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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUG ADVISORY COMMITTEE

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PUBLIC HEARING

NDA 20-871/NITAZOXANIDE

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OPEN SESSION

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WEDNESDAY,

MAY 6, 1998

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The hearing was conducted in Salons C, D, and E at the Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, Maryland at 8:00 a.m., SCOTT M. HAMMER, M.D. Chairman of the Committee, presiding.

MEMBERS PRESENT:

SCOTT M. HAMMER, M.D., Chairman
JUDITH FEINBERG, M.D., Member
HENRY MASUR, M.D., Member
LAMES J. LIPSKY, M.D., Member
JOHN D. HAMILTON, M.D., Member

RHONDA W. STOVER, R.Ph.
Executive Secretary

SAG, CORP
4218 LENORE LANE, N.W.
WASHINGTON, D.C. 20008
(202) 797-2525
VIDEO; TRANSCRIPTIONS

ALSO PRESENT:

CONSULTANTS PRESENT:

SUSAN COHEN, B.S.
MICHAEL MARCO
WILLIAM CHRISTOPHER MATHEWS, M.D., MSPH
CYNTHIA L. SEARS, M.D.
STEVE SELF, Ph.D.

Food and Drug Administration:

ALOKA CHAVKRAVARTY, Ph.D.
BARBARA DAVIT, Ph.D.
MARK GOLDBERGER, M.D., MPH
DIANNE MURPHY, M.D.
RIGOBERTO ROCA, M.D.
NANCY SILLIMAN, Ph.D.

UNIMED:

ROBERT T. DUDLEY, Ph.D.
SHELLEY GORDON, M.D., Ph.D.
CHERYL GRAHAM, M.D.
HOI LEUNG, Ph.D.
NESTOR ROHOWSKY, M.S.
ROSEMARY SOAVE, M.D.

I-N-D-E-X

I-N-D-E-X (Continued)

P-R-O-C-E-E-D-I-N-G-S

(8:01 a.m.)

CALL TO ORDER

CHAIRMAN HAMMER: Good morning. I'd like to call this session to order. I'd like to welcome the sponsor, Unimed, the panel members, and agency members.

Today we're going to consider the application of nitazoxanide, or Cryptaz, for the treatment of diarrhea associated with cryptosporidiosis in HIV-infected individuals.

I'd like to begin by having the panel members introduce themselves for the audience and for the transcript record. I'll begin on my left with Dr. Mathews.

DR. MATHEWS: Chris Mathews, Department of Medicine at UC-San Diego.

DR. SELF: Steve Self, Fred Hutchinson Cancer Center, University of Washington.

MEMBER FEINBERG: Judith Feinberg, University of Cincinnati.

MEMBER HAMILTON: John Hamilton, Infectious Disease, Duke University.

CHAIRMAN HAMMER: Scott Hammer from the Beth Israel Deaconess Medical Center and Harvard

Medical School in Boston.

EXECUTIVE DIRECTOR STOVER: Rhonda Stover, FDA.

MEMBER LIPSKY: Jim Lipsky, Clinical Pharmacology, Mayo Clinic, Rochester, Minnesota.

MEMBER MASUR: Henry Masur, our Critical Care Medicine and Clinical Center, NIH.

DR. ROCA: Rico Roca, FDA.

DR. SILLIMAN: Nancy Silliman, FDA.

DR. GOLDBERGER: Mark Goldberger, FDA.

DR. MURPHY: Dianne Murphy, FDA.

CHAIRMAN HAMMER: Thank you.

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

CONFLICT OF INTEREST STATEMENT

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

"Based on the submitted agendas for the meeting and all financial interests reported by the participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by

the participants present no potential for a conflict of interest at this meeting.

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

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

CHAIRMAN HAMMER: Thank you.

Dr. Mark Goldberger will give the FDA introductory remarks.

FDA INTRODUCTORY REMARKS

DR. GOLDBERGER: First of all, I would like to welcome everyone: Dr. Hammer; the Advisory Committee members; our invited consultants; the company, Unimed; and all of the other participants in the audience.

I would like to thank the company. This has obviously been very challenging to put this application together. This is the first application for cryptosporidial diarrhea ever to come before the

agency. And it's obviously been a lot of work. We would like to thank them for making this strong effort.

As I just noted, this is the first application for this indication. And, although that obviously produces opportunity, it also leads to multiple challenges. There is uncertainty in this setting regarding endpoints and methods of analysis, some of which you are going to see reflected in the presentations over the next hour or two. And I think the advice from Committee members will be crucial in thinking about some of these issues.

We would anticipate due to the fact that there really are no therapies for cryptosporidial diarrhea or for related situations of refractory diarrhea in patients with HIV other applications that may come in in the future. And giving us some good indication of your thinking as you look at the data will be very helpful as we give advice, both in this particular setting with this application and in applications that may come in in the future.

Other challenges include the fact that the design of the studies here are essentially historically controlled. That is certainly permissible under FDA regulations. Nonetheless, one

always looks at the historical controls to understand how applicable they are to current-day practice.

Inevitably, this will produce some issues in terms of, again, evaluating data. And, again, we would look to the Committee for their opinion and advice about how to approach this.

Finally, we would obviously like a drug in this situation that would produce a cure or a complete response. Yet, we also recognize that a drug with a lesser effect may be valuable, particularly in circumstances where patients do not have options.

Evaluating drugs in that situation with lesser effects, particularly if the disease in question may have some variability, can be quite challenging. And this is an area, again, where we are extremely interested in getting the advice and comment from the Committee.

Thank you.

CHAIRMAN HAMMER: Thank you.

I'd like to turn now to Dr. Robert Dudley, who will open the Unimed presentation.

UNIMED PRESENTATION

INTRODUCTION

DR. DUDLEY: Good morning. My name is Dr. Bob Dudley, and I serve as Unimed's Senior Vice

President of Clinical Research and Development. We are here today to discuss data collected and analyzed in support of nitazoxanide, our trade name Cryptaz, for use in treating cryptosporidial diarrhea in individuals with advanced HIV disease.

The data that I and others will present today demonstrate that nitazoxanide is, in fact, associated with a beneficial effect in patients suffering from a particularly devastating illness, one which has not responded well to any therapy, at least until now.

At the outset, I want to thank and extend my thanks to Dr. Goldberger and his colleagues at the FDA. As he said, this has been a challenge to FDA, I think for both parties, but the FDA has been extremely helpful in giving us advice that dates back two years and has been particularly helpful in the past several months as we have worked through several issues.

Many individuals have been heavily involved in the preparing of the NDA and have also been a part of creating today's presentation. These individuals bring a wealth of experience, not only in medicine but in statistics and other areas. And they will be available I believe this afternoon or this morning, as the case may be, for questions that would

be generated from the Committee.

I would like to publicly thank each of those individuals for their work and commitment on this project. And they are listed here; a few people of note, at least one, Dr. Rossignol, who is actually the inventor of the compound.

The presentation outline for this morning will follow this schedule. After a fairly brief introduction by me with an overview of NTZ, Rosemary Soave will follow. Dr. Soave is an Associate Professor of Medicine at Cornell Medical College and is a recognized expert in the field or area of cryptosporidiosis, particularly in AIDS patients.

I will come back and present the safety and efficacy trials that have been proffered in support of the application. I will be followed by Dr. Shelley Gordon, who is an infectious disease expert from San Francisco and who will share some of her own experience in treating patients with NTZ. And then Dr. Rosemary will close with some comments on benefit/risk.

NTZ OVERVIEW

DR. DUDLEY: The indication sought for nitazoxanide is as follows; that is, NTZ is indicated for the treatment of chronic diarrhea due to

Cryptosporidium parvum in AIDS patients with a CD_4 count less than 200 per cubic millimeter.

I might add here that orphan drug designation has been granted by the agency for the use of nitazoxanide in all immunocompromised patients, although today's application focuses specifically in patients with advanced HIV disease.

There are several data and public health-driven reasons that NTZ merits approval, in spite of the obvious fact that fairly nontraditional studies have been used to demonstrate beneficial effect, not without precedence but certainly not the norm.

This is clearly a devastating disease. It is hard to imagine in some ways how individuals live with this for as many months as you will see many have prior to entering into this trial.

As you will see, we have demonstrated about a 50 percent response rate, which we think is clinically meaningful in a patient population as sick as those in our studies.

Why does nitazoxanide merit approval? First, there is a substantial improvement in their diarrhea with use of NTZ. We will demonstrate that its use; that is, NTZ's use, leads to clinically

meaningful improvements in: quality of life, parasitologic profile, body weight loss, and the ability to basically function when you look at all of these in an integrated setting that are at one's work, home, and in the social environment. NTZ does have a very favorable safety profile in patients with AIDS. Fourthly, the regulated use of NTZ is clearly in the best public interest.

As we are all aware, cryptosporidiosis is serious and life-threatening. And that poses a significant public health risk for immunocompromised patients.

The health and quality of life consequences of cryptosporidial diarrhea in these patients are clearly devastating. And, as Dr. Goldberger mentioned in his opening remarks, there is no approved treatment for this chronic diarrhea.

And, finally, when all is said and done, we stand by the fact that we think that the risks associated with the use of NTZ are far less than those associated with its potential benefit.

This slide summarizes the basis for approval. Effectiveness data and safety data will be presented from three open-label trials in the United States. And I'll discuss each of these in some detail

in just a moment.

We've conducted subset analyses as additional techniques to demonstrate drug effect. We also pooled the data, as was mentioned at the outset, and compared this data with what we think are the best available placebo data for comparison, that data coming from two studies: ACTG 192 and Pfizer Study 143. I'd like to publicly thank both the ACTG Pfizer. for graciously providing us access to this data. And, then, finally we'll demonstrate for you this morning that NTZ is, in fact, safe.

So how did we come this far in NTZ's development without the kind of placebo data that clearly the Committee, the FDA, and Unimed would like to have? And I think the answer rests on these two slides, at least largely in part.

Our original plan was certainly always to conduct a placebo-controlled study of NTZ in patients with advanced HIV disease who were suffering from cryptosporidiosis. And we worked closely with ACTG to work on the protocol and initiation for this study, that study being 336, which was initiated in January of 1997. However, after 15 months of effort with numerous centers across the U.S., only 10 of 60 patients have been enrolled. And a decision has

recently been made to close that study as of the 15th of May.

One of the primary reasons I think for the failure of this study, in addition to the fact that therapy has changed a bit, has been the fact that the conduct of a placebo controlled trial in this patient population has basically become impossible and I think will be fairly impossible moving forward. And there are three primary reasons.

There are ethical issues involved in the treatment of these patients who are so seriously ill with a placebo, even for small periods of time. I think the ACTG study is a perfect example of patients not being willing to spend three weeks on placebo.

Secondly, NTZ, for a variety of reasons, has become on the street the de facto drug of choice. And, quite frankly, its availability is quite widespread across the U.S., particularly in major metropolitan areas. That is, in part, largely because of the availability of imported NTZ from Mexico.

With this problem and in conjunction with the FDA, Unimed has worked to develop a plan for the use of open-label data in support of safety and efficacy for nitazoxanide. And there was an agreement that we would attempt to look at the best possible

comparison of NTZ data versus historical control data sets.

Unimed's effort has resulted in the access to two placebo data sets: one from ACTG 192, which was a placebo-controlled study of paromomycin; and Pfizer 143, which was a placebo-controlled study of azithromycin. The only available data from these studies was at the time point of three weeks, and we were only allowed access to the placebo data, for obvious reasons.

Obviously this data is not without its problems. But, in spite of that, I think that there is sufficient data from these two and, arguably, the best possible placebo data sets for legitimate comparison as to historical control data to the data that we have derived from the NTZ studies. And when this is done, one sees that Unimed actually has a much better response than placebo.

I'd like now to focus on the drug itself before I turn the podium over to Dr. Soave for her presentation. This is nitazoxanide. It is a nitro-thiazolyl benzamide.

Those of you who are pharmacologists, like myself, appreciate that this is aspirin and this is a metronidazole-like compound. The bond in between the

primary moieties here is actually very stable in plasma. And so this molecule basically stays intact.

As a class, as an anti-infective, it has broad-spectrum activity against a host of antibacteria. And it has also a very broad spectrum of action against host of anti-parasites: nematodes, cestodes, trematodes, a whole variety of parasites. And, in fact, its use outside the U.S. has been primarily studied for these other indications. Its mechanism of action is currently unknown.

Pharmacologically, NTZ is very rapidly de-acetylated by esterases in the plasma. It's so fast that one can never actually track parent compound, when, instead, it is able to track the desacetyl-nitazoxanide or, in the materials provided to the Advisory Committee, tizoxanide.

About two-thirds of the doses excreted fecally based on carbon-14 studies and a third in urine, presumably as the glucuroninite conjugate.

I would like to now introduce Dr. Soave, who will make some comments about cryptosporidiosis itself as well as discuss the difficulties in conducting clinical trials in this patient population.

DR. SOAVE: Thank you very much, Dr. Dudley.

CRYPTOSPORIDIOSIS OVERVIEW

DR. SOAVE: *Cryptosporidium* was first described in 1907. And for nearly three-quarters of a century, this organism was considered rare and commensual, not a pathogen for humans. It took the profound immune defect of AIDS to so amplify this disease that physicians finally took note of its existence in the early 1980s.

In the 1980s we realized that cryptosporidiosis is a devastating complication for patients with AIDS. And in the 1990s with the Milwaukee outbreak, we realized that this parasite is globally a public health menace.

What I'd like to do this morning is to go over some of the salient features of the biology, epidemiology, and clinical characteristics of this parasite with the hope that I could lay some of the guidelines for evaluating the NTZ data that we are being asked to review here today.

If I may have the -- this is the *Cryptosporidium* oocyst. In addition to its small size, -- it's about approximately four microns in diameter -- it also has another very unique characteristic in that it is very environmentally resistant.

In fact, the phrase "environmentally resistant" has taken on new meaning with respect to *Cryptosporidium* in that this organism, withstands many types of disinfectants, particularly the common ones used, such as chlorine.

Just to give you an example, the chlorine inactivation contact time for *Cryptosporidium* is 640 times that for giardia and 640,000 times that for e. coli. Said a different way, in the laboratory, when we want a pure suspension of *Cryptosporidium*, we take stool and mix it with undiluted Chlorox. And we end up essentially with pure infective oocysts of *Cryptosporidium* and not very much else.

Now, when *Cryptosporidium* is ingested, it undergoes excystation to release four motile infective sporozoites, which, unlike the oocysts, are very fragile and immediately need to attach to an intestinal cell and be interiorized in order to develop and grow.

In order to understand how *Cryptosporidium* causes such profound, persistent disease in patients who are immunodeficient, we need to understand a couple of salient features with respect to its life cycle. *Cryptosporidium* life cycle is monogenous. All of it occurs in one host. And it basically has an

asexual and a sexual phase.

The sporozoite implants on the intestinal cell and develops into a schizont, within which merozoites are formed. These merozoites are indistinguishable from the sporozoites and have the unique feature that they can immediately reinfect the same host and set off the cycle of auto-infectivity within the same host.

Alternatively, these merozoites can enter the sexual phase of the life cycle, differentiated to micro and macrogamonts. Fertilization occurs, and oocysts are formed. And a certain percentage of the oocysts, thus formed, can also reinfect the same host.

Thus, you have multiple areas for auto-infectivity. And this imparts to this organism a tremendous reproductive capacity, such that patients who are infected with this parasite have intestines that are literally covered with these organisms.

So there are really three features of this parasite that suggest to us that definitely *Cryptosporidium* is here to stay. It is ubiquitous, found in five classes, all five classes, of animals as well as in humans. It has a tremendously high reproductive capacity and impressive environmental resistance.

When we look at histopathologic sections of *Cryptosporidium* attached to the intestinal epithelial cell, it appears that the organism is disappearing right in front of our very eyes.

(Laughter.)

DR. SOAVE: It appears that the organism is loosely attached to the intestinal wall. But, in fact, *Cryptosporidium* maintains a very special relationship with the intestinal cell that also is unique.

The cryptosporidial organism is interiorized by the intestinal cell. The intestinal cell wraps a membrane around it. And the organism attains an intracellular but extra-cytoplasmic position.

This is very different from most of the organisms that we have studied. And we don't know whether this peculiar location actually is protective for the parasite in terms of making it inaccessible to any of the chemotherapeutic agents that we administer to *Cryptosporidium*.

Now, we know very little about how *Cryptosporidium* causes the disease that it does cause in humans, but the tremendous outpouring of water electrolytes that occurs with this disease is very

reminiscent of mechanisms such as those caused by enteropathogenic e. coli and cholera toxin.

Now let me turn to the epidemiology of cryptosporidiosis. Although we have learned a lot in the past ten years, there are still many unanswered questions.

We know the organism is ubiquitous. It's been found just about every place that it's been looked for. But we really don't know the true prevalence of this disease in any specific populations.

Back in the late '80s, a number of studies were generated in the United States and Europe. And they showed that 11 to 21 percent of AIDS patients in these countries -- these are AIDS patients with diarrhea, now -- had cryptosporidiosis. And the number, of course, was much higher in the developing world.

The problem, again, is that there have been changes that have occurred over time. The prevalence has not been a constant. Certainly we have noticed that there have been decreases.

And these have occurred, for example, when AZT first came out, when behavioral practices started to change in terms of using safer sex, and perhaps

decreasing risk factors, such as contact with contaminated water.

So there has been definitely an evolution over time. Perhaps the biggest change has been the recent one with the initiation of use of highly active anti-retroviral therapy. Definitely the use of protease inhibitors has resulted in a significantly decreased incidence of this disease amongst the AIDS population, but by no means is cryptosporidiosis gone.

Just last week, we heard of a new case that we had in Brooklyn of a woman who is dying of this disease, in spite of the use of protease inhibitors. And over the past six months, we have lost three patients to this disease, again in spite of the use of protease inhibitors. So *Cryptosporidium* is definitely not completely gone because of the different response to these new agents amongst various patients.

Now, in the absence of effective therapy, obviously we have tried to prevent this disease. And in order to do this, we need to know how it's transmitted.

Initially, it was believed that zoonotic transmission from animals to man was the most important way by which this parasite was spread, but

we now know that person-to-person contact and transmission through contaminated water and food are probably much more important.

Cryptosporidium has been implicated in a number of waterborne outbreaks in the United States as well as in the United Kingdom and also in Japan. Perhaps the one that caught the attention of most of the public was the large waterborne outbreak that occurred in Milwaukee in 1993.

In this outbreak, 403,000 people, over half the population of Milwaukee, became ill. There were over 1,000 hospitalizations and over 100 deaths due to cryptosporidiosis, primarily in patients with AIDS and in the elderly.

This outbreak was estimated to cost approximately $150 million because of health care costs as well as litigation costs and costs to improve the water treatment plant in Milwaukee.

Now, how did an outbreak of such a magnitude occur in the United States? Well, public health officials and others have been scratching their heads for a long time now trying to determine that.

And some of the factors which seem to be operative include the fact that many physicians are still unaware of the fact that *Cryptosporidium* is an

important pathogen. Clinical laboratories do not routinely look for this organism. And in many states, it still is not a reportable disease.

In 1997, Warren and colleagues conducted a study in Connecticut. And they showed that over 75 percent of gastroenterologists, general practitioners, internists, and pediatricians did not order *Cryptosporidium* testing in patients who had signs and symptoms that were consistent with cryptosporidial disease.

Furthermore, over 30 percent of these physicians thought that if they ordered an parasite exam, *Cryptosporidium* would be looked for routinely. And this is definitely not the case. So there has been tremendous under-recognition of this disease, tremendous undiagnosis of the parasite.

In 1997, the United States Environmental Protection Agency mandated that the water utilities in all the states start to look for *Cryptosporidium* in water, in finished drinking water, under the information collection rule.

Now, as a result of gathering this information, -- and, actually, it had already been gathered over the past five to ten years because of many studies done prior to this in looking for

Cryptosporidium in water -- it has been found that there is indeed low-level contamination of drinking water in major cities with *Cryptosporidium*. The big dilemma is that the contamination is low-level. And no one really knows what this means.

Water companies are currently struggling with trying to determine what to advise their consumers to do. Should they tell the immunocompromised host to avoid drinking tap water? This has been the source of major problems for the public in the United States in terms of the safety of tap water.

Now, please note that all of the comments that I have made with respect to drinking water and *Cryptosporidium* also pertain to giardia, but we don't really discuss giardia very much. And that's because there's a known therapy, a known effective therapy, for that disease. And so it really isn't that big a problem.

Now if we turn to cryptosporidial infection and the clinical manifestations of the disease, we know, first of all, that anyone is susceptible to infection with *Cryptosporidium*: the young, the old, immunocompromised, immunocompetent men and women.

However, in the immunocompetent host, the disease is self-limited. And it's primarily localized to the gastrointestinal tract. However, it is a significant illness. And we should realize that if we had an effective agent to treat this disease, we would also want to use it in immunocompetent patients because it really is no different from treating giardiasis or amebiasis in this population.

In the immunocompromised host, *Cryptosporidium* causes persistent infection; that is, progressively more severe, and very often disseminates to extra-intestinal sites.

Now, we usually think of AIDS patients in terms of immunocompromised hosts, but other categories of patients affected by persistent cryptosporidiosis include: those with congenital immunodeficiency; those with acquired immunodeficiency, such as patients who are malnourished or have concurrent viral infections; and, interestingly, those who have been treated with exogenous chemotherapies, such as patients with neoplastic disease and solid organ transplants. And a number of recent studies seem to suggest that perhaps the incidence of cryptosporidial infection in these patients is really rather high and may have been under-diagnosed also in the past.

Watery diarrhea is the most common symptom associated with cryptosporidial infection. And this slide shows a diary from one of the patients that we enrolled in the nitazoxanide 004 study. This was baseline data gathering in the week prior to being enrolled into the trial.

Now, I'm not sure that you can make this out, but basically the patient was asked to track the bowel movements by jotting down the time at which he had the bowel movements and indicating whether they were: liquid, L; solid; or formed.

As you can see, all of this patient's bowel movements were liquid. He averaged about 15 a day. And I'm not sure that you can see the fact that they were evenly distributed between those that occurred in daytime hours and those that occurred during the night, between the hours of midnight and 8:00 o'clock in the morning.

In addition to being frequent, the diarrhea due to cryptosporidiosis is very often voluminous. A lot of water is poured out with each one of these bowel movements, leading to dehydration, which very often requires intravenous replenishment, either at home or the hospital.

The nighttime bowel movements are

particularly disturbing. They result in sleep deprivation, psychological distress, and further exacerbate the diarrhea.

Probably one of the most disturbing features of the diarrhea in AIDS patients, at least as reported to us by our patients, is the fact that it is explosive in nature. It results from a buildup of water and the pathogen in the intestinal tract. And very often patients have very little control over their bowel movements, and they suffer from urgency and incontinence.

This severely limits the ability of these patients to get around. Many of our patients have come to the clinic wearing diapers. The other alternative is merely to be homebound or bed-bound.

This is a very disturbing symptom, especially as the patients get more debilitated and are more unable to take care of themselves in that they have to depend on other people to clean up after them. This is psychologically distressing and results in a tremendous loss of dignity.

The other disturbing characteristics of cryptosporidial diarrhea include: abdominal pain, nausea, and vomiting. These patients, who on average are swallowing about 30 pills a day, have great

difficulty in getting them down and, again, get psychologically distressed when they can't. And these are also very debilitating signs and symptoms of the disease.

Most of the AIDS patients with cryptosporidiosis find it very difficult to ingest any kind of food. Most of the times, any food ingestion will trigger a bowel movement or they lose their taste for food or they actually just feel sick to their stomach and can't eat because of the nausea and vomiting. This, of course, contributes tremendously to the significant weight loss that they already have as a result of their HIV infection.

Now, about 25 percent of AIDS patients with cryptosporidiosis also have documented biliary disease. We don't know whether this is a true prevalence because it's a very difficult diagnosis to make. It involves using invasive techniques. And these are really not warranted in these patients because they don't benefit the patients very much.

Biliary cryptosporidiosis results in a lot of inflammation in the biliary tree. And there are a number of clinical syndromes that result from this, all of them manifesting clinically with more severe nausea, vomiting, and abdominal pain. And there has

been an accelerated mortality associated with biliary disease.

If you look at the Milwaukee outbreak, those patients who had AIDS and cryptosporidiosis complicated by biliary disease, 83 percent of that set were dead after a year of diagnosis, as compared to 43 percent of those who did not have biliary disease.

There have been a number of studies that have shown that *Cryptosporidium* has a significant morbidity and mortality attached to it. One of the more recent studies, Valdez and colleagues, looked at three sets of patients, AIDS with cryptosporidiosis, AIDS patients with chronic diarrhea, and compared them to AIDS patients without any enteritis, and showed that there was a significantly decreased mean survival in AIDS patients with cryptosporidiosis, as compared to the other two groups. And, most importantly, a significant part of those days that they did have remaining was spent in the hospital with a very poor quality of life.

So *Cryptosporidium* has a very important effect on morbidity and mortality. But, on the other hand, there is a spectrum of clinical illness with *Cryptosporidium* that can range anywhere from asymptomatic carriage all the way to the

progressive/fulminant disease that we sometimes see with this infection.

