---TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

BLA 98-0012, AVAKINE (infliximab)

SPONSORED BY CENTOCOR, INC.

FOR THE TREATMENT OF PATIENTS WITH CROHN'S DISEASE

Pages 1 thru 258

Bethesda, Maryland
May 28, 1998

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
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VOLUME I

Thursday, May 28, 1998

9:00 a.m.

Holiday Inn Bethesda
8120 Wisconsin Avenue
Bethesda, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
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PARTICIPANTS

Barbara Frank, M.D., Acting Chairperson
Joan Standaert, Executive Secretary

MEMBERS

Rosemary R. Berardi, Pharm. D.,
(Consumer Representative)
Janet Elashoff, Ph.D.
Loren Laine, M.D.
William M. Steinberg, M.D.
Christina M. Surawicz, M.D.

TEMPORARY VOTING MEMBERS

Sidney Getz, Patient Representative
Carole B. Miller, M.D.
Lee S. Simon, M.D.

TEMPORARY NON-VOTING MEMBER

William Tremaine, M.D.

FDA

Barbara Matthews, M.D.
Jay P. Siegel, M.D.
Kathryn E. Stein, M.D.
Karen Weiss, M.D.

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

2 **Call to Order**

3 DR. FRANK: Good morning and welcome. I would
4 like to call to order the meeting of the Gastrointestinal
5 Advisory Committee for May 28, 1998. I am Barbara Frank,
6 Acting Chairman.
7 I would like to have the members of the committee
8 introduce themselves, and let's start with Dr. Stein.
9 DR. STEIN: I am Kathryn Stein, Director of the
10 Division of Monoclinal Antibodies, CBER.
11 DR. WEISS: I am Karen Weiss, Director of the
12 Division of Clinical Trial Design and **Analysis,** CBER.
13 MR. GETZ: Sidney Getz, Bethesda, Maryland. I am
14 the patient representative.
15 DR. BERARDI: Rosemary Berardi, University of
16 Michigan. I am the consumer rep.
17 DR. ELASHOFF: Janet Elashoff, Dixon Associates
18 and Material. Sinai Medical Center.
19 DR. STEINBERG: Bill Steinberg, Gastroenterology
20 Section, George Washington University Medical Center.
21 DR. SURAWICZ: Chris Surawicz from
22 Gastroenterology at the University of Washington, Seattle.
23 MS. STANDAERT: Joan Standaert, Executive
24 Secretary, FDA.
25 DR. FRANK: Barbara Frank. I am from Allegheny

1 University of the Health Sciences in Philadelphia, and I am
2 acting as Chair today.
3 DR. LAINE: Loren Laine, Gastroenterology,
4 University of Southern California, Los Angeles.
5 DR. TREMAINE: William Tremaine, Division of
6 Gastroenterology, Mayo Clinic, Rochester, Minnesota.
7 DR. SIMON: Lee Simon, a rheumatologist from the
8 Beth Israel Deaconess Medical Center, Harvard Medical School
9 in Boston, and a visiting person from the Arthritis Advisory
10 Committee.
11 DR. MILLER: Carole Miller, Johns Hopkins Oncology
12 Center. I am a visiting member from the Biologics Advisory
13 Committee .
14 DR. FRANK: Thank you. Joan Standaert, would you
15 please read the conflict of interest statement.
16 Conflict of Interest Statement
17 MS. STANDAERT: The following announcement
18 addresses the issue of conflict of interest with regard to
19 this meeting and is made a part of the record to preclude
20 even the appearance of such at this meeting.
21 Based on the submitted agenda for the meeting and
22 all financial interests reported by the committee
23 participants, it has been determined that all interests in
24 Eirms regulated by the Center for Drug Evaluation and
25 Research present no potential for an appearance of a

1 conflict of interest at this meeting with the following
2 exceptions.
3 In accordance with 18 U.S.C. 208(b) 3), a full
4 waiver has been granted to Dr. Barbara Frank, and limited
5 waivers have been granted to Dr. William Tremaine and Dr.
6 Edward Loftus. Under the terms of the limited waivers, Dr,
7 Tremaine and Dr. Loftus will be permitted to participate in
8 the committee's discussions, but will be excluded from any
9 vote concerning Avakine.
10 Copies of these waiver statements may be obtained
11 by submitting a written request to the Agency's Freedom of
12 Information Office, Room 12A-30, Parklawn Building.
13 We would also like to note that Dr. Stephen
14 Hanauer is excluded from participating in the committee's
15 discussions and vote regarding Avakine.
16 In the event that the discussions involve any
17 other products or firms not already on the agenda for which
18 an FDA participant has a financial interest, the
19 participants are aware of the need to exclude themselves
20 from such involvement, and their exclusion will be noted for
21 the record.
22 With respect to all other participants, we ask in
23 the interest of fairness that they address any current or
24 previous financial involvement with any firm whose products
25 they may wish to comment upon.

1 That concludes the statement for May 28th, 1998.

2 DR. FRANK: Thank you.

3 Open Public Hearing

4 DR. FRANK: Now is the open forum session, the

5 open public forum, and we are very pleased to have with us

6 today members of Crohn's and Colitis Foundation of America,

7 who would like to speak to the issue Crohn's disease.

8 For those of you who don't know what CCFA is, it

9 probably raises more money for inflammatory bowel disease

10 research than any other private organization or foundation,

11 and we are very pleased to have some of the members here

12 today.

13 I would appreciate if each one would limit their

14 time to seven minutes, so that everyone has a chance to

15 speak.

16 First on the agenda is Greg Farrell.

17 MR. FARRELL: I would like to thank everybody for

18 the hearing today. For a brief moment I thought I was at

19 the MCI Center. It looks like we are -jam-packed in here for

20 a Caps game or something. It is good to see a lot of people

21 here today.

22 My name is Greg Farrell. I am a member of the

23 Crohn's and Colitis Foundation of America. Thank you for

24 inviting me here today to speak before this important FDA

25 Advisory Committee meeting regarding the approval for new

1 educations including infliximab.

2 The reason I am here today is because I have three

3 young kids -- and there they are -- and I have suffered from

4 Crohn's disease for over 20 years. I want to see my kids

5 grow up and they need me.

6 My oldest son is 10 years old, and I remember I

7 wasn't much older when Crohn's disease first hit me, and

8 this is my story. In 1976, despite frequent stomach cramps

9 and diarrhea I was ranked the number one tennis player in

10 the United States Tennis Association, Mid-Atlantic Region

11 out of Pennsylvania for men 18 years and under.

