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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.

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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

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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.

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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

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1 Medical School in Boston.

2 EXECUTIVE DIRECTOR STOVER: Rhonda Stover,
3 FDA.

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

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

8 DR. ROCA: Rico Roca, FDA.

9 DR. SILLIMAN: Nancy Silliman, FDA.

10 DR. GOLDBERGER: Mark Goldberger, FDA.

11 DR. MURPHY: Dianne Murphy, FDA.

12 CHAIRMAN HAMMER: Thank you.

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

15 CONFLICT OF INTEREST STATEMENT

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

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

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

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

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

13 CHAIRMAN HAMMER: Thank you.

14 Dr. Mark Goldberger will give the FDA
15 introductory remarks.

16 FDA INTRODUCTORY REMARKS

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

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

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

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

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

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

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

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

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

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

18 Thank you.

19 CHAIRMAN HAMMER: Thank you.

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

22 UNIMED PRESENTATION

23 INTRODUCTION

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

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

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

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

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

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1 be generated from the Committee.

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

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

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

22 NTZ OVERVIEW

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

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1 *Cryptosporidium parvum* in AIDS patients with a CD₄
2 count less than 200 per cubic millimeter.

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

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

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

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

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

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

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

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

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

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

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1 in just a moment.

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

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

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

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

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

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

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

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

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1 comparison of NTZ data versus historical control data
2 sets.

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

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

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

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

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

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

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

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

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

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

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CRYPTOSPORIDIOSIS OVERVIEW

1
2 DR. SOAVE: *Cryptosporidium* was first
3 described in 1907. And for nearly three-quarters of
4 a century, this organism was considered rare and
5 commensal, not a pathogen for humans. It took the
6 profound immune defect of AIDS to so amplify this
7 disease that physicians finally took note of its
8 existence in the early 1980s.

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

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

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

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

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

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

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

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1 asexual and a sexual phase.

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

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

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

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

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

5 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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1 decreasing risk factors, such as contact with
2 contaminated water.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 As you can see, all of this patient's
13 bowel movements were liquid. He averaged about 15 a
14 day. And I'm not sure that you can see the fact that
15 they were evenly distributed between those that
16 occurred in daytime hours and those that occurred
17 during the night, between the hours of midnight and
18 8:00 o'clock in the morning.

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

25 The nighttime bowel movements are

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

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

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

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

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

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

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

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

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

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1 been an accelerated mortality associated with biliary
2 disease.

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

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

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

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

3 It is clear to us that most of the
4 patients with CD₄ counts under 200 have a version of
5 the disease that is either chronic intermittent,
6 chronic persistent, or progressive/fulminant.

7 It is very uncommon for patients with CD₄
8 counts under 200 to have spontaneous remissions.
9 Spontaneous remissions have been seen. They have been
10 rare, and they have been most often associated with
11 initiation of either anti-retroviral therapy or other
12 immunomodulator therapy that has, in part, contributed
13 to enhancing the immune function of these patients.

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

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

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1 Four of the trials have been ACTG-sponsored.

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

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

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

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

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1 efficacious.

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

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

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

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

25 Our fears were really borne out recently

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

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

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

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

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

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

10 Most of these patients had other
11 opportunistic infections. And their CD₄ counts were
12 way below 50. These are not the type of patients who
13 spontaneously remit with this disease. These are very
14 ill patients, who are anxious to get on any kind of
15 therapy that you can put them on.

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

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

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

5 CLINICAL TRIAL DESIGN RATIONALE

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

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

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

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

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

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

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

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

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

25 For this, we devised this associated

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

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

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

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

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

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

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

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

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

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

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

25 There are many unanswered questions

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

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

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

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

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

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1 parasitologic response early on.

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

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

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

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1 This heterogeneity results in creating the
2 need for a sample size that is sufficient to
3 demonstrate a 20 percent difference in outcome with an
4 80 percent statistical power. It's very difficult to
5 get a sufficient number of patients to overcome the
6 problem of heterogeneity.

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

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

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

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

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SAFETY AND EFFICACY TRIALSUMD-95-004, UMD-95-009A, UMD-95-009B

1
2
3 DR. DUDLEY: The placement of NTZ within
4 a chronological context I think is important relative
5 to today's discussion. I'd like to do that now.

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

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

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

25 Eventually we had discussions with the FDA

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

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

14 In February of 1996, I was part of ACTG
15 336 protocol development team that developed the
16 placebo control study. I can tell you that the
17 discussions that Dr. Soave shared with you a moment
18 ago or the points about designing these trials really
19 came to full appreciation during those discussions.
20 I think Rosemary will remember we had at least 2
21 2-hour meetings on whether we should collect 24-hour
22 stool samples and how one would transport those across
23 the country.

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

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

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

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

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

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

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

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

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

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

18 004 was a Phase I/II dose escalation study
19 in AIDS patients with doses ranging from 500 to 2,000
20 milligrams per day.

21 009A was the initial compassionate-use
22 study that I described to you just a moment ago.
23 Patients were started at an initial dose of 1,000
24 milligrams per day. And that data cutoff was the 15th
25 of October in 1996. And that was included in the

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1 original NDA submission.

2 009B, which is still a study ongoing and
3 we continue to enroll patients in that study, is a
4 randomized, open-label study in AIDS patients, here
5 looking at 1,000 versus 2,000 milligrams per day. And
6 the data included in the materials provided to each of
7 you on the Committee and to the FDA is through the
8 20th of February this year.

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

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

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

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

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

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

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

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

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

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

7 These patients had significant HIV disease
8 with CD₄ counts well below 200. They had chronic
9 cryptosporidial diarrhea, at least defined for entry
10 as at least four or more stools per day. They needed
11 to have been on stable anti-retroviral or
12 antidiarrheal regimens. They were screened for the
13 absence of the other parasites, and there needed to be
14 a parasitologic evidence of *C. parvum*.

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

19 And their CD₄ count, as you will see,
20 averaged 25. And one could almost see a sequential
21 progression from the 500 to the 2,000 dose, with the
22 500 having the low CD₄ counts and those that enrolled
23 later in the study having the highest. But,
24 nonetheless, all of these patients are significantly
25 below 50 and not likely to be the spontaneous

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1 remitters that you might see in other patient
2 populations.

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

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

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

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

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

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

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

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

21 One will note initially that the
22 1,000-milligram dose appeared to be substantially
23 better than the others, having 5 of 7 patients, the
24 majority of whom were complete responders, that there
25 was no clear dose-response; that is, the response at

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

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

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

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

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

25 Parasitologically, we also studied these

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

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

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

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

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

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

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

9 What about quality of life? I want to
10 spend just a moment on this because the quality of
11 life assessments used in this study were, in fact, the
12 same instruments that we used in the studies 009A and
13 009B.

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

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

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

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

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

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

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

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1 cryptosporidial diarrhea.

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

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

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

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

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

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1 The primary inclusion criteria are very
2 similar to what were used in 004, in Study 004. The
3 patients had to have had AIDS, very low CD₄ counts,
4 chronic cryptosporidial diarrhea. It's notable that
5 we did allow microsporidiosis here because several
6 patients were co-infected with that.

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

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

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

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

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

6 So we established: a complete response in
7 009A and in the next study as at least a 50 percent
8 reduction in average daily stool count compared with
9 baseline; a partial, 25 to 49 percent, response; and
10 a failure, any response that was not either a partial
11 or a complete responder.

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

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

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

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1 report forms.

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

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

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

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

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

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

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

19 I'd like to now go through the
20 intent-to-treat analysis; that is, the analysis on the
21 139 patients in 009A. This slide summarizes the
22 clinical response.

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

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1 total stools through week eight.

2 And in this case, we had 114 patients in
3 this sample. The clinical response rate is right at
4 60 percent for both liquid and total stools. About 45
5 percent were in the case of liquid complete
6 responders. And, arguably, liquid is more important
7 in the discussion today than total.

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

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

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

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

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

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

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

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

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

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1 patients were dealing with.

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

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

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

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

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

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

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

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

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

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

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

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

9 This slide summarizes Protocol 009B, which
10 now is identical to Protocol 009A with the exception
11 that we are randomizing patients to either 1,000 or
12 2,000 milligrams per day to see whether or not there
13 was a clear dose benefit at that higher level.

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

18 Demographically these patients are
19 remarkably similar to the ones that we had seen in 004
20 and in 009A. There were 30 patients and 26 in the 2
21 different groups, respectively. Again, most patients
22 were men and they were white. The mean age was about
23 30; and the CD, again in that 25-cell range.

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

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

6 How about stool frequency? This is at the
7 1,000-milligram level with 25 patients and at the
8 2,000 with 21. Again, one sees, as one would expect,
9 there is a decrease, a significant decrease, in liquid
10 stools and total as well, but there's not a clear
11 difference between these with respect to the magnitude
12 of that difference.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 for the ACTG 192 and 143.

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

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

16 We only focused on patients that were on
17 1,000 milligrams for their initial dose. And we only
18 included patients that were 18 years of age or older.
19 I say that because we did have some patients that came
20 into the study who were children.

21 The per-protocol group, again, similar to
22 what we discussed a few moments ago, were those
23 evaluable patients. That is, it's a subset of this
24 group that had key baseline characteristics: liquid
25 stools, at least four per day; low CD₄ counts; and

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1 documented evidence of cryptosporidiosis in their
2 stool.

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

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

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

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

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

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

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

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

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

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

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

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

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

25 I'd like to conclude my portion of the

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

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

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

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

21 This slide summarizes the available data
22 sources that were used to compile the data. They come
23 from three areas of the world, if you will: the
24 United States. We had access to our own studies, to
25 228 patients; again, 2 non-AIDS patients but they were

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1 included in the safety analysis.

2 There are data from 2 Mexican studies, of
3 which there are 88 patients in an ongoing French
4 compassionate-use study, neither one of these studies
5 conducted by Unimed, I might add, giving us a total of
6 329 in a stacked notation, I see.

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 combined mild and moderate and severe and
2 life-threatening.

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

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

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

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

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1 population, particularly those patients with
2 cryptosporidiosis.

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

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

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

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

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

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

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

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

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

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

25 This then summarizes those 19 patients

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

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

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

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

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

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

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

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

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

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

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1 population; that is, those patients with
2 cryptosporidial diarrhea.

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

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

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

24 CLINICAL BENEFITS OF NTZ THERAPY

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

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

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

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

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

25 At that one-month visit, he was having

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

5 In April, his anti-retrovirals were
6 changed. We had a CD₄ count of five. He had a viral
7 load of half a million. His liver enzymes were still
8 abnormal, but he was sleeping through the night.

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

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

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

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

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

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

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

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

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

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

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

17 BENEFIT/RISK SUMMARY

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

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

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1 treated with nitazoxanide experienced some sort of
2 favorable benefit.

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

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

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

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

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1 Thank you.

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

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

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

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

18 I'd like to start with Dr. Mathews.

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

25 Secondly, some clarification on what

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

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

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

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

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

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

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

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

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

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

9 CHAIRMAN HAMMER: Dr. Sears?

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

14 DR. DUDLEY: This is Bob Dudley again.

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

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

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

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

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

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

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

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1 we got moving as fast as we did.

2 DR. SEARS: Thank you.

3 CHAIRMAN HAMMER: Thank you.

4 Mr. Marco?

5 MR. MARCO: I have two questions. First,
6 do you have the breakdown and possibly a slide to show
7 us of the concomitant antivirals that were used?
8 While we know these patients were very
9 immune-suppressed, mostly with under 50 CD₄'s, can you
10 attempt to tell me if they started to do
11 anti-retrovirals if they were on protease inhibitors
12 being that we know that people can clear
13 cryptosporidiosis if their CD₄'s go above 180 or 190?

14 And, secondly, I'm having trouble
15 understanding the true parasitologic response. In
16 004, it looks like you have an approximate 40 percent
17 response rate. In 009, it looks like you have an
18 approximate 50 percent response rate. But then in a
19 slide when you showed it compared to placebo, you put
20 down a 25 percent response rate with an n of 59. And
21 could you clarify that?