It is clear to us that most of the patients with CD_4 counts under 200 have a version of the disease that is either chronic intermittent, chronic persistent, or progressive/fulminant.

It is very uncommon for patients with CD_4 counts under 200 to have spontaneous remissions. Spontaneous remissions have been seen. They have been rare, and they have been most often associated with initiation of either anti-retroviral therapy or other immunomodulator therapy that has, in part, contributed to enhancing the immune function of these patients.

Because this disease is so devastating, there has been a tremendous effort to identify efficacious therapy for patients who are infected with this parasite. And in the past decade, we have jumped from study to study without really catching our breath in between these trials. And at the New York Hospital, we have conducted 11 clinical trials for cryptosporidiosis in AIDS since 1985.

In these trials, we enrolled over 350 patients. We have looked at anti-therapeutic agents that consisted of chemotherapeutic agents, immunomodulatory agents, as well as veterinary agents.

Four of the trials have been ACTG-sponsored.

And I must say that from this experience with all of this trial work with cryptosporidiosis, we have learned a great deal about the disease and a great deal about the problems related to conducting clinical trials for *Cryptosporidium*.

There are two salient features that need to be pointed out immediately. First of all, most of these trials were conducted with very little or no preclinical data in hand. We literally went from veterinary agents used in animals to giving them to humans because of the absence of preclinical data.

And the reason that we have very little preclinical data is that there is no good animal model of the disease, nor is there a good *in vitro* way to cultivate the parasite and do drug testing prior to going into clinical trials in humans.

Thus, a lot of these studies had to be studies in which we answered all of the questions related to a particular agent: what is the appropriate dose, what are the adverse effects and whether it's efficacious. They were literally dose-finding pharmacokinetic Phase I/II studies all wrapped into one because we had very little opportunity to determine whether something was

efficacious.

The second important point is that the first seven clinical trials that were conducted were all placebo-controlled trials. By 1993, it became very apparent to us that we would no longer be able to do clinical trials that were placebo-controlled for patients with AIDS and cryptosporidiosis.

We had great difficulty in finishing the paromomycin trial because paromomycin was readily available. Although there were plenty of patients to enroll, it was really very difficult to tell a patient who had this disease in its severe form, to ask them to enroll in a trial where they would postpone getting a potentially effective agent for as long as perhaps three weeks.

This is three weeks of suffering that most patients who are in this condition and have numbered days ahead of them are really not willing to do. They would just as soon go on the drug immediately if it is available. And that is really understandable.

Thus, it has become apparent to us that it is very difficult to do placebo-controlled trials, if not impossible. Many physicians and patients feel it is totally unethical.

Our fears were really borne out recently

with the closure of NTZ, as Bob Dudley mentioned. This study will be closed after having enrolled only ten patients.

And here we have two complications. One is that NTZ is readily available from Mexico. And the second complication is, of course, that there is a decreased incidence of the infection.

The patients that were available to be enrolled in this trial were indeed very, very ill. And, again, it was very difficult to put them into a placebo-controlled trial.

So why has it been so difficult to find a drug that works for this parasite? Well, there could be some parasite factors. Perhaps this oddball parasite lacks metabolic pathways that are targeted by most of the chemotherapeutic agents out there.

Perhaps its unique location under the intestinal cell makes it inaccessible to chemotherapeutic agents. But I think most importantly is the fact that the patients that we have been studying really have overwhelming disease. It is very likely that the lack of therapeutic efficacy in these patients could very well reflect their profound immune defect, as opposed to merely reflecting the absence of drug activity.

Let me just show you the baseline disease-specific characteristics for the 30 patients that we enrolled at Cornell in 004 nitazoxanide trial. As you can see, they were rather young, mean age of 39. They were about 5-foot-8 and weighed 140 pounds on average. And this was about 23 pounds less than what they weighed before the onset of cryptosporidiosis, which averaged 15 months at the time of entry into the study.

Most of these patients had other opportunistic infections. And their CD_4 counts were way below 50. These are not the type of patients who spontaneously remit with this disease. These are very ill patients, who are anxious to get on any kind of therapy that you can put them on.

Therefore, what we have been doing is we have been taking a subset of patients who are tremendously ill, who are on a fast downward curve going towards death. Their rate at which they're going towards this endpoint is increased by the fact that they have cryptosporidial infection. And what we try to do when we give them one of these agents is to put a brake on this rapid progression towards death.

How can we possibly show effectiveness of any agent in this kind of a situation? Do we have

instruments that are sensitive enough to measure a change? And what kind of a change can we accept as being important and significant given this kind of a situation?

CLINICAL TRIAL DESIGN RATIONALE

DR. SOAVE: Well, clinical trials have been very difficult. And in the remaining few minutes, I just want to point out some of the salient features involved in the nitty-gritty of trial design for these patients.

First of all, it's obviously very important to determine entry criteria and obtain a baseline. And here we often struggle with how much diarrhea and what kind of a parasitologic burden is enough to get someone into a trial.

We struggle with how long people should have cryptosporidiosis. Ideally we'd like to get them into a trial very early on so that they have a chance of responding, but we want to make sure that we don't enroll people who have a chance of spontaneous remission.

Concomitant medications, the panoply of these drugs that patients are on are, of course, very confounding and very difficult to control for. And then there's always the question of how aggressively

to work up for other pathogens, especially those that require invasive techniques, like CMV.

When you try to obtain a baseline in these patients, you're always struggling with the fact that here is a very sick person who is very anxious to get going on a trial. For how long do you ask them to remain ill and record all of their symptoms for you so that you can get a baseline that is really accurate and worth looking at in terms of response?

Then, of course, you have to pick endpoints. And the clinical endpoint most commonly looked at is diarrhea for this disease, but diarrhea is multifactorial in patients with AIDS. It can be due to concomitant pathogens and concomitant medications.

There's always a struggle with determining whether frequency or volume is more important to measure. And, of course, volume is very difficult to measure.

And then, as I suggested before, there's a complex of associated symptoms associated with this disease in patients with AIDS that really needs to also be entered into the equation of whether they're having a response or not.

For this, we devised this associated

symptoms questionnaire, which we administer to every AIDS patient who enrolls in our trials. And you'll hear about the data generated from Bob Dudley in the NTZ trial.

Basically we look at the six categories of symptoms that I mentioned before: nausea, vomiting, abdominal pain, urgency, incontinence, and bowel movements that wake patients up from sleep.

And we grade these according to the impact that they have on the activity of the patients; that is, the severity, and the frequency and come up with a score that we look at over time.

We also asked the patients to tell us whether they think that they're getting better, as compared to baseline, and generate a global assessment of symptoms' score on that basis.

And so when you look at the first patient that we enrolled in our NTZ trial, you see that over the first few weeks, he did have a decrease in bowel movement frequency. This was accompanied by weight gain and a tremendous decrease in the associated symptoms score as well as a perception that he was indeed getting better.

This patient when he first appeared to us was very debilitated, unable to leave the house, and

really was having tremendous problems dealing with the activities of daily living.

He felt so much better after eight weeks on NTZ that he decided to stop the drug and go visit some friends that he had been longing to see for a long time. The disease was re-exacerbated in the absence of taking NTZ. And he took a higher dose and reinduced a remission.

There are a couple of features that are important here. First of all, he did not always meet the criteria that we set forth for deciding that he had either a complete or partial clinical or parasitologic response. But, in point of fact, from the very beginning, he did feel a lot better. And his quality of life changed significantly. And this needs to be taken into consideration.

The second point is that there was a lag in the parasitologic response in this patient. In many patients, we don't even see a parasitologic response.

And this brings us to the second tricky point with respect to doing clinical trials in cryptosporidiosis in AIDS patients. And that is the parasitologic endpoints.

There are many unanswered questions

regarding what is the best technique to use to measure this. We have used the acid fast stain methodology because it is cheap, it is quick, and it is reproducible. It is not very sensitive, and it has its limitations. But our methods can be confirmed using IFA and ELISA technology, which is a little bit more sensitive.

Those latter two techniques, though more sensitive, are not easily adapted to quantitation, which the acid fast testing is. And so acid fast staining has stood us in good stead in terms of being able to quantitate at least partial responses.

The important feature, though, that we need to consider is: What do we expect patients to do in terms of clearing their parasite? Consider two things. In the immunocompetent host, parasitologic clearance occurs at least two to four weeks after clinical clearance.

This lag period can be prolonged in patients with AIDS. And, therefore, if you don't extend your study out far enough, you may not pick up the parasitologic effect.

Also, because of this lag in the parasitologic response, you may pick up a lot of discordance between a clinical response and a

parasitologic response early on.

The second important point to consider is: Prior to the use of protease inhibitors, did any of these patients ever clear any of their pathogens? If you look at patients with pneumocystis carinii pneumonia who were treated for 21 days with trimethoprin sulfa and you did bronchoscopy on them, weren't you very likely to find pneumocystis organisms? And isn't it very likely that if you give amphotericin to someone with cryptococcal meningitis, they will still have organisms in their cerebral spinal fluid after they're given two grams of the drug?

The problem is that AIDS patients can't clear their organisms completely if they don't have sufficient immunity. And, therefore, may be expecting a complete parasitologic response may not really be realistic.

So, in essence, we have a very heterogenous study population with respect to HIV infection, cryptosporidiosis, the panoply of medications that these patients are on, the differences in malabsorption that they're suffering, and their inability to actually get the medications that they're taking to the places you want to go.

This heterogeneity results in creating the need for a sample size that is sufficient to demonstrate a 20 percent difference in outcome with an 80 percent statistical power. It's very difficult to get a sufficient number of patients to overcome the problem of heterogeneity.

And then, of course, the subjects are very ill. This makes it very difficult for them to comply with taking the medications, recording the data, and also with going into placebo-controlled trials if that is what we want them to do.

So, in summary, cryptosporidiosis is definitely an unmet medical need. It's a debilitating and life-threatening disease that causes public health problems. And there is no currently approved therapy for this disease.

I submit to you that the design used to study nitazoxanide probably represents the best we have for the study in cryptosporidiosis. And the results that were obtained using that design were very strictly controlled, even in the absence of a placebo. So I think, from my point of view, that the data is quite strong in showing its efficacy.

So I'll now turn the podium over to Bob Dudley, who will show you the NTZ data.

SAFETY AND EFFICACY TRIALS

UMD-95-004, UMD-95-009A, UMD-95-009B

DR. DUDLEY: The placement of NTZ within a chronological context I think is important relative to today's discussion. I'd like to do that now.

In the late Summer of 1995, data had become available from Mali, West Africa suggesting that NTZ was, in fact, effective against cryptosporidiosis in about 15 AIDS patients. Each of these patients was terribly infected with a host of other parasites as well, which NTZ often eradicated, at least eradicated those parasites. But there was evidence of clinical effect.

We had worked with Romark Laboratories out of Tampa, Florida, from whom we licensed the U.S. rights to NTZ, on this project. And this resulted on a collective effort that initiated a Phase I/II study that I'll discuss momentarily, our study UMD-95-004.

Shortly thereafter and, really, in response to a variety of requests that Unimed had received from physicians in practice for NTZ, many of whom had initiated their own physician-sponsored INDs, we began with FDA's permission to provide drug to those patients through these IND programs.

Eventually we had discussions with the FDA

that suggested perhaps the best approach in this was for the company to initiate a compassionate-use program and fold in the physicians that had their own physician-sponsored IND, which is precisely what happened.

However, in the process of initiating the study, I want to make it very clear today that it was protocol-driven. We have a very comprehensive protocol. And from the outset, we collected data on case report forms and actually conducted this study as though it were your standard study. In other words, this was not just a free giveaway program for these patients.

In February of 1996, I was part of ACTG 336 protocol development team that developed the placebo control study. I can tell you that the discussions that Dr. Soave shared with you a moment ago or the points about designing these trials really came to full appreciation during those discussions. I think Rosemary will remember we had at least 2 2-hour meetings on whether we should collect 24-hour stool samples and how one would transport those across the country.

It was just a very difficult problem in figuring out the design of these studies.

Nonetheless, I think that the 336 design is an excellent design. Unfortunately, we will not see much data coming out of that study.

In April of 1996, nitazoxanide was approved in Mexico, originally for the treatment of a host of more easily treatable parasites, the nematodes, cestodes, trematodes, and the like, and later was approved for treatment of cryptosporidiosis.

This has actually led to a fair amount of importation into the U.S. And, in fact, as I mentioned earlier today, NTZ is quite readily available without looking too hard. And that has had an impact. It has compromised our ability I think, at least with this drug, to conduct the kind of trials that we would like to conduct.

In October of 1996, we began in earnest discussions with FDA to figure out how one might use the data that we were generating from these open-label studies. At the FDA's suggestion, about that time we enclosed enrollment into the initial compassionate-use study and initiated a second study, basically identical in design but in which patients were enrolled at one of two doses.

And then we arrived at an agreement in principle that we would as a team, if you will, look

at how one might use the open-label data as the basis of an NDA. And that has been the challenge moving forward.

The ACTG trial I've already mentioned was initiated. And, unfortunately, they only enrolled a small number of patients. Almost all of these patients are terribly ill, most hospitalized, as I understand.

The NDA through all of this process was submitted in December of last year. And just so that you are aware of what is going on to our neighbors to the north, an NDS was submitted for Canadian approval by Biochem Pharma, who was our licensor in Canada, recently.

This slide summarizes the Unimed's clinical trials of NTZ. And there are three primary studies in nature, the two largest being 009A and B.

004 was a Phase I/II dose escalation study in AIDS patients with doses ranging from 500 to 2,000 milligrams per day.

009A was the initial compassionate-use study that I described to you just a moment ago. Patients were started at an initial dose of 1,000 milligrams per day. And that data cutoff was the 15th of October in 1996. And that was included in the

original NDA submission.

009B, which is still a study ongoing and we continue to enroll patients in that study, is a randomized, open-label study in AIDS patients, here looking at 1,000 versus 2,000 milligrams per day. And the data included in the materials provided to each of you on the Committee and to the FDA is through the 20th of February this year.

I might add that those studies comprised a total of 228 patients with cryptosporidial diarrhea, all of whom had significant HIV disease with the exception of two immunocompromised patients that did not have HIV but were allowed to be enrolled in the study because of their desperate plight.

This slide summarizes the measurements used to determine effectiveness. They fall into two standard categories. The primary measure was stool frequency, collected both as liquid and total, reported as liquid and total. We actually collected it as liquid, soft, and formed.

The secondary parameters included the parasitology; that is, looking for the oocysts in stool. We looked at body weight. And then we looked at several key quality of life parameters that Dr. Soave has shared with you just a few moments ago.

This slide summarizes the protocol synopsis for Study 004. This was a study conducted at two sites: at the New York Hospital Cornell Medical Center, under Dr. Soave's direction; and in San Francisco at the Kaiser HIV Research Unit, under the direction of Dr. Fessel.

Its primary objective was to better determine the pharmacokinetics of NTZ at various doses. Its secondary effort was to look at evidence of safety and efficacy, again looking at the standard parameters that we discussed just a moment ago.

From a design perspective, it was an ascending dose, open-label study. The doses ranged from 500 to 2,000 milligrams per day in divided doses except on the initial day of treatment, where all of the doses were given as a single dose to look at the pharmacokinetics over a several-hour period.

The initial treatment phase was four weeks, after which depending upon the patients' response, there could, in fact, have been escalation and was escalation to higher doses.

A total of 30 patients were enrolled, 28 evaluable, 7 evaluable per group. They were enrolled sequentially beginning at the lowest dose and graduating upward. Quality of life was assessed by

questionnaire, and diaries were kept for antidiarrheal and stool frequency use.

The inclusion criteria are as you would expect. And, really, these are the lessons learned, if you will, from many of the studies that have gone before us.

These patients had significant HIV disease with CD_4 counts well below 200. They had chronic cryptosporidial diarrhea, at least defined for entry as at least four or more stools per day. They needed to have been on stable anti-retroviral or antidiarrheal regimens. They were screened for the absence of the other parasites, and there needed to be a parasitologic evidence of *C. parvum*.

This slide summarizes the demographics. The primary conclusions from this slide are as follows. Most of the patients were male and white. Their average age was 39 years of age.

And their CD_4 count, as you will see, averaged 25. And one could almost see a sequential progression from the 500 to the 2,000 dose, with the 500 having the low CD_4 counts and those that enrolled later in the study having the highest. But, nonetheless, all of these patients are significantly below 50 and not likely to be the spontaneous

remitters that you might see in other patient populations.

With respect to disease characteristics, the majority of these patients had longstanding cryptosporidial diarrhea with an average of seven bowel movements per day. You'll forgive me if I round that out, but I don't know what .7 of a bowel movement is.

The oocyst rate ran on a scale of zero to four to the three level in almost all of these patients. And the weight loss was substantial, on the order, as Dr. Soave mentioned earlier, of 23 pounds during the course of their cryptosporidial disease.

This summarizes very briefly the pharmacokinetics, which was provided in some more detail in the briefing documents. Again, the pharmacokinetic parameters are based on tizoxanide, which is desacetyl-NTZ; has a half-life of about two hours. And, although variable, the C_{max} and AUC over the initial 24-hour period increased in a dose-related manner.

When one looked at the day 14 pK, there was no evidence of accumulation. And, although not shown here, the protein binding in patients with HIV disease is about 95 to 99 percent.

Before talking about the clinical responses, I think it's important to go over some clinical response definitions. And there were three. In this particular study, a very conservative complete response category was used. That is, patients needed to have gone from whatever they were having with respect to their diarrhea to one to three predominantly formed stools per day.

A partial response was at least a 50 percent reduction in stools but still greater than 4. And no response was less than a 50 percent reduction and, again, still greater than 4.

I might point out that, again, these are based on diaries. And we did collect data from liquid, soft, and formed to have that information.

This shows the clinical response by dose. I'll point out that we've included both the partial and complete response because as we move forward, we've combined these into what in the future studies is a complete response.

One will note initially that the 1,000-milligram dose appeared to be substantially better than the others, having 5 of 7 patients, the majority of whom were complete responders, that there was no clear dose-response; that is, the response at

the higher doses, at 4 weeks. It was certainly less than one saw, even at the 500-milligram dose.

The reasons for this are not totally clear. Suffice it to say that we are working with heterogeneous groups of patients. And the time point, four weeks, I think is important as well.

Now, if one looks at the clinical response across all doses -- and the rationale for this is that at four weeks, these patients had the opportunity to dose-escalate and, in fact, essentially -- not essentially. I think all of the patients at 500 went to 1,000 and some at 1,000 went to slightly higher.

What one does see is that one looks at responses, the percent of patients responding for, again, partial and complete, that the last observation carried forward data through week four. This collects any patient, no matter how long they have been on the drug. It was about 31 percent. And that was about seven percent higher as one went out an additional four weeks at higher doses.

We think this is at least a slight indication that both duration of therapy and dose in this particular study needed to be higher than 500 milligrams and 4 weeks, respectively.

Parasitologically, we also studied these

patients. We were looking for eradication, substantial reduction, or persistence. Eradication was stool-negative for *C. parvum*. Substantial reduction was a significant decrease by at least two grades. And persistence was no change or an increase.

And the scales again ran from zero, four, to none. And these are based on the acid fast stain of stool samples. And these are the number of oocysts per high-powered light microscope field.

This, then, shows the response at four weeks, either for the patients that eradicated or had substantial reduction. And one can see that, again, there does not appear to be a significant difference between doses at this time point, where 2 of 7 patients in each of these 1,000 to 2,000 milligrams responded.

Perhaps more notably, again, with higher doses, again, these patients could have dose-escalated. And many did at week four to week eight.

One sees a doubling in the parasitology response. And by the end of study with a median duration of about six weeks, one sees that there was almost a 40 percent response rate for parasitology; again, consistent with Dr. Soave's comments and

certainly the observations of others that longer-term therapy with compounds like NTZ was probably justified.

This slide shows the effect of NTZ on weight. The take-home message from this slide, what I think we should be left with, is that over time weight was at least maintained. And I think that is a critical factor for these patients.

What about quality of life? I want to spend just a moment on this because the quality of life assessments used in this study were, in fact, the same instruments that we used in the studies 009A and 009B.

Again, it was questionnaire-based. And Dr. Soave showed portions of those questionnaires to you. Each patient was asked to evaluate six disease-related characteristics according to their debilitating effect or according to their frequency in each visit. These included: urgency, rectal incontinence, bowel movements that woke the patients from their sleep, abdominal pain, nausea, and vomiting.

A couple of points are important here. One, these kind of form a constellation, if you will, an integrated picture of the symptoms associated with

the disease. Secondly, not every patient has every symptom at every visit. And that's important as well.

I'll take a brief moment to orient you to the graph we have of the various doses at initial therapy for each of the four groups here. And this is data again at four weeks for the various parameters that we just discussed.

The top gray bar represents the percentage of patients that had any debilitating effect related to that particular symptom. In the case of urgency, essentially every patient across every group had problems with urgency.

What one wants to see in response to therapy is a movement of the bars to the left; that is, a regression towards zero. And, in fact, one does see that, even at the four-week data. And some of it is fairly striking. If you look at rectal incontinence, bowel movements that awoke the patient from sleep, abdominal pain are some that responded.

The conclusions for 004, then, are as follows. There was a trend toward greater clinical and parasitological response with longer duration of therapy and at higher NTZ doses, above 500; maintenance of body weight over the treatment period; and a decrease in symptoms associated with

cryptosporidial diarrhea.

Importantly from a safety perspective, there were no adverse events, serious adverse events, related to NTZ. And the quality of life data does suggest that the higher initial -- there was a slight suggestion at the higher doses that 2,000, for example, 2,000 milligrams might be slightly less well-tolerated.

Now, at the same time Study 004 was underway, we initiated 009A, which was the initial compassionate-use study. And that study is summarized here.

This was a multi-center study, it turns out, in about 75 sites across the United States that ranged from small clinical group practices to the largest medical centers in the country.

The objectives were: to provide initially compassionate treatment to patients with AIDS with cryptosporidiosis, assess efficacy, and determine safety and tolerability.

The design, as you know, is open-label. The initial dose was 1,000 milligrams given 500 milligrams b.i.d. for at least four weeks. And from this, we were able to establish a database of 139 patients as of October of 1996.

The primary inclusion criteria are very similar to what were used in 004, in Study 004. The patients had to have had AIDS, very low CD_4 counts, chronic cryptosporidial diarrhea. It's notable that we did allow microsporidiosis here because several patients were co-infected with that.

Perhaps most important is to point out that these patients needed to have been refractory to other putative cryptosporidiosis therapies; for example, paromomycin, clarithromycin, azithromycin, and the like. The point about ineligibility is that we did not want to enroll patients in this study prior to the enrollment in Dr. Soave's study.

We assessed efficacy: by looking at liquid and total stools on a daily basis; and, secondarily, by examining body weight, quality of life, and quantifying the oocysts.

Safety was reported based on investigator-initiated adverse event reports as well as laboratory evaluations, either by the investigators or in chart reviews conducted by Unimed based on the case report forms.

Now, complete response in this study is in many ways perhaps a more realistic endpoint than what we were looking for in the 004. We've come to

appreciate and the FDA would agree; in fact, we had some discussions about this, that asking the patient to come completely to one to four stools while clearly desirable in this patient population may not be achievable in the short run.

So we established: a complete response in 009A and in the next study as at least a 50 percent reduction in average daily stool count compared with baseline; a partial, 25 to 49 percent, response; and a failure, any response that was not either a partial or a complete responder.

This slide summarizes a portion of the demographics and disease characteristics. Again, the vast majority of patients were white male, men comprising 92 percent. And of those, of the total, 77 percent were white.

The age, again, was remarkably consistent with what was seen in 004. And the CD_4 counts were about 20. And these are very sick patients that came into this study; again, many of them, most of them, having failed at other therapies.

The purpose of this study flowchart is simply to demonstrate that we made a very significant and we think successful effort at collecting data. Again, this was a serious protocol with a lot of case

report forms.

And this simply shows that the data was collected on a regular basis over the period patients were on study. Notably, cryptosporidial oocyst confirmation stool was not a requirement for entry within the few months prior to baseline.

The reason for this was that many patients had been previously diagnosed based on that endpoint. And we wanted to give the physicians an opportunity based on the symptomatology, basically more of the real-world situation, to enroll those patients that in their clinical judgment were suffering from cryptosporidiosis. We did collect lab safety data and, of course, reviewed adverse events.

Now, listed here are the analyses of the primary endpoint; that is, stool frequency, for the data set 009A. And what we have tried to do is paint a picture where we have a very large patient population; that is, 139 and perhaps very large and not the right descriptor, from which we were able to do some subset analyses that not only confirmed our confidence in the data but also gave us additional pictures or additional demonstrations of drug effect.

In all of the studies, you'll see LOCF on the slides, which stands for last observation carried

forward. It's a statistical method which includes all patient data through that particular follow-up visit, whether or not they were a responder or not. If a patient was on NTZ for one day at a particular dose, it would be included in the LOCF at eight weeks at that time point.