12 That same year, 1976, I was diagnosed with Crohn's

13 disease. In the spring of 1978, I was a freshman in college

14 and I was the number one tennis player on the men's tennis

15 team, voted the Most Valuable Player.

16 In 1980, Crohn's ended all of that. Crohn's

17 disease hit with a wicked force. In January through March

18 of 1980, I was throwing up and had major stomach cramps,

19 sometimes throwing up four times a day.

20 At the time I kept thinking I would get better. I

21 was wrong. The pain only got worse due to a total

22 intestinal blockage from the Crohn's disease. The intense

23 cramps and pains totally devastated my life and knocked me

24 out of college for a semester. Major resection surgery was

25 performed at the Cleveland Clinic in March of 1980.

1 Since 1980, Crohn's disease has continued its
2 wicked and aggressive force and has ravaged my body. I may
3 look okay on the outside, but fully 7s percent of my small
4 intestine has been removed. My weight has dramatically
5 dropped from 170 pounds to 135 today. That is 35 pounds.
6 Every single aspect of my life and my family's
7 life is different now. Surgeons have told me that if I have
8 any more small intestine removed, I will have to live on a
9 feeding tube or a TPN tube for the rest of my life, and in
10 which case they don't predict that you will live long due to
11 infections .
12 Now , after seven different intestinal surgeries, I
13 have total abdominal disconfiguration, five fistulas, and I
14 now have an ostomy. Having an ostomy where surgeons remove
15 your small intestine from the large intestine, cut a hole in
16 your skin, and pull the intestine through the opening would
17 be okay if it prevented Crohn's disease. The problem is
18 that it doesn't. Unfortunately, in my case it hasn't. So,
19 let me repeat that. Having an ostomy would be okay if it
20 prevented the disease from coming back.
21 In my situation, the Crohn's disease has come back
22 and has given me serious life-threatening problems, life-
23 threatening health problems. Now when I eat, I see large
24 chunks of undigested food that come through the ostomy bag,
25 food that should have been digested, normal daily food, and

1 should have been absorbed is now passing through my small
2 intestine way too fast. Let me repeat. Every single time
3 that I eat, I see undigested food. You name it, chicken,
4 vegetables, salad, whatever I may have eaten, it is there.
5 So much of my small intestine has been removed. The
6 remaining portion simply cannot handle the normal digestion
7 and absorption. The short bowel has caused me serious life-
8 threatening problems.
9 Incredibly, I lived with five fistulas or holes in
10 my body for most of 1996 and 1997. It was a living hell.
11 When I would eat or drink, intestinal fluid would leak from
12 these holes, in these fistulas. This was especially true
13 when I would drink fruit juice or orange juice. Within 20
14 minutes, the bandages that covered these holes were wet from
15 the juice and intestinal fluid.
16 The abdominal fistulas are extremely serious.
17 They bleed, they leak, and they will not heal up on the
18 medicines that I am taking today. Two of the five are still
19 causing me daily problems: Just two weeks ago" I picked up
20 my daughter and I felt something pop, and one of the
21 fistulas started to bleed. It bled so much that I was
22 forced to immediately change the bandage. This is still
23 happening a full two years after my last surgery at GW
24 Hospital here in the District.
25 Moreover, due to a lack of absorption I have very

1 dry skin and must drink plenty of water to avoid
2 dehydration.
3 The Crohn's impact, the impact on my life, every
4 day I continue to fight for my life because I want to see my
5 kids make it through elementary school. With new, more
6 effective medications, I may even be able to see them
7 through high school, maybe longer.
8 My business career in sales and marketing, and my
9 ability to support my family has been dramatically reduced
10 because of Crohn's disease. It has gotten so bad that I am
11 now unable to have lunch with business clients and
12 colleagues . Think about that. I am unable to participate
13 in the most basic form of social activity in business,
14 having lunch.
15 I am forced to turn people down all the time for
16 most lunches because I am unable to eat most foods. Think
17 about your own life and try to imagine avoiding people and
18 avoiding social situations whenever food is involved - sales
19 meetings, luncheons, conferences, dinners, et cetera. You
20 name it, I avoid it.
21 The ostomy severely limits my ability to
22 participate in sports. I played tennis for over 20 years.
23 I now limit that severely. I limit sports because the skin
24 around the ostomy is so badly burned from hydrochloric-like
25 acid that seeps under the ostomy bag that the slightest

1 physical activity, if the seal of the ostomy bag is broken
2 or becomes a little bit loose, it causes serious skin
3 problems.
4 I also suffer from adhesions from the surgery,
5 little or no abdominal muscle support, and a major hernia.
6 Other members of my family, two brothers, three cousins have
7 also been diagnosed with Crohn's disease and have had very
8 similar medical histories over the last 20 years. Again,
9 two of my brothers have had major surgeries due to Crohn's
10 disease. My mom also suffers, but up to this point has
11 avoided surgery.
12 Two years ago we all donated blood for a genetic
13 study of Crohn's disease being conducted at Cedar Sinai in
14 Los Angeles, so I am happy to see that representatives are
15 here today. Thank you.
16 I am currently on about five to seven different
17 medications including 6-MP. It was not designed to treat
18 Crohn's disease, but it has serious side effects and is very
19 toxic. I also have an attached list for all prescription
20 medications that I am currently on. Not one of these drugs
21 were designed to treat Crohn's disease. Because of Crohn's
22 disease and the medications, I cannot be in the sun or swim
23 with my kids.
24 So, the major issue today is it is critical that
25 the FDA approve these new effective drugs or the anti-TNF

1 ability to halt aggressive non-responsive Crohn's disease.
2 It is my understanding that not one single drug has been
3 approved specifically to treat Crohn's disease, so I thank
4 you for holding this priority review case today.
5 In my case and in thousands of others, Crohn's
6 disease is very aggressive and does not respond to current
7 medications. I continue to suffer and have not found a
8 single drug that has halted the progression of this disease.
9 So, just to conclude here, I desperately think
10 that these treatments that you are studying today are of
11 value and I thank you for holding this hearing, and now is
12 the time to approve it if the data supports it because it is
13 the right thing to do.
14 Thank you very much.
15 DR. FRANK: Thank you, Greg.
16 Now, Anke Dannemann.
17 MS. ANKE DANNEMANN: Good morning, ladies and
18 gentlemen. I thank you for this opportunity.
19 Almost 23 years ago, at the age of 8, I was
20 vacationing with my family in Hilton Head Island, enjoying
21 the sun, ocean, and my youth. From one day to the next, I
22 had a fever, was in severe pain and bleeding. I had
23 diarrhea and was pretty much deathly ill.
24 I don't remember many of the details that
25 followed, but I do remember having to see a great number of