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

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

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

9 And Dr. Graham will address your first
10 question.

11 DR. GRAHAM: This is Cheryl Graham.

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

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

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

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1 all the old products that were on the market.

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

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

14 CHAIRMAN HAMMER: Okay. Ms. Cohen?

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

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

19 MS. COHEN: I know it is.

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

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

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

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

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

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

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

18 DR. SOAVE: Yes, yes.

19 MS. COHEN: Okay. Thank you.

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

25 DR. SOAVE: We have continued to follow

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

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

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

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

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

21 DR. SOAVE: The dropout rate over what
22 period?

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

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1 the reasons for it.

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

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

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

13 CHAIRMAN HAMMER: Dr. Self?

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

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

25 And the method that you have chosen to use

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

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

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

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

23 MR. ROHOWSKY: Nestor Rohowsky.

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

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

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

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

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

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

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

22 I actually have a slide that's going to
23 address the amount of missing data at week four for
24 the NTZ patients versus placebo patients. And it was
25 34 percent for the nitazoxanide patients at week four.

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1 I'm not sure about weeks two and eight.

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

4 DR. SILLIMAN: Yes, about a third.

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

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

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

25 I have another question. There is a claim

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

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

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

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

14 DR. SELF: That's it.

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

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

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

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

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

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

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

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

3 Now, this sensitized us a little bit in
4 the past because we were afraid that maybe this
5 occurred more often than not. And so in all trials
6 subsequent to the ones conducted before the early
7 1990s we've put in strict criteria that either
8 patients had to have a certain CD₄ count for entry or
9 if their cryptosporidiosis was newly diagnosed, they
10 would have to wait a certain period of time before
11 they could be entered into the trial. And that was
12 the reason for putting that stipulation in in order to
13 make sure that we weren't putting people in who might
14 be spontaneous remitters.

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

19 CHAIRMAN HAMMER: Dr. Sears?

20 DR. SEARS: I think I want to just
21 disagree with that. In Tim Flanigan's data published
22 in the annals, where the sort of cutoff for CD₄ for
23 160 for a difference in clinical course was published,
24 he had a 10 percent spontaneous remission rate in
25 individuals with a CD₄ under 160.

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

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

12 It's unclear to me why the clinical
13 pattern of disease is variable in individuals with
14 very low CD₄ counts. And in our patients, the CD₄
15 counts were almost exclusively under 50. But it
16 speaks for differences, potentially parasite
17 differences, potentially host differences.

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

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

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

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

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

15 CHAIRMAN HAMMER: Thank you.

16 Dr. Feinberg?

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

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

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

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

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

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

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

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1 Did that answer the second question?

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

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

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

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

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

7 MEMBER FEINBERG: I'd just also that the
8 animal model data are not really compelling, but they
9 were only done with the parent compound. And, again,
10 I don't know how gnotobiotic piglets and suckling mice
11 metabolize this drug. I don't know if you know, but
12 --

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

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

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1 kind of confounded that.

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

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

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

12 MEMBER FEINBERG: I'm sorry.

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

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

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

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

7 MEMBER FEINBERG: Thank you.

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

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

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

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1 biliary tract disease.

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

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

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

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

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

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

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

10 I'm not sure. Did I answer?

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

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

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

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1 *Cryptosporidium*. Do you want to --

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

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

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

13 Dr. Hamilton?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 was there.

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

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

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

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

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

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

4 Unfortunately, that didn't occur in the
5 004 study. We didn't need to do that. We have plenty
6 of patients with *Microsporidia*, but the patients that
7 we managed to enroll in the study were
8 *Cryptosporidium*-positive.

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

11 CHAIRMAN HAMMER: Sure.

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

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

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

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

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

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

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

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

12 MEMBER MASUR: On a single stool?

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

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

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

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

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

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

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

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

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

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

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1 of enteric pathogens that was found?

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

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

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

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

25 MEMBER HAMILTON: It's an enviable

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1 accession method.

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

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

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

19 CHAIRMAN HAMMER: Thank you.

20 Dr. Lipsky?

21 MEMBER LIPSKY: Thank you.

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

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

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

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

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

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

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

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

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

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

14 DR. DUDLEY: The answer to that is no.
15 The primary pharmacokinetic studies were, in fact, in
16 004, Dr. Soave's studies. And those patients were
17 followed only for the 14 days. We don't have
18 pharmacodynamic data relating blood levels to
19 efficacy, certainly not in the open-label study.
20 Blood samples weren't collected from those patients at
21 all.

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

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

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

9 DR. DUDLEY: Right.

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

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

16 MEMBER LIPSKY: Oh, I'm sorry.

17 DR. SOAVE: -- that the outbreak occurred.

18 MEMBER LIPSKY: I thought you said '95.

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

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

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

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

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

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

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

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

21 CHAIRMAN HAMMER: Dr. Masur?

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

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

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

10 CHAIRMAN HAMMER: Dr. Masur?

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

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

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

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

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

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

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

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

16 In the initial 004 study, where we
17 sequentially enrolled patients beginning at 500 and
18 1,000 and then above, recall that the 009 study, the
19 first, was started almost at the same time and, quite
20 frankly, at about the time when it appeared as though
21 the responses at the 1,000 dose were definitely better
22 than at the 500. And we didn't have any information
23 at the 1,500 to 2,000.

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

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

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

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

14 As it turns out, at least through our
15 experience today, there does not appear to be a
16 significant difference between those 2 doses, not to
17 say clearly that a patient might respond better at
18 2,000 and another at 1,000. I think that we don't
19 have enough data to suggest that.

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

25 There is a fairly complicated dose

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

8 Finally, this is an n of one, clearly
9 anecdotal. But I can tell you that Dr. Brogart in San
10 Francisco has the patient which I think is still on
11 NTZ and is the patient that has been on it the
12 longest. And he has been as high as 4,000 milligrams
13 before he saw a response, has dropped back down to
14 1,500 milligrams now. And she is maintaining him
15 prophylactically at that dose. So it gives you a
16 little idea of how we got to where we are today.

17 Was there another part to your question?

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

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

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

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

12 MEMBER MASUR: Okay.

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

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

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

25 I was interested in what Cindy said, that

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1 17 percent of her patients respond. And if you look
2 on Slide 94, 23 percent of the placebo patients
3 appeared to have a complete response.

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

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

15 DR. GRAHAM: Cheryl Graham again.

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

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

25 What we found was if they had a response

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

24 CHAIRMAN HAMMER: Anything else?

25 DR. DUDLEY: Just one follow-up there.

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

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

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

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

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

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

6 CHAIRMAN HAMMER: What about in the larger
7 data set? Because we're dealing with three studies,
8 009A and 009B? And 004 is only 28 patients.

9 MR. ROHOWSKY: This is Nestor Rohowsky
10 again.

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

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

25 CHAIRMAN HAMMER: Dr. Masur's question was

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

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

7 CHAIRMAN HAMMER: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

6 MR. ROHOWSKY: Yes.

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

9 MR. ROHOWSKY: Yes.

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

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

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

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

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

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1 drug needs to be and when.

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

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

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

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

22 DR. SOAVE: I have no idea.

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

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

4 MEMBER LIPSKY: Thank you.

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

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

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

17 DR. SOAVE: I don't know.

18 CHAIRMAN HAMMER: -- of the 228?

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

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

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

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

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

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

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

20 CHAIRMAN HAMMER: Thank you. Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 DR. DUDLEY: Yes.

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

7 DR. DUDLEY: There may be a slide --

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

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

12 CHAIRMAN HAMMER: Okay.

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

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

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

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

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

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

11 Does that answer your question?

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

17 MR. ROHOWSKY: Well, yes.

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

20 Dr. Sears, did you have any?

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

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

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

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

7 FDA PRESENTATION

8 CLINICAL SAFETY AND EFFICACY

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

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

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

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1 Shugal Bala, microbiology; Steve Kunder,
2 pharmacotoxicologist; and Mark Cavallé-Coll served as
3 the medical team leader.

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

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

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

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

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

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

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

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

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

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

17 There were some differences noted between
18 004 and the other two studies. And Dr. Silliman will
19 go into more detail regarding what analysis
20 modifications were performed in order to compensate
21 for these differences.

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

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

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

8 DR. SILLIMAN: Thank you, Dr. Roca.

9 STATISTICAL SUMMARY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 So specifically what we're doing today is

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

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

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

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

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

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

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

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

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

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

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

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

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

18 And what we have done here, the four
19 categories are: less than three and a half stools per
20 day. And this for notational convenience is written
21 as 3.5 to 6.4, but it actually means 3.5 to less than
22 6.5 stools per day. The third group was 6.5 to less
23 than 9.5 stools per day. And the final category was
24 9.5 or more stools per day.

25 And to analyze this categorical data,

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

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

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

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

22 This table shows reasons for exclusion
23 from this analysis. What we'll see is we had 226 AIDS
24 patients enrolled and treated in the nitazoxanide
25 group, 59 placebo patients enrolled and treated with

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1 at least one dose.

2 There are 91 NTZ patients in the
3 completers group and 43 placebo patients in the
4 completers group. This leaves 135 and 16 patients,
5 respectively, that were excluded from the analysis.

6 The reasons for exclusion are given in the
7 last three rows of this table. Essentially for
8 nitazoxanide, we lost a fair number of patients due to
9 the fact that they started on a dose other than 1,000
10 milligrams a day.

11 We lost just a handful of patients due to
12 their young age. And the majority of patients are
13 excluded from this analysis because of their missing
14 data. This is 34 percent of the nitazoxanide patients
15 that had missing data and 27 percent of the placebo
16 patients that had missing data.

17 And to address a question that Dr. Self
18 had earlier, if you incorporate these patients with
19 missing data as failure, -- that's sort of the
20 worst-case analysis -- in the primary outcome measure,
21 you end up with actually a higher response rate for
22 the placebo group, although it's, of course, not
23 statistically significant. It's 28 percent for the
24 placebo group versus 23 percent for the nitazoxanide
25 group.

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1 In the remainder of the presentation, the
2 results are just presented for people that actually
3 had data at both visits. And so what you can think of
4 is if we use that worst-case analysis and incorporate
5 these missing data points as failures, any difference
6 you see between the treatment arms will tend to be
7 diminished.

8 The last point that I would like to make
9 under general comments is about comparability of
10 treatment groups at baseline. There was some concern
11 that the placebo patients might be less ill. CD,
12 counts tended to be somewhat higher in placebo
13 patients. Daily total stool counts and daily liquid
14 stool counts tended to be somewhat lower in placebo
15 patients at baseline.

16 So in an attempt to control for some of
17 these baseline differences, the FDA analysis has
18 looked at the various outcome measures controlling for
19 these three factors, both uni-variately and
20 multi-variately. And essentially no effect was found
21 on conclusions when you control for these baseline
22 differences.

23 Now I'd like to turn to sort of the major
24 part of the presentation. These are six clinical
25 endpoints where controlled comparisons were possible.

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1 So we're going to compare how patients receiving
2 nitazoxanide did to patients receiving placebo.

3 And before I begin, I would just like to
4 point out that there were no significant treatment
5 differences observed on any of these six endpoints.
6 In addition, when we control for baseline factors, CD₄
7 count, total number of stools, and total number of
8 liquid stools, there are still no significant
9 treatment differences observed.

10 So let's first look at change from
11 baseline in total stool count to give you a feel for
12 the data that is available. In this analysis, I'm
13 only using the placebo patients from the ACTG study
14 since the Pfizer data was collected as a categorical
15 outcome.

16 And what we see here, the median stool
17 count at baseline is slightly higher for the
18 nitazoxanide patients, 7 stools per day versus 5.7
19 stools per day, about 6 stools per day, for the
20 placebo patients. So there is a difference of about
21 one stool per day at baseline.

22 The range was fairly wide in the
23 nitazoxanide patients. We had someone with no stools
24 at baseline and someone with 25 stools at baseline.
25 For the placebo patients, the range was also fairly

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1 large, from 2.3 stools to 19 stools per day.

