. Fletcher.

DR. WONG: To me, the issue here wasn't efficacy so I will agree that it would be very interesting to know the results of use of this drug in all those groups but, to me, if they got the safety data in order, this would be an approvable drug.

DR. GULICK: Dr. Fletcher?

DR. FLETCHER: I have probably three or four things. First, I think the drug-drug interactions. We talked about data with the oral contraceptives but there are clearly other drugs for which the inductive properties could be very important. I wouldn't want to try to right now construct a list but I think there do need to be interaction studies with other select drugs that are frequently used and that would have serious consequences of therapeutic failure.

I think these studies have to go beyond just a numerical pharmacokinetic study, in other words, was the area under the curve dropped by 30 percent or 20 percent. As we saw, I believe, with the oral contraceptive data a 30 percent drop did lead to a clinically significant interaction. So, the rules we would like to use, that it has to be more than 30 before it becomes clinically important I think are ones that we should try to move away from as rapidly as possible because it is just not an appropriate standard for us to have.

Second, the food effect. I think we need to understand that in a much clearer way. I am probably going to get this wrong but I think the

rule that our moms taught us was "starve a cold and feed a fever." "Feed a cold, starve a fever?"

[Laughter]

I knew I would get it wrong. Whatever way, if we are using a drug you have to take with food, we need to have a much clearer understanding of what is really necessary, what kind of a snack; what kind of a meal. So, that I think needs to be done.

Third on my list, and these really aren't in any particular order, would be resistance, I think in particular transmission of resistant viruses and response.

Lastly, I am still not willing yet to dismiss the race/ethnicity issue. I understand all the hazards about looking at subgroups but, to me, when I look at those data I see some signal there that says this is worth a little more exploration than has been done to date. I think that perhaps could start with some pharmacologic studies to see if there is a basis there for any differences in response between Caucasians and not Caucasians before you launch into thousands and thousands of patient studies. But I think a little more exploration of that would be worthwhile.

DR. GULICK: Dr. Schapiro?

DR. SCHAPIRO: To address some of the issues of resistance, first of all by the way, Courtney, my mother also said chicken soup. So, a combination of chicken soup with pleconaril I think would be optimal!

Some of the issues that came up in the discussion regarding resistance, I think characterizing the patients with resistance regarding if this is serotype or point mutation resistance would be very helpful. I think also focusing on maybe a pediatric population and looking there, and this could be done in a school or in other settings, to see to what degree there is transmission. It may be that we will find that there is not a lot going on, that there is not a lot of transmission and that much of this is not point mutation, but I think a pediatric setting might be a good place for a well-designed study to look at the virology there and characterizing that I think would be helpful. That is something to consider. Of course, we would want to see what the cause of resistance is and, to the degree that it is possible, I do think we want at least some laboratory studies looking at the issue of

cross-resistance with other compounds.

DR. GULICK: Dr. Brass?

DR. BRASS: I just want to reinforce the issue of generalizability. It is not only an efficacy issue because, again, I do believe the drug has efficacy, but it is a safety issue. If you want me to believe that as a primary care provider it is okay for me to give this drug to a 67-year old man status post-coronary bypass surgery on eight drugs, at least one of those has to be some place in a study population. So, I think the generalized population is very, very different than what we are seeing here. So, unless the label is going to be quite restrictive, I think that needs to be taken into account. Again, I pick that example because I do think the clarification of the cardiovascular adverse events and the theophylline reaction have to be at least agreed to, that there is no objective basis for them explicitly. And, the oral contraceptive issue I agree with as well.

DR. GULICK: Dr. Wood?

DR. WOOD: I would just like to add in terms of what has already been raised regarding drug-drug interactions that the analysis would look at repeated exposure since it is likely that

individuals will take this drug more than once within a cold season since people tend to get several colds a season so it wouldn't be a one time thing but potentially with repeated exposure.

DR. GULICK: Dr. Stanley?