1 doctors and specialists who couldn't help us. Since there
2 weren't any pediatricians who specialized in any of the
3 symptoms I displayed at Children's Hospital couldn't
4 diagnose me, I was forced to see the top specialists in
5 adult medicine, and none of them could help me either, let
6 alone diagnose me, until I found Dr. Theodore Bayless at
7 Johns Hopkins Hospital.
8 One look at my emaciated pale body was all he
9 needed to see that I had Crohn's disease. Back then Crohn's
10 disease wasn't a well-known disease and he was one of the
11 only specialists in this area. Few physicians had ever had
12 a patient with Crohn's, and to this day I feel I am much
13 better informed than your average doctor, nurse, or medical
14 researcher.
15 I ask myself frequently what does this mean about
16 this disease and what does it say about our culture,
17 education, our research into this disease. Not much. It
18 reveals that this disease is about diarrhea, loose
19 digestion, ulcers, abscesses, gas, cramps, dehydration,
20 Constipation, fever, and inflammation of the intestinal
21 lining, intestinal scarring and fistulas, hemorrhoids and
22 nausea doesn't make for excellent dinner conversation. It
23 certainly doesn't make itself obvious to a third party.
24 It was hard as a child growing up with this
25 disease because my disabilities weren't apparent to my

1 teachers, my friends, and their parents. Everybody thought
2 I was trying to get out of the responsibilities, tests, and
3 homework. It was hard for anyone to understand because I
4 wasn't sitting in a wheelchair, I wasn't wearing a
5 prosthesis, and I wasn't doing chemotherapy.
6 I was a picky eater who was tired and exhausted
7 all the time, couldn't sit still at the dinner table or in
8 the classroom because I had to get up and go to the bathroom
9 frequently. Teachers thought I was using this as an excuse
10 out of doing my homework and was a way to cheat on my exams.
11 I remember a childhood filled with anxiety of where the
12 nearest bathroom was and I probably wouldn't be able to
13 digest the meal my host would be serving at the dinner
14 table, if the next medical tests would be painful or
15 humiliating, and if my doctor would have a new medicine for
16 me that would help me and have fewer side effects.
17 I remember sleepless night of leg crams and
18 stomach cramps and frequent bathroom trips of bleeding and
19 painful diarrhea and hemorrhoids. I remember my growth
20 being stunted for two years from prednisone, and this is one
21 of the smaller symptoms people don't know about.
22 Crohn's isn't just about stomachaches and
23 diarrhea. It's about dehydration, malnutrition, infections,
24 fevers, fistulas, and many other problems that start with
25 bad digestion. Malnutrition and dehydration can make simple

(#-

1 colds and infections complex medical problems that required
2 antibiotics and even hospitalization.
3 In the past 23 years, I have had three major
4 operations and countless smaller ones. Two of the
5 operations were to remove inflamed, partially blocked
6 intestinal scar tissue from my large and small intestines,
7 and the first surgery, at the age of 16, nearly killed me.
8 The third one gave me the so-called temporary
9 colostomy which they still have to make non-temporary to
10 allow my large intestine and my body to heal from very bad
11 fistulas. Fistulas are infections that are created by the
12 erosion of the linings of the intestinal wall caused by
13 holes that are created in the eroded lining, and intestinal
14 fluids drain into what otherwise is normal, healthy tissue.
15 This is a not so very good thing. I can't imagine anything
16 more painful than having a very large pus-oozing infection
17 that pours its way, slowly may I add, through your
18 intestinal lining to another organ that will allow it to
19 drain or to the outer skin, so it can drain from there.
20 These fistulas and boils are, mildly put, a
21 nightmare. It can destroy wonderful emotions of romance,
22 sex, and sexuality, and ordinary fun, and turn them into
23 disgust, hate, embarrassment, and humiliation.
24 If you can bear with me for a moment, I would like
25 to make this disease a little more real to you all. First

1 of all, I would like to ask you, if you want to, to place.
2 your hand on your lower esophagus and you press inwards.
3 You will feel very much a discomfort in your throat and your
4 esophagus. If you place your hand in your chest between
5 your ribs and you press hard enough, if you have a belt and
6 you make it a couple notches too tight, you will also feel a
7 discomfort.
8 This discomfort stays with you and is always with
9 you, and that is what it is like to have some of the milder
10 symptoms of Crohn's. You probably will feel this funny
11 feeling if you try that, pretty much for an hour, and try to
12 not imagine feeling that. It just not describable.
13 Those are some of the daily symptoms I live with.
14 Also, I would like to describe to you what a day would be
15 like if you were having an active bout of Crohn's and you
16 had to go to work because your bills needed to be paid, such
17 as the bills that amounted up to $160,000 during my bout
18 with my fistulas when I was on TPN or total nutrition. That
19 lasted a duration of six months. I wasn't allowed to eat or
20 drink anything orally at all. That means I did not break
21 bread and sit at dinner tables and lunch tables with my
22 friends and family for more than six months. One doesn't
23 eat during this time to give your bowel a complete rest.
24 Back to a day with Crohn's. Your night of sleep
25 would have started late because you probably would have

1 gotten up several times before you fell asleep due to
2 painful burning, diarrhea, and gas. Then, you probably
3 would have gotten up around 2:00, 4:oo, and 6:00 a.m. to go
4 to the bathroom again. Although you may not have had
5 anything left in your intestine, it still spasms violently
6 enough to make you sit on the toilet.
7 After this not so restful night of sleep, you are
8 feeling very exhausted and dehydrated and hungry, and with
9 all the energy you can muster, you start the morning off
10 with a small bowl of cereal, toast, and some juice, and at
11 least 15 pills including anti-diarrhea, anti-spasmodic, a
12 steroid, an immunosuppressant, an antibiotic, a neuropeptic,
13 and painkiller to help you with this intestinal pain and the
14 cramping. At this point you are ready to join your carpool
15 to spend an hour in traffic without real access to a
16 bathroom, and with any luck, you will make it to the office
17 without having to stop at a McDonald's for another painful
18 and embarrassing session on the toilet, and this all happens
19 before your day really starts. Don't forget the meetings,
20 lunches, and dinners spent with others, continually excusing
21 yourself to go to the bathroom for diarrhea or gas.
22 Your workday ends with another miserable carpool
23 ride home, and ends having a bland meal of beige, soft,
24 mushy food, overcooked and non-stringy vegetables.
25 If all this sounds" exhausting it is, and none of