2 The median stool count at follow-up was
3 about four stools for both of the groups. And, again,
4 the ranges were somewhat variable. I should point out
5 that I'm using the median here since this data is
6 highly skewed. So it's misleading to look at
7 averages.

8 Okay. Next slide, please. Thank you.
9 What we see here is the median change from baseline in
10 stool count. So for the nitazoxanide patients, there
11 was a reduction of 2.5 stools per day. For the
12 placebo patients, the median reduction was two stools
13 per day. So the difference here was a half a stool
14 per day in the median reduction.

15 These p-values indicate that this change
16 from baseline is highly significant for the NTZ group.
17 It's also highly significant for the placebo group.
18 The p-value in the last row of the table indicates
19 that the difference in the magnitude of the change is
20 not statistically significant for NTZ versus placebo.

21 This is perhaps an easier way to look at
22 the data. These are side-by-side box plots of the
23 change in the total stool count for nitazoxanide
24 patients and placebo patients. And let me just remind
25 you how box plots are constructed.

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1 The lower line of the box here is the
2 first quartile. This means that 25 percent of the
3 patients in this group had a lower change in stool
4 count or larger if you want to look at it that way.

5 The line in the middle of the box is the
6 median. This indicates that 50 percent of the
7 patients had values less than that.

8 The top line of the box is the third
9 quartile. It indicates that 75 percent of the
10 patients had values less than that. And then the
11 whiskers extend one and a half times the length of
12 this box. And patients outside this are starred as
13 outliers. They're unusual for the group that was
14 considered.

15 So what we see here is essentially the
16 middle 50 percent of the data looks fairly similar for
17 nitazoxanide versus placebo. We do have several --
18 there are six nitazoxanide patients here that had
19 quite impressive reductions in their stool count.
20 There are also two nitazoxanide patients that had a
21 larger increase in their stool counts.

22 This slide is an attempt to look at
23 similar type of data for the Pfizer placebo patients.
24 Since this data is categorical, this is a fifth table.
25 And what it indicates is the rows are where the

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1 patient started at baseline. The columns are where
2 the patient ended up at week three.

3 So the data on the diagonal that's shaded
4 here, there were 13 patients that essentially had no
5 change. For example, these four patients started the
6 study with four to six stools and ended at week three
7 with four to six stools.

8 Patients above this diagonal had an
9 increase in their stool count. The first dot
10 diagonal, there's a total of four patients who
11 increased one category. The second diagonal shows us
12 there's one patient who increased two categories. And
13 then, finally, there's one patient who increased three
14 categories.

15 Similarly, there were ten patients who
16 decreased their stool count. They got better. There
17 were a total of eight patients on this first diagonal
18 that decreased one category, one patient who decreased
19 two categories, and one patient who decreased three
20 categories from baseline. So they started with ten or
21 more stools at baseline and ended up with one to three
22 stools at follow-up.

23 Next slide, please. A similar analysis
24 was done for change from baseline in liquid stool
25 count. The results are essentially identical. So

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1 they're not shown here, but I can show them to you
2 later if you're interested.

3 Again, we saw a highly significant change
4 from baseline for NTZ patients, a highly significant
5 change from baseline for placebo patients, and no
6 difference between the two treatment groups in the
7 amount of change.

8 The third outcome measure is Clinical
9 Response A. This was the outcome measure that was
10 prospectively defined and agreed upon by Unimed and
11 FDA. It's considered our primary endpoint I think by
12 both parties.

13 The definition of a responder here is a
14 patient you'll recall who either has a 50 percent or
15 higher reduction in their total stool count or a
16 patient who gets down to three or fewer total stools
17 per day at follow-up, having begun the study with more
18 than three liquid stools at baseline.

19 The difference between Unimed and FDA
20 analysis, FDA analysis excludes the Pfizer patients
21 due to the way their data was collected. Unimed has
22 actually analyzed this endpoint, both including and
23 excluding Pfizer patients. The results covered in
24 their presentation today include the Pfizer patients.
25 The results that they submitted in their NDA update

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1 excluded Pfizer patients.

2 Here are the FDA results for Clinical
3 Response A. And what I'd like you to focus on is this
4 first row. We are essentially seeing a 43 percent
5 response rate for NTZ patients compared to a 36
6 response rate for placebo patients. And this
7 difference is not statistically significant.

8 I would point out there are going to be
9 several more tables that follow. And if you want to
10 try to remember one table, I think this is the table
11 to remember because this is the closest that we have
12 to what was actually submitted in the initial NDA.
13 There were other methods developed later after the
14 Pfizer data became available, which we consider more
15 of a sensitivity analysis.

16 That said, they still give you a feel for
17 the data. So if you include the Pfizer patients after
18 converting their data, they have about a 24 percent
19 response rate. So that brings the combined placebo
20 rate down to 28 percent. And that 43 versus 28
21 percent is not statistically significant.

22 I should also point out the rates in
23 Unimed's presentation this morning are about five
24 percentage points lower than 43 and 28 because they're
25 using last observation carried forward. So they're

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1 getting about a five percent reduction in both
2 treatment arms. But the difference between the
3 treatment arms remains the same.

4 Also, these rates are lower than you might
5 recall when we were talking about the individual study
6 results. Those were in the 50s to 60s. That's
7 because for Study 009A and 009B, there we were looking
8 at responders as anyone who had a 25 percent or
9 greater reduction in their stool counts. Here we're
10 looking at patients that had to have at least a 50
11 percent reduction in their stool count, which may
12 provide more clinical benefit to the patient.

13 This table shows the results for Clinical
14 Response A in somewhat more detail. You'll recall
15 there were two ways that you could be counted as a
16 cure. So what this table does is it shows you the
17 first row is patients who were cured because they met
18 both criteria. The next row is patients who were
19 cured because they had a 50 percent reduction but they
20 didn't get down to 3 or fewer stools at follow-up.
21 The third row is patients that got down to 3 or fewer
22 stools at follow-up, having had less than a 50 percent
23 reduction. And then finally are the patients with no
24 response.

25 And what we see here is essentially the

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1 only difference is in the patients that had a 50
2 percent reduction which did not bring them down to 3
3 or fewer stools at follow-up. And this is partially
4 explained by the fact that there is more variability
5 in the nitazoxanide patients. And there were a
6 greater number that started out with higher stool
7 counts.

8 So a 50 percent reduction is not going to
9 bring them to 3 stools per day at follow-up, although
10 the magnitude of the reduction that was seen between
11 the two treatment groups tended to be similar.

12 That's good. Next slide, please. The
13 fourth outcome I'd like to look at is Clinical
14 Response B. This was defined by the applicant after
15 the Pfizer data became available.

16 Here a responder is defined as a patient
17 who shifts down one or more categories from baseline
18 to follow-up. So, for example, if you started with
19 9.5 stools per day, you had to get down to fewer than
20 9.5 at follow-up to be a responder. This is a fairly
21 easy criterion to meet. So what we'll see is that the
22 response rates are fairly high for this analysis.

23 The difference between Unimed and FDA
24 analysis, FDA analysis excludes patients in the lowest
25 category at baseline. That is, we excluded patients

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1 who had less than three and a half stools per day at
2 baseline because by definition, there's no way for
3 them to be assessed as a cure. There's not another
4 category for them to go down to. Unimed analysis
5 includes these patients and calls them all failures.

6 FDA results for Clinical Response B. What
7 we see here -- this is a fairly easy criterion to
8 meet. So the response rates are high: 65 percent for
9 NTZ, 61 percent for placebo. And there is no
10 treatment difference, no significant treatment
11 difference.

12 The next outcome that I would like to look
13 at is Modified Clinical Response B. This was defined
14 by the FDA after the Pfizer data became available and
15 was an attempt to look at a more clinically meaningful
16 change from baseline in stool count.

17 Here a responder is defined as a patient
18 who shifts down two or more categories. So, for
19 example, if you had 9.5 stools per day at baseline,
20 you had to get down to less than 6.5 at follow-up to
21 be cured.

22 The difference between Unimed and FDA
23 analysis, the applicant did not perform this analysis.

24 Here are the results for Modified Clinical
25 Response B. These results look more promising. We

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1 have a 43 percent response rate for nitazoxanide
2 patients and only a 20 percent response rate for
3 placebo patients. This difference is not
4 statistically significant.

5 And also in looking at this difference,
6 one has to recall that we're looking at many different
7 endpoints and many different sensitivity analyses. So
8 we would really need a very tiny p-value to have any
9 confidence that there was a true treatment difference
10 here.

11 Okay. The last outcome that I'd like to
12 look at is Clinical Response C. This was suggested by
13 the FDA after the time of NDA submission and after the
14 Pfizer data became available and is an attempt to look
15 at what are usually called complete responders. So
16 here to be a response, you had to get down to 3 or
17 fewer total bowel movements at follow-up. And
18 obviously patients who began in that category are
19 excluded because it doesn't make sense to include
20 them. The difference between Unimed and FDA analysis,
21 the same approach was used by both parties.

22 Here are the results from clinical
23 Response C. What we see is about a 31 percent
24 response rate in the nitazoxanide patients, compared
25 to a 38 percent response rate in the placebo patients.

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1 This difference was not statistically significant.

2 The placebo group has a slightly higher
3 rate here. And you'll notice in the FDA background,
4 there are Tables 15, 16, and 17 you might want to look
5 at at the end of the presentation.

6 They present this variable by baseline CD,
7 counts, baseline total stool count, and baseline
8 liquid stool count, respectively. And the difference
9 does not appear to be explained when you control for
10 those baseline factors. You still get similar rates
11 between NTZ and placebo in each of the strata that
12 were examined.

13 Finally I would like to talk a little bit
14 about the quality of life data that was collected for
15 the nitazoxanide patients. Unfortunately, we didn't
16 have similar data for the placebo patients. So this
17 is an uncontrolled comparison.

18 There were six quality of life symptoms
19 that were considered. You'll recall they were nausea,
20 vomiting, abdominal pain, urgency, incontinence, and
21 nocturnal bowel movements.

22 They were scored on the four-point scale:
23 one meaning not at all, two meaning mild, three
24 meaning moderate, and four meaning that the symptom
25 was marked.

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1 What I'd like you to focus on in this
2 table is the final column. This is the results for
3 NTZ week four completers before the time of -- there
4 was an efficacy update, which added two more patients.
5 And this is taken from the sponsors, the applicant's
6 submission.

7 This shows the average change from
8 baseline for each of the symptom scores. And what we
9 see is that the amount of change ranged from -.2 for
10 vomiting to -.8 for bowel movements that woke the
11 patient from sleep.

12 Now, each of these changes from baseline
13 was statistically significant. However, there are two
14 questions that the Advisory Committee needs to
15 consider. The first is the fact that this is
16 uncontrolled data. And if you'll recall the analysis
17 of change from baseline and total stool count, there
18 we also saw a highly significant change from baseline
19 for nitazoxanide patients. We saw a highly
20 significant change from baseline for placebo patients.
21 And there was no difference between the two groups.

22 The second question for the Advisory
23 Committee we need help on is whether these changes
24 from -.2 to -.8 are clinically meaningful on a 4-point
25 scale.

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1 So, to summarize my part of the
2 presentation, in FDA's analysis, NTZ response rates
3 range from 31 to 43 percent. And this is excluding
4 Clinical Response B because those rates were unusually
5 high. And you'll recall there was a median reduction
6 of two and a half stools per day from baseline.

7 The placebo response rates ranged from 20
8 to 38 percent, again including Clinical Response B.
9 And there was a median reduction of two stools per day
10 from baseline.

11 No significant differences, treatment
12 differences, were observed on any of the six endpoints
13 that were considered here. And when we control for
14 baseline differences, there were still no significant
15 treatment differences.

16 Finally, we had a significant change from
17 baseline for nitazoxanide patients on all of the
18 quality of life scores. However, the results are
19 uncontrolled. And so we need a little bit of help
20 interpreting this data.