DR. STANLEY: Courtney beat me to it since he is there and I am not, but I do want to emphasize again that we really need to understand in other ethnicities how this drug works and if it is equivalent. In this day and age I think it is unconscionable to just assume that you can prove something in a particular Caucasian population and extrapolate it to others.

DR. GULICK: Dr. Fletcher and then Dr. Gardner.

DR. FLETCHER: I was just going to add to Dr. Wood's comment, I think not only repeated exposures but longer duration than five days. I think it is likely, if the drug is approved, that some will receive it for a course that is longer than five days. Not yet fully understanding the time frame of induction, one could imagine that you might not have something that appears if you have a five-day course and could appear if you have a seven- or ten-day course because you reach a

different level of CYP induction. So, besides repeat exposures, I would probably extend the interval out a little bit longer.

DR. GULICK: Dr. Gardner?

DR. GARDNER: A couple of things. First, I hope the sponsor doesn't get the idea that we are going to try to hold them to pregnancy as an outcome or contraceptive interactions because I don't think any of us are thinking that way. But we would like a whole lot more information on the oral contraceptive interaction by analogy, by other studies, pharmacokinetically, all kinds of ways that we can get it, but the number of pregnancies and powering up for that is not it.

The second thing is that I think possibly we may be struggling with it being the first in this class, that is, a prescribed medication, and some of what we have talked about today is related to what we would be discussing if we had an over-the-counter medication. So, I, for one, would like to have some insight from them, possibly from focus groups or other kinds of studies, about how this drug is likely to find its customary use and what they suggest, other than labeling which I will systematically reject every time it comes before me

at least, as a risk management tool. What are some innovative ways that they might find to explain to people the important things about this product once it becomes available because even though it may be a prescribed product, being first in its class, the sense of all of us that it will be prescribed and used very likely, we think, much more like an over-the-counter product. I don't know about actual use studies but certainly label comprehension studies for people who are about to use it, or other ways that we could be assured that when it finds its usual use some of our concerns will not be magnified, would be very helpful.

DR. GULICK: Dr. Brass?

DR. BRASS: I just want to follow-up on something Dr. Fletcher said in the context of drug interaction studies, their duration, off/on rates, etc., that we not overly focus on mean responses. Because this is safety data, it is going to be the outliers that matter, and there very well may be ethnicity differences in the drug interactions where there are examples too. So I care about the 99th percentile, not the mean, and the 30 percent is the mean magnitude.

DR. GULICK: Other comments on additional

studies we would like to see? Dr. Birnkrant?

DR. BIRNKRANT: With all of these recommendations, would this necessarily translate into another Phase III trial for the applicant to think about conducting or not?

DR. GULICK: Anyone want to tackle that one?

DR. BRASS: Well, it is usually a bad idea for committees to design trials for sponsors. I think if somebody can think of another way to do it, more power to them.

DR. GULICK: Dr. Kumar?

DR. KUMAR: I personally think that they have shown efficacy. It all comes down to safety. So, in whatever format the sponsor can show common drug-drug interactions, intermenstrual bleeding, and reassure us that there will not be increased failure of oral contraceptives is all that I would look for being able to safely use this agent.

DR. GULICK: Dr. Reller?

DR. RELLER: Since we did not see any data on the effect of this compound on prevention of complications, and I am not aware of any secondary benefits that might be important or should be considered, such as prevention of transmission to

other patients, in reality we have a drug for an illness where we are talking only about symptom reduction. So, the level of safety that I would want to see, however it be demonstrated, is basically the same level of safety that would be required for an over-the-counter preparation, which means with all the ramifications of drug interactions etc., it is a very substantial bar because I think the benefit from reduction in symptoms is pretty small.

DR. GULICK: Yes, Dr. Stanley?