1 what I have described discusses the side effects of this
2 disease, medication, malnutrition, dehydration, hair loss,
3 migraines, headaches, skin rashes, eye disease caused by
4 prednisone, tooth decay and thrush caused by antibiotics,
5 bloating, inflammation, and blockages, fevers, infections,
6 fistulas, infertility and sterility from the steroids and
7 the methotrexate, kidney stones, liver disease, joint pain,
8 depression, humiliation, and low self-esteem.
9 If you don't find a cure or treatment for Crohn's
10 soon I will literally use my large intestine and temporary
11 colostomy to a permanent ileostomy due to some very serious
12 and ugly ulcers. If we can't approve a treatment soon,
13 someone else will have to walk a mile in my shoes, and I
14 wouldn't wish this on my worst enemy.
15 It might not be apparent when you look at me, but
16 I am slowly being eaten alive from the inside. We need fast
17 approval for new treatments and medications because time is
18 our enemy. As each day progresses, more than my digestive
19 tract will be permanently scarred with any ability to
20 reverse the damages of this disease.
21 There is no going back. We can only prevent any
22 future scarring and damage.
23 Thank you.
24 DR. FRANK: Thank you .
25 Now, Anke's mother, Jutta.

1 MRS. JUTTA DANNEMANN: Good morning. My name is
2 Jutta Dannemann. I appreciate greatly the opportunity to
3 speak before you today. I want to relate to the FDA my
4 experiences and observations as a parent of a child with
5 severe Crohn's disease.
6 My daughter, Anke Dannemann, was born June 20,
7 1967. She had no health problems until the age of 8. At
8 that time, she suddenly developed violent diarrhea, the
9 symptoms of hemorrhoids and bleeding that could not be
10 controlled with conventional medications. Thus, began one
11 nightmarish year of going from one hospital to another in
12 the Washington area involving invasive testing, which was
13 very often very humiliating for a little girl, before she
14 was finally diagnosed at Johns Hopkins Hospital with Crohn's
15 disease.
16 During the 23 years since then, I watched my
17 daughter struggle with the disease, watched her body and
18 nind being terribly affected, not only by the disease, but
19 also by the destructive side effects of the various
20 dedications, like brittle bones, premature dental
21 deterioration, swelling in her joints, bloating of her body,
22 and often extreme pain.
23 During these 23 years, she had numerous invasive
24 tests and surgery. Some of these produced very frightening
25 experiences . One of her lungs collapsed while they inserted

1 a TPN, a large cyst burst open during one of her surgeries.
2 Her health has now deteriorated to the point where
3 a renowned specialist at Johns Hopkins had recommended the
4 removal of her colon, but the disease has invaded her whole
5 intestines, and the removal of her colon is not expected to
6 restore her health.
7 The financial and emotional impact on our family
8 has been significant, and it was especially hard also on her
9 sister who lived with her during the last eight years and
10 put her own life on hold to help her sister get through all
11 the terrible times.
12 But the focus has always been on Anke's well-
13 being. There have been numerous trips to the schools to
14 retrieve my sick child at the school's request. She had to
15 interrupt her college education and shift her major in
16 midstream.
17 There have been numerous emergency trips to
18 hospitals, interrupted and canceled vacation plans, and last
19 but not least, I watched my daughter change over the years.
20 One day she was a spunky, healthy little girl full of life
21 and mischief, whom everybody liked, including her teachers,
22 and the next day she turned into a pale, whiny, sickly
23 little child who had problems participating in the simplest
24 of activities.
25 She stopped growing for almost two years because

1 the disease depleted her of all nutrients. Her friends also
2 avoided her because she was different all of a sudden. I
3 tried to make up for it by letting her participate whenever
4 she was physically able to in activities like ballet,
5 gymnastics, swim team, et cetera. She was very talented.
6 The beautiful person she is today is wracked by
7 this debilitating disease, and she has had to miss out on
8 many things in life including having a family with children,
9 She had to quit her job with the National Museum for Women
10 in the Arts because they could not accept the fact that she
11 had frequent doctors' appointments.
12 After a hospital stay, she returned soon to work
13 because she was afraid of losing her job. As a consequence,
14 she became really sick afterwards. Now she is working in
15 our family business where she is able to adjust her schedule
16 according to her health.
17 The social consequences for Anke included the loss
18 of friends, a very limited lifestyle, lack of intimacy and
19 relationships . She never had a chance to live a real life.
20 There have been good efforts made by all concerned, that is,
21 doctors, hospitals, patients, and family. All such efforts
22 have been followed, but Anke is running out of time.
23 Right now there are no medications that really
24 help her. In fact, she almost lost her life with the latest
25 round of treatments. My personal pain is only exceeded by

her pain. I do not want to see her completely debilitated or to lose her life to this disease.

Thank you very much for listening to me.

DR. FRANK: Thank you.

Amy Berkeley.

MS. BERKELEY: Good morning. I am pleased to be with you today to share my experiences living with Crohn's disease. I have been diagnosed with Crohn's disease for 23 years, the same length of time as Anke, and in that time I have taken countless drugs, been hospitalized five times, had two major and two minor surgeries, and nearly died.

Yet, my experiences pale beside those of the many hundreds of patients I have been privileged to meet and work with as a volunteer with, and past president, of the Crohn's and Colitis Foundation of America.

I would like to share some of those stories with you now to illustrate the devastating emotional, physical, and financial impact this disease has on the millions of Americans who live with it.

My own story is all too typical. I was diagnosed with Crohn's disease in 1975, but before I was diagnosed I lived through nearly a year of agonizing pain, sleepless nights, and symptoms that were brushed off by my doctor as eating the wrong diet.

When I finally found out what I had, the doctor

1 had to explain to me what it was, and I could tell from the
2 tone of his voice that it wasn't good. Learning at such a
3 young age that I had an incurable illness that might recur
4 again and again, even if this present bout were cleared up,
5 that I would probably have to have surgery at some point in
6 my life, and the chances for repeat surgery were high, that
7 there was simply no effective treatment in sight was a
8 realization that sent me into a depression that took me a
9 long time to recover from.
10 At an age when my peers were dreaming of a future,
11 I was confronted with my own mortality. I knew no one else
12 with this illness, there was no one in the news or the media
13 with it, and people didn't talk about it. So, when I found
14 out about the Crohn's and Colitis Foundation, I joined and
15 quickly found relief in knowing others with this illness,
16 and I became a volunteer.
17 Over the years, I have met hundreds, perhaps
18 thousands, of people with Crohn's disease. I have
19 discovered that no case of Crohn's is like another, but
20 still all Crohn's patients share a common bond, the
21 experience of often unimaginable physical and emotional
22 pain, the inability to participate in even some of the
23 simplest things of everyday life, terrible financial stress,
24 and the isolation that comes from living with a disease that
25 saps you of your energy, chains you to a bathroom isn't

1 pretty to talk about.