The per-protocol subgroup took a subgroup of patients for which we really had substantial evidence of baseline diarrhea, documented *C. parvum* by laboratory evidence in their stool within two months of baseline, and data at baseline in at least one post-baseline visit.

And then, finally and quite serendipitously, we had some patients who initiated treatment, stopped therapy, and then came back on therapy. And so we have challenge/re-challenge data, which is particularly in my view strong evidence of drug effect.

I'd like to now go through the intent-to-treat analysis; that is, the analysis on the 139 patients in 009A. This slide summarizes the clinical response.

One can see here again partial. The partial responder portion of this bar is in orange, and the complete responders are in blue for liquid and

total stools through week eight.

And in this case, we had 114 patients in this sample. The clinical response rate is right at 60 percent for both liquid and total stools. About 45 percent were in the case of liquid complete responders. And, arguably, liquid is more important in the discussion today than total.

This slide summarizes the mean change from baseline in stool frequency by week. That is, what is the trend these patients are experiencing in their stool frequency?

And, as one would hope to see, over time there is, in fact, a decrease in the number of liquid and total stools, consistent with some effect of drug. The liquid are the purple bars, and the total are the bars in more the aqua color.

One looks at all of the data available again for those 114 patients that we saw in the last slide and compares this response, which is about a little over a 3-decrement -- roughly a decrease of 3 stools per day for each of these 3 categories. This is highly significant compared to baseline.

Well, what does that mean? Not to be trivial, but so what? What is the benefit to the patient? In one way, it should be obvious. The

treating diarrhea is actually going to improve the patient's clinical situation.

But if you talk to these patients, they're also interested in the formation of softer and formed stools. And we took a look at that data as well.

This is the baseline data of 125 patients, of which only 18 percent had formed or soft. Over time, as this component decreased, you saw what you would expect to see: an increase in the number of formed and soft.

This slide summarizes body weight. Again, the message here, the conclusion here, is that over time, there was a consistent maintenance of body weight and, actually, a slight increase over time such that at about week eight, as a group, this patient had about one kilogram increase in body weight. And each of these bars represents about 60 to 70-plus percent of the patients in that group of patients.

How about debilitation scores? This shows the debilitation scores. Again, the gray bar, as in the earlier study, is the baseline. The pink is the last observation carried forward data through week eight. And one again sees that there is improvement essentially in all of these parameters with respect to the debilitating effect of the symptoms that these

patients were dealing with.

I'd like to move now to the per-protocol analysis or analyses. Again, this was a subset of patients that met key inclusion criteria of four liquid stools per day, documented *C. parvum*, and they had to have a baseline visit and a visit at at least one subsequent post-baseline time point.

We used it as an internal consistency to check our own data. That is, did we see the same response in the per-protocol patients as we did in the intent-to-treat? The answer is yes, unquestionably yes. The results are similar for stool frequency, clinical response, and oocyst quantification.

This shows, in fact, the clinical response comparing the intent-to-treat versus the per-protocol, both for liquid and total stools. Along the ordinate, you have the percent of patients responding.

One can see again about 60 to 70 percent of patients responded either completely or partially, the vast majority again being complete responders. And the same was true for total stools.

Now, there were data, as I said earlier, on some patients who had been exposed to NTZ, stopped therapy, for a variety of reasons, many of whom early on in 004 because as that study was initially started,

we had a cap on how long the patients were treated as we were gathering additional safety data.

So these patients stopped, relapsed, and then started therapy again. And this really provided us with a very serendipitous opportunity to look at what happens when a patient is re-challenged.

And the question obviously is: On re-challenge, does one see the same effect as one did on the initial response to treatment? And what you see is what precisely you would like to see.

This graph shows two side-by-side comparisons for patients for which we had original treatment course data as well as re-challenge data. And the time point between these on average was about a month, four weeks.

If you see, there are five of seven responders that were in that category of partial or complete that had the negative slopes; that is, a downward movement, meeting the response criteria that we have already mentioned. On re-challenge, four or five of those initial responders again responded when they were provided NTZ.

In conclusion, then, beneficial drug effects for NTZ at 1,000 milligrams were demonstrated in this study by: a partial or complete response in

approximately 60 percent of patients; significant decreases in liquid and total stools by 3 to 4 per day; significant reduction in debilitating effects; improvements in oocyst shedding, although not shown here; -- if you look at the ITT group, 48 percent of the evaluable patients had lower oocysts or improved oocyst scores -- stabilization of body weight; and the drug was effective on re-challenge.

This slide summarizes Protocol 009B, which now is identical to Protocol 009A with the exception that we are randomizing patients to either 1,000 or 2,000 milligrams per day to see whether or not there was a clear dose benefit at that higher level.

All of the objectives remained the same as in the other study. And, again, we collected safety based on adverse events reported by the investigator and on laboratory evaluations.

Demographically these patients are remarkably similar to the ones that we had seen in 004 and in 009A. There were 30 patients and 26 in the 2 different groups, respectively. Again, most patients were men and they were white. The mean age was about 30; and the CD_4 again in that 25-cell range.

This shows the clinical response, again reported by the patients on their diaries at last

observation carried forward through week eight. One sees 68 percent of patients in both groups showing at least a partial or complete response. And, again, the blue bars are the complete response, no obvious difference between those two dose levels.

How about stool frequency? This is at the 1,000-milligram level with 25 patients and at the 2,000 with 21. Again, one sees, as one would expect, there is a decrease, a significant decrease, in liquid stools and total as well, but there's not a clear difference between these with respect to the magnitude of that difference.

How about change from baseline over time, again comparing the two doses? For orientation, these are the weeks across the very top here. And under each week are the two dose levels.

So what one wants to look at are in this case under week one, the purple bars compared to the aqua bars or the purple bars compared to one another and the aqua bars compared to one another.

You see again a trend over time for there to be a decrease in the number of liquid stools. And you at eight weeks arrive at the same number as you did before, a reduction of three to four liquid stools per day. It is not evident, however, if you line each

of these up under their respective weeks that there is an advantage to a 2,000-milligram dose.

This shows the effect of treatment on body weight. Again one sees at 2,000 this is the salmon-colored bars compared to the 1,000. When I look at this data, I am not overwhelmed that there is a difference, a significant difference, between these two. Although one might perhaps see a trend towards a slight advantage to 2,000 milligrams, I think that these are quite equivocal.

This shows debilitation scores presented as decreases from baseline. And one sees again, what one hopes to see in these patients is that as their symptomatology with respect to stool frequency improves, so do the symptoms that have been debilitating. And, in fact, you do see decreases in all of these. For reasons unknown, both in this study and in the prior study, the effect of NTZ on nighttime bowel movements seemed to be fairly significant.

In conclusion, again we saw evidence of: beneficial drug effect at both doses, complete and partial response in about 68 percent of the patients, a significant decrease in liquid and total stools by about 3 per day, stabilization of body weight, and a reduction in the debilitating effects. But over all

of these, there really was not a significant difference between the 1,000 and 2,000-milligram doses.

And now to the fun part of today's meeting: the historical control. We've tried to take a very reasonable and common sense approach how we could best avail ourselves of the placebo data that was in the literature or available to us to lay against the NTZ response rate that we observed in our studies.

We used the same NTZ study response criteria as the primary basis of our analyses. That is, we laid our response criteria on top of the data that we had available to us for historical controls.

And, as I'll show you in a minute, we had to convert in the case of the Pfizer data from categorical to continuous data. That is, in the NTZ study and in the ACTG studies that we had access to, our Study 192, the actual values for a certain number of stools per day were collected.

That was not the case in the Pfizer data. It was, instead, a range. So a patient could have had like three to five. And so we did a sensitivity analysis, which confirmed that the best approach was probably to take the midpoint.

The goal over all of this -- and this has been the challenge I think for the agency and for Unimed -- is to look at the fairest comparison and in our case to get the highest number of patients within that placebo group as possible. It's very hard to make judgments when one only has 10 or even 12 placebo patients to which you're comparing data in this kind of patient population.

Now, with those introductory remarks about the methodology or the process that we used, this slide summarizes the published data that we had available to us that provided placebo response rates.

And you'll see that there are three studies for paromomycin -- ACTG 192 is a study of particular importance; there are several others as well -- and then azithromycin, which was Pfizer 143 at the bottom.

One of the important messages from this slide is that if you look back historically, these studies had remarkably small numbers of placebo patients in them.

The two exceptions were: the ACTG 192 trial, which had 18 patients, of which 14 were evaluable; and then the Pfizer 143, which had a fairly large group, the largest of any study, at 41.

Now, I've listed in this column the complete response based on stool frequency. And the other message from this slide, although you'll have to take my word for it, is that the methodology used to assess response differed between these studies.

So the same methodology in the Kanyok study was actually a little bit different than used in the ACTg study for assessing response. Nonetheless, by their definitions for stool response, I think one can appreciate that the response varies from none to about 24 percent. It's hard to put much credence in one of 2, which would be 50 percent.

And that's consistent, actually, with what the ACTG 336 development team decided upon as a reasonable historical control rate. In that study, the rate used to power that study and determine sample size was ten percent.

When we lay our response criteria against the 3-week data, you can see that in the case of the ACTG 192 study and in the Pfizer study, we get response rates, placebo response rates, of anywhere from 20 to 30 percent.

So what were, then, the data sets that we used to compare to one another? We combined NTZ data from 004, 009A, and 009B. We also took placebo data

for the ACTG 192 and 143.

And the key comparison was looking at the combined NTZ two and four-week response versus the combined three-week data from those two studies. And we did that in two ways. We did it on a last observation carried forward, where we just took everybody out to those time points. And then we looked at completers, where we actually had data for each patient at each of the key time points.

The evaluable patients out of these two data sets were defined as follows. They had to have received at least one NTZ dose or one placebo dose. There needed to be efficacy data available at baseline and at week three for placebo or week two and four for NTZ.

We only focused on patients that were on 1,000 milligrams for their initial dose. And we only included patients that were 18 years of age or older. I say that because we did have some patients that came into the study who were children.

The per-protocol group, again, similar to what we discussed a few moments ago, were those evaluable patients. That is, it's a subset of this group that had key baseline characteristics: liquid stools, at least four per day; low CD_4 counts; and

documented evidence of cryptosporidiosis in their stool.

The response definition was singular. In other words, it was only complete response. We did not lay any partial responders against this data. And the definition here was at least a 50 percent reduction from baseline in total stools per day or less than 3 stools per day with greater than 3 liquid stools at baseline.

And here are the responses you see when you do those analyses. Again, if one looks at the percent responding, this is in the evaluable, last observation carried forward. For NTZ at 2 weeks, we saw about a 36 percent response rate. That was in 138 patients, the mean over 138.

At 4 weeks, we had 140 patients in a slightly higher 37 percent but, again, about 36 to 37 for here versus 23 percent for placebo based on an *n* of 56.

Now, when one looks at the per-protocol group; that is, those subjects who would gain entry in a very tightly controlled study if we were to do one today, one sees a substantially larger response in the NTZ group, twice that we've seen to placebo: 43 percent versus 21 percent.

What other pieces of information were we able to glean from this process? Well, in fact, we had oocyst data from some of these patients in these studies. And we asked the question: How many of those patients reverted from positive or progressed from positive to negative in their stool?

And we looked at four weeks versus three weeks. Again, we had a 25 percent response in the NTZ completed patients and a 14 percent response in those patients that had been on placebo.

What about body weight? Again, NTZ consistently maintained body weight, small increases for the two and four-week period. During the same time period in the case of the evaluable patient populations, placebo patients lost about a kilogram of body weight.

And the same response held true but is more pronounced if one looks at the per-protocol group where the placebo patients lost two kilograms over that period at week three versus maintenance at week four for patients on NTZ.

So, in spite of the fact that these are not perfect data sets, I think there has been evidence demonstrated for drug effect. And one looks at that. NTZ does show a better response than placebo.

So there was a consistent trend which favored placebo in the case of the per-protocol patients and a response rate twice that seen. The higher number of NTZ patients converted from *C. parvum* positive to negative. And NTZ again was associated with maintenance of body weight compared to a decrease in placebo patients.

Overall, then, these are the safety conclusions across all of our studies, that, in fact, NTZ treatment is associated with the drug effect, beneficial drug effect. There were decreases in the number of total and liquid stools. About 60 percent of patients had a complete or partial response.

There was improvement in quality of life associated with cryptosporidial diarrhea. There was a maintenance or in some cases slight increases in body weight. There were consistent decreases in oocyst shedding.

And across all of the analyses, whether we looked at the intent to treat, whether we looked at the per-protocol, whether we looked at the challenge/re-challenge, whether we looked at our data compared to placebo, NTZ always comes out with a significant, clinically significant, effect.

I'd like to conclude my portion of the

presentation by reviewing the safety data, after which Dr. Shelley Gordon from San Francisco and Dr. Rosemary Soave will make a few concluding remarks.

This slide summarizes the key safety findings. First, NTZ is generally well-tolerated by AIDS patients at doses up to 2,000 milligrams per day.

Second, no deaths were attributable to NTZ therapy. There was no pattern of organ-linked toxicity with respect to NTZ use, something we'll explore in more detail in a moment but important to point out that, as you know, many of these patients are on a whole host of medications that in and of themselves are associated with clinical laboratory abnormalities, let alone those seen with cryptosporidiosis.

There is some data perhaps when one looks at all of the studies that the 2,000-milligram dose is a little less well-tolerated. But overall I think the data do clearly support the safe use of NTZ in this patient population.

This slide summarizes the available data sources that were used to compile the data. They come from three areas of the world, if you will: the United States. We had access to our own studies, to 228 patients; again, 2 non-AIDS patients but they were

included in the safety analysis.

There are data from 2 Mexican studies, of which there are 88 patients in an ongoing French compassionate-use study, neither one of these studies conducted by Unimed, I might add, giving us a total of 329 in a stacked notation, I see.

Now, allow me to orient you. Well, I'm sorry. I got ahead of myself. This slide summarizes the extent of exposure across the U.S. studies. And again we focused on those studies because that was the most available data and the data for which we had the most comfort with respect to source documents and case report forms.

The starting daily dose of NTZ is listed here across the top and the extent of exposure along the vertical axis. The conclusion that I'd like you to derive from this study is that if one looks at those patients that had been on therapy for at least four weeks that is summarized in this column down, you'll see that that's somewhere between 50 and 60 percent of the patients.

Perhaps just as important are those patients that had been on therapy for more than four weeks; that is, that had been on for greater than two months. And if you add this up and divide it by 179,

you should get about 33 percent, or about a third, that were on therapy for at least 8 weeks.

This slide summarizes the causes of death reported for patients in this study. And I'll take a moment to orient you to this slide because there are several slides like this that will follow.

The body systems are located here. In this case, it's any body system, and then it's body as a whole, digestive, respiratory, following the COSTART terminology. The middle column in this slide causes the reports on the cause of death, under which we have separated out those items that were considered potentially to be related to the study, and then the overall number of patients here. One sees that in this case that 62, or about 27 percent, of the patients died in the course of our studies.

The events are not surprising. If one looks under body as a whole, one sees HIV syndrome accounted for almost half of the deaths, infections and sepsis as well. These are common problems that these patients face.

If you look in the digestive system, again one sees nine patients, or about four percent. I want to point out here that the hepatic failures observed here, none of these were considered to be related to

treatment. Several of these others; for example, the diarrhea, sclerosing cholangitis, are, in fact, not uncommon in patients with cryptosporidial disease as well.

If one explodes -- excuse me. I think there's very little difference. Let me go back one here. Sorry. Okay. If one now looks at the number of patients that are reporting adverse events over the course of our studies, one sees that about 65 percent of patients in our study had some adverse event reported while they were on the trial.

Again, body as a whole accounted for the vast majority of these. And, as you'll see in a moment, again these were related primarily to HIV syndrome. The digestive accounted for about a third again. And these tended to be related to the cryptosporidiosis that these patients had as well.

You see metabolic and nutritional in this category, about 15 percent of patients, are many of the increases in the liver enzymes that were tracked. And then respiratory was the third or fourth highest category here, with 12 percent of patients.

Now, as a whole again there were 65 patients that had an adverse event of some sort. This slide tries to relate that to NTZ treatment. We

combined mild and moderate and severe and life-threatening.

Again, one sees that the vast majority of the events for the body as a whole were not related to treatment but looks at the digestive system, where there were approximately 68. Half of those were at least possibly related. And if one looks at metabolic and nutritional, again you see about a 50/50 split.

This slide summarizes in the same fashion, then, -- and if you could focus that, it would help me, anyway -- those patients for which a serious adverse event was reported and, again, its relatedness to treatment.

One sees the total was 71 events, comprising 30 of the percents in the study, had an adverse event. If one looks at body as a whole, one sees that none of those were considered to be at least possibly related.

Of the 30 that you saw in the previous slide, 5 of those were deemed by the investigators to be at least possibly related. And these fell into these categories. Four patients had pancreatitis, one each colitis, liver function abnormalities, a rectal disorder or sclerosing cholangitis. None of these would be unexpected in this particular patient

population, particularly those patients with cryptosporidiosis.

Again, if one looks at the metabolic and nutritional increases, in this case AST, one sees there is one patient that might possibly be related.

This slide summarizes the discontinuations for the study pooled across all of the U.S. studies. There were 55 patients who discontinued for one reason or another, representing roughly 25 percent, 24 percent.

Body as a whole again accounted for the majority of these. And the majority of these were not related to treatment but were, in fact, related to HIV disease.

In the digestive category as well, roughly half of the 16 patients were considered to have been at least possibly related to treatment. Again, if one looks at each of these, one sees that the diarrhea, nausea, nausea and vomiting is almost the checklist from our patient questionnaire with respect to symptoms associated with cryptosporidiosis.

Finally, there were some patients that had elevated liver transaminases. And, again, some were considered related, and others were not. And I'll discuss that in more detail in just a moment.

Now, really, based on our review of the data, we wanted to be much more sure that, in fact, NTZ was not associated with any hepatobiliary toxicity. And we conducted that search or that analysis in the following way.

There were 87 patients that had reported hepatobiliary abnormalities out of the total 228. Three of those patients entered the study and had a slight increase or an increase in their liver function tests while on therapy. One was deemed not to be related to treatment. And two others, the data was not available at subsequent visits.

Fifty-three of the original 87 entered the study with elevated liver enzymes, which was permissible. Of these, one had any further increase in their transaminase levels.

And there were no reported hepatobiliary events for those patients. That left 31 patients for which there could possibly be hepatobiliary abnormalities associated with treatment.

Twelve of the 31 were lab abnormalities that were identified by Unimed. Nineteen were adverse events reported to us by the investigator, comprising, then, the 31 patients.

This then summarizes those 19 patients

reported to us by the investigators. You can see half of those were increased liver function tests along with some of the other adverse events here: hepatic failure, increased bilirubin, cholecystitis, interhepatic cholestasis, and hepatitis.

If one looks at the relationship to treatment, only in the case of interhepatic cholestasis was there any possible relation as deemed by the investigator.

The majority of relatedness occurred in increased liver function tests. One of these resolved during treatment. One resolved upon discontinuation. In four we do not have data to follow those patients. It's important to note that these increases all occurred early in those patients after they had been put on therapy.

If one looks at the 12 Unimed-identified laboratory abnormalities, one sees that the vast majority, 11 of 12, were increases in the liver function enzymes, varying from 3 to 11 times their baseline.

Eight of these occurred early, four several months later in the case of this one included. Three of the patients resolved while on drug with no change.

Let me go back. There was resolution in three of the patients in this category while on therapy. Two patients remained on therapy with no further increase. And the outcome on three others was unknown.

In conclusion, cryptosporidiosis is itself known to involve the hepatobiliary system and to be associated with a variety of adverse effects related thereto, not the least of which is abnormal LFTs as well as some of the biliary tract problems that these patients faced.

In addition, the treatments that these patients often take are associated with some of these same elevations. And it was not clear during our analysis, therefore, that there was, in fact, any toxicity that could be clearly associated with NTZ in this hepatobiliary system.

To conclude, then, these are again the key safety findings. NTZ is well-tolerated. There were no deaths. There is no pattern of organ toxicity that was demonstrated by NTZ use.

The higher dose, although data we didn't discuss a great deal, may be less well-tolerated. That's very unclear. And overall the data from these patients clearly supports its safe use in this patient

population; that is, those patients with cryptosporidial diarrhea.

This, then, is our proposed dosage and recommendation that the initial adult dose is 500 milligrams twice per day; that is, 1,000 milligrams, preferably taken with food, -- all of the studies recommended that the drug be taken with food to take the edge off any nausea that might be produced, and it was actually observed in the Mali patients -- and that treatment should be for a duration of at least 4 weeks depending upon clinical response. However, for patients with an inadequate response, we believe the safety of the product does warrant that higher dose be at least an option to the physician.

Let me now introduce Dr. Gordon. Dr. Gordon is an infectious disease specialist from San Francisco who has been a principal investigator in both our 009A and B studies. She will briefly discuss the clinical benefits of NTZ, as illustrated by at least one case study.

And Dr. Gordon will be followed by Dr. Soave, who will then make some concluding remarks with respect to benefit/risk.

CLINICAL BENEFITS OF NTZ THERAPY

DR. GORDON: I just have one slide, and I

will go through this very quickly. This is a patient that I enrolled last year. Eric was 29 years old when he came to me. He had had *Cryptosporidium* for about two years and had regulated his diarrhea on deotoricetine trib opium to six to eight watery stools.

He was on epivir zairite. And the virus at the time I first saw him, he had kind of a level without measuring. His viral loads were depressing. He had enteopathy, both by clinical symptoms and by ultrasound. He had a sickened gall bladder, dilated and irregular bile ducts. He had fatty food intolerance, nausea, vomiting. He was incontinent at least one to two times a week and was awakened by water stools at least once a night.

We started NTZ in February. And at his two-week follow-up visit, he felt that he was perhaps having more nausea and was having diarrhea two hours after NTZ.

We continued. He had initially lost about six pounds of weight. He put on four pounds by his one-month follow-up visit. I should also mention his alkaline phosphatase of GGT also correlated with his cholangiopathy.

At that one-month visit, he was having

less nausea. He felt that he could tolerate continuing with the drug. He was no longer incontinent, but he was still not clearly responding to the drug.

In April, his anti-retrovirals were changed. We had a CD_4 count of five. He had a viral load of half a million. His liver enzymes were still abnormal, but he was sleeping through the night.

And there was a subjective, perhaps improved, but we weren't clear, by June. By June his weight had increased to 156. And we saw the first indication that his cholangiopathy was getting better, with a decrease in his alkaline phosphatase to 431. His stools had gone down to three soft and two formed. And his stool was for the first time negative for *Cryptosporidium*.

What I'd like to point out now is that he continued to improve over time. His weight went up in July to 164. His stools became soft, formed. And, actually, in July of '97, we stopped his TPN.

In October, he actually enrolled in graduate school. He got his life back. He was able to go out and participate in activities. And you can see his changes in anti-retrovirals, though, without a clear response in his t-cells or viral load.

In January, he actually had an episode of rectal bleeding from the fissure. His stools had gotten so hard, he started to use stool softeners. And he continues on the directive to this day. He has two formed stools a day.

And he actually would have been delighted to come here and address this audience, but he was previously committed to participate in a conference at Acelyn Institute.

So several points I'd like to raise regarding this patient. The first is the duration that it took to get a clinical response. His first subjective response was at 12 weeks, and his objective response was at 16 weeks. And he would have been considered a nonresponder by many of the criteria that you heard presented today.

He also continued to have improvement over the course of the year that he has been treated. And we feel that he's probably at about baseline. Now we have discussed stopping his therapy, but he's very reluctant to do so. He has tolerated the drug beautifully and is very delighted with the response.

The second issue is that his response appears to be independent of the effective anti-retrovirals. And I know that's been an issue

with interpreting some of this data, but in this case I think it's real clear that the drug had the effect, the nitazoxanide had the effect, not the anti-retrovirals.

The third thing is that we got resolution of his cholangiopathy over time. And I think this is really impressive. Many of us who care for these patients had had concerns about the cholangiopathy and whether we would need to perform cholecystectomies to remove a reservoir of *Cryptosporidium*. And in this case, we have both clinical and laboratory resolution of cholangiopathy.

I think those were the major points that I'd want to make. And now I'd like to reintroduce Dr. Soave, who will discuss the risk/benefit of nitazoxanide.

BENEFIT/RISK SUMMARY

DR. SOAVE: In summary, therefore, what do we have here today? Well, cryptosporidiosis, undoubtedly, is a life-threatening and serious disease for patients with AIDS. There is currently no approved therapy for this disease. It results in severe misery and makes people very ill.

If we look at the data that was presented here today, clearly over 50 percent of the patients

treated with nitazoxanide experienced some sort of favorable benefit.

Now, I've tried to point out the difficulties with doing clinical trials for cryptosporidiosis. And clearly the data sets are not perfect. It's not the kind of data we would like to present because of the difficulties with doing trials in these patients.

But there was a benefit, both clinical and parasitologic, in a significant number of patients. The question really is: Was this benefit significant enough to warrant the use of this drug? I submit to you that definitely for the patients who are helped by this, it is.

The drug is very well-tolerated. It lacks any serious toxicity, even when given over the long term. Three of our patients from the 004 study are still on this agent now without any significant toxicity. And so from that point of view, there really is no problem with giving it.