21 Thank you. And I'd like to turn the
22 podium back over to Dr. Roca.

23 DR. ROCA: I think we have caught up on
24 time a little bit. So I will slow down.

25 As we discuss in the beginning, there were

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1 four points that we wanted to bring to the Committee's
2 attention. And the last one is safety.

3 Next slide, please. This slide shows the
4 number of patients in the applicant's current safety
5 database. And even if one were to include the 88
6 patients in the overseas studies, -- and this would be
7 in Mali and Mexico -- it would still be quite less
8 than the total amount of database that one is usually
9 expected to see or one would like to see.

10 It is noted that there is a much larger
11 database in non-AIDS patients. And there are our
12 overseas patients. However, these are for different
13 indications, shorter durations of therapy, and for
14 different dose. Although this information is very
15 helpful, it is not exactly applicable to the patient
16 population for which the applicant seeks approval.

17 This slide is here to remind you and to
18 refresh your memory of the extent of drug exposure in
19 the safety databases, essentially the same slide that
20 the applicant showed before.

21 And there are three points that I'd like
22 to bring out about this slide. First, there is no
23 control safety data except for some comparison between
24 1,000-milligram and 2,000-milligram dose per day. And
25 the 2,000-milligram did suggest that the higher dose

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1 was less well-tolerated.

2 Second, there was an overall 117 patients
3 which received 1,000 milligrams for at least one month
4 or four weeks.

5 And the last point is 22 patients received
6 2,000 milligrams for at least one month.

7 Next slide, please. This slide summarizes
8 the incidence of the liver enzyme elevations that were
9 observed. And two of these events were considered
10 Grade 4 or life-threatening. One of them was an
11 alkaline phosphatase, and it was felt not to be
12 drug-related. And the other one was an AST. That was
13 felt to be drug-related, and it did improve after
14 discontinuation of nitazoxanide.

15 The pediatric database consists of 13
16 patients ranging from ages of 3 to 15. And in this
17 group, 8 out of 13 experienced an adverse event. The
18 type of adverse events observed are similar to the
19 ones that were seen in the adult patients.

20 In summary, nitazoxanide demonstrated
21 variable results in the different experimental models.
22 And, as mentioned before, there is no consensus
23 regarding a valid animal model. Therefore, it is not
24 clear which one would be representative of
25 nitazoxanide's activity in humans.

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1 Next slide, please. No significant
2 differences were observed between nitazoxanide and
3 placebo for any of the six clinical endpoints. No
4 significant differences were observed between
5 nitazoxanide and placebo in analyses that controlled
6 for baseline factors.

7 There is the potential concern for
8 hepatotoxicity in the intended patient population.
9 And we concur with the applicant, as they mention in
10 their background package, that patients on
11 nitazoxanide therapy should be monitored for these
12 toxicities.

13 Thank you for your attention.

14 CHAIRMAN HAMMER: Thank you.

15 Are there questions from the panel members
16 for the FDA presenters? Dr. Mathews?

17 DR. MATHEWS: The response definition for
18 number of stools, say, at four weeks, was that based
19 on diaries for the preceding week? And was the method
20 of specification of that outcome variable similar,
21 effectively similar, in the placebo-controlled group
22 as in the nitazoxanide group?

23 In other words, there's a lot of
24 variability from day to day. And Dr. Soave showed us
25 a sample diary. Is that what was used in defining

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1 response in terms of stool frequency?

2 DR. SILLIMAN: The applicant can also jump
3 in here if I say anything wrong. At baseline I think
4 for the NTZ patients, they were looking at a week of
5 data. For most of the other time points, I think it
6 was an average over the prior three days.

7 DR. MATHEWS: And it was actually based on
8 diaries or report of the patient: On average how many
9 stools did you have over the last week?

10 DR. SILLIMAN: I think it was based on
11 patient diaries. That was my understanding.

12 DR. MATHEWS: Is there a difference, then?
13 The placebo patients had it collected a different way?
14 Do you know, Dr. Soave?

15 DR. SOAVE: Yes. At least the Pfizer
16 patients, it was a report. The NTZ was based on
17 diaries.

18 DR. MATHEWS: Okay. And the ACTG trial,
19 how is that?

20 DR. SILLIMAN: That was also based on
21 diaries.

22 CHAIRMAN HAMMER: Dr. Lipsky?

23 MEMBER LIPSKY: With the negative results,
24 can you give us an idea of the Type II error? And
25 where there were differences, how many patients might

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1 it take to show a difference?

2 DR. SILLIMAN: I think the company had
3 looked at that. There was only like a 38 percent --

4 DR. LEUNG: Yes. With trying to detect
5 the difference between, say, a 43 percent of NTZ
6 compared to the 28 percent in the combined placebo
7 study, the observed power is only 38 percent with a
8 Type I error of 105. If you want to have 80 percent
9 power, than you need 159 patients per arm in order to
10 achieve that.

11 CHAIRMAN HAMMER: Please identify yourself
12 for the transcript.

13 DR. LEUNG: Hoi Leung, a Unimed
14 consultant.

15 CHAIRMAN HAMMER: Thank you.

16 DR. SILLIMAN: Yes. The power for the
17 primary comparison was low, but you also recall, I
18 mean, there were many, many sensitivity analyses that
19 were conducted. So you would expect, just due to
20 natural variability, that at least one of those
21 analyses would have shown a significant treatment
22 difference. And that didn't happen.

23 CHAIRMAN HAMMER: Dr. Hamilton?

24 MEMBER HAMILTON: Was the use of a
25 microbiologic comparison simply not possible?

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1 DR. SILLIMAN: For the placebo patients?

2 MEMBER HAMILTON: Yes.

3 DR. SILLIMAN: Yes. I guess we didn't
4 focus on the micro data because there was a little bit
5 of a disconnect between the clinical and the
6 microbiology.

7 CHAIRMAN HAMMER: Any other questions?

8 (No response.)

9 CHAIRMAN HAMMER: We'll have a chance to
10 come back with our critical questions at the beginning
11 of the afternoon. I think we'll break for lunch.
12 We'll reconvene in one hour, approximately 1:20. And
13 we will start with the open public hearing at that
14 time.

15 (Whereupon, a luncheon recess was taken
16 at 12:18 p.m.)

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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

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1 Ziegler Foundation, which is a nonprofit organization
2 that has as its mission access to state-of-the-art
3 care for all people with HIV without regard for
4 ability to pay. So that's specifically what we are
5 interested in promoting.

6 I had submitted an article that comes from
7 the recent April issue of the *Bulletin of Experimental*
8 *Treatments for AIDS* for inclusion in the record. And
9 I'm not sure that has happened. If not, I can yet
10 give you a copy of that.

11 To come to the conclusion that I'm now
12 going to present, we went through a series of steps
13 that I think are briefly worth discussing. The
14 Scientific Advisory Committee of the San Francisco
15 AIDS Foundation has reviewed the data which I had
16 collected from presentations by Unimed on two
17 different occasions earlier this year and has come to
18 the conclusion that based on their clinical experience
19 as well as upon some of the pharmacological analysis
20 done by a pharmacist that is in charge of something
21 that's called the National HIV Teleconference and
22 Teleconsultation Service that there be a specific
23 recommendation made today to the panel that they
24 consider the dosing; if this is approved, that dosing
25 not be restricted in such a way that people will have

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1 difficulty with third party payers. So that what
2 they're suggesting is that no specific ceiling dose be
3 established but, rather, that each individual
4 physician in consultation and with best judgment be
5 allowed to titrate up to the most effective dose for
6 the individuals involved.

7 A similar process was undertaken with the
8 medical staff of the Andrew Ziegler Foundation, which
9 is, again, another six physicians who are in community
10 practice in San Francisco. And the same conclusion
11 was reached with the same recommendation.

12 So input from these individuals weighs
13 heavily in any decision to either support or oppose
14 the approval of any given drug by the San Francisco
15 AIDS Foundation. And I believe you have seen in a
16 consensus statement which has been widely circulated
17 here that the San Francisco AIDS Foundation has been
18 a signatory to a consensus statement that has strongly
19 advised this Committee to accept and to agree to the
20 NDA for this particular drug.

21 Let's see. I believe that the consensus
22 statement does not include the Andrew Ziegler
23 Foundation. I would like that to at least be a mental
24 note on your part that that as well is now a
25 signatory. And I believe that if we had more time, we

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1 would get more organizations to sign on to that
2 particular consensus statement. So I would encourage
3 you to take that quite seriously as part of community
4 input.

5 Personal experiences with this I will not
6 refer to because they fall outside of the specific
7 indication that is being asked for, but let me just
8 say sort of in a parenthetical kind of way that there
9 are other diarrhea-causing kinds of conditions that
10 people can have for which NTZ seems to be effective.
11 At least in my case that has been true with Crohn's
12 disease but doesn't bolster the case in this
13 particular instance.

14 However, anecdotal evidence as it seems to
15 collect seems to have a stronger case, at least in the
16 data presented so far, than does the analysis that was
17 presented by FDA. So I would hope that you will
18 listen to me and to the other two speakers who come to
19 provide you with some testimony on this.

20 I believe that I'm missing some parts of
21 what I'm supposed to say. I disclose that my two
22 organizations, neither of them takes any money from
23 Unimed. And I was authorized to use my own credit
24 card to fly here. That was quite gracious on the part
25 of the AIDS Foundation. I hope that they can change

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1 their mind on that.

2 (Laughter.)

3 CHAIRMAN HAMMER: Thank you very much.

4 The next speaker is Bill Bahlman.

5 MR. BAHLMAN: Good afternoon. My name is
6 Bill Bahlman. I am a founding member of Act Up New
7 York, which was founded in March of 1987. And I was
8 a treatment advocate in AIDS going back to 1985. I
9 have been living with AIDS for over ten years now.

10 I also serve on the Community Advisory
11 Board of NYU-Bellevue and their AIDS Clinical Trials
12 Program, which is one of the most active and proactive
13 community advisory boards in the country, where for
14 each and every single clinical trials protocol that
15 comes before our NYU-Bellevue's Clinical Trials
16 Program, we review those protocols very carefully and
17 quite often make comments on those protocols and have
18 initiated a number of changes to those protocols when
19 they're in their early form and even once those
20 programs become protocols that are up and running.

21 I have thought long and hard on the
22 approval of Cryptaz that's here before the Committee
23 today and got more aggressively involved in terms of
24 dealing with the issues around the approval of this
25 drug as I began to be aware that there's some degree

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1 of potential that the outcome from the Advisory
2 Committee or the FDA might be in question.

3 I hope it is not in question, and I hope
4 it will be approved today. But I thought it was
5 important that a number of members of the community be
6 somewhat involved in the process and to voice our
7 concerns about the issues surrounding the approval of
8 this drug.

9 I was very concerned about the
10 placebo-controlled study that was attempted to be run
11 through the ACTG program that over the course of the
12 15 months was only able to accrue 10 people with AIDS
13 and crypto.

14 I think if we went back and there was more
15 community involvement in the design of that protocol,
16 we might have been able to come up with a more
17 significant protocol that people with AIDS would want
18 to enroll in. And we might have more significant data
19 here today to deal with whether we should move ahead
20 with approval or to say to the company that we want to
21 see this drug go back for further analysis before
22 we're able to say that it should be approved.

23 I think that's an unfortunate position for
24 people with AIDS because what mistakes might have been
25 made at ACTG, whether they were well-intentioned or

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1 whatever, you know, that's the way things were set up
2 and the way Unimed worked with the ACTG. It was a
3 protocol that was not too friendly to people with
4 AIDS, unfortunately. And I think they are the people
5 who should not be held hostage to the limited data
6 that we currently have here today.

7 And I think we need to take a bit of a
8 leap of faith and understand that we have to work with
9 the data we have now and figure out whether this drug
10 should be made available to people with AIDS or not.

11 We look at the fact that it's been said a
12 number of times today that there is access to Cryptaz
13 at this point. That is true. It is not wide-scale
14 access. It is available through a number of buyers'
15 clubs, which means that if you want to gain access to
16 it, you have to pay for it.