2 I have lived through some pretty terrible times

3 with my Crohn's disease, but not anywhere nearly as bad as

4 Greg and Anke have described. Although I have had numerous

5 flare-ups, the worst time for me came when I had an

6 undiagnosed bowel obstruction that had me in the hospital

7 numerous times, down to 108 pounds and looking like a

8 walking skeleton. I had had surgery, was being fed

9 intravenously, and I couldn't even go to the bathroom by

10 myself because I was hooked up to three machines and my I.V.

11 line that I was too weak to drag with me, and every time I

12 pressed for the call button, it took up to an hour for a

13 nurse to respond.

14 I was released from the hospital after five weeks

15 to go home on total parenteral nutrition, which meant that I

16 had to have a catheter surgically implanted in my chest, so

17 that I could be tethered to a portable pump for up to 12

18 hours a day of intravenous nutrition.

19 It wasn't so bad when I was too weak" to do

20 anything anyway, but when I finally started to gain strength

21 after several months, I came to regard myself as a prisoner

22 of that pump, which I had to use for about five months until

23 I got back to a semblance of my normal weight, and that is

24 with eating, as well.

25 Of course, anytime you have that catheter and that

1 sort of wound, you have a substantial risk of infection, and
2 that is exactly what happened to me, landing me right back
3 into the hospital for another month. My line had started
4 dripping and the home health care company nurse didn't
5 respond to my pagers, so I was forced to lie in bed with my
6 solution dripping onto a fresh wound, terrified, and unable
7 to stop it.
8 The day I got off of the total parenteral
9 nutrition was the happiest day of my life, but I wasn't
10 through yet with the TPN. My obstruction was still there
11 although undiagnosed. I kept dropping weight, was unable to
12 eat, and throwing up what little I could eat, until finally
13 my doctor forced me to go to the hospital and have every
14 painful, embarrassing, and humiliating gastrointestinal
15 related tests known to mankind.
16 Anyone who has ever had a barium enema will know
17 exactly how I feel. It compares to a medieval torture
18 chamber but without some of the human touch.
19 I kept being told that I might have an
20 obstruction, but they couldn't find one. In fact, they were
21 even wondering whether I ever really had Crohn's disease at
22 all, despite the fact that I had gone to that same hospital
23 and had several colonoscopies and had biopsies that had
24 proven the existence of the Crohn's disease.
25 so, all they could do in the end was put a

1 nasogastric tube down my nose and throat for 10 days, only
2 it took 12 attempts to get it there. That was yet more
3 torture, but at least it got me a little bit better until
4 the next time I had to be hospitalized, which was just a few
5 months later.
6 During this time, I had to have yet another
7 catheter surgically implanted because in a fit of misguided
8 optimism I had had the first removed, a big mistake as it
9 turned out.
10 I went to a number of major medical centers for
11 treatment and none were able to help until I went to the
12 Mayo Clinic, so I am pleased to see a representative from
13 the Mayo Clinic here today.
14 Finally, I got the surgery I needed and I had 18
15 inches of my small intestine removed. Again, my experience
16 pales next to that of Greg and Anke. None of it was
17 currently diseased, but that part of my gut was so scarred
18 and fibrotic from past inflammation that it simply wasn't
19 working anymore, and what I understand is had there been
20 more effective treatments during the 18 or so years that
21 that infection had been working its way through my body,
22 perhaps that scar tissue would not have been so bad and
23 perhaps I wouldn't have had to have that surgery.
24 However, that operation gave me back my life, and
25 I am so grateful to the doctors there for their kindness and

1 skills, but even they warned me that the improvement I had
2 night not hold, and they were right. Within a few months I
3 had started to experience the symptoms of an active flare-up
4 again. Since that time, I have had two major flare-ups and
5 am currently in the middle of one right now.
6 I have taken numerous drugs for Crohn's disease.
7 I have tried various diets, alternative treatments,
8 everything you can think of, and the only thing that seems
9 to work for me is prednisone. I can't say it's a good drug
10 at all, but I have been lucky so far. The worst side
11 effects I have had have been the moon face and gaining 40
12 pounds. I consider that lucky because others I have known
13 have had far, far worse.
14 I have known an 18-year-old man who had to have
15 cataract surgery due to glaucoma because of prednisone, a
16 31-year-old woman who had to have two knee replacements, a
17 25-year-old woman who had osteoporosis, all due to
18 prednisone.
19 I have known many people how refused to take it
20 because it makes them psychotic, for instance, they get
21 violent mood swings or they feel invincible and run red
22 lights. I think they are choosing safety over death.
23 It is hard for me to detail my experiences with
24 Crohn's because so much of my life during the past 23 years
25 has been about trying to minimize the effects of Crohn's -

1 no letting other see how badly I hurt, trying to fulfill my
2 family and work obligations while having no energy
3 whatsoever, keeping the awful details to myself while I
4 listen to well-meaning but ill-informed people comment look
5 that I look so healthy or that all I have to do is deal
6 better with stress or eat a certain diet and this disease
7 will just melt away.
8 The common ground that most people with Crohn's
9 share is the frustration of being victimized twice - by the
10 disease itself and the isolation and the misunderstanding
11 that come with it.
12 Over the years, I have led support groups for
13 patients and their families, and I have talked to hundreds,
14 maybe thousands, of Crohn's patients about their struggles
15 with this illness. I have heard stories that could break
16 your heart.
17 I think of the family of 10 children of whom 4 had
18 Crohn's, the professional couple who both have Crohn's and
19 decided not to have children of their own because of the
20 risk that their children, too, would have it. I think of
21 the terrible burden placed on young children with Crohn's
22 and want nothing more than to be like other children,
23 therefore, won't accept the support they need because it
24 means acknowledging that they are different.
25 I think of the man with short bowel syndrome who

1 was on disability and in and out of the hospital for years.
2 His wife actually wondered aloud in the support group one
3 day if he wouldn't be better off dead.
4 I think of the pain and suffering of the parents
5 of children with Crohn's who watch helplessly as their
6 children's growth is stunted and they have to undergo tests
7 and procedures that even adults find hard to bear.
8 I think of the brave children with Crohn's who
9 learn to insert their own nasogastric tube every night, so
10 they can be fed enough parenteral nutrition to keep them
11 alive and growing.
12 I think of families who have lost houses due to
13 the crushing burden of medical bills not covered by
14 insurance. I could give you a hundred more examples, but
15 the bottom line is this. The suffering caused by this
16 illness is enormous and the treatments we have simply aren't
17 good enough.
18 I am living proof that they really don't work. We
19 need more treatments, newer forms of treatment; and more
20 options.
21 I thank you for your time and attention, and I
22 urge you to keep in mind what I and the other patients have
23 to say as the human backdrop to your deliberations today.
24 Thank you.
25 DR. FRANK: Thank you, Amy. I appreciate all your

1 comments.