So clearly nitazoxanide is currently the best available therapy for cryptosporidiosis. And so when you take the potential benefits and weigh them against the risks, definitely the potential benefits far outweigh the risks for use of this agent.

Thank you.

CHAIRMAN HAMMER: Can we have the lights, please? Thank you very much.

I think we will take a 20-minute break and then return. And we'll initiate some panel questions at that time. Thank you.

(Whereupon, the foregoing matter went off the record at 9:55 a.m. and went back on the record at 10:20 a.m.)

CHAIRMAN HAMMER: I'd like to reconvene. What we'll do next is take some questions from the panel members and go in sequence. I'd like to ask the panel members to please prioritize their questions and perhaps ask their two or three most critical questions to start so that we can move around the table. There will be a time for further questions, either this morning or at the beginning of the afternoon session.

I'd like to start with Dr. Mathews.

DR. MATHEWS: I have a few questions about the characteristics of the patients in all of the three trials that were presented and wanted some clarification on what was the diagnostic workup required to exclude other pathogens. Specifically, did it include endoscopy with biopsies?

Secondly, some clarification on what

exactly is meant by a stable antidiarrheal regimen and also during the course of the studies whether antidiarrheal regimens were allowed to be changed.

I think I'll just limit myself to those two questions.

DR. SOAVE: Let me try to answer those for you. With respect to doing endoscopy and ruling out CMV and other organisms that can be ruled out by using the invasive procedure, for the most part, we stopped doing that three trials before the nitazoxanide because we found it to be very expensive, invasive, and not very high-yield. Normally we would find maybe one patient out of a series of 30 who would have that.

So we decided to look for all the pathogens we could look for using stool studies, open parasite, stool culture, and clostridium difficile assay. And if patients appeared to have a significant parasitologic response, complete eradication of crypto, but their diarrhea persisted, that subset would have been studied, would have been investigated further, subsequent to being put in the trial, for CMV or some other pathogen that we might have missed, both from the point of view of having the data and also from the clinical management point of view of the patient.

Now, with respect to antiviral, antidiarrheal therapies, it's very difficult because most of these patients are on numerous different types of antidiarrheals. And they're fairly wedded to them in the sense that they try to get themselves on a regimen that really controls them in the best possible way. And altering that in any way very often results in either rebound or some sort of distortion of the baseline that you try to attain.

So what we sought to do was to make sure that patients maintained whatever they were on throughout and that the baseline data was obtained on the regimen that they came to us with that they found to be a useful regimen.

We encouraged them not to change the regimen, if possible, during the course of the trial. But, of course, if they responded, most of them would stop or decrease their antidiarrheals because of the need to decrease the amount of pill-taking. And that, of course, was further indication that some of these patients were doing better. What we didn't want was for them to go on new antidiarrheals or increase them.

DR. MATHEWS: I understand that was a preference, but if someone's diarrhea got worse on the study and you decided to add opiates or the doctor did

since these were compassionate use for two of the three trials, that that was done, did you track that?

DR. SOAVE: Yes, yes. We tracked that. And it didn't really happen at all, at least in the first four weeks of the trial for the patients that were being studied very, very aggressively. It may have happened on rare occasions further on, but it was tracked.

CHAIRMAN HAMMER: Dr. Sears?

DR. SEARS: Were there any differences in the data collected between the two sites: San Francisco and New York City? And what were the number of patients enrolled at each site?

DR. DUDLEY: This is Bob Dudley again.

The vast majority of the patients were at Cornell Medical Center. I think we had four patients in San Francisco. And I'm not sure all of those were evaluable. Only two of the four turned out to be evaluable. So the vast majority were at a single site.

DR. SEARS: Okay. And given the repeated observation that cryptosporidiosis shortens the lives of AIDS patients, was there any attempt made to look at the effect on long-term mortality in the group that responded to nitazoxanide versus those that did not?

DR. SOAVE: Maybe I can answer that, Cindy, in the sense that we didn't look at it in a systematic way. But clearly; whereas, for other studies -- we did the study in 1994, 1995, '96. And over half of the people we enrolled are still alive right now. In previous studies within a year of ending a study, everyone would be dead.

This to a certain degree, though, has been confounded by the advent of protease inhibitors. So it's very difficult to get the data right now that you're asking for if you want to look at NTZ effect.

DR. SEARS: And I guess the question about anti-motility absorptive agents, I agreed with. And the same thing: Did you track your anti-retrovirals relative to your apparent responses or what you termed "responses"?

DR. SOAVE: Yes. In the 004 study, only one of the responders in the first eight weeks had been on anti-retrovirals prior to coming into the study. He was on a stable regimen prior to coming in. None of the other people were.

And I think the fact is that we were favored by the window of opportunity there in the sense that the anti-retroviral use came a considerable time after we started 004. So it was fortunate that

we got moving as fast as we did.

DR. SEARS: Thank you.

CHAIRMAN HAMMER: Thank you.

Mr. Marco?

MR. MARCO: I have two questions. First, do you have the breakdown and possibly a slide to show us of the concomitant antivirals that were used? While we know these patients were very immune-suppressed, mostly with under 50 CD_4's, can you attempt to tell me if they started to do anti-retrovirals if they were on protease inhibitors being that we know that people can clear cryptosporidiosis if their CD_4's go above 180 or 190?

And, secondly, I'm having trouble understanding the true parasitologic response. In 004, it looks like you have an approximate 40 percent response rate. In 009, it looks like you have an approximate 50 percent response rate. But then in a slide when you showed it compared to placebo, you put down a 25 percent response rate with an *n* of 59. And could you clarify that?

DR. DUDLEY: Let me answer the second question first. The improvement in parasitologic scores of 40 to 50 percent is accurate based on stool oocyst change in scale or in the broader 009A and B

studies as improvement because many of the laboratories there simply designated it was improved or that it got worse.

The slide that I showed near the end of my presentation showing a 25 percent versus a 14 percent response in placebo was patients that had converted from oocyst-positive to oocyst-negative. And that was the difference there.

And Dr. Graham will address your first question.

DR. GRAHAM: This is Cheryl Graham.

In the compassionate-use studies, we collected concomitant drug use. At the time that the patient was discontinued from the study, we collected the case report forms.

So the number of patients that are represented in the slide that you see up here is a sample of the number of patients that were in the study. And what you see, what I can't see, is a breakdown according to the -- okay.

The top line -- and this is using a WHO code methodology. So what you see on the top line here is the number of patients that were taking an agent that was intended to be an antiviral agent. That includes all of the new protease inhibitors plus

all the old products that were on the market.

We just recently went through and looked to see how many of these were actually protease inhibitors. And there's a subset of these patients. Probably somewhere around 39 or 40 of these patients were actually on protease inhibitors. And I suppose more to the point, when we actually tried to see if that was influencing the outcome of these patients, we didn't see any change in their response rate.

The rest of these lines give you the number of other kinds of agents. These are sort of a typical array of products that all of these patients are on.

CHAIRMAN HAMMER: Okay. Ms. Cohen?

MS. COHEN: I'm just curious to know what you use for a placebo.

DR. SOAVE: That's a very interesting question.

MS. COHEN: I know it is.

DR. SOAVE: We struggled with this one for the azithromycin study because most placebos contain lactose. And, in fact, the company had a lot of trouble putting one together.

I'm not sure I can actually tell you what was in that placebo, but the azithromycin that was

used for that study was lactose-free purposely so that we wouldn't confound things. So I'm not really sure what was in the placebos that were used previously.

MS. COHEN: You wouldn't mind if I told you that was very troubling to me, I hope.

I'm also interested in the questionnaire. And it seems as thought I couldn't figure out if there was a cross-section of the AIDS population or not. But in terms of filling out the questionnaires, were these people then interviewed to determine what they answered really was true?

DR. SOAVE: I'm sorry. I guess we didn't get the point across, but the data was obtained by interview. We questioned the patients about each and every symptom and --

MS. COHEN: So you, in fact, filled out the questionnaire?

DR. SOAVE: Yes, yes.

MS. COHEN: Okay. Thank you.

I'm also curious about the follow-up. I think the follow-up probably is just as important almost as the beginning phases of the clinical study. What kind of follow-up? And when did you do that after the patient stopped taking the medication?

DR. SOAVE: We have continued to follow

all of the *Cryptosporidium* patients we have ever treated in any of our trials to the end, either death or clearance. And even after they completely clear, we still continue to follow them because many of them are very interested in being assured that they have maintained that clearance. So we have continued to follow the patients out to this day, the ones that have not moved away.

We have three patients who are still on drug, in fact, two and a half years later.

MS. COHEN: What about the ones who are not? What happened?

DR. SOAVE: Some of them discontinued because they were clinical complete responders. Some of them moved away. And some of them chose to discontinue drug. Some of them died.

MS. COHEN: I just have one more question: What was the dropout rate? And what was the major reason for dropping out besides, unfortunately, someone who would die?

DR. SOAVE: The dropout rate over what period?

MS. COHEN: Well, over the period -- I mean, I would assume you have it all traced as to who dropped out when and how far along in the study and

the reasons for it.

DR. SOAVE: Right. The initial trial was four weeks long. Of the patients that finished that 4-week period, that number at Cornell, anyway, was 26 patients.

Of those patients, it was like 95 percent went on to complete 8 weeks. And of that number, it was something like 20 of those patients went on to complete at least another 3 months in the study.

So the dropout rate was not very significant over time in the sense that everyone didn't just disappear.

CHAIRMAN HAMMER: Dr. Self?

DR. SELF: As you've said in your presentations so far, there are many methodologic challenges here. And that's certainly true. I think it's useful to distinguish difficulties in study design, which seemed to be largely out of your control, with problems with data in the conduct of the trials that were done.

And there seems to be a fair amount of missing data. And this is of particular concern since missing data typically happened among those whose response is not particularly favorable.

And the method that you have chosen to use

to deal with the missing data, this LOCF method, I think does little to remedy that situation. In fact, it might actually aggravate the biases that might come from missing data.

It's clear that if data on patients who are not doing particularly well are missing, that will rise the overall response rate, but there were many slides that were presented showing some modest trends of improvement over time.

And if patients who are not doing well over time begin to drop out and you either analyze only those who remain or, as I understand this LOCF method, you take their last observed data point and use that to impute future, you will create those trends when, in fact, there are no trends that are really going on.

So two questions about this. One is what the extent is of the missing data. Of the 228 patients that were described in this experience across the several trials, what fraction of these is missing out from data at two weeks, four weeks, and eight weeks?

MR. ROHOWSKY: Nestor Rohowsky.

I can tell you that the fraction as you go farther out into time gets larger. At 2 weeks, I'd

say it's fairly small, maybe 15 or so percent. By 4 weeks, it's probably around 20 percent. And at later times -- well, overall there was some estimate made of missing data through the whole eight-week period or through eight weeks at any time point. And that was estimated to be somewhere in the area of 30 percent.

DR. SELF: Do you have a slide of that or can you get the specific numbers for us by early this afternoon?

MR. ROHOWSKY: I don't have a slide, and I'm not sure about the other. Okay. Well, I guess we can.

DR. SELF: Could you also comment about the method that you've chosen to use for handling that missing data, this LOCF method?

MR. ROHOWSKY: Okay. The idea behind the LOCF method -- and that's --

DR. SILLIMAN: Can I just interrupt and address the point about the amount of missing data at week four? Sorry. I guess I didn't speak into the microphone at the beginning.

I actually have a slide that's going to address the amount of missing data at week four for the NTZ patients versus placebo patients. And it was 34 percent for the nitazoxanide patients at week four.

I'm not sure about weeks two and eight.

DR. SELF: So about a third of the patients are --

DR. SILLIMAN: Yes, about a third.

MR. ROHOWSKY: Okay. The idea behind using the LOCF, knowing that there was missing data, -- some patients had data at one time period, and then it was missing and then came back for more with more data -- was that we were using the worst-case approach.

The LOCF data didn't discriminate whether the last non-missing observation was of benefit or of detriment to NTZ. So we basically used whatever was available, good or bad, to estimate what the response would be at the time point of interest. And we felt that using this approach was a good approximation of real-life conditions.

DR. SELF: I'd suggest that there's a lot of experience to suggest that that's probably not a worst case. One standard approach to this would be to really impute a worst case, a no response kind of outcome for missing observations. So it would be interesting to see in terms of sensitivity analysis what the response rates would be with that approach.

I have another question. There is a claim

of a dose and duration of treatment effect based on the 004 data, I believe, that I didn't quite follow. I wonder if that slide could be put back up and someone could talk through the rationale for that claim.

DR. DUDLEY: Yes. Just give us a moment to find that slide, please. That would be on the primary presentation.

DR. SELF: Slide 58 maybe, 57 and 58 I think.

DR. DUDLEY: Thank you. We need to come back. The next slide. Was this the slide that you were interested in?

DR. SELF: That's it.

DR. DUDLEY: Okay. I think the point to be made here is that at this week four period using LOCF in spite of the concerns that you may have about that, there is a 32 percent response across all of those doses. And at this point, at week four, the patients had an opportunity to dose-escalate. And I can tell you that every patient on 500 escalated to at least 1,000.

And so by looking at week four, admittedly it's confounded in the sense that you're looking at all patients on a whole variety of doses. But what I

think that it does argue for is that the 500 certainly is not in this higher number. And there are four weeks longer of treatment.

And that's the point I was trying to make. I certainly wasn't trying to overstate the issue because there is, after all, only about an eight percent difference.

DR. SELF: One last question. There was a mention of some spontaneous remissions have been seen, although they're rare. I was wondering if there's any information about that relative to some of the dramatic case histories that you have shown here that also look like remissions, although perhaps due to the drug.

DR. SOAVE: The spontaneous remissions that we brought up mostly occurred in the past when we were doing trials and at the same time drugs like AZT became available and patients concomitantly started anti-cryptosporidial therapy and AZT. And within a matter of a week or two, they would have a complete response; whereas, everybody else in the trial was not.

There might have been a spontaneous remitter who did this totally on their own, but for the most part, the rare occasions that we have seen

this in the past, it was concomitant with starting something that had some immunomodulator-type effect.

Now, this sensitized us a little bit in the past because we were afraid that maybe this occurred more often than not. And so in all trials subsequent to the ones conducted before the early 1990s we've put in strict criteria that either patients had to have a certain CD_4 count for entry or if their cryptosporidiosis was newly diagnosed, they would have to wait a certain period of time before they could be entered into the trial. And that was the reason for putting that stipulation in in order to make sure that we weren't putting people in who might be spontaneous remitters.

I really truly believe that the spontaneous remission rate in the patients that we have enrolled in these trials is negligible, if at all existent.

CHAIRMAN HAMMER: Dr. Sears?

DR. SEARS: I think I want to just disagree with that. In Tim Flanigan's data published in the annals, where the sort of cutoff for CD_4 for 160 for a difference in clinical course was published, he had a 10 percent spontaneous remission rate in individuals with a CD_4 under 160.

And we have in the press a review of all of our patients at Hopkins in clinical infectious disease. In reviewing all of our patients from 1986 through 1996, we identified a 17 percent spontaneous remission rate that could not be linked to anti-retroviral use.

So, in addition, there are several papers now suggesting there are different clinical patterns, some very serious with cholera-like diarrhea, if you will, and some with disturbing diarrhea and weight loss that are seen in AIDS patients.

It's unclear to me why the clinical pattern of disease is variable in individuals with very low CD_4 counts. And in our patients, the CD_4 counts were almost exclusively under 50. But it speaks for differences, potentially parasite differences, potentially host differences.

In addition, there is some other data published by Goodgame and his colleagues showing that the histologic pattern of cryptosporidiosis in the intestine is varied depending on the type of inflammatory response.

So I think there are a lot of things we don't understand. And I would not be certain that this is rare. I think it's a clinical pattern that's

seen, and we don't understand the reasons for it. It's not common, but I don't know if it's rare.

DR. SOAVE: Cindy, in the patients you're describing, though, were you able to control for the possibility of their being on drugs that might have had an impact on cryptosporidial diarrhea? Because with the wide availability of paromomycin and azithromycin and nitazoxanide, et cetera, you wonder always whether there is some other concomitant event.

DR. SEARS: Nitazoxanide has not been used, at least that we're aware of, in our population. And the data did not appear to be confounded with paromomycin. And beyond that I don't think there's anything to discuss.

CHAIRMAN HAMMER: Thank you.

Dr. Feinberg?

MEMBER FEINBERG: Well, some of the questions I had have already been asked. So let me move on to a different area. In going through the preclinical microbiologic and animal model data, I noted that the *in vivo* studies for cryptosporidiosis itself were only done with nitazoxanide; whereas, a lot of the other microbiologic studies were done with both nitazoxanide and tizoxanide, the major metabolite. And I wonder if there's any clarity on

what the active moiety against cryptosporidiosis really is because these studies seem to have only been done with the initial chemical entity.

I guess the other issue is knowing whether in these animal models the drug is as rapidly and completely metabolized as it is in people, which was sort of another piece of uncertainty, in trying to understand that.

A parallel question to that: If the drug in man is almost immediately and completely metabolized, then I'm interested in a hypothesis about how the drug has an effect on an intestinal parasite if the active moiety is nitazoxanide itself.

DR. DUDLEY: I'll go in the reverse order. My memory is better.

With respect to the ingestion of NTZ, the absorbed quantity that is about 30 percent of the drug is rapidly acted upon by esterases to form tizoxanide. That's the circulating portion, of course.

It is not clear how much of the remaining two-thirds remains as parent, although some of it clearly probably will also be de-acetylated on the benzamide ring. So you really have, in actuality, in the gut probably both the parent and some tizoxanide, while in the circulation you have tizoxanide.

Did that answer the second question?

MEMBER FEINBERG: Well, so are you positing that it's the drug at the gut lumen that is effective or is it the circulating drug? I mean, I know you don't know a molecular mechanism of action, but I'm just logically trying to piece this together.

DR. DUDLEY: Well, I think it's probably both. And perhaps Dr. Soave or others who are more familiar with the pathophysiology than I can discuss that.

In most parasitic diseases that are lumenal, you want high lumenal concentrations of a compound. And, in fact, NTZ is highly effective, although data not shown here, against a host of intraluminal parasites, different from *Cryptosporidium* in that they are not intracellular.

It's unclear whether having high lumenal concentrations of NTZ in close approximation can be absorbed across that membrane or whether the drug needs to come in from the back side or whether the response is due to the fact that over time you're interrupting some life cycle stage that we don't understand. We understand the life cycle stages, but we don't understand the potential effect of either of those compounds in those various stages.

So there's not a clear answer to the question as to whether it's one or the other. I believe that Dr. Soave and others would agree, Dr. Rossignol perhaps, too, that, in fact, it may well be a combination of activity, but we don't understand the mechanism well.

MEMBER FEINBERG: I'd just also that the animal model data are not really compelling, but they were only done with the parent compound. And, again, I don't know how gnotobiotic piglets and suckling mice metabolize this drug. I don't know if you know, but --

DR. DUDLEY: I know enough about the comparative physiology to know that the esterases present in their system will absolutely cleave off the acetyl group from that compound. So you will get the formation of tizoxanide.

The animal models themselves historically are very poor indicators for any kind of assessment of human activity. And that's problematic I think in this disease particularly because it is true that there was some evidence of positivity in the skid mouse, perhaps a little bit in the gnotobiotic pig, but we feel fairly comfortable that NTZ is diarrheagenic in the gnotobiotic pig. And so that

kind of confounded that.

In addition, outside of the piglet model, I don't know of any model where the infection of *Cryptosporidium* actually causes a pathophysiology similar to that seen in humans. You don't see diarrhea, for example, in the rodent model.

MEMBER FEINBERG: Okay. And I had a question in a completely different area. With regard to the --

CHAIRMAN HAMMER: Dr. Feinberg, I'm sorry to interrupt, but I think you had a comment.

MEMBER FEINBERG: I'm sorry.

DR. DAVIT: Yes. I'm Barbara Davit. And I'm the FDA pharmacokinetic reviewer. I just wanted to comment on some of my observations from the mass balance data.

You can correct me if I'm wrong, but from my interpretation of the data, there did not appear to be any evidence of NTZ in the intestine. It's in the mass balance study the fecal samples were analyzed. And the analysts could not find any evidence of NTZ. That's not to say that it's not there at some point, but there was no evidence of it.

When we were reviewing the metabolic data, we were never entirely sure because NTZ is converted

to desacetyl-NTZ so rapidly and spontaneously we were never entirely sure whether this was occurring in the plasma or in the intestine, in the gut wall, intracellularly, where it was happening, but there was just never any evidence that I could find of parent NTZ in any biological fluid or excreta.

MEMBER FEINBERG: Thank you.

My second question, which is in a completely different area, as regards these hepatobiliary or potential hepatobiliary adverse effects, -- I guess maybe Dr. Soave knows the answer to this -- were these patients adequately evaluated for hepatobiliary cryptosporidiosis? I mean, do we know in these patients whether that was confounded by that or not?

DR. SOAVE: Well, they were evaluated insofar as we looked at the alkaline phosphatase. And those who had elevated alkaline phosphatases for the most part had sonograms or some sort of imaging study to look to see if they had dilated bile ducts or dilated gall bladder.

Nothing beyond that in terms of invasive procedures were done for the purposes of study entry. A few of the patients had had that done previous to coming into the study and, therefore, had documented

biliary tract disease.

I can't give you off the top of my head the actual number of people who we thought had biliary tract disease. I believe it was in the range of the quarter that we sort of see in any population of this sort that we take.

MEMBER FEINBERG: So no one has looked to see if there's sort of a one-to-one correlation of those patients in that branching diagram that was shown for the hepatobiliary AEs, whether those patients were also the patients in whom hepatobiliary disease was suspected?

DR. SOAVE: Oh, I assume that in looking at it, it depends on whether you're looking at the biliary tract involvement from the point of view of efficacy or if you're looking at it from the point of view of adverse events.

Looking at it from the point of view of adverse events, definitely there were people with abnormalities that were thought to be due to hepatobiliary crypto that did not change on nitazoxanide therapy.

Basically we couldn't blame the nitazoxanide therapy for the hepatobiliary events, but it made it very difficult initially oftentimes to put

people in the trial if they had significant enough abnormalities because then you wondered if you were stacking things against you in terms of developing adverse events.

In terms of the efficacy part of it, you always worry if people who have the hepatobiliary disease are more prone to not responding to anything because they have this reservoir of infection which is going to be very hard to eradicate.

I'm not sure. Did I answer?

MEMBER FEINBERG: Yes, I'm not sure you have either, but I'm really not looking to either blame or exculpate the drug. I'm just trying to figure out: Was there a substantial proportion of people in whom hepatobiliary adverse events were reported who might have also been confounded by having hepatobiliary disease?

And I don't think that that piece of it's yet answered, but maybe people from the company know that and that's something that can be --

DR. SOAVE: Right. I think on that slide that you're referring to where they get broken down, you can almost assume that anyone who had an alkaline phosphatase abnormality but not transaminase abnormalities was more likely to have that due to the

Cryptosporidium. Do you want to --

CHAIRMAN HAMMER: But I think, just to amplify, no direct workup for involvement, cryptosporidial involvement, of the hepatobiliary system was done?

DR. SOAVE: In terms of invasive procedures, no.

CHAIRMAN HAMMER: It's either like a per-quadrant ultrasounds or endoscopy in ERCP. That's the kind of definitive data that would answer Dr. Feinberg's question. And so we're left with possibly a confounder.

Dr. Hamilton?

MEMBER HAMILTON: Given the complexity of the clinical events in the patient population under discussion today, certainly from a patient management point of view, precision of diagnosis is absolutely essential.

And certainly in the interpretation of results of clinical trials, it also I think rises to the top among my priorities here. And, to that end, I'd like to return to an issue touched upon by Dr. Mathews in his initial question.

And that is: What level of certainty do we have, actually, that cryptosporidio was indeed the

illness being treated and being responded to or being responsive to NTZ?

So let me get a point of clarification here. I thought one of the slides indicated that identification of *Cryptosporidia* were essential for incorporation in one or another of the substudies or studies. I can't remember which. Presumably it pertained to all. And then I thought Dr. Dudley said that the patient only needed to have had that diagnosis in the prior two months or something like that.

So have I mistaken those facts or could you corroborate that conclusion?

DR. DUDLEY: Yes, I can respond. The one subset of patients for which there is absolute documentation for cryptosporidiosis at baseline was the per-protocol group, which was about 40, 39 patients from that larger group. And one of the purposes of our doing that analysis was, in fact, to unknowingly address your very question.

And that was given the fact that this more mimicked the real world and that not every physician was, in fact, going to rely on a stool-positive identification for *Cryptosporidium* but might well rely on his clinical judgment with respect to symptoms,

this we thought was a way in which one could hone in on the question and ask: Okay. Out of that bigger set, let's look at those patients that absolutely have the diarrhea, absolutely have the cryptosporidiosis, and had enough visits on which one could make an analysis.

When one does that, the consistency and I think what gave us comfort, in fact, quite frankly, this was a no go/go for us. Had the data fallen completely out of bed at this stage, we would have been very comfortable making some of the statements we have about ITT.