17 And how many people with AIDS who have
18 crypto need to gain access to this drug or would like
19 to be able to try it because it might be able to help
20 them based on the limited data that we have who cannot
21 afford to pay for it? They cannot get their insurance
22 companies to pay for it.

23 So that's one of the other reasons I hope
24 that this Committee recommends its approval, so there
25 is more of a wider scale and more of a uniform access

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1 to this drug that does not discriminate against people
2 who cannot afford to pay for it.

3 I think we have to look at what we have
4 here in terms of data. This drug was studied in
5 people with very, very low CD₄ counts. It was also
6 studied significantly in patients who did not have
7 access to HAART, highly active anti-retroviral
8 treatment regimens. Protease inhibitors were not so
9 widely available when these studies were conducted.

10 So that sort of confounds things in terms
11 of where we are, but it also tells us that the drug
12 had an impact in these patients who were very sick and
13 also did not have protease inhibitors to help them
14 out.

15 We also look at the fact that it clearly
16 I think shows that there was benefit to patients. You
17 can compare it to the placebo-controlled analysis from
18 Unimed and, with worse results, from the FDA's
19 analysis, which didn't seem to take into account the
20 differences in the characteristics of the patients
21 that were used in the analysis in the 143 and the 192
22 studies.

23 I think one has to make a closer
24 comparison and pair off the baseline characteristics
25 of CD₄ count and how sick these patients were in the

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1 Unimed studies, as compared to the other studies that
2 were used in the analysis.

3 So in terms of what we do know, I do
4 believe and on analysis of this data and I think a lot
5 of community activists who have looked at the data see
6 that there really appears to be a significant benefit
7 to patients. How confident we can be about that
8 benefit is in doubt, but it really appears as if there
9 is benefit there. We see also in terms of the weight
10 maintenance of the patients who are in the studies.
11 And I think that's important.

12 In terms of the dosing regimens, we can
13 see from the data a 500-milligram dose is not
14 adequate. We appear to get good results from the
15 1,000-milligram dose. And we also see with the
16 2,000-milligram dose that that dose may be too high to
17 start with a patient.

18 We're seeing more problems with
19 gastrointestinal problems, which possibly might be
20 compounded by the fact that the compound, one of the
21 components is aspirin in the compound.

22 And, therefore, the 2,000-milligram dose
23 starting with patients who have really bad diarrhea
24 might lead to more problems with the patients. And,
25 therefore, I don't think we necessarily should be

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1 dosing up higher than that or be looking for a higher
2 dose for initiation of therapy.

3 So I think the starting of the
4 1,000-milligram dose, 500 milligrams b.i.d., is an
5 adequate choice. When I first looked at the data, I
6 was thinking that the higher dose was necessary, but
7 the more one looks at the data, the more it seems as
8 if the indication that the company is looking for
9 right now is the adequate one.

10 We also have to consider, as Rosemary
11 Soave put forth, the condition of crypto in patients
12 who are very sick. It is very debilitating. I
13 suffered from crypto late last year. And I'll tell
14 you the way one feels, the personal toll that it takes
15 on your life, not just the losing of weight but also,
16 as Rosemary put it, the self-esteem that one suffers
17 when you're lying in bed incontinent, waking up
18 through the middle of the night and you're a mess, not
19 being able to go out, not being able to be with
20 friends because you're concerned about that.

21 It's a problem we have now with
22 anti-retroviral therapy as well. Taking nelfinivir
23 can make one incontinent and give one uncontrollable
24 diarrhea over a period of time. And I think it's
25 downplayed a bit in terms of what patients suffer, but

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1 it's very real and it's a hard thing for people to
2 deal with.

3 So, with all of that, I believe very
4 strongly that we should move toward approving this
5 drug. I think we should monitor how it's being used.
6 And I think it's going to fall amongst the physicians
7 who use this drug when it's out there in clinical
8 practice. With the experience that they have when
9 they prescribe it to patients and they see success,
10 they're going to use it again. And if they find that
11 it's not helping their patients, they're going to wind
12 up not using it.

13 I think the toxicity profile that you see
14 before you is fairly good. I think that should give
15 us some confidence to take a chance on data on a drug
16 that we don't have the data that we would love to
17 have.

18 So, with those things said, Act Up New
19 York strongly urges its approval and that we should
20 continue to monitor this drug over the coming years
21 because I believe that crypto is not going away.

22 There has been talk about how there's a
23 much less incidence of crypto thanks to HAART, but the
24 water supply is probably worse than ever and may get
25 worse in the future.

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1 Sexual practices that people with AIDS
2 engage in can lead to the spread of this disease and
3 is no likelihood that that is going to get any better
4 in the future.

5 I think there needs to be greater
6 education around crypto and AIDS, particularly within
7 the gay community but throughout all communities
8 affected by AIDS. So I believe that we need to put an
9 emphasis on education.

10 We need to better understand how crypto
11 affects people with AIDS. There needs to be more
12 research in there because there is a dearth of
13 research, particularly due to the fact that we haven't
14 had effective drugs, but I think it is very important
15 we have that research and the education.

16 And so I just think, ending with that, I
17 urge you to please support its approval.

18 CHAIRMAN HAMMER: Thank you very much.

19 The next speaker is Laura Morrison.

20 MS. MORRISON: Thanks. As noted, I'm
21 Laura Morrison. And I'm here today on behalf of 17
22 AIDS organizations and publications, including The
23 Treatment Action Group, Act Up East Bay, AIDS Action
24 Baltimore, AIDS Project Arizona, AIDS Project Los
25 Angeles, AIDS Treatment Initiatives in Atlanta, the

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1 Center for AIDS-Houston, Foundation for AIDS and
2 Immunology Research, Gay Men's Health Crisis, John
3 James AIDS Treatment News, National Minority AIDS
4 Council, Pause L.A., Pause Magazine, Project Inform,
5 PWA Coalition Colorado, Resolute, and the Whitman
6 Walker Clinic here in D.C., to urge the approval of
7 Cryptaz for treatment of cryptosporidial diarrhea in
8 people with AIDS.

9 I have distributed outside -- there's a
10 consensus statement that we all signed onto as well as
11 a background document that was based on data we
12 received prior to today's hearing.

13 The groups who have reached this consensus
14 position recommend approval, despite our recognition
15 that the data package is rather marginal and is based
16 largely; in fact, entirely, on open-label
17 compassionate-use data.

18 While we typically believe that open-label
19 compassionate-use study data are valuable solely or
20 primarily for safety of a given drug and we're
21 typically uncomfortable using it as an indicator of
22 efficacy or as the sole basis for approval of a drug,
23 in this case we don't see a choice.

24 We believe that in the case of
25 anti-cryptosporidial agents, there really isn't a

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1 possibility of doing placebo-controlled trials at this
2 time and that the historical data that has been
3 presented so far is not a reasonable comparison due to
4 differences in study design and number of patients
5 enrolled.

6 Also we believe there are ethical problems
7 with conducting placebo-controlled trials at this
8 point and actually don't think they are going to be
9 feasible with the HAART regimens that people are now
10 on, regardless of whether there's a decrease in the
11 actual instance of cryptosporidiosis.

12 We see small numbers that are actually
13 diagnosed, as we'll address, in the number of patients
14 in the 226-patient population that was presented today
15 who actually had confirmed, microbiologically
16 confirmed, crypto.

17 People have access to other unapproved
18 therapies. Whether they are actually effective, they
19 can get them through off-label use. We've mentioned
20 the buyers' club that have provided NTZ to people.

21 So there are a lot of problems with having
22 controlled data, and we just have to accept the
23 limitations, as Bill Bahlman said, with this data set
24 and present our argument based on that.

25 That said, looking at the data that was

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1 presented by the sponsor, we see an undeniable
2 clinical response with an excellent safety profile.

3 We have limited our efficacy analysis as
4 a community consensus group to those patients who had
5 had microbiologically confirmed cryptosporidiosis.
6 That was, at baseline we had 28 patients in 004 who
7 fit that criteria and 39 in 009, for a total of 67.

8 Within those patient groups, we saw
9 clinical response rates of nearly 40 percent of those
10 in 004. And that was on a very stringent definition
11 of what a clinical response was. We saw nearly 50
12 percent for the people in 009A.

13 And we saw microbiological parasitological
14 response of nearly 40 percent in the 004 and close to
15 60 percent in 009A, which we believe clearly shows
16 there is actively for Cryptaz for people with
17 cryptosporidiosis.

18 It should be noted also, as Bill Bahlman
19 did and Mark did, that the people in these studies
20 were profoundly ill. They had advanced
21 cryptosporidiosis and were profoundly
22 immunosuppressed.

23 There is reason to believe that Cryptaz
24 might have an even greater efficacy in people who are
25 healthier at baseline. Right now for people who are

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1 healthy, who are early in their cryptosporidiosis,
2 maybe have a higher CD₄ count, there isn't an approved
3 therapy. There is nothing else out there.

4 So it's really important for people to
5 have a chance. And give people a one in two or even
6 a four in ten chance of having something that is going
7 to limit this debilitating diarrhea of this really
8 devastating disease. I think we have to give them
9 that opportunity. Without this, there is nothing.

10 That said, we urge you to recommend
11 approval of Cryptaz and suggest that the FDA work with
12 Unimed to develop post-marketing studies that might
13 actually give us more answers about how to best use
14 this, what duration of treatment we should have and
15 what dose.

16 Thank you.

17 CHAIRMAN HAMMER: Thank you.

18 MR. BAHLMAN: This is Bill Bahlman.

19 I just wanted to say very quickly that I
20 didn't make a disclosure because I was running from
21 quick notes because when I prepared full text in
22 advance of these hearings, I often chuck them and have
23 written new remarks as I have been sitting here.

24 I just wanted to say that early on in
25 discussions a couple of months ago, the company,

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1 Unimed, offered to pay or take care of my expenses to
2 be able to be here today, and I accepted that offer.
3 And that's the only gratuity I've received at all,
4 just to take care of my expenses to be here today.

5 CHAIRMAN HAMMER: Thank you.

6 Is there anyone else who wishes to make a
7 public statement?

8 (No response.)

9 CHAIRMAN HAMMER: If not, I would just
10 reiterate that the community consensus position paper
11 is outside. And copies are available.

12 We have also received a letter from a
13 patient involved in one of the studies supporting
14 approval. I believe a copy is available outside.

15 And also Act Up Golden Gate has submitted
16 a statement, copies of which are also available,
17 supporting approval but supporting it under conditions
18 and not supporting full approval but conditional
19 approval. And, again, those statements are available
20 for review.

21 That being said, we'll close this part of
22 the meeting and move on. Before we have the charge to
23 the Committee, I would just ask the panel members
24 whether there are any last important questions that
25 anyone has for either the sponsor or the agency.

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1 Please, Doctor?

2 DR. SELF: There was a question raised
3 about the FDA's data analysis, whether there was
4 appropriate adjustment for differences in baseline
5 characteristics between historical placebo-controlled
6 and the NTZ patients. Could you comment on those
7 adjustments and what you found?

8 DR. SILLIMAN: Sure. We looked at the
9 outcome measures controlling for three baseline
10 factors: CD₄ count, total stool count at baseline,
11 and total liquid stool count at baseline. We did this
12 both uni-variately using categories and
13 multi-variately using logistic regression.

14 And controlling for differences in
15 baseline factors we still found no significant
16 treatment differences and no trends that were
17 consistently in favor of nitazoxanide.

18 CHAIRMAN HAMMER: Thank you.

19 Dr. Sears?

20 DR. SEARS: Along the same lines, the
21 question was raised whether the placebo group used for
22 comparison is valid -- do you have any comments about
23 that? -- in terms of the characteristics of the
24 population.

25 DR. SILLIMAN: The placebo patients were

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1 slightly less ill. We can actually show a couple of
2 slides. Slide 57. These are side-by-side box plots
3 of the CD₄ count at baseline. And what you'll see is
4 the NTZ patients -- there we go. My pointer doesn't
5 seem to be working.