DR. STANLEY: Which reminds me of another issue we talked about, which is more thorough virologic studies to show the effect of actually perhaps decreasing viral burden in the secretions. I mean, if you could show that more convincingly with a better time decay curve, or whatever, now you are looking at a public health impact which gets beyond just saving the individual half a day or a day of symptom relief.

DR. GULICK: Let me try to summarize. Again, from the committee's point of view, we were really focused on additional information that would fill in the blanks in terms of safety information. That is really what we concentrated on.

People noted once again that the generalizability of the current Phase III studies should be expanded, and that we need to see additional studies in other populations, specifically pediatrics, other non-white race and ethnicities, the elderly, people with concomitant diseases such as asthma or chronic cardiac or pulmonary disease and immunosuppression, also those taking other medications.

We spent a lot of time again talking about drug interactions. As Dr. Fletcher pointed out, these aren't just changes in numbers but there are physiological changes such as breakthrough bleeding. Everyone agreed that we need more information on that interaction and, in addition, drugs with a high probability of clinical failure. Also, just common drugs that are taken quite frequently.

Other issues, pharmacokinetic, better definition of the food effect; better definition of longer duration or repeated exposures of the medication. Then, as Dr. Brass pointed out, increased characterization of the outliers rather than focusing on the mean.

The other major area we touched upon was

virological and resistance issues. Everyone felt that further characterization of resistance, serotypes, point mutations, does this have an effect on transmission and people suggested pediatrics or family situations is the best place to look for that.

Does the drug really decrease the viral burden, and are there subsequent effects on transmissibility? Then, once again, cross-resistance among other drugs that are in development right now.

Finally, one other suggestion was from Dr. Gardner, how would this drug really be used, and increase the amount of information considered, perhaps in a focus group; thinking about innovative ways to convey safety information given the likelihood that this drug would be prescribed in advance. And, Dr. Brass would like to add.

DR. BRASS: No, I just want to clarify something because you included the issue of pediatric populations, and not presuming what the sponsor is or isn't doing in the pediatric population, I hope the intent was not to imply that an adult only indication could not be achieved. Because when you say you have to do studies in

children or imply that you have to do studies in children you are shifting things a lot from what we have before us as an adult indication.

DR. GULICK: Yes, let me clarify. I think the spirit of this discussion is what kinds of things would the committee like to see done to find out more about this drug. Clearly, studies in the pediatric population, for the many reasons that were discussed, would be helpful and valuable. I don't think I meant to imply, or anyone on the committee, is that you must do the following things to get your drug approved. Dr. Goldberger?

DR. GOLDBERGER: Just to follow-up then on Dr. Birnkrant's question about an additional Phase III study, we recognize Dr. Brass' comment and we do not expect the committee to go through the detailed elements of the design of such a study. Yet, listening to you just summarize the discussion about additional data that was required, you spoke about the concerns about the generalizability of the information that was here; issues about certain ethnic groups not being adequately represented; about certain patient populations including the elderly, asthmatics, etc.

As you know, we will need to have some

discussions with the firm about appropriate ways to proceed. It does sound, listening to that, as though the committee would like a substantial amount of additional clinical trial data, and we would just like as much clarification as we can have from you so that when we discuss these issues with the firm we can ensure that they have the best possible advice about how to proceed.

DR. GULICK: Maybe I can just jump in and say that we all recognized around the table is that these were very large studies, thousands of people, yet, 80 to 90 percent were white. The elderly were in a very low minority; and patients were excluded with many serious concomitant diseases. I think I got a consensus from the committee that we are concerned about that. There are other diseases, other clinical trials that we have seen which may not have complete representation of every group but at least are a much more diverse group and you get the sense of a performance of a drug in many different populations. Generalizability I think is always a concern with clinical trials. Having these very large studies be so homogeneous I think gave a lot of us pause about trying to apply to the entire world of people that get colds. Yes, Dr.

Wong?

DR. WONG: I would agree with that with respect to safety but I saw enough to conclude that this is an efficacious drug for picornavirus infections. So, I would not recommend that efficacy necessarily be shown in all those groups, but I would like to see that it can safely be used in all those groups.