On the other hand, the consistency one sees looking at an, arguably, much more well-defined patient population, that data is so consistent with the whole that we feel, by and large, that the ITT was a reasonable approach. So I think that in part answers your question.

The open-label study did allow for entry of patients that had a cryptosporidial diarrhea diagnosis. In the absence of oocysts, many of which I think -- the exact statement in the protocol does not come to mind, but if there had been a diagnosis within two months prior to that and the symptoms were consistent with cryptosporidial diarrhea, those

physicians were, in fact, allowed to enroll patients into the study.

MEMBER HAMILTON: So, if I understand that correctly, then, 41 patients or 40-something, out of some 200 constitute the group for which we have incontrovertible evidence that *Cryptosporidia* was present.

DR. DUDLEY: Well, it's actually in Dr. Soave's 004 study. They all had incontrovertible evidence. And 39 of the 139 had incontrovertible evidence in 009A.

MEMBER HAMILTON: And then the other part of that question, then, is: What didn't they have? I heard some comments by Dr. Soave, I think, and perhaps by yourself that stools were examined for other parasites. But can you tell us what the range of other enteric pathogens that might have been present and caused an indistinguishable illness were excluded?

DR. SOAVE: The pathogens were excluded were: those that we could detect using stool culture, namely salmonella, shigella, campylobacter, yersinia; those detectable by open parasite exam: Giardia, meba, blastocystis if you think that that's a pathogen; and where the clostridium difficile toxin

was there.

So the range of pathogens that are picked up basically on stool exam were the ones that were excluded. The only one that is not in that list that might be important is cytomegalovirus in patients with AIDS. And we did not actively exclude that in the patients by doing biopsies.

However, at least for the 004, none of these patients had other CMV infection elsewhere at the time and had not been worked up previously for CMV infection in the gut.

So there wasn't someone who came in, for example, with a history of or possibly ongoing cytomegalovirus infection who was not looked at from the intestinal point of view. It was just those patients who had no indication that they had cytomegalovirus. We did not actively do biopsies on those patients.

CHAIRMAN HAMMER: What about *Microsporidium*, which on one of the slides was not rigorously excluded?

DR. SOAVE: I'm sorry. *Microsporidia*. I forgot that. That's a good point. *Microsporidia* was looked for in all of the patients who were in the 004 study. And we had decided because of the fact that it

does occur concomitant with cryptosporidiosis very commonly not to exclude those patients from the study but to subset them out.

Unfortunately, that didn't occur in the 004 study. We didn't need to do that. We have plenty of patients with *Microsporidia*, but the patients that we managed to enroll in the study were *Cryptosporidium*-positive.

MEMBER MASUR: Scott, could I ask a clarification on that?

CHAIRMAN HAMMER: Sure.

MEMBER MASUR: There are a couple of things, Rosemary. Are you suggesting that none of these patients at any time had co-pathogens other than *Cryptosporidia* found in their stool?

DR. SOAVE: I'm suggesting that the co-pathogens, I'm stating that the co-pathogens, that I mentioned were all ruled out upon entry into the study.

If someone came in with giardia, for example, they would have been treated for the giardia until they had negative stool before being entered into the study.

So yes, they didn't have any of those other pathogens.

MEMBER MASUR: Okay. And in terms of when the baseline stool was gotten, was there information that was gotten on day zero in the subset of 39 patients you're talking about?

DR. SOAVE: It was within a week of study entry.

MEMBER MASUR: And how did you look for *Microsporidia*?

DR. SOAVE: We used the trichrome stain, the modified trichrome stain, in our parasitology laboratory.

MEMBER MASUR: On a single stool?

DR. SOAVE: Yes. We did it on a single stool to rule it out. However, again, all of the stools that were subsequently looked at on a weekly basis also were looked at for other open parasites.

And, again, had these parasites popped up during the course of the study, we would have known. And that wasn't the case.

MEMBER HAMILTON: So as an -- I'm sorry. Did you have something you wanted to say?

DR. GORDON: Yes. Let me just make one other comment about looking for CMV and other pathogens. At least in the open-label, compassionate-use trial in San Francisco, many of

these patients were chronically infected with *Cryptosporidium* and had clinicians who were very astute to their symptoms and the patients were astute and would be evaluated intermittently for a change in stool pattern.

And there are also triggers that would be used to look for things like CMV, for example, if they became hemacult-positive, had gross blood, or had focal consistent abdominal pain. They might be colonoscoped looking for CMV.

So it was not done systematically for the study, but it was done as part of their routine clinical care. And I feel pretty comfortable that at least in my site, there was no concomitant untreated CMV.

MEMBER HAMILTON: So, to give us a sense of the concomitant and in parallel endomicity of other enteric diseases, how many such other patients did you find seeking those that you ultimately enrolled? Do you understand my question?

DR. SOAVE: I'm not sure that I do.

MEMBER HAMILTON: You must have done some screening of the larger population to find those who had *Cryptosporidium*. So I'm asking: How many others of those were there? And what was the representation

of enteric pathogens that was found?

DR. SOAVE: Actually, it didn't quite work out that way. What happened more commonly in almost all of the cases was that patients who were already known to have cryptosporidiosis were referred to us for the study or people sought us out because they knew they had the disease. It wasn't that we were just looking at AIDS patients with diarrhea for patients that had crypto.

Because there always seems to be a backlog of patients with this disease looking for a therapy, we drew from the patients that already had the fine disease. And we confirmed that they had cryptosporidiosis and ruled out that they didn't have other pathogens at the time of study entry.

There might have been one or two patients that didn't have cryptosporidiosis in the 003 study who were not entered. I don't remember off the top of my head if one or two had another pathogen. Most of the others are treatable. So we would have treated them and then subsequently enrolled them.

So there really wasn't a number of patients that were screened and not enrolled because of concomitant pathogens.

MEMBER HAMILTON: It's an enviable

accession method.

DR. SOAVE: Well, I think it reflects, though, sort of the way this disease behaves and sort of the tremendous need for a therapy out there. I think that's one of the points that's very hard to bring across, but it's a different subset of patients who have this. There really is not very much for them.

The fact that many of them had cryptosporidiosis for a long time, the mean was 15 months definitely suggests that these are patients who are sick with this disease. It most likely is causing their problem. And, therefore, they're willing to try something. They're anxious to try something. They're anxious to get going. And they're readily available.

That has changed now significantly, fortunately, but that was not the case when we started these nitazoxanide trials.

CHAIRMAN HAMMER: Thank you.

Dr. Lipsky?

MEMBER LIPSKY: Thank you.

One of the statements was very intriguing in the background information about the metabolism of the drug, and that is the possibility of undergoing nitro-reduction analogous to metronidazole. If that's

the case, I believe nitro-reductase is a non-mammalian. And this would depend on the intestinal bacteria.

So I wonder first: Do you have any more besides that intriguing statement, any more evidence, of nitro-reduction? And, secondly, if that is the case an active metabolite is potentially a product of nitro-reductase, that would mean that the efficacy of the drug would depend upon the quantity and the quality, if you will, of the stool, which was the bacteria nearly the drug. And, thus, one might be able to relate the possible efficacy to the nature of the stool.

So, first, any evidence of nitro-reduction? And, secondly, was there any relationship of the bacteriology of the stool in relationship to efficacy?

DR. DUDLEY: Yes. No, there is no evidence at all that studies looking at this molecule specifically with respect to nitro-reductase activity have not been conducted.

So the comment in the briefing document was to put it in some context that at least that portion of the nitro-thiazolyl portion of the molecule has the attributes that might enabled it to be

nitro-reduced in a manner similar to, for example, nitazoxanide? And, as you know, it's that nitro-reduction of metronidazole that is the reason for its activity.

We just don't have that data. There's no data of that kind.

MEMBER LIPSKY: So it seems like some mechanistic studies would be useful. And you would hope that no one would go off and get a use patent on a nitro-reduction product of the drug.

Anyway, okay. In addition to that, has there been any relationship to any pharmacokinetic parameter and efficacy, patient outcome for this drug?

DR. DUDLEY: The answer to that is no. The primary pharmacokinetic studies were, in fact, in 004, Dr. Soave's studies. And those patients were followed only for the 14 days. We don't have pharmacodynamic data relating blood levels to efficacy, certainly not in the open-label study. Blood samples weren't collected from those patients at all.

MEMBER LIPSKY: So that's pretty basic. Of course, we don't know if you want to have zero absorption as better than greater absorption. So there's a lot of unanswered questions there.

DR. SOAVE: Definitely, that's true. I'm not so sure I'd ever want to have zero absorption, though, because there still is this problem that the organism is intracellular and it does get to the biliary tree in a fair number of patients. So maybe I'd definitely want both.

MEMBER LIPSKY: Of course, we don't necessarily know if it's really active there.

DR. DUDLEY: Right.

MEMBER LIPSKY: And, finally, since you're at the microphone, Dr. Soave, you mentioned Milwaukee in, I think it was, over 1,000 hospitalizations. Was this drug used in Milwaukee?

DR. SOAVE: No. Milwaukee antedated this drug. That was 1993 --

MEMBER LIPSKY: Oh, I'm sorry.

DR. SOAVE: -- that the outbreak occurred.

MEMBER LIPSKY: I thought you said '95.

DR. SOAVE: And we didn't hear about nitazoxanide until '95, I guess.

MEMBER LIPSKY: And you also mentioned a few patients that had died with this disease recently. Were these treatment failures?

DR. SOAVE: These were patients who were on protease inhibitors and had cryptosporidiosis in a

fairly severe form. And they died, in spite of therapy with protease inhibitors and nitazoxanide. They were very, very ill.

MEMBER LIPSKY: And then, finally, there was just a statement in the toxicity about patients dying with HIV syndrome death. Could you or anyone define exactly what that means?

DR. DUDLEY: Well, "HIV syndrome" is a COSTART term that I would interpret -- and physicians around me should pipe in -- is basically end-stage AIDS, but it's in the COSTART terminology as "HIV syndrome." And some physicians did report by that methodology that it was HIV syndrome that caused the death.

Put around that whatever constellation of diseases or symptoms that you like, but the point I think to be made is that the patients died of their HIV infection.

MEMBER LIPSKY: That's I think complicated. Thank you.

CHAIRMAN HAMMER: Dr. Masur?

DR. SOAVE: Let me just add one comment to that, I guess, and that is that it's always very difficult in these trials to remind ourselves constantly that the patients we're treating, although

we're looking at the cryptosporidiosis per se, have a fatal underlying disease that continues to progress throughout the course of the trial.

And so when they do die or when they develop other infections, it becomes difficult to sort out what's happening with respect to the agent and the disease you're treating and the overall course of the disease. It is terribly complicated in terms of actually defining events.

CHAIRMAN HAMMER: Dr. Masur?

MEMBER MASUR: I have a couple of different areas I want to ask about. First of all, you alluded in your oral presentation, then it says in the written material that the initial two-gram dose may be less well-tolerated.

I was wondering, first of all, what the intolerance to an initial two-gram dose would be; and, second of all, how you determine this particular dosing range.

Did you define MTD? And is there some reason to think that higher doses might not be more effective or lower doses might be as effective?

DR. GORDON: I can speak to the toxicity of both the two-gram and the one-gram doses. The commonest side effect that I saw with both dosing

regimens was nausea, which seemed to be alleviated after the first couple of weeks of therapy. And it was more pronounced in the two-gram patients. There was also some degree of diarrhea with the two-gram dose.

MEMBER MASUR: Did I miss in your safety data how much nausea you attribute to this drug?

DR. DUDLEY: We will put that slide back up so that everyone can see that. This would be the summary of adverse events by system for the digestive system.

While we're looking for that slide, perhaps I could elucidate a little bit how we got to that 1,000-milligram dose fairly -- I won't say serendipitously. That sounds too cavalier.

In the initial 004 study, where we sequentially enrolled patients beginning at 500 and 1,000 and then above, recall that the 009 study, the first, was started almost at the same time and, quite frankly, at about the time when it appeared as though the responses at the 1,000 dose were definitely better than at the 500. And we didn't have any information at the 1,500 to 2,000.

In addition, we didn't have a lot of -- rephrase that. We wanted to have more comfort at a

lower dose with respect to what one might observe from a clinical side effect benefit before we catapulted up to in this case 2,000. So that's how the initial patients came in at 2,000.

Having said that, if there were a nonresponder, we wanted to provide them an opportunity to, in fact, dose-escalate. And that was most of the patients went from 1,000 if they dose-escalated and needed to to 2,000.

By the time we got to 009B, there was enough comfort with both doses to feel, on both our part and I think the agency's part, that it made sense to look at an arm with 1,000 and an arm with 2,000.

As it turns out, at least through our experience today, there does not appear to be a significant difference between those 2 doses, not to say clearly that a patient might respond better at 2,000 and another at 1,000. I think that we don't have enough data to suggest that.

One related piece of information that may be of value to the Committee, in the design of the 336 protocol, which is the placebo-controlled study of nitazoxanide that will, unfortunately, be closed in the middle of this month.

There is a fairly complicated dose

escalation tree. Patients can have -- now I'm doing this from memory. But it's at 1,000 or 2,000. And then if they don't respond, they can go to 3,000. And then they can drop back to 1,500. It was well-intentioned in its design to try and tease some of that data out. But, unfortunately, we know that will not happen.

Finally, this is an *n* of one, clearly anecdotal. But I can tell you that Dr. Brogart in San Francisco has the patient which I think is still on NTZ and is the patient that has been on it the longest. And he has been as high as 4,000 milligrams before he saw a response, has dropped back down to 1,500 milligrams now. And she is maintaining him prophylactically at that dose. So it gives you a little idea of how we got to where we are today.

Was there another part to your question?

MEMBER MASUR: Well, the other question is about the nausea. We can look at the slide, but one of the questions is how much of the nausea that occurred -- I mean, whether one can determine how much was due to the drug, this drug, versus other drugs versus other diseases.

DR. GORDON: At least in my patients when they went on NTZ, there was no other change. Whatever

nausea they had due to the *Cryptosporidium* was stable nausea. And they reported nausea above and beyond what they had had previously.

But, at least at the one-gram dose, I found that if they were forewarned about this nausea during the first two-week interval and, as I understand it, this doesn't correlate with no metabolite of the drug, if they were forewarned about it, were able to self-medicate with compazine, they could get through that initial period. And then the nausea became self-limited.

MEMBER MASUR: Okay.

DR. SOAVE: Let me just add to that with the 004 study, we had no problems, actually, with nausea, even at the two-milligram dose. And some people were eventually in the follow-up period pushed to three milligrams.

There were no instances where people in the study wanted to decrease their dose because of that symptom. It was not really a problem.

MEMBER MASUR: Another issue relates to the chronicity of this disease. I guess, as you eloquently state, this is a chronic disease, and it tends to wax and wane.

I was interested in what Cindy said, that

17 percent of her patients respond. And if you look on Slide 94, 23 percent of the placebo patients appeared to have a complete response.

I guess I had, really, a two-part question. First of all, were the people who responded at two weeks, four weeks, and eight weeks the same people or were some of the people who responded at two weeks perhaps not the same people who responded at four weeks?

In other words, some people might wax and wane in terms of their diarrhea. Were these consistent responses or was this a subset of people who would bounce down to gradual diarrhea for a few weeks, then more diarrhea, then down again?

DR. GRAHAM: Cheryl Graham again.

I asked that question initially when I looked at this data. And what we did is we took responders at eight weeks. And I don't have the specific slide here. So I can't show it to you.

We took responders at eight weeks and patients who had data at one, two, four, and all the interval times and looked to see at what point they actually responded and whether they sustained the response.

What we found was if they had a response

at two weeks, they held that response. And that showed it in the data. It was reflected in the data. If they responded at four weeks, they retained that response.

And there was very little gain in the clinical response, the stool frequency, after four weeks.

MEMBER MASUR: And very little dropout because the second part of that -- and maybe, Rosemary, you can respond to that -- is if you look at Slide 104, the impressive thing about long-term drug is that very few patients stay on the drug for very long.

I guess I wasn't clear. If patients are having a response, why do they stop the drug? Is the presumption they're cured, that their stools are negative, and they're not going to relapse or is the fact that their response is fairly transient and they relapse then and then drop off? Because only about 20 percent of patients are still taking the drug at 6 months. And that would be your placebo response rate.

DR. SOAVE: Let me address your first question first. We, too, were conflicted. If you look at the bowel movement frequency data on a day-to-day basis, you end up with these incredibly

hectic curves and in order to try to make sense of that, obviously you have to pick some way of interpreting it. And one of the ways is the way that was presented to you. And you always wonder about this variation in the disease.

Although my experience has not been that we have had that many spontaneous remitters, certainly there is variation in this disease. And I respect the findings that it might be higher than I think that it is.

We have actually gone back to the responders in 004, actually all of the patients in 004. And we have applied logistic regression, linear regression analysis, to look to see how real those responses were.

And, indeed, again, as Cheryl just said, all of the patients who had a response, had a sustained response over time, the slope was definitely in the right direction and there was a significant decrease in the slope over time.

So I feel very comfortable that the patients who responded in 004, this was a real response. It was sustained, and it went on over time.

MEMBER MASUR: But, Rosemary, one of the issues is that, I mean, it's a terribly difficult

problem to deal with. And I'm not suggesting that there are any easy answers as to how to express the data, but, for instance, one way of looking at it that might be more helpful is if, for instance, there were a Kaplan-Meier plot of how many people were still free of diarrhea over time because the way the data is presented, you know that people are free of diarrhea or improved at a given time point. But you don't know if they're retaining their response from, as far as I can see, any of the data that is presented here.

DR. SOAVE: Okay. We actually have done Kaplan-Meier plots on these patients. And I could try to see if I have those with me.

But, again, with respect to the sustained nature of the response to rule out the variation, in looking in a number of different ways at the clinical response in the responders in 004, it was sustained, certainly over the first four weeks, certainly over the first eight weeks for those who continued on to eight weeks.

MEMBER MASUR: When we're looking at a lifelong disease, are you suggesting that the response is only transient, that the best you can get is four to eight weeks, or how many patients get a sustained response? I would assume that for a chronic disease

like this, we're talking about 12 weeks, 24 weeks, 48 weeks, something that's long-term.

DR. SOAVE: Right. Those who continued -- and this goes back, I guess, to the question that Ms. Cohen asked before. And I'll try to have the data for you in a little while. We actually do have that spelled out.

Basically, the patients who responded did one of two things. They either continued on the drug -- and three of them are still on the drug now two and a half years later.

Two of those patients are totally *Cryptosporidia*-free and diarrhea-free. One is diarrhea-free but intermittently has *Cryptosporidium* in his stool. And those three have chosen to stay on the drug.

MEMBER MASUR: Okay. But one or two patients aren't going to sway things one way or the other, the question really is of this larger number. Is it possible to say how many have the sustained response or to show us some data about that?

DR. SOAVE: Yes, we could pull that together.

CHAIRMAN HAMMER: Anything else?

DR. DUDLEY: Just one follow-up there.

Keep in mind that in the 009A study when that was first initiated, the patients actually were forced to come off therapy, responder or not responder, at two and four weeks because we were working with the agency to collect kind of rolling safety. So you have a certain cohort of patients that might have stayed on longer, and it messes up the data just a little bit.

MEMBER MASUR: No. I mean, I appreciate that. And, again, it's a very difficult problem. But if what we're looking at is how many people get a long-term benefit, the short-term data doesn't help us terribly much.

CHAIRMAN HAMMER: Can I ask a follow-up/related question as far as the response? Some of the data were looked at as far as eradication or *Cryptosporidia*-positive to negative at a certain week.

Of the individuals who were negative, for example, after week four, was that consistent? Did anybody bounce back with positive cryptosporidial stool smears after a time point labeled as "Eradication"?

DR. SOAVE: In the 004 for the follow-up on all of the patients that we've looked at, both within the study and also post-study. For the most

part, any patient who came up as negative, we repeated the stool within a week to make sure it was still negative. And if it remained negative, we would do other testing on it, such as ELISA testing, to confirm that that was the case as well.

CHAIRMAN HAMMER: What about in the larger data set? Because we're dealing with three studies, 009A and 009B? And 004 is only 28 patients.

MR. ROHOWSKY: This is Nestor Rohowsky again.

I have some information on responses for one of the studies. This happens to be study 009B, which goes beyond eight weeks. Here, as you could see, the data cut off was February 20 of this year. So the first two columns by dose is through eight weeks, and then the second two columns are through February 20th.

Now, these include, these last two columns include, patients here and also one or two extras. Some of these patients have been on drug for the better part of a year. And you could see here clinical response in the first eight weeks is about 52 percent, mid 50s. And in the longer term, it goes up to about 60. So it's consistent.

CHAIRMAN HAMMER: Dr. Masur's question was

whether those are all the same patients. And my question was related to the microbiologic response, also consistently within the same patients.

MR. ROHOWSKY: Okay. The vast majority of the patients who went out through February 20th are the same as in the eight-week period.

CHAIRMAN HAMMER: Thank you.

DR. SELF: Could I ask one more feature of these data? This is, again, this LOCF method. What fraction of this data -- well, how to ask the question. What time points do the actual observations represent in this slide? You're moving data, earlier data, forward. How long a term of follow-up is this really?

MR. ROHOWSKY: Okay. I'm not sure I completely understand what you're saying.

CHAIRMAN HAMMER: What proportion were data carried forward versus actual data at the last data collection time point? Does that translate the question? How much was imputed versus how much was actual?

MR. ROHOWSKY: Was actual data? I could give you an estimate. I don't have an exact figure. Well, I could give you some idea; unfortunately, not through eight weeks. At 2 weeks, it was 14 percent

that were carried forward. At 4 weeks, it was 35 percent. And so we have to figure it might have been somewhere in that area of 35 to 40 percent at 8 weeks.

One thing that may have an impact here, these patients who were carried forward, they're not always patients who discontinued. These patients did not always have data at each time point. So they may have had data at four weeks, at six weeks, but not at eight weeks.

MEMBER MASUR: What is the *n* here; like, for instance, that 220? It says *n* equals 27 out of 30. What does that *n* equals 27 out of 30 refer to?

MR. ROHOWSKY: Okay. What that means is there were 30 patients who had some data somewhere at the 1,000 dose. But of those 30, 27 had data at baseline and at the follow-up so that a change from baseline could be calculated.

MEMBER MASUR: So change at baseline probably meaning it wasn't imputed data; it was real data? I think it's --

MR. ROHOWSKY: Well, meaning that they had, some patients had, data at baseline only and no follow-up. Others, for whatever reason, did not have data at baseline but did at follow-up.

DR. SELF: At at least one follow-up?

MR. ROHOWSKY: The 27 means that they had baseline and data at their last non-missing time point.

DR. SELF: So there is at least one follow-up --

MR. ROHOWSKY: Yes.

DR. SELF: -- visit with data plus baseline? We don't know exactly when that is, --

MR. ROHOWSKY: Yes.

DR. SELF: -- whether that's two, four, or eight weeks? Is that right?

MR. ROHOWSKY: Or for the 228, it could have been 50 weeks.

CHAIRMAN HAMMER: Dr. Masur, any other questions? Did you have one follow-up, Doctor? Yes, please, Dr. Lipsky? Then we need to move on to the FDA presentation.

MEMBER LIPSKY: We're talking about the microbiology. In a parasitic infection like malaria, it's complicated that there are suppressive and curative therapies, there are tissue exoerythrocytic phase, et cetera, what gets delivered or not.

Do you have any idea what your drug is doing to what part of the life cycle of this parasite? And that also would have implications on where the

drug needs to be and when.

DR. SOAVE: I wish I did. I don't know. I've spent a significant portion of my life studying this organism in the lab and clinically as well. And there still are many more questions to be answered about this bug than there are answers.

It's very difficult to do those studies because there are just no good models to use in the laboratory to look to see. I mean, now we're beginning finally to sequence some of the *Cryptosporidia* genes. People are beginning to make a little progress in that direction, but every time we make a little bit of progress, we're faced with a whole host of other problems.

For example, when you finally get enough of these organisms from one source and you do all of this work of sequencing and finding an enzyme or finding a gene, is that relevant for all the organisms or are you dealing --

MEMBER LIPSKY: Excuse me. But, still, just from the clinical outcome, --

DR. SOAVE: I have no idea.

MEMBER LIPSKY: -- is this behaving like it's -- you know, are you getting a radical cure or is it just a suppressive therapy?

DR. SOAVE: In some patients, in a very, very small subset, it was a radical cure. In most of the patients, it was suppressive therapy.

MEMBER LIPSKY: Thank you.

CHAIRMAN HAMMER: I just have two quick questions. One relates to other interventions at the time of entry into the study. What proportion of subjects since many of these were quite ill, patients were quite ill and were hospitalized, received total parenteral nutrition or had dietary manipulations at the initiation of the nitazoxanide treatment?

DR. SOAVE: In the 004, it was approximately a third who were either on IV hydration intermittently at home or were on TPN.

CHAIRMAN HAMMER: And in the total study population, the three studies in aggregate --

DR. SOAVE: I don't know.

CHAIRMAN HAMMER: -- of the 228?

DR. DUDLEY: Unfortunately, we don't have good data to respond to that.