2 Is there anyone else who would like to speak

3 before we begin the remainder of the session?

4 If there isn't, I am going to turn it over to the

5 sponsor, but I would like to just mention to the panel I am

6 going to have the sponsor give the presentations, and I

7 would like any questions from the panel to be for

8 clarification of specific items, if possible, and the major

9 questions will wait until after the FDA presentation, as

10 well.

11 Mr. Martin Page.

12 Sponsor Presentation

13 Introduction

14 MR. PAGE: Good morning. Dr. Frank, committee

15 members: On behalf of Centocor, may I express appreciation

16 for this opportunity to present data on infliximab, the

17 first biological agent to be submitted to this committee.

18 [Slide.]

19 Infliximab is a chimeric monoclinal antibody

20 directed against human tumor necrosis factor alpha, a pro-

21 inflammatory cytokine that is considered an important

22 mediator of inflammation in Crohn's disease.

23 [Slide.]

24 As we have heard eloquently this morning, Crohn's

25 disease is a severely disabling disease, occurring with the

1 highest incidence in patients between the ages of 20 and 35.

2 The major clinical features include diarrhea,

3 fever, abdominal pain, weight loss, and generalized fatigue.

4 Up to 30 percent of afflicted patients will develop fistulas

5 and 70 percent will eventually require surgery. Even after

6 surgery, the disease frequently recurs.

7 [Slide.]

8 In practice, medical management of Crohn's disease

9 involves use of various drugs, such as aminosalicylates,

10 antibiotics, antidiarrheals, corticosteroids, and immuno

11 modulators to control the signs and symptoms.

12 With the exception of corticosteroids, no drugs

13 have FDA approval for treatment of this disease. Many of

14 the drugs are relatively toxic, and the treatment benefit is

15 often not maintained. Even in patients treated with

16 corticosteroids, 80 percent relapse or become steroid-

17 dependent after on year.

18 No drug in a controlled clinical trial has been

19 show to heal enterocutaneous fistulas. There is therefore a

20 clearly unmet need for a new medical treatment.

21 [Slide.]

22 The prevalence of Crohn's disease is variously

23 estimated at 20 to 80 per 100,000 population. Based on this

24 prevalence, infliximab has been granted orphan drug status

25 for the treatment of Crohn's disease.

1 [Slide.]

2 The indication we are requesting for infliximab is
3 for the treatment of patients with active Crohn's disease
4 for the reduction of symptoms and signs including
5 enterocutaneous fistulas.

6 This reworded indication, which has recently been
7 submitted to FDA, has been phrased more closely in line with
8 the current draft guideline for Crohn's disease as published
9 by Dr. Steven Fredd in the Journal Inflammatory Bowel
10 Disease in 1995.

11 In addition to this currently proposed indication,
12 a draft protocol is under discussion with the FDA for a
13 large multi-center, randomized trial to investigate the
14 long-term maintenance of clinical benefit. We plan to
15 finalize this protocol with guidelines resulting from the
16 committee's discussions tomorrow.

17 [Slide.]

18 Centocor conducted four clinical trials of
19 infliximab in Crohn's disease consisting of two open-label
20 trials and two placebo-controlled, randomized, double-blind
21 trials .

22 The open-label trials provided the preliminary
23 pharmacokinetics and dose-ranging information...

24 The two controlled trials investigated safety and
25 efficacy in patients with active Crohn's disease including

1 patients with draining enterocutaneous fistulas.

2 Both trials provide compelling efficacy results

3 and show internal consistency across all patient subgroups

4 evaluated. The primary endpoints are supported by the

5 secondary clinical and laboratory endpoints.

6 Moreover, given the common underlying

7 pathophysiology, we believe that these two independent

8 trials, using different endpoints, cross-substantiate each

9 other and support a conclusion of effectiveness more

10 convincing than repetition of the identical study. This

11 view is consistent with FDA's recent guidance document on

12 providing clinical evidence of effectiveness.

13 [Slide.]

14 The safety database, comprising patients with

15 rheumatoid arthritis and other indications, as well as

16 Crohn's disease, totals 514 patients. Additional safety

17 experience from 447 patients is available from two sepsis

18 trials and ongoing trials in rheumatoid arthritis and AIDS.

19 [Slide.]

20 Our objective this morning is to provide an

21 overview of the clinical data, and assist you in your task

22 of advising FDA with respect to the safety and efficacy of

23 infliximab.

24 Following this introduction, our agenda consists

25 of four presentations.

L--

1 Dr. Sander van Deventer, Professor of Experimental
2 Medicine at the University of Amsterdam in The Netherlands,
3 will present the scientific rationale and clinical
4 pharmacology. Dr. van Deventer was the first investigator
5 to explore the use of infliximab in a patient with Crohn's
6 disease.
7 The main efficacy and safety results will be
8 described by Dr. Thomas Schaible, Director, Immunology
9 Clinical, at Centocor.
10 Dr. Roger Cohen, Associate Professor of Medicine,
11 and Director, Cancer Center Clinical Trials, at the
12 University of Virginia, will provide a safety perspective in
13 which he assesses the infliximab safety data in the context
14 of the types of lymphoproliferative disorders that occur in
15 patients with inflammatory diseases of long duration. Dr.
16 Cohen is a hematologist/oncologist and was formerly Deputy
17 Director of the Division of Monoclinal Antibodies at FDA
18 Center for Biologics.
19 Finally, Dr. Daniel Present, Clinical Professor of
20 Medicine at Mt. Sinai School of Medicine, New York, will
21 provide an overall clinical perspective on the use of
22 infliximab for the treatment of Crohn's disease.
23 [Slide.]
24 In addition to the presenters, the following
25 consultants are also present to assist in answering your

1 questions if necessary.