6 The CD₄ counts are somewhat lower for the
7 nitazoxanide patients. The difference here was not
8 statistically significant. And you'll note that while
9 the placebo patients were slightly less ill, still the
10 majority of patients had CD₄ counts of less than 100.
11 So it's not like they're healthy patients.

12 And then if we could go to the next slide?
13 This shows the total number of stools at baseline for
14 nitazoxanide and placebo patients. And, again, the
15 nitazoxanide patients had slightly higher stool counts
16 at baseline. There's also more variability in the
17 nitazoxanide patients.

18 And then let's see. If we go to Slide 61,
19 this is the number of liquid stools at baseline.
20 Again, nitazoxanide patients had slightly higher stool
21 counts at baseline than the placebo patients.

22 So to control for these differences, maybe
23 I can show one of the tables to give you an idea of
24 what we looked at. Slide 67, please. This shows
25 results for the primary efficacy variable by CD₄.

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1 count.

2 And we looked at three categories which we
3 felt were clinically meaningful: CD₄ count of zero to
4 50 at baseline, 50 to 150 at baseline, and greater
5 than 150 at baseline.

6 Unfortunately, the number of placebo
7 patients is small. As the Pfizer data was collected,
8 it was the categorical outcome you'll recall. So here
9 this is just the ACTG placebo patients versus the
10 nitazoxanide patients.

11 And what you'll see is there is no
12 consistent trend in favor of either treatment arm.
13 And the p-value indicates that when you control for
14 these three different levels of CD₄ count at baseline,
15 there's no significant treatment difference or there
16 is no trend in favor of either arm that's consistent
17 across the strata. That's perhaps a better way to
18 think about it.

19 Similar analyses were done looking at
20 total stool count at baseline and total liquid stool
21 count. Those are the next two slides. Here again we
22 don't see any consistent trend in favor of either
23 nitazoxanide or placebo. Numbers again are small,
24 unfortunately. And the p-value indicates that
25 controlling for these four different categories there

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1 is no trend in favor of either arm that is consistent
2 across the strata.

3 And then the next slide is we looked at
4 number of liquid stools at baseline. And for this, we
5 used patients who had less than or equal to three
6 liquid stools at baseline -- so they're less ill
7 patients -- and then greater than or equal to three
8 liquid stools at baseline, the more ill patients.
9 And, again, the rates were essentially similar in the
10 treatment arms and there was no significant
11 difference.

12 We also used logistic regression to look
13 at all three of these factors together. And,
14 actually, none of those factors were significant
15 predictors of clinical response. And treatment was
16 also not a significant predictor of clinical response.

17 CHAIRMAN HAMMER: Thank you. Thanks.
18 Lights, please.

19 If there are no additional questions, then
20 we'll turn to Dr. Dianne Murphy for the charge to the
21 Committee.

22 CHARGE TO COMMITTEE

23 DR. MURPHY: Before we go to the
24 questions, I just want to make a few statements.
25 Today you've heard of a need for a good therapeutic

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1 option for an infection which is life-threatening,
2 devastating in an already vulnerable population.

3 You've also heard of a company which
4 stepped forward and, despite concerted efforts by the
5 company and cooperative efforts with NIH and ACTG,
6 there is no concurrently placebo-controlled trial for
7 you to evaluate.

8 You have heard of their efforts to obtain
9 historical controls and of the limitations involved in
10 using placebo patients from differently designed
11 studies with differently designed endpoints.

12 Thus, you have been presented open-label
13 historically controlled data where the placebo
14 population had -- pick the middle here -- 20 percent
15 positive response and other uncontrolled open-label
16 data.

17 The proposal of the sponsor is not that
18 there is a statistically significant difference. They
19 propose that there is a non-statistically significant
20 clinical benefit as demonstrated by persistence of a
21 positive clinical benefit in numerous analysis that
22 this therapy provides as a needed option for patients.

23 In this context, could we have a slide?
24 You are presented with these questions. Is
25 nitazoxanide safe and effective for use in the

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1 treatment of cryptosporidial disease in AIDS? If yes,
2 is there a specific patient population for which the
3 drug is intended? And what in the data was
4 convincing, keeping in mind future applicants? If no,
5 what additional data is required in order to be able
6 to make the above determination?

7 And I would hope that we wouldn't leave
8 today without defining for this population what this
9 Committee would want to see for a successful study
10 and, in particular, the endpoints they felt are most
11 relevant.

12 Next slide, please. And does the
13 Committee have any additional advice regarding future
14 studies with respect to: design, duration, and choice
15 of comparator?

16 Thank you. And we look forward to your
17 comments.

18 CHAIRMAN HAMMER: Thank you.

19 We will now turn to the Committee. The
20 first question will be a voting question. And I'll
21 just restate it, and then we'll go around the room.
22 Is nitazoxanide safe and effective for use in the
23 treatment of cryptosporidial diarrhea in AIDS? And
24 I'll start on my left with Dr. Mathews.

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OPEN COMMITTEE DISCUSSION

1
2 DR. MATHEWS: The brief answer in my
3 opinion is it appears to be safe, but I'm not
4 convinced that it's effective.

5 And if I could just make a couple of
6 comments, first of all, I share with the other members
7 of the Committee admiration for the company,
8 particularly the investigators who brought this
9 forward and have worked in it for years.

10 Out on the West Coast, I have read all of
11 Dr. Soave's articles on this and looked for the latest
12 hope in the treatment of a devastating illness. But,
13 for a number of reasons that I think have been
14 highlighted in the course of the morning's discussion,
15 I am not convinced that the difference between the
16 placebo arms of the other studies and the combined two
17 compassionate-use and one open-label study are
18 meaningfully different. And they're certainly not
19 statistically different. In my own mind, I'm not sure
20 that we would be doing a favor to the community at
21 large to state that efficacy has been demonstrated.

22 There are reasons that have to do with the
23 diagnostic criteria, the varied diagnostic intensity,
24 for good reasons certainly, but in use of a new agent
25 for which there has not been clear-cut proof of

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1 efficacy in any population by a randomized controlled
2 trial, I am more persuaded by the history of trials in
3 this disease, that it's been one agent after another
4 brought forward based on open-label, uncontrolled
5 observations, which when subjected to randomized
6 controlled trials failed to prove the test.

7 The issues of loss to follow-up, short
8 duration of observation I think have been raised and
9 are cogent. The disease itself is so heterogeneous.
10 And even the endpoint as it was defined, reduction to
11 less than or equal to three stools per day, would
12 include a whole range of patients, even on some of the
13 graphs, where people dropped from, say, 20 to 25
14 stools a day down to less than less 3, others who had
15 very small changes but still were able to meet the
16 endpoint. I'm not convinced we're dealing with the
17 same process, the same disease.

18 So, in conclusion, I just don't believe
19 that the weight of evidence is there. And, therefore,
20 I would vote no. There are other comments I'd make on
21 possible ideas on how to study the drug more
22 effectively.

23 CHAIRMAN HAMMER: Thank you.

24 We will return to the other questions that
25 Dr. Murphy asked us, but the primary question, Dr.

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1 Sears?

2 DR. SEARS: I don't think I can state it
3 any better than Dr. Mathews. I agree that the
4 nitazoxanide appears safe, but I concur with all of
5 his comments on a relative lack or a lack of efficacy
6 demonstrated in the study as presented.

7 CHAIRMAN HAMMER: Thank you.

8 Mr. Marco?

9 MR. MARCO: Well, I do believe that the
10 drug is safe, but I also agree with some of the FDA's
11 comment, especially Dr. Murphy, who said that doing
12 cross-protocol analysis is often difficult, especially
13 with confounding variables.

14 And so if I take her 20 percent median for
15 placebo response rate and compare it to the FDA's 43
16 percent, it makes me feel confident that there's at
17 least some marginal clinical benefit. And even in
18 only looking at the patients who all had microbiologic
19 evidence of crypto at baseline, I think that the
20 risk/benefit ratio is in favor of NTZ.

21 And so I do see a soft yes for approval.

22 CHAIRMAN HAMMER: Thank you.

23 Ms. Cohen?

24 MS. COHEN: Well, if you say a soft yes,
25 do I have to say a hard no? I have some concerns. I

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1 don't think there's any absorption information. I
2 don't think there's any information on the placebo.
3 I'm not satisfied with the follow-up. I think the
4 missing data I think overall someone said was 34
5 percent. They haven't had a decent animal model.
6 There's no pharmacokinetic information.

7 And, you know, when one talks about buying
8 clubs, it concerns me because I sat on the panel for
9 thalidomide. That's not reason enough to pass a drug
10 that you really don't know about.

11 And if we make this available, I always
12 worry. It's for a certain population, but other
13 people might think that: If it works for them, it
14 will work for us.

15 And I just don't think there's enough
16 information to make me comfortable. In the
17 comparisons, I'm not even sure how they picked the
18 patients, frankly, and whether they were similar. I
19 just think it's a very difficult problem. And in my
20 good conscience, I can't vote for it.

21 CHAIRMAN HAMMER: Thank you.

22 Dr. Self?

23 DR. SELF: In the briefing materials, the
24 sponsor provided some criteria by which efficacy could
25 be evaluated in the absence of placebo-controlled

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1 trials. These were a dose-response relationship,
2 which was not demonstrated.

3 The criteria also included comparison with
4 historical controls, which I think, in spite of all of
5 the difficulties given the problems with mounting a
6 trial in this disease, is probably as best one can do.

7 So, contrary to an earlier statement, if
8 all attempts have been made to mount a
9 placebo-controlled trial and those fail, it's just not
10 feasible. I think the approval shouldn't be held
11 hostage to that. So I'm perfectly willing to
12 entertain that sort of comparison.

13 However, in the analyses, I think
14 primarily due to limitations of the data on the
15 NTZ-treated patients, rather than the challenges with
16 comparing to historical controls, that there was no
17 consistent trend in favor of NTZ. And I found that
18 particularly compelling.

19 Given that there isn't any other treatment
20 available and the severity of the disease, I in this
21 case actually wouldn't even hold the process to strict
22 statistical significance since the amount of data from
23 historical controls is limited.

24 Having said that, I might have to turn in
25 my statistician's card, but, again, giving I think

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1 every benefit to the doubt in good conscience, I think
2 the comparison is not favorable to NTZ.

3 What's left I think is and perhaps is most
4 intriguing is the analysis of detailed
5 characterization of relatively few patients, clinical
6 course.

7 In the slide presented by the FDA, there
8 are these five patients out of '91 with large
9 decreases in the numbers of stools. And that's
10 intriguing. There are also the plots presented from
11 a few select patients of I think what was referred to
12 as the challenge/re-challenge data.

13 But, again, even though those are
14 intriguing and suggestive, that type of data is very
15 difficult to carry into a recommendation for use of
16 drug in a population.

17 And so in the end, I don't see the
18 evidence for the effectiveness of NTZ.

19 CHAIRMAN HAMMER: Thank you.

20 Dr. Hamilton?

21 MEMBER HAMILTON: I'm very sympathetic to
22 the views expressed by some articulate, impassioned,
23 personally involved individuals who are making a plea
24 for approval.

25 I've also been very impressed with the

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1 level of effort expended by the sponsor in pursuing
2 the solution to a very important and difficult
3 problem.

4 I think it's completely appropriate that
5 various perspectives be directed at whether the case
6 has been made to make this more generally available in
7 a forum such as this with representatives from areas
8 of different expertise.

9 I myself have been involved in HIV
10 research for some time and am actively engaged in
11 patient care. That having been said, I'm certain I'm
12 not as close to the real tragedy as many of you are.

13 That having been said, however, I have
14 kind of made the decision in my own mind based on what
15 I think is close to a sacred trust between individual
16 patients and myself that I will advise to them only
17 what I really think will work. And I can do no less
18 in this situation.

19 I find, as have many of my predecessors
20 here, the data to be wanting. And I would in all
21 conscience I think be ill-advised to recommend this
22 drug either for a large number of patients with this
23 disease or to an individual. And, therefore, I will
24 not approve this drug by my vote.