CHAIRMAN HAMMER: Okay. One last question. The quality of life instrument, was that devised specifically for these studies? Was it validated previously or in parallel or was it a fairly unique instrument for these studies?

DR. DUDLEY: It was not designed specifically for this study. It was actually developed over time at Cornell in all of those studies that had been done with cryptosporidiosis.

CHAIRMAN HAMMER: Has it been applied to other diarrheal disease? And how do you find it as far as a validated instrument?

DR. SOAVE: We actually used it successfully in two studies prior to the nitazoxanide study. And that's what caused us to prove on it minimally and actually use it for this study.

We have found it to be very, very useful because it also helps use tease out what might be drug-related toxicity versus what might be toxicity or signs and symptoms due to the disease itself. So we have found it tremendously helpful.

It is somewhat based on other similar type instruments that have been used in other types of diarrheal studies.

CHAIRMAN HAMMER: Thank you. Thank you.

DR. SOAVE: I don't know if it's appropriate to bring this up at this time, but this might help enlighten. We don't have a slide of this, and we could make this available to the Committee I guess if we get a few seconds of break. But we do

have the Kaplan-Meier plots basically that Dr. Masur suggested might be helpful. And this also responds, in part, to Ms. Cohen's question before of how long these patients go out.

If we look at the Kaplan-Meier plots that are generated here for clinical response and parasitologic response, -- and I guess, again, we'll make it available, but just very briefly -- this goes out 24 weeks. And it's basically 8 of the 30 patients that went out that entire period of time. And there is accumulative both parasitologic and clinical response.

So for 8 of the patients out of the 30, there definitely was sustained effect over time.

CHAIRMAN HAMMER: Maybe I could suggest we could Xerox that and distribute it. And if there are questions, we can come back to that for clarification later.

Just one last question. I certainly have seen and understand the situation of the clinical response without a clear microbiologic response or at least a delayed one.

Did you have any circumstances where the durable absence of *Cryptosporidia* in the stool on repeated measure without clinical response, basically

with the correlation as of your parasitologic and clinical responses when you had a parasitologic clearing? Did you have any patients that continued to be symptomatic?

DR. SOAVE: We didn't see it in this study. We saw it in the previous study. And that was the instance where we decided then to be aggressive and do biopsies and look for something else. And, indeed, our patient ended up having CMV as being a primary problem. This study, that didn't happen.

CHAIRMAN HAMMER: By "This study," you mean --

DR. SOAVE: In the 004, in the 30 patients.

CHAIRMAN HAMMER: In the overall study, do we know that if you cleared and durably cleared, that you also clinically cleared? Is there any discordance there or do we not know?

DR. DUDLEY: We're looking. I can say that some patients that durably cleared went off treatment. We did have some patients who were complete responders. And, as has been stated earlier, they came off drug.

Unfortunately, we didn't follow those patients for long periods of time, as is the case in

this kind of study. And I guess we would --

CHAIRMAN HAMMER: I'm just trying to relate the --

DR. DUDLEY: Yes.

CHAIRMAN HAMMER: -- activity of the drug against this organism and the --

DR. DUDLEY: There may be a slide --

CHAIRMAN HAMMER: -- just general infectious disease fashion to clinical response.

DR. DUDLEY: There may be a slide here that will help.

CHAIRMAN HAMMER: Okay.

DR. SOAVE: The discordance most commonly comes in the other direction, actually, which we --

CHAIRMAN HAMMER: That I understand. It would be very helpful to know if discordance happens in the direction that I asked about.

MR. ROHOWSKY: I think this may help answer your question here. We have a correlation of parasitologic and clinical responses for study 009A. So this is the largest of the three.

On the *y*-axis, this is the number of patients with a clinical response for different parasitologic responses. So of those who improved parasitologically, we have: one, complete response;

four, a partial response; three, failures. Of those with no change in their parasitologic status, it's four, one, and four. And of those who worsened parasitologically, there is one complete responder.

Now, this is a limited subset. Everyone who is represented in this graph had to have both a parasitologic response and a clinical response, meaning they had crypto at baseline and at some time point up through eight weeks and the same for clinical.

Does that answer your question?

CHAIRMAN HAMMER: If I interpret this correctly, the second and third bars, you would have five patients who had a complete clinical response, who had either no change or a worsened parasitologic response?

MR. ROHOWSKY: Well, yes.

CHAIRMAN HAMMER: Okay. That's very helpful. Thank you.

Dr. Sears, did you have any?

DR. SEARS: So would you interpret that as discordant?

CHAIRMAN HAMMER: I wouldn't interpret personally. Yes, that would be my interpretation, some evidence of discordance.

Okay. I think we need to move on. And, for the audience's sake, we will catch up with the day's schedule since we're somewhat behind. Thank you very much.

We're going to move on to the FDA presentation. And Dr. Roca will lead that off.

FDA PRESENTATION

CLINICAL SAFETY AND EFFICACY

DR. ROCA: Good morning. Dr. Hammer, members of the Committee, representatives from Unimed Pharmaceuticals, and guests, I'm Dr. Roca from the Division of Special Pathogens and Immunologic Drug Products and the reviewing medical officer for this NDA.

First of all, I would like to thank Unimed Pharmaceuticals for their presentation this morning, to commend them for their efforts. They have brought nitazoxanide from Phase I/II studies to NDA filing status in a little bit over two years.

Next slide. I would also like to take a quick moment to recognize a few of my colleagues, whose help has been invaluable to the performance of this review. You have met Dr. Silliman and Dr. Davit from before. Ellen Frank was the regulatory management officer; Gene Holbert, chemistry reviewer;

Shugal Bala, microbiology; Steve Kunder, pharmacotoxicologist; and Mark Cavaillé-Coll served as the medical team leader.

Next slide. This application presented several challenges, several of which we would like to bring to your attention right now: microbiological issues, study design, data analysis, and safety.

First I will discuss certain microbiological issues that became apparent during the review and which some of you have already touched upon this morning.

The *in vitro* studies performed gave limited information and demonstrated some variability in their results. The *in vivo* studies were performed in three different animal models, with one model showing conflicting results in repeated studies.

Furthermore, since there is no current consensus regarding a valid animal model, it is difficult to say which one is predictive of nitazoxanide's activity in humans. And, as mentioned before, the mechanism of nitazoxanide is unknown.

Regarding the study design, there are three points that need to be highlighted. The first is the open-label study design of the three studies. The applicant has already described to you the history

of the clinical drug development and their rationale for their designs.

The study designs were reasonable given the circumstances. However, all the objective data were obtained next to a frequency. A portion of the study's results depended on subjective evaluation of symptomatology.

The second point to consider is whether the three trials do allow for pooling of the data.

And, finally, the third point is the use of a historical control.

Next slide, please. This slide summarizes the three studies performed by the applicant. And, as noted before, 009A and 009B were very similar, had the same conclusion and exclusion criteria as with the study endpoints.

There were some differences noted between 004 and the other two studies. And Dr. Silliman will go into more detail regarding what analysis modifications were performed in order to compensate for these differences.

Next slide, please. The third issue to be highlighted regarding the study design is the use of a historical control. As this slide shows, this is one of the types of controls that is recognized as a

component of an adequate and well-controlled trial. However, it is acknowledged that a study design may present difficulties during the data analysis.

Next slide, please. I would like now to turn the podium over to Dr. Nancy Silliman, who will discuss the data analysis issues pertaining to the NDA.

DR. SILLIMAN: Thank you, Dr. Roca.

STATISTICAL SUMMARY

DR. SILLIMAN: Good morning. My name is Nancy Silliman, and I was the statistical reviewer for this new drug application.

Next slide, please. Today I'd like to share with you the results of our clinical and statistical review of this NDA. What I'm planning to do is focus on the patient population, which was considered primary at the time of NDA submission.

I'd like to explore the primary clinical endpoint in some detail. And then I'm also planning to summarize results for other endpoints that were of interest and that were examined.

An outline of the remainder of my part of the presentation. I'd like to begin with some general comments. And then I'm going to address six measures of clinical response where controlled comparisons

where possible. That is, these are going to be six outcomes where we could compare how patients receiving nitazoxanide did with patients receiving a placebo.

The first two measures that I'll look at, change from baseline in total and liquid stool count, are just simple measures to give you a feel for the data, sort of what's there.

The next outcome that I'll focus on I'm calling here Clinical Response A. And this was the primary endpoint. This is the only endpoint that was prospectively defined and agreed upon by Unimed and FDA before at the time of NDA submission.

And then I'd like to talk about three other measures of clinical response that were produced after the Pfizer data became available. And let me just clarify that the Pfizer placebo data became available after the time of initial NDA submission. And so there were no prospectively defined methods to deal with this data. That said, you can consider these three outcome measures sort of sensitivity analyses.

And then at the end I'd like to talk a little bit about the quality of life symptom data that was collected for the nitazoxanide patients. Unfortunately, we do not have similar data for the

placebo patients. So this is an uncontrolled comparison. And then, finally, I'll summarize the results.

There are four general comments that I'd like to touch upon. The first is the fact that we're interested in controlled comparisons.

The second is that there were differences in how the data was collected between the studies. And this has affected how outcomes were analyzed.

The third is that we're focusing on the completers patient population, which was primary at the time of NDA submission.

And the fourth point is I'll mention a little bit about comparability of treatment groups at baseline.

So, in more detail, the first point, we're interested in controlled comparisons. Unfortunately, for reasons that we've heard earlier today, there are no placebo-controlled trials of nitazoxanide.

Since the interpretation of uncontrolled data is problematic at best, what we have chosen to do in our review and in the presentation today is to focus on the comparison between NTZ and a historical placebo group.

So specifically what we're doing today is

we're going to look at the comparison between NTZ patients receiving 1,000 milligrams per day -- and I should say these are patients who began on that dose -- from the 3 Unimed studies: 004, 009A, and 009B. And we'll compare them to historical placebo patients from two trials: an AIDS clinical trial group study of placebo versus paromomycin and the Pfizer study of placebo versus azithromycin.

The second general comment that I wanted to make was that there are differences in how the data were collected. And there are actually two things that I'd like to point out here. The first is that there were differences in the timing of the visits.

As you've heard, we have data on nitazoxanide patients from the three Unimed studies available at baseline, weeks one, two, and four, and then further time points. However, the placebo data from the two, the AIDS clinical trial group study and the Pfizer study, unfortunately, we only have data available for baseline and weeks one and three.

Since week one is too early to assess a drug effect, what was done was we used the week three time point for the placebo patients and compared that to the week four time point for the nitazoxanide patients. That was the primary analysis.

As a sensitivity analysis, to try to determine whether the difference in the length of follow-up affects our conclusions, we compared NTZ week two data for placebo week three data. And there were no differences in our conclusions. So today we'll focus on the primary analysis, NTZ week four versus placebo week three.

The second comment that I wanted to make about differences in data collection was -- and Dr. Dudley touched upon this before -- some of the data was collected as a continuous outcome. Other data was collected as a categorical outcome.

So in the three Unimed studies and the AIDS clinical trial group study, data was collected as number of stools per day, either total or liquid; in other words, a continuous outcome. However, the Pfizer study collected only a categorical outcome.

That is, the most that we know about the placebo patients from the Pfizer studies is whether they had zero stools per day, one to three stools per day, four to six stools per day, seven to nine stools per day, or ten or more stools per day.

Two analysis approaches were taken to try to incorporate the Pfizer data. And, as I've said, this data became available after the time of NDA

submission. So these are post hoc analyses. And they're considered sensitivity analyses by the FDA.

The first approach was to convert categorical data to continuous using the midpoints of the ranges for the Pfizer study. So, for example, if you were in this category, you were assigned a value of five as your stool count for that visit. For the highest category, patients were assigned a value of ten.

So once this data was converted to continuous, we then incorporated it into the analysis of the original, the primary efficacy endpoint.

The second approach that was taken, which is more straightforward, was to convert the continuous data to categorical. And we collapse here into four categories, basically due to the fact that there was no one in this zero stool category.

And what we have done here, the four categories are: less than three and a half stools per day. And this for notational convenience is written as 3.5 to 6.4, but it actually means 3.5 to less than 6.5 stools per day. The third group was 6.5 to less than 9.5 stools per day. And the final category was 9.5 or more stools per day.

And to analyze this categorical data,

there were three new outcome measures that were looked at. These are: Clinical Response B, Modified Clinical Response B, and Clinical Response C, which I'll define in a few more slides.

The third general comment that I wanted to make was that we're focusing on the completer population. This was primary at the time of NDA submission. And the results were similar for other analysis populations that were considered.

The definition of the completer population let me just remind you. NTZ week four completers were patients who had received at least one dose of nitazoxanide, were at least 18 years old, had data available for the baseline and week 4 visits, and were assigned to 1,000 milligrams per day initially.

Placebo week three completers were defined similarly. They had to have received at least one dose of placebo. They had to be at least 18 years old. And they needed data available for baseline and week three because you recall there is no week four placebo data.

This table shows reasons for exclusion from this analysis. What we'll see is we had 226 AIDS patients enrolled and treated in the nitazoxanide group, 59 placebo patients enrolled and treated with

at least one dose.

There are 91 NTZ patients in the completers group and 43 placebo patients in the completers group. This leaves 135 and 16 patients, respectively, that were excluded from the analysis.

The reasons for exclusion are given in the last three rows of this table. Essentially for nitazoxanide, we lost a fair number of patients due to the fact that they started on a dose other than 1,000 milligrams a day.

We lost just a handful of patients due to their young age. And the majority of patients are excluded from this analysis because of their missing data. This is 34 percent of the nitazoxanide patients that had missing data and 27 percent of the placebo patients that had missing data.

And to address a question that Dr. Self had earlier, if you incorporate these patients with missing data as failure, -- that's sort of the worst-case analysis -- in the primary outcome measure, you end up with actually a higher response rate for the placebo group, although it's, of course, not statistically significant. It's 28 percent for the placebo group versus 23 percent for the nitazoxanide group.

In the remainder of the presentation, the results are just presented for people that actually had data at both visits. And so what you can think of is if we use that worst-case analysis and incorporate these missing data points as failures, any difference you see between the treatment arms will tend to be diminished.

The last point that I would like to make under general comments is about comparability of treatment groups at baseline. There was some concern that the placebo patients might be less ill. CD_4 counts tended to be somewhat higher in placebo patients. Daily total stool counts and daily liquid stool counts tended to be somewhat lower in placebo patients at baseline.

So in an attempt to control for some of these baseline differences, the FDA analysis has looked at the various outcome measures controlling for these three factors, both uni-variately and multi-variately. And essentially no effect was found on conclusions when you control for these baseline differences.

Now I'd like to turn to sort of the major part of the presentation. These are six clinical endpoints where controlled comparisons were possible.

So we're going to compare how patients receiving nitazoxanide did to patients receiving placebo.

And before I begin, I would just like to point out that there were no significant treatment differences observed on any of these six endpoints. In addition, when we control for baseline factors, CD_4 count, total number of stools, and total number of liquid stools, there are still no significant treatment differences observed.

So let's first look at change from baseline in total stool count to give you a feel for the data that is available. In this analysis, I'm only using the placebo patients from the ACTG study since the Pfizer data was collected as a categorical outcome.

And what we see here, the median stool count at baseline is slightly higher for the nitazoxanide patients, 7 stools per day versus 5.7 stools per day, about 6 stools per day, for the placebo patients. So there is a difference of about one stool per day at baseline.

The range was fairly wide in the nitazoxanide patients. We had someone with no stools at baseline and someone with 25 stools at baseline. For the placebo patients, the range was also fairly

large, from 2.3 stools to 19 stools per day.

The median stool count at follow-up was about four stools for both of the groups. And, again, the ranges were somewhat variable. I should point out that I'm using the median here since this data is highly skewed. So it's misleading to look at averages.

Okay. Next slide, please. Thank you. What we see here is the median change from baseline in stool count. So for the nitazoxanide patients, there was a reduction of 2.5 stools per day. For the placebo patients, the median reduction was two stools per day. So the difference here was a half a stool per day in the median reduction.

These *p*-values indicate that this change from baseline is highly significant for the NTZ group. It's also highly significant for the placebo group. The *p*-value in the last row of the table indicates that the difference in the magnitude of the change is not statistically significant for NTZ versus placebo.

This is perhaps an easier way to look at the data. These are side-by-side box plots of the change in the total stool count for nitazoxanide patients and placebo patients. And let me just remind you how box plots are constructed.

The lower line of the box here is the first quartile. This means that 25 percent of the patients in this group had a lower change in stool count or larger if you want to look at it that way.

The line in the middle of the box is the median. This indicates that 50 percent of the patients had values less than that.

The top line of the box is the third quartile. It indicates that 75 percent of the patients had values less than that. And then the whiskers extend one and a half times the length of this box. And patients outside this are starred as outliers. They're unusual for the group that was considered.

So what we see here is essentially the middle 50 percent of the data looks fairly similar for nitazoxanide versus placebo. We do have several -- there are six nitazoxanide patients here that had quite impressive reductions in their stool count. There are also two nitazoxanide patients that had a larger increase in their stool counts.

This slide is an attempt to look at similar type of data for the Pfizer placebo patients. Since this data is categorical, this is a fifth table. And what it indicates is the rows are where the

patient started at baseline. The columns are where the patient ended up at week three.

So the data on the diagonal that's shaded here, there were 13 patients that essentially had no change. For example, these four patients started the study with four to six stools and ended at week three with four to six stools.

Patients above this diagonal had an increase in their stool count. The first dot diagonal, there's a total of four patients who increased one category. The second diagonal shows us there's one patient who increased two categories. And then, finally, there's one patient who increased three categories.

Similarly, there were ten patients who decreased their stool count. They got better. There were a total of eight patients on this first diagonal that decreased one category, one patient who decreased two categories, and one patient who decreased three categories from baseline. So they started with ten or more stools at baseline and ended up with one to three stools at follow-up.

Next slide, please. A similar analysis was done for change from baseline in liquid stool count. The results are essentially identical. So

they're not shown here, but I can show them to you later if you're interested.

Again, we saw a highly significant change from baseline for NTZ patients, a highly significant change from baseline for placebo patients, and no difference between the two treatment groups in the amount of change.

The third outcome measure is Clinical Response A. This was the outcome measure that was prospectively defined and agreed upon by Unimed and FDA. It's considered our primary endpoint I think by both parties.

The definition of a responder here is a patient you'll recall who either has a 50 percent or higher reduction in their total stool count or a patient who gets down to three or fewer total stools per day at follow-up, having begun the study with more than three liquid stools at baseline.

The difference between Unimed and FDA analysis, FDA analysis excludes the Pfizer patients due to the way their data was collected. Unimed has actually analyzed this endpoint, both including and excluding Pfizer patients. The results covered in their presentation today include the Pfizer patients. The results that they submitted in their NDA update

excluded Pfizer patients.

Here are the FDA results for Clinical Response A. And what I'd like you to focus on is this first row. We are essentially seeing a 43 percent response rate for NTZ patients compared to a 36 response rate for placebo patients. And this difference is not statistically significant.

I would point out there are going to be several more tables that follow. And if you want to try to remember one table, I think this is the table to remember because this is the closest that we have to what was actually submitted in the initial NDA. There were other methods developed later after the Pfizer data became available, which we consider more of a sensitivity analysis.

That said, they still give you a feel for the data. So if you include the Pfizer patients after converting their data, they have about a 24 percent response rate. So that brings the combined placebo rate down to 28 percent. And that 43 versus 28 percent is not statistically significant.

I should also point out the rates in Unimed's presentation this morning are about five percentage points lower than 43 and 28 because they're using last observation carried forward. So they're

getting about a five percent reduction in both treatment arms. But the difference between the treatment arms remains the same.

Also, these rates are lower than you might recall when we were talking about the individual study results. Those were in the 50s to 60s. That's because for Study 009A and 009B, there we were looking at responders as anyone who had a 25 percent or greater reduction in their stool counts. Here we're looking at patients that had to have at least a 50 percent reduction in their stool count, which may provide more clinical benefit to the patient.

This table shows the results for Clinical Response A in somewhat more detail. You'll recall there were two ways that you could be counted as a cure. So what this table does is it shows you the first row is patients who were cured because they met both criteria. The next row is patients who were cured because they had a 50 percent reduction but they didn't get down to 3 or fewer stools at follow-up. The third row is patients that got down to 3 or fewer stools at follow-up, having had less than a 50 percent reduction. And then finally are the patients with no response.

And what we see here is essentially the

only difference is in the patients that had a 50 percent reduction which did not bring them down to 3 or fewer stools at follow-up. And this is partially explained by the fact that there is more variability in the nitazoxanide patients. And there were a greater number that started out with higher stool counts.

So a 50 percent reduction is not going to bring them to 3 stools per day at follow-up, although the magnitude of the reduction that was seen between the two treatment groups tended to be similar.

That's good. Next slide, please. The fourth outcome I'd like to look at is Clinical Response B. This was defined by the applicant after the Pfizer data became available.

Here a responder is defined as a patient who shifts down one or more categories from baseline to follow-up. So, for example, if you started with 9.5 stools per day, you had to get down to fewer than 9.5 at follow-up to be a responder. This is a fairly easy criterion to meet. So what we'll see is that the response rates are fairly high for this analysis.

The difference between Unimed and FDA analysis, FDA analysis excludes patients in the lowest category at baseline. That is, we excluded patients

who had less than three and a half stools per day at baseline because by definition, there's no way for them to be assessed as a cure. There's not another category for them to go down to. Unimed analysis includes these patients and calls them all failures.

FDA results for Clinical Response B. What we see here -- this is a fairly easy criterion to meet. So the response rates are high: 65 percent for NTZ, 61 percent for placebo. And there is no treatment difference, no significant treatment difference.

The next outcome that I would like to look at is Modified Clinical Response B. This was defined by the FDA after the Pfizer data became available and was an attempt to look at a more clinically meaningful change from baseline in stool count.

Here a responder is defined as a patient who shifts down two or more categories. So, for example, if you had 9.5 stools per day at baseline, you had to get down to less than 6.5 at follow-up to be cured.

The difference between Unimed and FDA analysis, the applicant did not perform this analysis.

Here are the results for Modified Clinical Response B. These results look more promising. We

have a 43 percent response rate for nitazoxanide patients and only a 20 percent response rate for placebo patients. This difference is not statistically significant.

And also in looking at this difference, one has to recall that we're looking at many different endpoints and many different sensitivity analyses. So we would really need a very tiny *p*-value to have any confidence that there was a true treatment difference here.

Okay. The last outcome that I'd like to look at is Clinical Response C. This was suggested by the FDA after the time of NDA submission and after the Pfizer data became available and is an attempt to look at what are usually called complete responders. So here to be a response, you had to get down to 3 or fewer total bowel movements at follow-up. And obviously patients who began in that category are excluded because it doesn't make sense to include them. The difference between Unimed and FDA analysis, the same approach was used by both parties.

Here are the results from clinical Response C. What we see is about a 31 percent response rate in the nitazoxanide patients, compared to a 38 percent response rate in the placebo patients.

This difference was not statistically significant.

The placebo group has a slightly higher rate here. And you'll notice in the FDA background, there are Tables 15, 16, and 17 you might want to look at at the end of the presentation.

They present this variable by baseline CD_4 counts, baseline total stool count, and baseline liquid stool count, respectively. And the difference does not appear to be explained when you control for those baseline factors. You still get similar rates between NTZ and placebo in each of the strata that were examined.

Finally I would like to talk a little bit about the quality of life data that was collected for the nitazoxanide patients. Unfortunately, we didn't have similar data for the placebo patients. So this is an uncontrolled comparison.

There were six qualify of life symptoms that were considered. You'll recall they were nausea, vomiting, abdominal pain, urgency, incontinence, and nocturnal bowel movements.

They were scored on the four-point scale: one meaning not at all, two meaning mild, three meaning moderate, and four meaning that the symptom was marked.

What I'd like you to focus on in this table is the final column. This is the results for NTZ week four completers before the time of -- there was an efficacy update, which added two more patients. And this is taken from the sponsors, the applicant's submission.

This shows the average change from baseline for each of the symptom scores. And what we see is that the amount of change ranged from -.2 for vomiting to -.8 for bowel movements that woke the patient from sleep.

Now, each of these changes from baseline was statistically significant. However, there are two questions that the Advisory Committee needs to consider. The first is the fact that this is uncontrolled data. And if you'll recall the analysis of change from baseline and total stool count, there we also saw a highly significant change from baseline for nitazoxanide patients. We saw a highly significant change from baseline for placebo patients. And there was no difference between the two groups.

The second question for the Advisory Committee we need help on is whether these changes from -.2 to -.8 are clinically meaningful on a 4-point scale.

So, to summarize my part of the presentation, in FDA's analysis, NTZ response rates range from 31 to 43 percent. And this is excluding Clinical Response B because those rates were unusually high. And you'll recall there was a median reduction of two and a half stools per day from baseline.

The placebo response rates ranged from 20 to 38 percent, again including Clinical Response B. And there was a median reduction of two stools per day from baseline.

No significant differences, treatment differences, were observed on any of the six endpoints that were considered here. And when we control for baseline differences, there were still no significant treatment differences.