2 In alphabetical order, they are: Drs. Brian

3 Feagan, James Fries, Paul Rutgeerts, Josef Smolen, and

4 Stephan Targan.

5 May I now introduce Dr. Sander van Deventer to

6 present the scientific rationale and clinical pharmacology.

7 Scientific Rationale and Clinical pharmacology

8 DR. van DEVENTER: Dr. Frank, members of the

9 committee : Cytokines are insoluble proteins that enable

10 immune cells to communicate with other immune cells and also

11 with non-immune cells. Tumor necrosis factor alpha or TNF

12 was one of the first cytokines to be characterized, and it

13 is considered to be a major pro-inflammatory cytokine.

14 [Slide.]

15 Macrophages, monocytes, and T-lymphocytes produce

16 TNF, and it is translated as a precursor molecule that is

17 retained within the cell outer membrane. After cleavage by

18 a specific protease, the mature trimeric molecule is

19 released, and it is now able to diffuse to target cells

20 where it binds to one of two specific TNF receptors.

21 Engagements of three of these receptors leads to

22 signal transduction and activation of the target cell, and

23 then using a whole lot of pro-inflammatory effects.

24 It is important to note that the cell surface-

25 bound TNF, as well as the soluble TNF can be biologically

1 active, so in order to fully neutralize TNF, one would need
2 a reagent that addresses both the soluble and the cell
3 surface-bound TNF.
4 [Slide.]
5 The activities of TNF on target cells are
6 numerous. For example, in macrophages, TNF induces the
7 production of other pro-inflammatory cytokines, in fact,
8 inducing TNF itself, including TNF itself, and also of
9 chemokines . Chemokines are small cytokines that act to
10 recruit other inflammatory cells into local sites of
11 inflammation, and all this serves to amplify inflammation.
12 On endothelial cells, TNF expresses or induces the
13 expression of specific adhesion molecules that make the cell
14 sticky, so that inflammatory cells like neutrophils can
15 adhere and transmigrate through the endothelium, and this
16 also leads to increased cell infiltration.
17 In fibroblasts and other cells like endothelial
18 cells, TNF induces another cytokine, interleukin-6, which
19 induces the acute phase response. The acute phase response
20 is characterized by an increase of C-reactive protein in
21 serum, CRP, and this is one of the parameters that has been
22 studied, and you will see it later coming back in the
23 clinical studies.
24 TNF also up-regulates the synthesis of
25 netalloproteinases and down-regulates collagen production,

1 and all this leads to tissue remodeling.

2 Finally, of importance for Crohn's disease is the

3 effect on the epitheliums, that is, TNF increases ion

4 transport and it also increases permeability, and these are

5 two characteristics of the inflamed bowel in Crohn's

6 disease.

7 [Slide.]

8 Now, there are two major lines of evidence to

9 indicate that TNF is involved in the pathogenesis of Crohn's

10 disease, and the first line comes from animal models.

11 In several animal models which are considered

12 relevant for inflammatory bowel disease, including Crohn's

13 disease, there is increased production of TNF in the mucosa,

14 and these models are spontaneous colitis, which occurs in

15 nonkeys, in cotton-top tamarins, and it includes several

16 models in mice, which are T-lymphocyte dependent, and by

17 nany investigators considered to be very relevant for

18 Crohn's disease.

19 Importantly, the administration of anti-TNF

20 monoclonal antibodies or polyclonal antibodies is able not

21 only to prevent disease in these models, but it has been

22 also shown that in most of severe Crohn's disease, such

23 interventions can treat already established disease, and,

24 Eor example, this is the case in the cotton-top tamarin

25 monkeys.

1 It is also very difficult to induce disease in
2 animals that are deficient for production of TNF, TNF
3 knockout mice. The TNF knockout mice do not develop disease
4 when you challenge them with haptens, which is a lymphocyte-
5 dependent, T-1ymphocyte-dependent model of disease.
6 [Slide.]
7 There is also evidence from clinical data that TNF
8 is important for the development of Crohn's disease. I have
9 to stress that the circulating TNF levels in patients with
10 even very active Crohn's disease usually are low, or
11 something even undetectable, but in contrast, there is
12 substantial production of TNF messenger RNA and also protein
13 localized and confined to the bowel mucosa.
14 It has been reported that stool TNF concentrations
15 nicely parallel the disease activity in children with
16 Crohn's disease, and when you take biopsies and culture the
17 biopsies or when you isolate mononuclear cells from these
18 biopsies, TNF production is clearly increased in patients
19 with Crohn's disease.
20 To this I can add that there is a paper which in
21 press, in the Lancet, and this paper showed that even in
22 patients with quiescent Crohn's disease, if you take their
23 nonocytes, their T-lymphocytes, out of the biopsies, and
24 neasure the TNF production, this is a very reliable
25 predictor of relapse. The more TNF that is produced, the

1 higher the chance of relapse.

2 [Slide.]

3 Infliximab is human mouse chimeric monoclinal

4 antibody that consists of a TNF binding site, which is

5 murine, which is grafted on an IgG1 heavy tail, and the

6 constant region for the lychain is kappa.

7 [Slide.]

8 The antibody binds with a high affinity, 10^{10}

9 molar, to both transmembrane TNF, the TNF that this

10 expressed on the cell surface, and to soluble TNF.

11 The antibody is specific for human and chimpanzee

12 TNF . It doesn't cross-react with TNF from other primates,

13 and not with TNF from 13 other animal species tested.

14 The antibody neutralizes TNF in a wide variety of

15 functional bioassays, and it blocks TNF by forming stable

16 complexes with the TNF, that is, once the TNF is bound by

17 the antibody, it is not released from the complex.

18 In addition to the TNF-neutralizing effect, it

19 binds to TNF that is expressed on the cell surface, and it

20 can lyse cells that express transmembrane TNF in in vitro

21 experiments when complement is added or in the presence of

22 effecter cells.

23 [Slide.]

24 This is one example of a biological function that

25 is blocked by infliximab. In this assay, endothelial cells

1 are exposed to TNF, and the ability of TNF antibody is
2 tested to block the expression of two cell adhesion
3 molecules - E-selectin and ICAM-1. These two cell adhesion
4 molecules both are important for the recruitment of
5 neutrophils into the inflamed bowel mucosa.
6 Note that a control antibody has no effect on the
7 expressed of the two cell adhesion molecules. In contrast,
8 infliximab concentration independently decreased the
9 expression of these cell adhesion molecules.
10 I would like to point to the fact that an
11 important inhibition is already noted at an antibody
12 concentration of 0.1 mcg/mL, and you have to remember this
13 concentration because I will come back to that in discussing
14 the pharmacokinetic data.
15 [Slide.]
16 There have been several nonclinical safety
17 studies, but in the case of infliximab, these have been
18 necessarily restricted to chimpanzee studies because this is
19 the only animal species other than humans in which the
20 antibody recognizes TNF.
21 The chimpanzee studies consisted of single dose
22 and multiple dose, up to 30 mg/kg x 3 days dosing. There
23 were no signs of toxicity, of hypersensitivity, no symptoms
24 of immune system suppression, and no infections, and the
25 maximum follow up in these studies for the multiple dosing

1 has been six weeks.