DR. GULICK: Dr. Reller?

DR. RELLER: I thought the efficacy, when you didn't restrict it to those who had some evidence of picornavirus infection, was a split decision and I don't know how you are going to find out information in the broad span of patients unless one eliminates some of the exclusions and studies those patients. At the same time, in addition to safety, with a more diverse patient population you might as well see if the efficacy holds up as the drug would actually be used. I am not convinced that it would.

DR. GULICK: Dr. Englund?

DR. ENGLUND: I think that the studies that need to be done do need to be broader, but I think you should compare the elderly with the elderly, the COPD 50-year old with the 50-year old,

and forget to compare an 18-year old college student with a 65-year old who is on hypertensive meds and has smoked for 50 years. So, I would like to see more focused clinical studies in hundreds, not thousands, because I think that could be pin-pointed for investigators that have a high minority population and it could still get us the right answer. But I think you need to keep on comparing oranges with oranges and apples with apples because we are never going to get efficacy. With rhinovirus I don't believe you will get efficacy if you compare a huge population unless the sample size approaches 10,000 or 20,000.

DR. GULICK: Dr. Gordin and then Dr. Brass.

DR. GORDIN: I was just going to make the point that if future studies are done I think it would be up front, for the FDA and the company, to agree whether it is intent-to-treat of all people or only those with proven picornavirus, given how difficult it is going to be for any clinician to tell the two apart if the drug is marketed.

DR. GULICK: Dr. Brass?

DR. BRASS: My issue with efficacy boils down to what the label population is going to be.

If the label is going to be limited to young, healthy women who are not on oral contraceptives and who are not smoking, I think the efficacy has been nicely demonstrated. If we want to extrapolate that result to other populations and so reflect it in the label, that is where I think the issue of studying other patient populations becomes a judgment call. But I am unconvinced that the efficacy extends beyond that population in a substantial manner.

DR. GULICK: Dr. DeGruttola?

DR. DEGRUTTOLA: I just want to comment that I would certainly agree they have demonstrated efficacy within the restrictions of the populations studied, and it would be interesting to go outside those populations and learn more about efficacy elsewhere. I also wanted to mention that I think that the comment that was made about studying families was particularly interesting because, for example, if it were feasible to do this, if you could randomize families to use pleconaril versus placebo at the time of colds, then you might be able to study the resistance issues as well as the transmission issues and find out not only if the number of colds in the families were reduced, but

also something about what viruses they became infected with and so on. So, I think that would be a challenging study to do, obviously, and I wouldn't personally think that would be required for reconsideration of the drug. I agree with the concern about focus on safety, as I mentioned before, but if there were interest in looking more broadly at the questions of resistance and transmission, I think that would be a fascinating way to proceed.

DR. GULICK: Have we answered that question to your satisfaction? I see a "yes." We have one additional question to consider. This is more kind of global, asking the committee to think about rhinovirus infections in general.

DR. BIRNKRANT: That is, how to develop a drug for rhinovirus infections. In addition to issues outlined on that slide that was up there, could we hear some discussion about which population we should actually be focusing on for efficacy? Should it be the intent-to-treat infected, or should it be the all randomized, or should it be both?

DR. GULICK: Dr. Schapiro?

DR. SCHAPIRO: I would probably agree with

Dr. Gordin that it is important for this to be clinically relevant. We saw a very nice presentation and good data from the sponsor but we were really seeing symptomatic relief with a drug that is antiviral, and when we went with the risk/benefit that impacted what we were willing to accept. I think that was a repeated motif. If we are looking to reduce symptoms, then we should also do that in a way that would be widespread. It would have to be not diagnosed as the virus but on the symptoms. So, as Dr. Gordin said, it wasn't appropriate to have here PCR positive patients. That just wouldn't work. If, on the other hand, we are looking at targeting complications and high risk patients, then that would.