Finally, we had a significant change from baseline for nitazoxanide patients on all of the quality of life scores. However, the results are uncontrolled. And so we need a little bit of help interpreting this data.

Thank you. And I'd like to turn the podium back over to Dr. Roca.

DR. ROCA: I think we have caught up on time a little bit. So I will slow down.

As we discuss in the beginning, there were

four points that we wanted to bring to the Committee's attention. And the last one is safety.

Next slide, please. This slide shows the number of patients in the applicant's current safety database. And even if one were to include the 88 patients in the overseas studies, -- and this would be in Mali and Mexico -- it would still be quite less than the total amount of database that one is usually expected to see or one would like to see.

It is noted that there is a much larger database in non-AIDS patients. And there are our overseas patients. However, these are for different indications, shorter durations of therapy, and for different dose. Although this information is very helpful, it is not exactly applicable to the patient population for which the applicant seeks approval.

This slide is here to remind you and to refresh your memory of the extent of drug exposure in the safety databases, essentially the same slide that the applicant showed before.

And there are three points that I'd like to bring out about this slide. First, there is no control safety data except for some comparison between 1,000-milligram and 2,000-milligram dose per day. And the 2,000-milligram did suggest that the higher dose

was less well-tolerated.

Second, there was an overall 117 patients which received 1,000 milligrams for at least one month or four weeks.

And the last point is 22 patients received 2,000 milligrams for at least one month.

Next slide, please. This slide summarizes the incidence of the liver enzyme elevations that were observed. And two of these events were considered Grade 4 or life-threatening. One of them was an alkaline phosphatase, and it was felt not to be drug-related. And the other one was an AST. That was felt to be drug-related, and it did improve after discontinuation of nitazoxanide.

The pediatric database consists of 13 patients ranging from ages of 3 to 15. And in this group, 8 out of 13 experienced an adverse event. The type of adverse events observed are similar to the ones that were seen in the adult patients.

In summary, nitazoxanide demonstrated variable results in the different experimental models. And, as mentioned before, there is no consensus regarding a valid animal model. Therefore, it is not clear which one would be representative of nitazoxanide's activity in humans.

Next slide, please. No significant differences were observed between nitazoxanide and placebo for any of the six clinical endpoints. No significant differences were observed between nitazoxanide and placebo in analyses that controlled for baseline factors.

There is the potential concern for hepatotoxicity in the intended patient population. And we concur with the applicant, as they mention in their background package, that patients on nitazoxanide therapy should be monitored for these toxicities.

Thank you for your attention.

CHAIRMAN HAMMER: Thank you.

Are there questions from the panel members for the FDA presenters? Dr. Mathews?

DR. MATHEWS: The response definition for number of stools, say, at four weeks, was that based on diaries for the preceding week? And was the method of specification of that outcome variable similar, effectively similar, in the placebo-controlled group as in the nitazoxanide group?

In other words, there's a lot of variability from day to day. And Dr. Soave showed us a sample diary. Is that what was used in defining

response in terms of stool frequency?

DR. SILLIMAN: The applicant can also jump in here if I say anything wrong. At baseline I think for the NTZ patients, they were looking at a week of data. For most of the other time points, I think it was an average over the prior three days.

DR. MATHEWS: And it was actually based on diaries or report of the patient: On average how many stools did you have over the last week?

DR. SILLIMAN: I think it was based on patient diaries. That was my understanding.

DR. MATHEWS: Is there a difference, then? The placebo patients had it collected a different way? Do you know, Dr. Soave?

DR. SOAVE: Yes. At least the Pfizer patients, it was a report. The NTZ was based on diaries.

DR. MATHEWS: Okay. And the ACTG trial, how is that?

DR. SILLIMAN: That was also based on diaries.

CHAIRMAN HAMMER: Dr. Lipsky?

MEMBER LIPSKY: With the negative results, can you give us an idea of the Type II error? And where there were differences, how many patients might

it take to show a difference?

DR. SILLIMAN: I think the company had looked at that. There was only like a 38 percent --

DR. LEUNG: Yes. With trying to detect the difference between, say, a 43 percent of NTZ compared to the 28 percent in the combined placebo study, the observed power is only 38 percent with a Type I error of 105. If you want to have 80 percent power, than you need 159 patients per arm in order to achieve that.

CHAIRMAN HAMMER: Please identify yourself for the transcript.

DR. LEUNG: Hoi Leung, a Unimed consultant.

CHAIRMAN HAMMER: Thank you.

DR. SILLIMAN: Yes. The power for the primary comparison was low, but you also recall, I mean, there were many, many sensitivity analyses that were conducted. So you would expect, just due to natural variability, that at least one of those analyses would have shown a significant treatment difference. And that didn't happen.

CHAIRMAN HAMMER: Dr. Hamilton?

MEMBER HAMILTON: Was the use of a microbiologic comparison simply not possible?

DR. SILLIMAN: For the placebo patients?

MEMBER HAMILTON: Yes.

DR. SILLIMAN: Yes. I guess we didn't focus on the micro data because there was a little bit of a disconnect between the clinical and the microbiology.

CHAIRMAN HAMMER: Any other questions?

(No response.)

CHAIRMAN HAMMER: We'll have a chance to come back with our critical questions at the beginning of the afternoon. I think we'll break for lunch. We'll reconvene in one hour, approximately 1:20. And we will start with the open public hearing at that time.

(Whereupon, a luncheon recess was taken at 12:18 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:21 p.m.)

CHAIRMAN HAMMER: I'd like to call to order the afternoon session. And we'll start the afternoon session with the open public hearing. There are three people signed up in advance. The first individual is Mark Bowers. We would ask for identification of affiliations and any disclosures that are necessary.

MR. BOWERS: Is this okay?

CHAIRMAN HAMMER: Use any microphone.

MR. BOWERS: Good. Thanks.

CHAIRMAN HAMMER: Thank you.

OPEN PUBLIC HEARING

MR. BOWERS: Well, as you introduced me, I'm Mark Bowers. I'm Managing Editor of the *Bulletin of Experimental Treatments for AIDS*, which has been reporting on the HIV epidemic and on treatment for HIV and opportunistic infections for the last ten years.

It's published by the San Francisco AIDS Foundation, of which I am an employee. It has a readership now of about 22,500, approximately evenly divided between health care providers and educated patients and their relations and their friends.

I also represent at this point the Andrew

Ziegler Foundation, which is a nonprofit organization that has as its mission access to state-of-the-art care for all people with HIV without regard for ability to pay. So that's specifically what we are interested in promoting.

I had submitted an article that comes from the recent April issue of the *Bulletin of Experimental Treatments for AIDS* for inclusion in the record. And I'm not sure that has happened. If not, I can yet give you a copy of that.

To come to the conclusion that I'm now going to present, we went through a series of steps that I think are briefly worth discussing. The Scientific Advisory Committee of the San Francisco AIDS Foundation has reviewed the data which I had collected from presentations by Unimed on two different occasions earlier this year and has come to the conclusion that based on their clinical experience as well as upon some of the pharmacological analysis done by a pharmacist that is in charge of something that's called the National HIV Teleconference and Teleconsultation Service that there be a specific recommendation made today to the panel that they consider the dosing; if this is approved, that dosing not be restricted in such a way that people will have

difficulty with third party payers. So that what they're suggesting is that no specific ceiling dose be established but, rather, that each individual physician in consultation and with best judgment be allowed to titrate up to the most effective dose for the individuals involved.

A similar process was undertaken with the medical staff of the Andrew Ziegler Foundation, which is, again, another six physicians who are in community practice in San Francisco. And the same conclusion was reached with the same recommendation.

So input from these individuals weighs heavily in any decision to either support or oppose the approval of any given drug by the San Francisco AIDS Foundation. And I believe you have seen in a consensus statement which has been widely circulated here that the San Francisco AIDS Foundation has been a signatory to a consensus statement that has strongly advised this Committee to accept and to agree to the NDA for this particular drug.

Let's see. I believe that the consensus statement does not include the Andrew Ziegler Foundation. I would like that to at least be a mental note on your part that that as well is now a signatory. And I believe that if we had more time, we

would get more organizations to sign on to that particular consensus statement. So I would encourage you to take that quite seriously as part of community input.

Personal experiences with this I will not refer to because they fall outside of the specific indication that is being asked for, but let me just say sort of in a parenthetical kind of way that there are other diarrhea-causing kinds of conditions that people can have for which NTZ seems to be effective. At least in my case that has been true with Crohn's disease but doesn't bolster the case in this particular instance.

However, anecdotal evidence as it seems to collect seems to have a stronger case, at least in the data presented so far, than does the analysis that was presented by FDA. So I would hope that you will listen to me and to the other two speakers who come to provide you with some testimony on this.

I believe that I'm missing some parts of what I'm supposed to say. I disclose that my two organizations, neither of them takes any money from Unimed. And I was authorized to use my own credit card to fly here. That was quite gracious on the part of the AIDS Foundation. I hope that they can change

their mind on that.

(Laughter.)

CHAIRMAN HAMMER: Thank you very much.

The next speaker is Bill Bahlman.

MR. BAHLMAN: Good afternoon. My name is Bill Bahlman. I am a founding member of Act Up New York, which was founded in March of 1987. And I was a treatment advocate in AIDS going back to 1985. I have been living with AIDS for over ten years now.

I also serve on the Community Advisory Board of NYU-Bellevue and their AIDS Clinical Trials Program, which is one of the most active and proactive community advisory boards in the country, where for each and every single clinical trials protocol that comes before our NYU-Bellevue's Clinical Trials Program, we review those protocols very carefully and quite often make comments on those protocols and have initiated a number of changes to those protocols when they're in their early form and even once those programs become protocols that are up and running.

I have thought long and hard on the approval of Cryptaz that's here before the Committee today and got more aggressively involved in terms of dealing with the issues around the approval of this drug as I began to be aware that there's some degree

of potential that the outcome from the Advisory Committee or the FDA might be in question.

I hope it is not in question, and I hope it will be approved today. But I thought it was important that a number of members of the community be somewhat involved in the process and to voice our concerns about the issues surrounding the approval of this drug.

I was very concerned about the placebo-controlled study that was attempted to be run through the ACTG program that over the course of the 15 months was only able to accrue 10 people with AIDS and crypto.

I think if we went back and there was more community involvement in the design of that protocol, we might have been able to come up with a more significant protocol that people with AIDS would want to enroll in. And we might have more significant data here today to deal with whether we should move ahead with approval or to say to the company that we want to see this drug go back for further analysis before we're able to say that it should be approved.

I think that's an unfortunate position for people with AIDS because what mistakes might have been made at ACTG, whether they were well-intentioned or

whatever, you know, that's the way things were set up and the way Unimed worked with the ACTG. It was a protocol that was not too friendly to people with AIDS, unfortunately. And I think they are the people who should not be held hostage to the limited data that we currently have here today.

And I think we need to take a bit of a leap of faith and understand that we have to work with the data we have now and figure out whether this drug should be made available to people with AIDS or not.

We look at the fact that it's been said a number of times today that there is access to Cryptaz at this point. That is true. It is not wide-scale access. It is available through a number of buyers' clubs, which means that if you want to gain access to it, you have to pay for it.

And how many people with AIDS who have crypto need to gain access to this drug or would like to be able to try it because it might be able to help them based on the limited data that we have who cannot afford to pay for it? They cannot get their insurance companies to pay for it.

So that's one of the other reasons I hope that this Committee recommends its approval, so there is more of a wider scale and more of a uniform access

to this drug that does not discriminate against people who cannot afford to pay for it.

I think we have to look at what we have here in terms of data. This drug was studied in people with very, very low CD_4 counts. It was also studied significantly in patients who did not have access to HAART, highly active anti-retroviral treatment regimens. Protease inhibitors were not so widely available when these studies were conducted.

So that sort of confounds things in terms of where we are, but it also tells us that the drug had an impact in these patients who were very sick and also did not have protease inhibitors to help them out.

We also look at the fact that it clearly I think shows that there was benefit to patients. You can compare it to the placebo-controlled analysis from Unimed and, with worse results, from the FDA's analysis, which didn't seem to take into account the differences in the characteristics of the patients that were used in the analysis in the 143 and the 192 studies.

I think one has to make a closer comparison and pair off the baseline characteristics of CD_4 count and how sick these patients were in the

Unimed studies, as compared to the other studies that were used in the analysis.

So in terms of what we do know, I do believe and on analysis of this data and I think a lot of community activists who have looked at the data see that there really appears to be a significant benefit to patients. How confident we can be about that benefit is in doubt, but it really appears as if there is benefit there. We see also in terms of the weight maintenance of the patients who are in the studies. And I think that's important.

In terms of the dosing regimens, we can see from the data a 500-milligram dose is not adequate. We appear to get good results from the 1,000-milligram dose. And we also see with the 2,000-milligram dose that that dose may be too high to start with a patient.

We're seeing more problems with gastrointestinal problems, which possibly might be compounded by the fact that the compound, one of the components is aspirin in the compound.

And, therefore, the 2,000-milligram dose starting with patients who have really bad diarrhea might lead to more problems with the patients. And, therefore, I don't think we necessarily should be

dosing up higher than that or be looking for a higher dose for initiation of therapy.

So I think the starting of the 1,000-milligram dose, 500 milligrams b.i.d., is an adequate choice. When I first looked at the data, I was thinking that the higher dose was necessary, but the more one looks at the data, the more it seems as if the indication that the company is looking for right now is the adequate one.

We also have to consider, as Rosemary Soave put forth, the condition of crypto in patients who are very sick. It is very debilitating. I suffered from crypto late last year. And I'll tell you the way one feels, the personal toll that it takes on your life, not just the losing of weight but also, as Rosemary put it, the self-esteem that one suffers when you're lying in bed incontinent, waking up through the middle of the night and you're a mess, not being able to go out, not being able to be with friends because you're concerned about that.

It's a problem we have now with anti-retroviral therapy as well. Taking nelfinivir can make one incontinent and give one uncontrollable diarrhea over a period of time. And I think it's downplayed a bit in terms of what patients suffer, but

it's very real and it's a hard thing for people to deal with.

So, with all of that, I believe very strongly that we should move toward approving this drug. I think we should monitor how it's being used. And I think it's going to fall amongst the physicians who use this drug when it's out there in clinical practice. With the experience that they have when they prescribe it to patients and they see success, they're going to use it again. And if they find that it's not helping their patients, they're going to wind up not using it.

I think the toxicity profile that you see before you is fairly good. I think that should give us some confidence to take a chance on data on a drug that we don't have the data that we would love to have.

So, with those things said, Act Up New York strongly urges its approval and that we should continue to monitor this drug over the coming years because I believe that crypto is not going away.

There has been talk about how there's a much less incidence of crypto thanks to HAART, but the water supply is probably worse than ever and may get worse in the future.

Sexual practices that people with AIDS engage in can lead to the spread of this disease and is no likelihood that that is going to get any better in the future.

I think there needs to be greater education around crypto and AIDS, particularly within the gay community but throughout all communities affected by AIDS. So I believe that we need to put an emphasis on education.

We need to better understand how crypto affects people with AIDS. There needs to be more research in there because there is a dearth of research, particularly due to the fact that we haven't had effective drugs, but I think it is very important we have that research and the education.

And so I just think, ending with that, I urge you to please support its approval.

CHAIRMAN HAMMER: Thank you very much.

The next speaker is Laura Morrison.

MS. MORRISON: Thanks. As noted, I'm Laura Morrison. And I'm here today on behalf of 17 AIDS organizations and publications, including The Treatment Action Group, Act Up East Bay, AIDS Action Baltimore, AIDS Project Arizona, AIDS Project Los Angeles, AIDS Treatment Initiatives in Atlanta, the

Center for AIDS-Houston, Foundation for AIDS and Immunology Research, Gay Men's Health Crisis, John James AIDS Treatment News, National Minority AIDS Council, Pause L.A., Pause Magazine, Project Inform, PWA Coalition Colorado, Resolute, and the Whitman Walker Clinic here in D.C., to urge the approval of Cryptaz for treatment of cryptosporidial diarrhea in people with AIDS.

I have distributed outside -- there's a consensus statement that we all signed onto as well as a background document that was based on data we received prior to today's hearing.

The groups who have reached this consensus position recommend approval, despite our recognition that the data package is rather marginal and is based largely; in fact, entirely, on open-label compassionate-use data.

While we typically believe that open-label compassionate-use study data are valuable solely or primarily for safety of a given drug and we're typically uncomfortable using it as an indicator of efficacy or as the sole basis for approval of a drug, in this case we don't see a choice.

We believe that in the case of anti-cryptosporidial agents, there really isn't a

possibility of doing placebo-controlled trials at this time and that the historical data that has been presented so far is not a reasonable comparison due to differences in study design and number of patients enrolled.

Also we believe there are ethical problems with conducting placebo-controlled trials at this point and actually don't think they are going to be feasible with the HAART regimens that people are now on, regardless of whether there's a decrease in the actual instance of cryptosporidiosis.

We see small numbers that are actually diagnosed, as we'll address, in the number of patients in the 226-patient population that was presented today who actually had confirmed, microbiologically confirmed, crypto.

People have access to other unapproved therapies. Whether they are actually effective, they can get them through off-label use. We've mentioned the buyers' club that have provided NTZ to people.

So there are a lot of problems with having controlled data, and we just have to accept the limitations, as Bill Bahlman said, with this data set and present our argument based on that.

That said, looking at the data that was

presented by the sponsor, we see an undeniable clinical response with an excellent safety profile.

We have limited our efficacy analysis as a community consensus group to those patients who had had microbiologically confirmed cryptosporidiosis. That was, at baseline we had 28 patients in 004 who fit that criteria and 39 in 009, for a total of 67.

Within those patient groups, we saw clinical response rates of nearly 40 percent of those in 004. And that was on a very stringent definition of what a clinical response was. We saw nearly 50 percent for the people in 009A.

And we saw microbiological parasitological response of nearly 40 percent in the 004 and close to 60 percent in 009A, which we believe clearly shows there is actively for Cryptaz for people with cryptosporidiosis.

It should be noted also, as Bill Bahlman did and Mark did, that the people in these studies were profoundly ill. They had advanced cryptosporidiosis and were profoundly immunosuppressed.

There is reason to believe that Cryptaz might have an even greater efficacy in people who are healthier at baseline. Right now for people who are

healthy, who are early in their cryptosporidiosis, maybe have a higher CD_4 count, there isn't an approved therapy. There is nothing else out there.

So it's really important for people to have a chance. And give people a one in two or even a four in ten chance of having something that is going to limit this debilitating diarrhea of this really devastating disease. I think we have to give them that opportunity. Without this, there is nothing.

That said, we urge you to recommend approval of Cryptaz and suggest that the FDA work with Unimed to develop post-marketing studies that might actually give us more answers about how to best use this, what duration of treatment we should have and what dose.

Thank you.

CHAIRMAN HAMMER: Thank you.

MR. BAHLMAN: This is Bill Bahlman.

I just wanted to say very quickly that I didn't make a disclosure because I was running from quick notes because when I prepared full text in advance of these hearings, I often chuck them and have written new remarks as I have been sitting here.

I just wanted to say that early on in discussions a couple of months ago, the company,

Unimed, offered to pay or take care of my expenses to be able to be here today, and I accepted that offer. And that's the only gratuity I've received at all, just to take care of my expenses to be here today.

CHAIRMAN HAMMER: Thank you.

Is there anyone else who wishes to make a public statement?

(No response.)

CHAIRMAN HAMMER: If not, I would just reiterate that the community consensus position paper is outside. And copies are available.

We have also received a letter from a patient involved in one of the studies supporting approval. I believe a copy is available outside.

And also Act Up Golden Gate has submitted a statement, copies of which are also available, supporting approval but supporting it under conditions and not supporting full approval but conditional approval. And, again, those statements are available for review.

That being said, we'll close this part of the meeting and move on. Before we have the charge to the Committee, I would just ask the panel members whether there are any last important questions that anyone has for either the sponsor or the agency.

Please, Doctor?

DR. SELF: There was a question raised about the FDA's data analysis, whether there was appropriate adjustment for differences in baseline characteristics between historical placebo-controlled and the NTZ patients. Could you comment on those adjustments and what you found?

DR. SILLIMAN: Sure. We looked at the outcome measures controlling for three baseline factors: CD_4 count, total stool count at baseline, and total liquid stool count at baseline. We did this both uni-variately using categories and multi-variately using logistic regression.

And controlling for differences in baseline factors we still found no significant treatment differences and no trends that were consistently in favor of nitazoxanide.

CHAIRMAN HAMMER: Thank you.

Dr. Sears?

DR. SEARS: Along the same lines, the question was raised whether the placebo group used for comparison is valid -- do you have any comments about that? -- in terms of the characteristics of the population.

DR. SILLIMAN: The placebo patients were

slightly less ill. We can actually show a couple of slides. Slide 57. These are side-by-side box plots of the CD_4 count at baseline. And what you'll see is the NTZ patients -- there we go. My pointer doesn't seem to be working.

The CD_4 counts are somewhat lower for the nitazoxanide patients. The difference here was not statistically significant. And you'll note that while the placebo patients were slightly less ill, still the majority of patients had CD_4 counts of less than 100. So it's not like they're healthy patients.

And then if we could go to the next slide? This shows the total number of stools at baseline for nitazoxanide and placebo patients. And, again, the nitazoxanide patients had slightly higher stool counts at baseline. There's also more variability in the nitazoxanide patients.

And then let's see. If we go to Slide 61, this is the number of liquid stools at baseline. Again, nitazoxanide patients had slightly higher stool counts at baseline than the placebo patients.

So to control for these differences, maybe I can show one of the tables to give you an idea of what we looked at. Slide 67, please. This shows results for the primary efficacy variable by CD_4

count.

And we looked at three categories which we felt were clinically meaningful: CD_4 count of zero to 50 at baseline, 50 to 150 at baseline, and greater than 150 at baseline.

Unfortunately, the number of placebo patients is small. As the Pfizer data was collected, it was the categorical outcome you'll recall. So here this is just the ACTG placebo patients versus the nitazoxanide patients.

And what you'll see is there is no consistent trend in favor of either treatment arm. And the *p*-value indicates that when you control for these three different levels of CD_4 count at baseline, there's no significant treatment difference or there is no trend in favor of either arm that's consistent across the strata. That's perhaps a better way to think about it.

Similar analyses were done looking at total stool count at baseline and total liquid stool count. Those are the next two slides. Here again we don't see any consistent trend in favor of either nitazoxanide or placebo. Numbers again are small, unfortunately. And the *p*-value indicates that controlling for these four different categories there

is no trend in favor of either arm that is consistent across the strata.

And then the next slide is we looked at number of liquid stools at baseline. And for this, we used patients who had less than or equal to three liquid stools at baseline -- so they're less ill patients -- and then greater than or equal to three liquid stools at baseline, the more ill patients. And, again, the rates were essentially similar in the treatment arms and there was no significant difference.

We also used logistic regression to look at all three of these factors together. And, actually, none of those factors were significant predictors of clinical response. And treatment was also not a significant predictor of clinical response.

CHAIRMAN HAMMER: Thank you. Thanks. Lights, please.

If there are no additional questions, then we'll turn to Dr. Dianne Murphy for the charge to the Committee.

CHARGE TO COMMITTEE

DR. MURPHY: Before we go to the questions, I just want to make a few statements. Today you've heard of a need for a good therapeutic

option for an infection which is life-threatening, devastating in an already vulnerable population.

You've also heard of a company which stepped forward and, despite concerted efforts by the company and cooperative efforts with NIH and ACTG, there is no concurrently placebo-controlled trial for you to evaluate.

You have heard of their efforts to obtain historical controls and of the limitations involved in using placebo patients from differently designed studies with differently designed endpoints.

Thus, you have been presented open-label historically controlled data where the placebo population had -- pick the middle here -- 20 percent positive response and other uncontrolled open-label data.

The proposal of the sponsor is not that there is a statistically significant difference. They propose that there is a non-statistically significant clinical benefit as demonstrated by persistence of a positive clinical benefit in numerous analysis that this therapy provides as a needed option for patients.

In this context, could we have a slide? You are presented with these questions. Is nitazoxanide safe and effective for use in the

treatment of cryptosporidial disease in AIDS? If yes, is there a specific patient population for which the drug is intended? And what in the data was convincing, keeping in mind future applicants? If no, what additional data is required in order to be able to make the above determination?

And I would hope that we wouldn't leave today without defining for this population what this Committee would want to see for a successful study and, in particular, the endpoints they felt are most relevant.

Next slide, please. And does the Committee have any additional advice regarding future studies with respect to: design, duration, and choice of comparator?

Thank you. And we look forward to your comments.

CHAIRMAN HAMMER: Thank you.

We will now turn to the Committee. The first question will be a voting question. And I'll just restate it, and then we'll go around the room. Is nitazoxanide safe and effective for use in the treatment of cryptosporidial diarrhea in AIDS? And I'll start on my left with Dr. Mathews.

DR. MATHEWS: The brief answer in my opinion is it appears to be safe, but I'm not convinced that it's effective.

And if I could just make a couple of comments, first of all, I share with the other members of the Committee admiration for the company, particularly the investigators who brought this forward and have worked in it for years.