25 CHAIRMAN HAMMER: Thank you.

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1 Dr. Lipsky?

2 MEMBER LIPSKY: Rather than answer the
3 question "Is the drug safe and effective?" with a no,
4 I would say the answer is more like a not proven. And
5 I think others have made comments which I might have
6 made.

7 CHAIRMAN HAMMER: Thank you.

8 Dr. Masur?

9 MEMBER MASUR: I concur with what Jim
10 said. I think, again, I'm impressed that the sponsor,
11 the investigators have made a real effort to look at
12 a very difficult problem. And, yet, what we're left
13 with is a relatively small cohort of patients with a
14 lot of missing data.

15 We're left with some scientific voids in
16 that the discrepancy between the microbiologic and the
17 clinical response is a little bit disturbing. The
18 lack of a dose-response is disturbing.

19 So I would hope that this drug is going to
20 continue to be investigated because there do seem to
21 be patients who have dramatic responses. But based on
22 the scientific evidence here, efficacy has not been
23 demonstrated.

24 And, even with safety, I'm concerned that
25 we don't have very much data about the long-term

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1 effects, particularly at some of the higher doses that
2 might be used. So we don't have any evidence of
3 toxicity, but I'm not sure that we have convincing
4 data that this drug at the higher doses for long
5 periods of time is, in fact, safe.

6 CHAIRMAN HAMMER: Thank you.

7 Dr. Feinberg had to leave, but she left me
8 her comments. They, briefly stated, were that she
9 felt there was no statistically significant benefit
10 demonstrated when compared to historical controls,
11 although those are, admittedly, somewhat inadequate;
12 no understanding of what the active moiety is or what
13 the mechanism of action of the drug is; and no
14 biologic measure; for example, parasite load, which
15 was indicative of a treatment effect. And she didn't
16 comment on the safety, but she did not feel that there
17 were data to support its effectiveness.

18 My own comments basically echo what's been
19 stated before. I think for the record, though, it's
20 also important to note that this Committee has an
21 extended history of attempting to be flexible in
22 dealing with agents related to HIV disease recognizing
23 many factors, including the needs that are out there,
24 access, need for further drug development, et cetera,
25 and has even low response rates.

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1 But there is still a minimum level of
2 efficacy, even accepting historical controls, which
3 for this disease one certainly could accept. And if
4 that's what we're left with accepting, one still needs
5 some relatively convincing evidence of a treatment
6 benefit.

7 I would echo the comments earlier that
8 access is important, but it's access to a drug that
9 one feels there's an adequate safety database for and
10 some level of efficacy.

11 Continued development of this drug in this
12 field is certainly important, but I echo my
13 colleagues' statements about the data set that we have
14 seen today.

15 And I say that with regret, too, because
16 I think the tradition of this Committee is really to
17 try to look positively on agents that have come before
18 it.

19 With that being said, I think we need to
20 take an official vote. The voting members for today
21 are: Drs. Feinberg, Lipsky, Hamilton, Self, Mathews,
22 Sears, Mr. Marco, Ms. Cohen, and me.

23 So I will restate the question: Is
24 nitazoxanide safe and effective for use in the
25 treatment of cryptosporidial diarrhea in AIDS? If you

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1 feel the answer to the question is yes, please raise
2 your hand.

3 (Whereupon, there was a show of hands.)

4 CHAIRMAN HAMMER: If you feel the answer
5 to the question is no, please raise your hand of the
6 voting members.

7 (Whereupon, there was a show of hands.)

8 CHAIRMAN HAMMER: Okay. We now have a
9 second part to this question based on the consensus of
10 the Committee: If the answer to the above question is
11 no, what additional data is required in order to be
12 able to make the above determination?

13 I also think for efficiency's sake, we can
14 combine that with the second question, if you will.
15 And I would ask you to try to comment on both of
16 these: Does the Committee have any additional advice
17 regarding future studies, particularly with respect
18 to: study design, duration of treatment, and choice
19 of comparator?

20 So first 1(b) and then Question 2. And
21 I'll start on my right with Dr. Masur.

22 MEMBER MASUR: I think we have alluded to
23 the fact that since this is a chronic disease, it
24 would be nice to have long-term data about the
25 sustained benefits and toxicities of these drugs.

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1 So I would hope that, first of all, some
2 comparative studies could be done either looking at
3 different doses or it seems to me that there are still
4 some open questions about some other drugs out there.
5 Whether this could be compared to them or not I guess
6 is less clear, but certainly doing dose comparisons is
7 a possibility.

8 There are also some other models there in
9 which patients have been blinded to what drugs they're
10 on for periods of weeks so that one can compare time
11 on drug, time off drug to make this period relatively
12 short before deciding whether to use open-label drug
13 or not because, again, with a disease that has this
14 uncertain a natural history, I think you clearly do
15 need some kind of comparison.

16 In our experience, some of the patients
17 who were the most convinced they benefitted from other
18 agents we've looked at were patients who were on
19 placebo. So I think that it's very important to have
20 comparative data and it's very important to have
21 regular evaluations and be able to look over a long
22 period of time, six months or a year, as to whether
23 patients are benefitting in terms of GI function, in
24 terms of weight. Admittedly, survival is a hard
25 endpoint to look at in a study of a feasible size

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1 given other issues.

2 CHAIRMAN HAMMER: Thank you.

3 Dr. Lipsky?

4 MEMBER LIPSKY: It would seem that you
5 would want a trial that could be done that would have
6 rigorous microbiologic criteria, both to establish a
7 diagnosis and for its outcome, even with the
8 understanding that there might be a delay in that
9 response prior to a clinical delay. Perhaps a dose
10 escalation study could be entertained.

11 It would seem that you would want to have
12 some better understanding of the pharmacodynamics
13 because if one did determine that the drug was
14 eventually efficacious, -- and that would not surprise
15 me if that were the result -- you might want to know:
16 Gee, do you need to have a level of something, even
17 though that something might be a surrogate for the
18 active metabolite?

19 And, for instance, a basic question, does
20 it need to be absorbed? Does it not need to be
21 absorbed? Would you want to promote absorption?
22 Would you want to promote levels? Would you want it?
23 How would you rationally dose this drug? That would
24 be I think rather crucial to the situation.

25 More basic work on mechanisms, of course,

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1 might help that along the line. But doing I think a
2 study which perhaps could avoid a placebo if it were
3 done in a dose escalation trial might be useful.

4 CHAIRMAN HAMMER: Thank you.

5 Dr. Hamilton?

6 MEMBER HAMILTON: The Achilles heel of
7 this study, it seems to me, has been a series of
8 methodologic issues that either couldn't be addressed
9 or weren't addressed, which further suggests to me
10 that there has been insufficient engagement of several
11 vested interest groups here.

12 I'm including now the scientific community
13 and those people living with AIDS and perhaps others
14 in a meaningful way to develop the kind of strategy
15 that would be necessary to provide compelling data one
16 way or another.

17 Had we that in our hands today, our task
18 would have been substantially easier. I think my
19 predecessors here have described what we find the
20 deficits in data are. And I agree with those.

21 I think a more important question is how
22 to proceed at this moment to resolve and replace those
23 deficits because it is evident to me from the comments
24 made by many in the room that there remains a need
25 here to solve this problem.

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1 And I would not like to feel that I
2 personally or that the Committee in general was
3 walking away from this problem. I would like to see
4 us strongly recommend that this whole series of
5 questions be meaningfully readdressed, readdressed
6 with resources.

7 I'm not laying this at the doorstep of the
8 sponsor. The sponsor has gone a long ways I think
9 toward attempting to resolve this. It's evidence, at
10 least if our opinion is correct, that the data was
11 insufficient.

12 But I believe if they are to persevere
13 productively, I would think they're going to need some
14 help. And I knock on several doors and expect some
15 answers in that regard.

16 CHAIRMAN HAMMER: Thank you.

17 Dr. Self?

18 DR. SELF: I was intrigued by one of the
19 comments of one of the presenters in the open session
20 about ACTG 336 not being particularly friendly
21 protocol. And along the lines of the last comments,
22 I wonder if there might be some creative thinking
23 about a study design that would allow some comparative
24 type of trial to be done, even if it's not necessarily
25 a placebo.

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1 Failing that, at the very least, a much
2 more detailed characterization of clinical course in
3 a larger group of patients, more thorough in the sense
4 of making sure that follow-up, at least over the first
5 month or maybe two, is effectively complete would go
6 a long way I think and perhaps characteristics of such
7 an open-label study could be identified that would
8 facilitate its comparison to what little historical
9 placebo data there is available.

10 CHAIRMAN HAMMER: Thank you.

11 Ms. Cohen?

12 MS. COHEN: As the non-scientist, we have
13 been congratulating the sponsor, but I would like to
14 say something about what the FDA did because I found
15 this a very useful tool. I particularly like the
16 graphs and the information in the back.

17 And for someone like me, I really
18 appreciate the effort put into this and the
19 information. And that's not a political statement.
20 That's just Susan Cohen.

21 In terms of what I see, I am concerned it
22 wasn't multicultural enough. I think that it's very
23 important that it be far more multicultural than it's
24 been.

25 I am concerned about the patients that

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1 they have. And maybe it's comparing apples and
2 oranges, but I'd like to know about people who are
3 just starting with diarrhea and what it does for those
4 people who just start.

5 I'd like to know -- and it's kind of a
6 strange question, but because there's been a weight
7 increase in the patients, I'm wondering if it isn't
8 because they're also being seen by professionals and
9 perhaps being guided to take better care of
10 themselves. It's interesting how people respond when
11 people listen to them and take care of them.

12 The follow-up to me is extremely
13 important. Yes, I think that clinical trials should
14 be better designed, and I think that there are people
15 who are much more equipped to handle that than I am.

16 And I am concerned about the drug dosage,
17 and I am concerned again that there are other patients
18 who will be taking this if it is approved. And I want
19 to know how it responds to other drugs that are being
20 taken care of. And I am interested about absorption.

21 So I'm walking about thinking they tried.
22 I give them A for trying, but we have to do better
23 than that.

24 CHAIRMAN HAMMER: Thank you.

25 Mr. Marco?.

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1 MR. MARCO: Let me first respond to ACTG
2 336. For the past three years, I have been a member
3 of the leadership of the community constituency group,
4 which oversees all the AIDS clinical trials done in
5 the ACTG. And we do and we do not give the trials our
6 blessing. And we actually gave the placebo-controlled
7 Study 336 our blessing. And we sat on the protocol
8 teams, in fact.

9 The reason it did not accrue is because it
10 took a while to get the study started. It didn't
11 start until last year. We approved protease
12 inhibitors in 1996.

13 I mean, myself and Dr. Sears have both
14 told you that there is data showing that when patient
15 CD₄'s go above 160, 170, to 190, they will clear their
16 crypto. So we're just not seeing it as much. I think
17 the same thing is with the other OIs.

18 So, even though I don't think a
19 placebo-controlled study is wrong, I just don't know
20 if it's possible any more just because of the limited
21 number of patients. I just don't think we'll see that
22 many.

23 The only possibility is that you could
24 take 009B and make it up front, instead of refractory,
25 because I don't really understand this refractory

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1 thing since paromomycin and azithromycin don't have an
2 indication for crypto. It's not like they really
3 failed an approved treatment.

4 So if you open it up to those who are
5 naive and you possibly put in a placebo arm, that
6 might help. From the data right now, it doesn't look
7 like we're going to see a dose-response difference
8 between 1,000 and 2,000.

9 That's an idea, but I guess the big answer
10 is I have no idea if you'll ever be able to answer
11 these questions for this drug or any other drug for
12 crypto.

13 CHAIRMAN HAMMER: Dr. Sears?

14 DR. SEARS: I think it's an incredibly
15 difficult problem. And I think the likelihood that
16 we're going to be able to study large numbers of
17 patients with *Cryptosporidium* in the United States
18 approaches zero in the era of HAART and newly
19 developing HIV therapies.