So, focusing on specific patient patients, of course, depends on what diagnostics become available. We may see new and nice improvements but I think it has to be relevant to what the sponsor is going for. If it is similar to what we saw today, I think it would have to be a general population. I think also it would have to be generalizable as far as how quickly the treatment was given. We were able to eventually define that only a third of those that were screened were able

to be enrolled. That is clinically relevant. So, I think those are some of the things that have to do into the design. I think if we are targeting specific populations where maybe you are able to have a diagnosis first, in that case it would be applicable. But I think here that was a little bit part of the discrepancy between what the sponsor was presenting and how we critiqued it. The same I think for toxicity and interactions.

DR. GULICK: Dr. Brass and then Dr. Wong.

DR. BRASS: While the endpoint was symptomatic, I think it is worth pointing out, as I said before but to reemphasize, that this was a very rigorously defined symptomatic endpoint. It was not just a composite score of a bunch of things; you had to meet substantive standards in multiple categories, and it had to be sustained for 48 hours. Remember, when you reached the endpoint that really means the last day you had symptoms was on day six and so one and a half days was a high percentage of the six-day symptomatic period. So, I was actually pretty comfortable with the endpoint, as defined, as being clinically relevant and rigorous enough to have that kind of meaning.

The issue about the ITT population versus

the truly infected population goes back to how you make the population risk/benefit ratio. Again, if one tries to understand who is actually going to be exposed to this drug when it is available 12 months out of the year in a more generalized way, what is the percentage of patients who you think will be deriving benefit from the universe that is actually prescribed the drug? When a physician is making the decision and maybe even discussing it with the patient, they have to have some sense of what the probability is of even getting that day, day and a half of relief.

As I indicated, I think that the 45, 50 percent is a top bar and the actual percent in a more generalized population might be much lower. That may still be fine, but if one is going to make an informed decision with an individual patient about the risk and benefit and truly understand what the probability of success is going to be, one has to relate it to the overall population that is going to be exposed to the drug, not only the subpopulation that has been shown to benefit from the drug because you can't identify that cohort prospectively.

DR. GULICK: Dr. Wong?

DR. WONG: I guess my answer to Dr. Birnkrant's question would be that I would ask them for both analyses. I have a hard time imagining any circumstance in which I would not want to see them both. Clearly, having the intent-to-treat populations compared really does tell you the most about the effects that will be seen in real life, but not giving the other population takes the risk that you will not be able to see a true biological effect and I think that that is something that we would want to know. Even if we were not able to extrapolate that to a clinically identifiable treatment population today, it might well be important to know that a new drug or a class of drugs is biologically active in and of itself.

DR. GULICK: Other comments? Dr. Goldberger?

DR. GOLDBERGER: It was, of course, entirely appropriate for the company to conduct their clinical trials versus placebo. Nonetheless, there are questions that came up here, not surprisingly, perhaps intensified a little bit by some of the potential safety issues, about how a drug like this would actually compare to the type of over-the-counter therapies that are commonly

used. Does the committee have any perspective or view about clinical trials that would utilize that comparison as opposed to simply utilizing a placebo control?

DR. GULICK: Dr. Brass?

DR. BRASS: It would be of interest but should not be required.

DR. GULICK: Do you want to say more about that?

DR. BRASS: Again, we talked about how hard it is to do trials in this population. We have referred to the limitations of symptomatic therapy, and without understanding all those variables, I think demonstrating that the drug was efficacious against placebo would be an appropriate standard that would allow physicians and other healthcare providers to make an appropriate decision about whether it is an appropriate use in an individual patient. Obviously, we would all be interested in how it would compare to those other drugs but I think all you are doing is adding a series of design complications to a problem that we have spent all day talking about how difficult it is to study.

DR. GULICK: Yes, Dr. Stanley.