Out on the West Coast, I have read all of Dr. Soave's articles on this and looked for the latest hope in the treatment of a devastating illness. But, for a number of reasons that I think have been highlighted in the course of the morning's discussion, I am not convinced that the difference between the placebo arms of the other studies and the combined two compassionate-use and one open-label study are meaningfully different. And they're certainly not statistically different. In my own mind, I'm not sure that we would be doing a favor to the community at large to state that efficacy has been demonstrated.

There are reasons that have to do with the diagnostic criteria, the varied diagnostic intensity, for good reasons certainly, but in use of a new agent for which there has not been clear-cut proof of

efficacy in any population by a randomized controlled trial, I am more persuaded by the history of trials in this disease, that it's been one agent after another brought forward based on open-label, uncontrolled observations, which when subjected to randomized controlled trials failed to prove the test.

The issues of loss to follow-up, short duration of observation I think have been raised and are cogent. The disease itself is so heterogeneous. And even the endpoint as it was defined, reduction to less than or equal to three stools per day, would include a whole range of patients, even on some of the graphs, where people dropped from, say, 20 to 25 stools a day down to less than less 3, others who had very small changes but still were able to meet the endpoint. I'm not convinced we're dealing with the same process, the same disease.

So, in conclusion, I just don't believe that the weight of evidence is there. And, therefore, I would vote no. There are other comments I'd make on possible ideas on how to study the drug more effectively.

CHAIRMAN HAMMER: Thank you.

We will return to the other questions that Dr. Murphy asked us, but the primary question, Dr.

Sears?

DR. SEARS: I don't think I can state it any better than Dr. Mathews. I agree that the nitazoxanide appears safe, but I concur with all of his comments on a relative lack or a lack of efficacy demonstrated in the study as presented.

CHAIRMAN HAMMER: Thank you.

Mr. Marco?

MR. MARCO: Well, I do believe that the drug is safe, but I also agree with some of the FDA's comment, especially Dr. Murphy, who said that doing cross-protocol analysis is often difficult, especially with confounding variables.

And so if I take her 20 percent median for placebo response rate and compare it to the FDA's 43 percent, it makes me feel confident that there's at least some marginal clinical benefit. And even in only looking at the patients who all had microbiologic evidence of crypto at baseline, I think that the risk/benefit ratio is in favor of NTZ.

And so I do see a soft yes for approval.

CHAIRMAN HAMMER: Thank you.

Ms. Cohen?

MS. COHEN: Well, if you say a soft yes, do I have to say a hard no? I have some concerns. I

don't think there's any absorption information. I don't think there's any information on the placebo. I'm not satisfied with the follow-up. I think the missing data I think overall someone said was 34 percent. They haven't had a decent animal model. There's no pharmacokinetic information.

And, you know, when one talks about buying clubs, it concerns me because I sat on the panel for thalidomide. That's not reason enough to pass a drug that you really don't know about.

And if we make this available, I always worry. It's for a certain population, but other people might think that: If it works for them, it will work for us.

And I just don't think there's enough information to make me comfortable. In the comparisons, I'm not even sure how they picked the patients, frankly, and whether they were similar. I just think it's a very difficult problem. And in my good conscience, I can't vote for it.

CHAIRMAN HAMMER: Thank you.

Dr. Self?

DR. SELF: In the briefing materials, the sponsor provided some criteria by which efficacy could be evaluated in the absence of placebo-controlled

trials. These were a dose-response relationship, which was not demonstrated.

The criteria also included comparison with historical controls, which I think, in spite of all of the difficulties given the problems with mounting a trial in this disease, is probably as best one can do.

So, contrary to an earlier statement, if all attempts have been made to mount a placebo-controlled trial and those fail, it's just not feasible. I think the approval shouldn't be held hostage to that. So I'm perfectly willing to entertain that sort of comparison.

However, in the analyses, I think primarily due to limitations of the data on the NTZ-treated patients, rather than the challenges with comparing to historical controls, that there was no consistent trend in favor of NTZ. And I found that particularly compelling.

Given that there isn't any other treatment available and the severity of the disease, I in this case actually wouldn't even hold the process to strict statistical significance since the amount of data from historical controls is limited.

Having said that, I might have to turn in my statistician's card, but, again, giving I think

every benefit to the doubt in good conscience, I think the comparison is not favorable to NTZ.

What's left I think is and perhaps is most intriguing is the analysis of detailed characterization of relatively few patients, clinical course.

In the slide presented by the FDA, there are these five patients out of '91 with large decreases in the numbers of stools. And that's intriguing. There are also the plots presented from a few select patients of I think what was referred to as the challenge/re-challenge data.

But, again, even though those are intriguing and suggestive, that type of data is very difficult to carry into a recommendation for use of drug in a population.

And so in the end, I don't see the evidence for the effectiveness of NTZ.

CHAIRMAN HAMMER: Thank you.

Dr. Hamilton?

MEMBER HAMILTON: I'm very sympathetic to the views expressed by some articulate, impassioned, personally involved individuals who are making a plea for approval.

I've also been very impressed with the

level of effort expended by the sponsor in pursuing the solution to a very important and difficult problem.

I think it's completely appropriate that various perspectives be directed at whether the case has been made to make this more generally available in a forum such as this with representatives from areas of different expertise.

I myself have been involved in HIV research for some time and am actively engaged in patient care. That having been said, I'm certain I'm not as close to the real tragedy as many of you are.

That having been said, however, I have kind of made the decision in my own mind based on what I think is close to a sacred trust between individual patients and myself that I will advise to them only what I really think will work. And I can do no less in this situation.

I find, as have many of my predecessors here, the data to be wanting. And I would in all conscience I think be ill-advised to recommend this drug either for a large number of patients with this disease or to an individual. And, therefore, I will not approve this drug by my vote.

CHAIRMAN HAMMER: Thank you.

Dr. Lipsky?

MEMBER LIPSKY: Rather than answer the question "Is the drug safe and effective?" with a no, I would say the answer is more like a not proven. And I think others have made comments which I might have made.

CHAIRMAN HAMMER: Thank you.

Dr. Masur?

MEMBER MASUR: I concur with what Jim said. I think, again, I'm impressed that the sponsor, the investigators have made a real effort to look at a very difficult problem. And, yet, what we're left with is a relatively small cohort of patients with a lot of missing data.

We're left with some scientific voids in that the discrepancy between the microbiologic and the clinical response is a little bit disturbing. The lack of a dose-response is disturbing.

So I would hope that this drug is going to continue to be investigated because there do seem to be patients who have dramatic responses. But based on the scientific evidence here, efficacy has not been demonstrated.

And, even with safety, I'm concerned that we don't have very much data about the long-term

effects, particularly at some of the higher doses that might be used. So we don't have any evidence of toxicity, but I'm not sure that we have convincing data that this drug at the higher doses for long periods of time is, in fact, safe.

CHAIRMAN HAMMER: Thank you.

Dr. Feinberg had to leave, but she left me her comments. They, briefly stated, were that she felt there was no statistically significant benefit demonstrated when compared to historical controls, although those are, admittedly, somewhat inadequate; no understanding of what the active moiety is or what the mechanism of action of the drug is; and no biologic measure; for example, parasite load, which was indicative of a treatment effect. And she didn't comment on the safety, but she did not feel that there were data to support its effectiveness.

My own comments basically echo what's been stated before. I think for the record, though, it's also important to note that this Committee has an extended history of attempting to be flexible in dealing with agents related to HIV disease recognizing many factors, including the needs that are out there, access, need for further drug development, et cetera, and has even low response rates.

But there is still a minimum level of efficacy, even accepting historical controls, which for this disease one certainly could accept. And if that's what we're left with accepting, one still needs some relatively convincing evidence of a treatment benefit.

I would echo the comments earlier that access is important, but it's access to a drug that one feels there's an adequate safety database for and some level of efficacy.

Continued development of this drug in this field is certainly important, but I echo my colleagues' statements about the data set that we have seen today.

And I say that with regret, too, because I think the tradition of this Committee is really to try to look positively on agents that have come before it.

With that being said, I think we need to take an official vote. The voting members for today are: Drs. Feinberg, Lipsky, Hamilton, Self, Mathews, Sears, Mr. Marco, Ms. Cohen, and me.

So I will restate the question: Is nitazoxanide safe and effective for use in the treatment of cryptosporidial diarrhea in AIDS? If you

feel the answer to the question is yes, please raise your hand.

(Whereupon, there was a show of hands.)

CHAIRMAN HAMMER: If you feel the answer to the question is no, please raise your hand of the voting members.

(Whereupon, there was a show of hands.)

CHAIRMAN HAMMER: Okay. We now have a second part to this question based on the consensus of the Committee: If the answer to the above question is no, what additional data is required in order to be able to make the above determination?

I also think for efficiency's sake, we can combine that with the second question, if you will. And I would ask you to try to comment on both of these: Does the Committee have any additional advice regarding future studies, particularly with respect to: study design, duration of treatment, and choice of comparator?

So first 1(b) and then Question 2. And I'll start on my right with Dr. Masur.

MEMBER MASUR: I think we have alluded to the fact that since this is a chronic disease, it would be nice to have long-term data about the sustained benefits and toxicities of these drugs.

So I would hope that, first of all, some comparative studies could be done either looking at different doses or it seems to me that there are still some open questions about some other drugs out there. Whether this could be compared to them or not I guess is less clear, but certainly doing dose comparisons is a possibility.

There are also some other models there in which patients have been blinded to what drugs they're on for periods of weeks so that one can compare time on drug, time off drug to make this period relatively short before deciding whether to use open-label drug or not because, again, with a disease that has this uncertain a natural history, I think you clearly do need some kind of comparison.

In our experience, some of the patients who were the most convinced they benefitted from other agents we've looked at were patients who were on placebo. So I think that it's very important to have comparative data and it's very important to have regular evaluations and be able to look over a long period of time, six months or a year, as to whether patients are benefitting in terms of GI function, in terms of weight. Admittedly, survival is a hard endpoint to look at in a study of a feasible size

given other issues.

CHAIRMAN HAMMER: Thank you.

Dr. Lipsky?

MEMBER LIPSKY: It would seem that you would want a trial that could be done that would have rigorous microbiologic criteria, both to establish a diagnosis and for its outcome, even with the understanding that there might be a delay in that response prior to a clinical delay. Perhaps a dose escalation study could be entertained.

It would seem that you would want to have some better understanding of the pharmacodynamics because if one did determine that the drug was eventually efficacious, -- and that would not surprise me if that were the result -- you might want to know: Gee, do you need to have a level of something, even though that something might be a surrogate for the active metabolite?

And, for instance, a basic question, does it need to be absorbed? Does it not need to be absorbed? Would you want to promote absorption? Would you want to promote levels? Would you want it? How would you rationally dose this drug? That would be I think rather crucial to the situation.

More basic work on mechanisms, of course,

might help that along the line. But doing I think a study which perhaps could avoid a placebo if it were done in a dose escalation trial might be useful.

CHAIRMAN HAMMER: Thank you.

Dr. Hamilton?

MEMBER HAMILTON: The Achilles heel of this study, it seems to me, has been a series of methodologic issues that either couldn't be addressed or weren't addressed, which further suggests to me that there has been insufficient engagement of several vested interest groups here.

I'm including now the scientific community and those people living with AIDS and perhaps others in a meaningful way to develop the kind of strategy that would be necessary to provide compelling data one way or another.

Had we that in our hands today, our task would have been substantially easier. I think my predecessors here have described what we find the deficits in data are. And I agree with those.

I think a more important question is how to proceed at this moment to resolve and replace those deficits because it is evident to me from the comments made by many in the room that there remains a need here to solve this problem.

And I would not like to feel that I personally or that the Committee in general was walking away from this problem. I would like to see us strongly recommend that this whole series of questions be meaningfully readdressed, readdressed with resources.

I'm not laying this at the doorstep of the sponsor. The sponsor has gone a long ways I think toward attempting to resolve this. It's evidence, at least if our opinion is correct, that the data was insufficient.

But I believe if they are to persevere productively, I would think they're going to need some help. And I knock on several doors and expect some answers in that regard.

CHAIRMAN HAMMER: Thank you.

Dr. Self?

DR. SELF: I was intrigued by one of the comments of one of the presenters in the open session about ACTG 336 not being particularly friendly protocol. And along the lines of the last comments, I wonder if there might be some creative thinking about a study design that would allow some comparative type of trial to be done, even if it's not necessarily a placebo.

Failing that, at the very least, a much more detailed characterization of clinical course in a larger group of patients, more thorough in the sense of making sure that follow-up, at least over the first month or maybe two, is effectively complete would go a long way I think and perhaps characteristics of such an open-label study could be identified that would facilitate its comparison to what little historical placebo data there is available.

CHAIRMAN HAMMER: Thank you.

Ms. Cohen?

MS. COHEN: As the non-scientist, we have been congratulating the sponsor, but I would like to say something about what the FDA did because I found this a very useful tool. I particularly like the graphs and the information in the back.

And for someone like me, I really appreciate the effort put into this and the information. And that's not a political statement. That's just Susan Cohen.

In terms of what I see, I am concerned it wasn't multicultural enough. I think that it's very important that it be far more multicultural than it's been.

I am concerned about the patients that

they have. And maybe it's comparing apples and oranges, but I'd like to know about people who are just starting with diarrhea and what it does for those people who just start.

I'd like to know -- and it's kind of a strange question, but because there's been a weight increase in the patients, I'm wondering if it isn't because they're also being seen by professionals and perhaps being guided to take better care of themselves. It's interesting how people respond when people listen to them and take care of them.

The follow-up to me is extremely important. Yes, I think that clinical trials should be better designed, and I think that there are people who are much more equipped to handle that than I am.

And I am concerned about the drug dosage, and I am concerned again that there are other patients who will be taking this if it is approved. And I want to know how it responds to other drugs that are being taken care of. And I am interested about absorption.

So I'm walking about thinking they tried. I give them A for trying, but we have to do better than that.

CHAIRMAN HAMMER: Thank you.

Mr. Marco?.

MR. MARCO: Let me first respond to ACTG 336. For the past three years, I have been a member of the leadership of the community constituency group, which oversees all the AIDS clinical trials done in the ACTG. And we do and we do not give the trials our blessing. And we actually gave the placebo-controlled Study 336 our blessing. And we sat on the protocol teams, in fact.

The reason it did not accrue is because it took a while to get the study started. It didn't start until last year. We approved protease inhibitors in 1996.

I mean, myself and Dr. Sears have both told you that there is data showing that when patient CD_4's go above 160, 170, to 190, they will clear their crypto. So we're just not seeing it as much. I think the same thing is with the other OIs.

So, even though I don't think a placebo-controlled study is wrong, I just don't know if it's possible any more just because of the limited number of patients. I just don't think we'll see that many.

The only possibility is that you could take 009B and make it up front, instead of refractory, because I don't really understand this refractory

thing since paromomycin and azithromycin don't have an indication for crypto. It's not like they really failed an approved treatment.

So if you open it up to those who are naive and you possibly put in a placebo arm, that might help. From the data right now, it doesn't look like we're going to see a dose-response difference between 1,000 and 2,000.

That's an idea, but I guess the big answer is I have no idea if you'll ever be able to answer these questions for this drug or any other drug for crypto.

CHAIRMAN HAMMER: Dr. Sears?

DR. SEARS: I think it's an incredibly difficult problem. And I think the likelihood that we're going to be able to study large numbers of patients with *Cryptosporidium* in the United States approaches zero in the era of HAART and newly developing HIV therapies.

So, for large-scale studies of efficacy, I think consideration has to be given to the international setting, both where the disease, in particular, is an issue in children, although the FDA one slide on toxicity in children is of concern and safety issues are obviously paramount.

But in that setting, immunocompetent children who acquire *Cryptosporidium*, a non-trivial percentage go on to develop persistent diarrhea which has long-term effects on morbidity and mortality in that population and is also a setting where HIV is rampant and additional therapies are obviously not available in many instances.

So in terms of large-scale studies of efficacy, in truth, in my mind that's the only setting I see where studies will be able to be done. In the United States, though, where we have some patients and we have more resources, I wonder if what might be helpful is to intensively study a smaller group of patients with concomitant data on microbiology, pharmacology, and clinical responses.

I think one of the major issues we face is that this is a very variable disease. And I believe it is a variable disease, even in patients with advanced HIV infection.

And I'm wondering if -- even though I think the preponderance of data didn't support overall efficacy, I in my own mind still wonder whether there's a subset of patients who, in fact, are truly responsive, given some of the dramatic anecdotal evidence for responsiveness. But what makes a patient

responsive to this disease is what's unidentified. So I wonder.

For example, in our studies in the northeast of Brazil, our most recent observations are that children who asymptomatically carry *Cryptosporidium* have no evidence of inflammation in their stools; whereas, all of the children who were symptomatic had evidence of inflammation in their stools.

There's evidence that prostaglandin production, they've got "correlate with symptomatic disease." There's evidence that interleukins as well as beta defensins as well as other cytokines have some modulary effect on disease.

So I'm wondering if there's a subset where there's a particular host response or there's a particular parasite infection who, in truth, are responsive to nitazoxanide and may be responsive to paromomycin.

So what I would suggest is that a small group of patients intensively studied to try to develop the correlates to try to understand who responds and who doesn't might help us direct future studies.

Thank you.

CHAIRMAN HAMMER: Thank you.

Dr. Mathews?

DR. MATHEWS: I agree with Dr. Sears' comments in total. You know, I think it's very unfortunate a drug like this came around at this point in time, as opposed to a few years ago. But in a sense, you know, this is not unique to cryptosporidiosis.

If we were trying to study disseminated *Mycobacterium avium* disease in 1998 with many of the drugs that we initially started in trials, we would be in exactly the same position. And so in a sense we're delighted that these very horrible opportunistic events have diminished in incidence. It makes it much, much more challenging to study drugs.

I think with a disease that is so variable like this, unless you have a home-run drug, the only way you're going to be able to convince is a randomized trial that includes very tight control of co-variates that could affect disease severity.

And anti-retroviral therapy, even without HAART, I mean, it's known that even half-log drops in viral load translate into measurable clinical benefit.

So if you don't randomize and you have all of these post-initiation changes in antiviral therapy

which have obvious impacts on disease severity, it's going to become less and less convincing.

So I agree with Dr. Sears. There may be settings where there are people who don't have access to these therapies where an international study could be mounted or people who have failed all existing anti-retroviral therapies who may experience a recrudescence of these infections.

DR. LEUNG: Thank you.

Dr. Feinberg had left some comments which really echo what has been stated. And they will be put into the record.

For my part, I don't really have what to add to what has been said. I share the hope that the study of the drug will still go forward because the issue is: Is there a subset of patients that we just can't tease out that really do respond?

The question is again how to study this. In answer I think Dr. Sears' suggestion is really the most practical because it will not be possible to enroll large numbers of patients in any trial, let alone trying to do a placebo-controlled trial solely within the borders of the United States. But it is possible to think about mounting a placebo-controlled trial in other areas with the crossover designs, et

cetera, even with the limitations there, but one could do that, at least to find out whether this drug has efficacy clearly in the short term.

In the United States, what we need and I think one of the issues that the Committee was wrestling with here is the characterization of the patients both for the variability of the disease but also the clear issue of the parasite burden at baseline exclusion of other pathogens, the issue of co-variates that may be influencing the interpretation. All of those issues that I think were teased out today that were given concern should be placed into a new study.

And the study of a relatively small number of patients who are extremely well-characterized would I think perhaps tease out clearly whether there is any drug effect.

I think incorporating the pharmacodynamic issues Dr. Lipsky mentioned would also be important. And those studies can also be involved in trying to perhaps tease out some more issues about the potential mechanisms and metabolite issues in relation to efficacy.

So I think a pair of trials looking at broader populations, perhaps on the international

scene, with well-done perhaps dose comparison studies that try to control for the factors that have wrestled with today and, most importantly, including the follow-up information because I think that was clearly an additional problem here as far as the follow-up and the missing data that were giving individuals problems.

And it will be hard and I think to also develop new drugs, any new agent beyond the one that we're discussing today is going to face exactly the same problems. And I would hope that we can think of incredible ways to overcome that. But it will be a cooperative effort. One can't just look probably within our borders to solve this issue for this particular pathogen at the moment.

Dr. Murphy? Dr. Goldberger?

DR. GOLDBERGER: I just wanted to ask if any of the Committee members wanted to comment a little bit on the issue of endpoints. As you saw, we saw analyses using a 25 to 49 percent reduction in stool number, greater than 50 percent reduction, greater than 50 percent reduction to less than 3 stools. Plus, there are issues of durability -- whether there are any comments or advice any of the Committee members would like to give about this for

future trials.

MR. MARCO: Well, I guess first, even before you get to your criteria, how you choose evaluable patients, I don't think you should ever allow patients to be considered evaluable if there's not microbiologic confirmation.

You know, in cancer, you ask for biopsies. This all we need is a stool sample. I think you should at least require that.

CHAIRMAN HAMMER: I would just add to that I think where one is contemplating, as is likely, small, intensive studies in the United States, perhaps paired, as Dr. Sears mentioned, with an international trial, stool studies -- and I don't actually think that endoscopies on a relatively limited scale are beyond the pale.

In our own clinical experience, they're used all the time in patients with chronic diarrhea and will be particularly valuable both clinically and certainly would be valuable in a study setting, trying to get a better handle on the issue of microbiologic. Eradication or at least quantitation in relation to response would be very important.

One can sort of obviously appreciate in this disease persistence of pathogens and

disassociation with persistence with clinical outcome, but there still should be -- if the drug is active by a mechanism of action that's antimicrobial should be able to see some antimicrobial effect in quantitative measures. And that may require an expensive intensive study, but if you really want to know what the drug is doing, I think that's one way to do it.

The other issue I think that came up today as far as because of the variable history of this disease, weeks two, four, six, eight are a snapshot of the longer picture. And I think the trials should have probably both short-term and more durable endpoints with patients that one can try to encourage to commit to that follow-up that we need.

Obviously we look at group comparative data, but also the issue of the variability of measurements within subject has to be taken into account in the analysis so that we know that responders are durable, responders both individually and as a group.

And, again, unless you have, as Dr. Mathews mentioned, a home-run drug, it's going to be difficult. If you have a great drug and everybody responds, it's easy. If you've got a 40, 60, 70 percent response rate, you have to tease that out.

So one has to look at group responses but also intrapersonal responses that are durable and correlate in a very careful fashion the clinical response with the microbiologic response.

Now, as far as the clinical, it's difficult, but one can sort of probably deal with the microbiologic endpoint more easily than the clinical endpoint. Diarrhea is a difficult disease to study. And anyone tries to quantitate stool numbers, et cetera, et cetera.

And I think the ACTG team, as was described, wrestled with this and other studies obviously have wrestled with it. And the sponsor's studies were about two. I don't think you can really get away from some sort of combined endpoint.

It seems to me that from what we have seen today, looking at diary as a continuous variable, rather than a categorical variable, makes a little bit more sense than trying to say you have one to three or four to six or seven to nine stools per day. But I think it's the durability issue that's key.

And I think both proportion reduction and total number of stools have to be looked at separately but also probably can be combined in a primary endpoint analysis.

I think that decrement can be argued about, but I think that you really need some substantial decrease because of the variability. At least a 50 percent decrease would be what I would personally state, but I think also the absolute number of stools is important.

I don't see a clinical -- obviously survival and other things are there, but in our current here in the United States again, thank goodness, because of the progress we've made, that's not going to be an endpoint. It's going to be disease severity as measured primarily by stool output, which I would say is going to be combining numbers of stools and how many and then looked at individually. And correlative issues of weight and quality of life, as was demonstrated today, should be part of that measure.

But I think we need durability of data, good follow-up, and issues of trying to take into account the intra-subject variability of this disease in any study that's designed.

MEMBER LIPSKY: Just one comment which I forgot, which reminded me of the comment about Milwaukee. Perhaps there should be a contingency plan that if that event should ever occur again in another

city, that perhaps for the CDC or whatever, that there would be some sort of design so that one and rapidly could go into a community and perhaps treat some people.

If it's at the same extent that happened before, there may be enough comparative patients around. And it's possible that through a public health tragedy, you could get efficacy data within a couple of weeks, --

CHAIRMAN HAMMER: Are there other responses?

MEMBER LIPSKY: -- although I understand that also that would be with the immune -- mostly the immune status of people might be different, but that it could be helpful.

CHAIRMAN HAMMER: Are there other responses to Dr. Goldberger's question about endpoints?

(No response.)

CHAIRMAN HAMMER: I think the silence indicates the difficulty faced.

DR. MURPHY: Yes. I just wanted to thank everybody for very thoughtful comments and for everyone who has participated today in providing their thoughts and recommendations to this field.

CHAIRMAN HAMMER: On behalf of the committee, I'd like to thank our consultants and guests; the agency; certainly the sponsor; the audience, in particular, the individuals who spoke at the public session.

With that, I would like to adjourn.

(Whereupon, the foregoing matter was concluded at 2:36 p.m.)

C E R T I F I C A T E

This is to certify that the foregoing transcript in the matter of: Meeting of the Antiviral Drugs Advisory Committee

Before: DHHS/FDA/CDER

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represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

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