20 So, for large-scale studies of efficacy,
21 I think consideration has to be given to the
22 international setting, both where the disease, in
23 particular, is an issue in children, although the FDA
24 one slide on toxicity in children is of concern and
25 safety issues are obviously paramount.

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1 But in that setting, immunocompetent
2 children who acquire *Cryptosporidium*, a non-trivial
3 percentage go on to develop persistent diarrhea which
4 has long-term effects on morbidity and mortality in
5 that population and is also a setting where HIV is
6 rampant and additional therapies are obviously not
7 available in many instances.

8 So in terms of large-scale studies of
9 efficacy, in truth, in my mind that's the only setting
10 I see where studies will be able to be done. In the
11 United States, though, where we have some patients and
12 we have more resources, I wonder if what might be
13 helpful is to intensively study a smaller group of
14 patients with concomitant data on microbiology,
15 pharmacology, and clinical responses.

16 I think one of the major issues we face is
17 that this is a very variable disease. And I believe
18 it is a variable disease, even in patients with
19 advanced HIV infection.

20 And I'm wondering if -- even though I
21 think the preponderance of data didn't support overall
22 efficacy, I in my own mind still wonder whether
23 there's a subset of patients who, in fact, are truly
24 responsive, given some of the dramatic anecdotal
25 evidence for responsiveness. But what makes a patient

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1 responsive to this disease is what's unidentified. So
2 I wonder.

3 For example, in our studies in the
4 northeast of Brazil, our most recent observations are
5 that children who asymptotically carry
6 *Cryptosporidium* have no evidence of inflammation in
7 their stools; whereas, all of the children who were
8 symptomatic had evidence of inflammation in their
9 stools.

10 There's evidence that prostaglandin
11 production, they've got "correlate with symptomatic
12 disease." There's evidence that interleukins as well
13 as beta defensins as well as other cytokines have some
14 modulary effect on disease.

15 So I'm wondering if there's a subset where
16 there's a particular host response or there's a
17 particular parasite infection who, in truth, are
18 responsive to nitazoxanide and may be responsive to
19 paromomycin.

20 So what I would suggest is that a small
21 group of patients intensively studied to try to
22 develop the correlates to try to understand who
23 responds and who doesn't might help us direct future
24 studies.

25 Thank you.

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1 CHAIRMAN HAMMER: Thank you.

2 Dr. Mathews?

3 DR. MATHEWS: I agree with Dr. Sears'
4 comments in total. You know, I think it's very
5 unfortunate a drug like this came around at this point
6 in time, as opposed to a few years ago. But in a
7 sense, you know, this is not unique to
8 cryptosporidiosis.

9 If we were trying to study disseminated
10 *Mycobacterium avium* disease in 1998 with many of the
11 drugs that we initially started in trials, we would be
12 in exactly the same position. And so in a sense we're
13 delighted that these very horrible opportunistic
14 events have diminished in incidence. It makes it
15 much, much more challenging to study drugs.

16 I think with a disease that is so variable
17 like this, unless you have a home-run drug, the only
18 way you're going to be able to convince is a
19 randomized trial that includes very tight control of
20 co-variates that could affect disease severity.

21 And anti-retroviral therapy, even without
22 HAART, I mean, it's known that even half-log drops in
23 viral load translate into measurable clinical benefit.

24 So if you don't randomize and you have all
25 of these post-initiation changes in antiviral therapy

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1 which have obvious impacts on disease severity, it's
2 going to become less and less convincing.

3 So I agree with Dr. Sears. There may be
4 settings where there are people who don't have access
5 to these therapies where an international study could
6 be mounted or people who have failed all existing
7 anti-retroviral therapies who may experience a
8 recrudescence of these infections.

9 DR. LEUNG: Thank you.

10 Dr. Feinberg had left some comments which
11 really echo what has been stated. And they will be
12 put into the record.

13 For my part, I don't really have what to
14 add to what has been said. I share the hope that the
15 study of the drug will still go forward because the
16 issue is: Is there a subset of patients that we just
17 can't tease out that really do respond?

18 The question is again how to study this.
19 In answer I think Dr. Sears' suggestion is really the
20 most practical because it will not be possible to
21 enroll large numbers of patients in any trial, let
22 alone trying to do a placebo-controlled trial solely
23 within the borders of the United States. But it is
24 possible to think about mounting a placebo-controlled
25 trial in other areas with the crossover designs, et

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1 cetera, even with the limitations there, but one could
2 do that, at least to find out whether this drug has
3 efficacy clearly in the short term.

4 In the United States, what we need and I
5 think one of the issues that the Committee was
6 wrestling with here is the characterization of the
7 patients both for the variability of the disease but
8 also the clear issue of the parasite burden at
9 baseline exclusion of other pathogens, the issue of
10 co-variates that may be influencing the
11 interpretation. All of those issues that I think were
12 teased out today that were given concern should be
13 placed into a new study.

14 And the study of a relatively small number
15 of patients who are extremely well-characterized would
16 I think perhaps tease out clearly whether there is any
17 drug effect.

18 I think incorporating the pharmacodynamic
19 issues Dr. Lipsky mentioned would also be important.
20 And those studies can also be involved in trying to
21 perhaps tease out some more issues about the potential
22 mechanisms and metabolite issues in relation to
23 efficacy.

24 So I think a pair of trials looking at
25 broader populations, perhaps on the international

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1 scene, with well-done perhaps dose comparison studies
2 that try to control for the factors that have wrestled
3 with today and, most importantly, including the
4 follow-up information because I think that was clearly
5 an additional problem here as far as the follow-up and
6 the missing data that were giving individuals
7 problems.

8 And it will be hard and I think to also
9 develop new drugs, any new agent beyond the one that
10 we're discussing today is going to face exactly the
11 same problems. And I would hope that we can think of
12 incredible ways to overcome that. But it will be a
13 cooperative effort. One can't just look probably
14 within our borders to solve this issue for this
15 particular pathogen at the moment.

16 Dr. Murphy? Dr. Goldberger?

17 DR. GOLDBERGER: I just wanted to ask if
18 any of the Committee members wanted to comment a
19 little bit on the issue of endpoints. As you saw, we
20 saw analyses using a 25 to 49 percent reduction in
21 stool number, greater than 50 percent reduction,
22 greater than 50 percent reduction to less than 3
23 stools. Plus, there are issues of durability --
24 whether there are any comments or advice any of the
25 Committee members would like to give about this for

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1 future trials.

2 MR. MARCO: Well, I guess first, even
3 before you get to your criteria, how you choose
4 evaluable patients, I don't think you should ever
5 allow patients to be considered evaluable if there's
6 not microbiologic confirmation.

7 You know, in cancer, you ask for biopsies.
8 This all we need is a stool sample. I think you
9 should at least require that.

10 CHAIRMAN HAMMER: I would just add to that
11 I think where one is contemplating, as is likely,
12 small, intensive studies in the United States, perhaps
13 paired, as Dr. Sears mentioned, with an international
14 trial, stool studies -- and I don't actually think
15 that endoscopies on a relatively limited scale are
16 beyond the pale.

17 In our own clinical experience, they're
18 used all the time in patients with chronic diarrhea
19 and will be particularly valuable both clinically and
20 certainly would be valuable in a study setting, trying
21 to get a better handle on the issue of microbiologic.
22 Eradication or at least quantitation in relation to
23 response would be very important.

24 One can sort of obviously appreciate in
25 this disease persistence of pathogens and

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1 disassociation with persistence with clinical outcome,
2 but there still should be -- if the drug is active by
3 a mechanism of action that's antimicrobial should be
4 able to see some antimicrobial effect in quantitative
5 measures. And that may require an expensive intensive
6 study, but if you really want to know what the drug is
7 doing, I think that's one way to do it.

8 The other issue I think that came up today
9 as far as because of the variable history of this
10 disease, weeks two, four, six, eight are a snapshot of
11 the longer picture. And I think the trials should
12 have probably both short-term and more durable
13 endpoints with patients that one can try to encourage
14 to commit to that follow-up that we need.

15 Obviously we look at group comparative
16 data, but also the issue of the variability of
17 measurements within subject has to be taken into
18 account in the analysis so that we know that
19 responders are durable, responders both individually
20 and as a group.

21 And, again, unless you have, as Dr.
22 Mathews mentioned, a home-run drug, it's going to be
23 difficult. If you have a great drug and everybody
24 responds, it's easy. If you've got a 40, 60, 70
25 percent response rate, you have to tease that out.

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1 So one has to look at group responses but
2 also intrapersonal responses that are durable and
3 correlate in a very careful fashion the clinical
4 response with the microbiologic response.

5 Now, as far as the clinical, it's
6 difficult, but one can sort of probably deal with the
7 microbiologic endpoint more easily than the clinical
8 endpoint. Diarrhea is a difficult disease to study.
9 And anyone tries to quantitate stool numbers, et
10 cetera, et cetera.

11 And I think the ACTG team, as was
12 described, wrestled with this and other studies
13 obviously have wrestled with it. And the sponsor's
14 studies were about two. I don't think you can really
15 get away from some sort of combined endpoint.

16 It seems to me that from what we have seen
17 today, looking at diary as a continuous variable,
18 rather than a categorical variable, makes a little bit
19 more sense than trying to say you have one to three or
20 four to six or seven to nine stools per day. But I
21 think it's the durability issue that's key.

22 And I think both proportion reduction and
23 total number of stools have to be looked at separately
24 but also probably can be combined in a primary
25 endpoint analysis.

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1 I think that decrement can be argued
2 about, but I think that you really need some
3 substantial decrease because of the variability. At
4 least a 50 percent decrease would be what I would
5 personally state, but I think also the absolute number
6 of stools is important.

7 I don't see a clinical -- obviously
8 survival and other things are there, but in our
9 current here in the United States again, thank
10 goodness, because of the progress we've made, that's
11 not going to be an endpoint. It's going to be disease
12 severity as measured primarily by stool output, which
13 I would say is going to be combining numbers of stools
14 and how many and then looked at individually. And
15 correlative issues of weight and quality of life, as
16 was demonstrated today, should be part of that
17 measure.

18 But I think we need durability of data,
19 good follow-up, and issues of trying to take into
20 account the intra-subject variability of this disease
21 in any study that's designed.

22 MEMBER LIPSKY: Just one comment which I
23 forgot, which reminded me of the comment about
24 Milwaukee. Perhaps there should be a contingency plan
25 that if that event should ever occur again in another

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1 city, that perhaps for the CDC or whatever, that there
2 would be some sort of design so that one and rapidly
3 could go into a community and perhaps treat some
4 people.

5 If it's at the same extent that happened
6 before, there may be enough comparative patients
7 around. And it's possible that through a public
8 health tragedy, you could get efficacy data within a
9 couple of weeks, --

10 CHAIRMAN HAMMER: Are there other
11 responses?

12 MEMBER LIPSKY: -- although I understand
13 that also that would be with the immune -- mostly the
14 immune status of people might be different, but that
15 it could be helpful.

16 CHAIRMAN HAMMER: Are there other
17 responses to Dr. Goldberger's question about
18 endpoints?

19 (No response.)

20 CHAIRMAN HAMMER: I think the silence
21 indicates the difficulty faced.

22 DR. MURPHY: Yes. I just wanted to thank
23 everybody for very thoughtful comments and for
24 everyone who has participated today in providing their
25 thoughts and recommendations to this field.

SAQ, CORP

4218 LENORE LANE, N.W.
WASHINGTON, D.C. 20008

1 CHAIRMAN HAMMER: On behalf of the
2 committee, I'd like to thank our consultants and
3 guests; the agency; certainly the sponsor; the
4 audience, in particular, the individuals who spoke at
5 the public session.

6 With that, I would like to adjourn.

7 (Whereupon, the foregoing matter was
8 concluded at 2:36 p.m.)

SAG, CORP

4218 LENORE LANE, N.W.
WASHINGTON, D.C. 20008

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
Date: May 6, 1998
Place: Gaithersburg, MD

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
typewriting.



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