DR. STANLEY: Again, if you are just going to look at symptom relief as your endpoint, then there may be some validity to having it compared to what is already available over-the-counter. On the other hand, if you are looking at an antiviral effect and you can really show a significant antiviral effect, then it shouldn't be held up next to the other standard.

DR. GULICK: Two parts of the question that we haven't really touched on are the first and fourth, although we have been talking about them all day. But do people have general suggestions about diagnostic criteria for the potential for drug interactions in a more general sense?

DR. BIRNKRANT: We would also specifically like to know if, up front, all patients should be cultured, not just those who are deemed to be PCR positive.

DR. GULICK: Dr. Englund?

DR. ENGLUND: I think that the sponsor needs to provide us with some data, not necessarily on all patients but on a subset of patients, so that we can take a look at see. I believe that PCR is a great assay and I believe their PCR is probably a good assay. I don't believe that I have

seen it published; I don't believe I have seen references. I have just read through here and I would like more information. So, I would say we wouldn't need it on all patients but they had thousands of patients and if we could have had a subset of that it would have been great. And, I would like to know what the effect of the freezing is. I mean, there are things in terms of diagnostics that they could provide some information without greatly affecting their effort and cost.

DR. GULICK: Dr. Fletcher?

DR. FLETCHER: On drug interaction, for the drugs that we talked about that would be very commonly used or that would have serious consequences of therapeutic failure, I think those probably ought to be discrete drug-drug interaction studies. I don't think I would try to embed those into another large clinical trial. I think if another large clinical trial was done, one could think about an opportunity to look for any signals for drug-drug interactions in that study. You know, there are population pharmacokinetic techniques that are talked about.

The only comment I would have is if you go

down that road you would need to pay very close attention to the design of that. I think far too often we have just said, well, we will collect some random samples and try to use that as a screen for drug-drug interactions. I don't believe that is an adequate way to proceed. If you are going to do that you need to pay as much attention to the design of that component of the study as you would any other components of a large study.

DR. GULICK: Dr. Atmar?

DR. ATMAR: In addressing the issue of doing the cultures at baseline, I think the sponsor did address that issue in their Phase II 032, if I remember the number correctly, trial. By my calculation, they came up with three additional culture-positive specimens at baseline that were RT-PCR negative by the two assays. In an ideal world, sure, do all the tests but I think at this time the best method to diagnose picornavirus, rhinovirus infection is RT-PCR, and it is an assay that has adequate controls to ensure that there is no carryover contamination. That is the new gold standard. I think there is adequate proof in the literature to substantiate that. So, if I had a bottomless pocketbook, yes, I would do cultures on

everything but I think that the approach that the sponsor took for these two studies is realistic.

DR. GULICK: Any other thoughts? Not to belabor it but just to say our additional suggestions are for diagnostic criteria. We heard a difference of opinion on the use of PCR versus culture, and a plea for at least embedding a pilot study into larger studies.

People were convinced that we should look at both intent-to-treat and intent-to-treat infected because they tell us different things.

In terms of the population, most of the consensus was that we need to have a population for the real world, and consideration about the within the 24 hours rule needs to be done, again, looking at the intent-to-treat infected as a valuable subpopulation, and then consideration of the use of over-the-counter meds since that is so common.

In terms of endpoints, people once again complimented the sponsor on using a very well thought out symptomatic endpoint which people thought was clinically relevant, although many people reiterated that we are interested in the virologic effect as well.

Dr. Goldberger's question about

randomizing people, what is the appropriate randomization between a rhinovirus drug and whether it should be placebo or over-the-counter meds, and finally drug interaction studies and Dr. Fletcher's suggestion of doing formal small pharmacokinetic studies and then trying to glean signals about other possible drug interactions from the larger studies.

Did we do our job? I am getting a "yes." Any final comments from anyone?

I would like to thank the sponsor, the agency, the members of the committee and the audience, and we will close this session. Thank you.

[Whereupon, at 3:30 p.m., the proceedings were adjourned.]

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