2 In addition to this, there has been a

3 reproduction/developmental study in mice using another

4 antibody that is specific for mouse TNF, and in this study,

5 two administrations of different doses of the monoclinal

6 antibody didn't produce any fetal abnormalities.

7 To this, I can add that TNF knockout mice, mice

8 that cannot produce TNF, do not display developmental

9 abnormalities either, and therefore it seems that TNF is not

10 necessary for normal fetal development.

11 [Slide.]

12 so, to sum up this part of my talk, I can conclude

13 that TNF is a potent pro-inflammatory cytokine which

14 contributes to the pathophysiology of Crohn's disease.

15 The antibody infliximab is a chimeric monoclinal

16 antibody that has the ability to bind to soluble, as well as

17 transmembrane TNF and to neutralize its biological effects,

18 and the nonclinical safety studies revealed no evidence of

19 toxicity.

20 [Slide.]

21 In the next part of my talk, I would like to

22 discuss some data on clinical pharmacology of infliximab, in

23 particular dose data that have led to the dose selection

24 used in the efficacy trials.

25 [Slide.]

1 The clinical pharmacology studies that happened
2 prior to the dose selection or that led to the dose
3 selection have been three studies.
4 There was one study in healthy volunteers, which
5 is called the T03 study, which was a placebo-controlled
6 study in endotoxin-challenged volunteers.
7 There has been one study in patients with
8 rheumatoid arthritis, again, a placebo-controlled trial,
9 looking at two doses of the antibody, called the T09 study,
10 and in the T11 study, which was a nonplacebo-controlled
11 trial, dose escalating study in patients with Crohn's
12 disease, the pharmacokinetics were evaluated in patients
13 with active Crohn's disease.
14 I will briefly discuss these three studies.
15 [Slide.]
16 The T03 study was a single-blind, placebo-
17 controlled study. In this study, infliximab was infused in
18 healthy volunteers at four different doses: 0.01, 0.1, 1.0
19 and 10 mg/kg. Placebo was given, and it was followed two
20 hours later by a challenge with 4 rig//kg of E. coli
21 endotoxin. Of course, the endotoxin here was used to induce
22 TNF secretion in vivo.
23 In this study, there were five subjects per group,
24 and I will show you the effect of these different doses on
25 three TNF concentrations.

1 [Slide.]

2 The red line here is the placebo group, so this
3 shows you what happens if you give endotoxin to volunteers.
4 As you can see here, the endotoxin challenge leads to an
5 increase in the TNF serum concentration up to 400 pg/mL with
6 the peak occurring at about 90 minutes after the challenge.
7 Infliximab dose dependently reduced the amount of
8 free TNF in the volunteers. The 0.01 dose showed some
9 effect here, 0.1 was better, so the full neutralization of
10 TNF only occurred at 1 mg and the 10 mg dose.
11 So, from a pharmacodynamic point of view, one
12 would need a dose of at least 1 mg/kg in order to fully
13 neutralize TNF.
14 [Slide.]
15 The T09 study was a multi-center, placebo-
16 controlled trial in patients with rheumatoid arthritis, that
17 had active disease despite prior treatment with at least one
18 disease-modifying drug.
19 The antibody was infused as a single" infusion.
20 There were 24 patients per group, and placebo was given and
21 the antibody at a dose of 1 or 10 mg/kg dose. The
22 predefined endpoint parameter here was clinical response.
23 It was defined as a 20 percent improvement in Paulus
24 criteria. This is a validated composite score for
25 rheumatoid arthritis, and the 20 percent improvement is

1 considered to be clinically relevant for an improvement of
2 rheumatoid arthritis.
3 [Slide.]
4 As you can see on this slide, using these
5 endpoints, placebo had no effect whatsoever on disease
6 activity. Both antibody doses, 1 mg and the 10 mg/kg dose,
7 have a significant effect when looking at the endpoint.
8 Note, however, that in the 1 mg/kg dose, there were less
9 patients responding. The endpoint here was determined at
10 four weeks, and this difference is statistically
11 significant, so there is a smaller proportion of patients
12 responding, and also the duration of the response appears to
13 be less in the lower dose than in the higher dose of
14 infliximab.
15 [Slide.]
16 The T11 study was a multi-center, open-label,
17 dose-escalating trial in patients with active Crohn's
18 disease despite treatment with corticosteroids. The
19 antibody was infused as a single infusion, there were five
20 patients per group, and the doses used were 1, 5, 10 and 20
21 mg/kg. I want to show you the pharmacokinetic assessment of
22 this study.
23 [Slide.]
24 As you can see, all the doses led to a significant
25 concentration of infliximab in the circulation, and there

1 was a dose-response relationship.

2 There is also, infliximab, in time, as you can see

3 here, and for three of the four doses, the antibody

4 persisted for more than four weeks. The only exception was

5 the 1 mg/kg dose, where you can see that there was no

6 antibody detectable at four weeks. The detection limit of

7 the assay is 0.1 mcg/mL here. So, all these other doses led

8 to antibody in the circulation for longer than four weeks.

9 I would also like to stress that antibody levels

10 in this dose range, that is, 0.1 to 10 mcg/mL are relevant

11 because I have shown you that at this dose of TNF still has

12 biological effects, so all these doses were are relevant, so

13 with these doses, 1, 5, 10, and 20 mg/kg, you have

14 biologically active antibodies in the circulation for more

15 than four weeks.

16 For a disease that is a chronic disease, one would

17 like to see a durable effect of the antibody, so these

18 concentrations seem more appropriate for this indication

19 than this antibody dose.

20 [Slide.]

21 The T16 study was not a pharmacokinetic study. It

22 was primarily an efficacy trial, and it will be extensively

23 discussed in the next presentation.

24 This was a trial in patients with active Crohn's

25 disease despite treatment with corticosteroids,

1 immunomodulatory agents and/or aminosalicylates. The
2 initial infusion or the initial treatment consisted of a
3 single infusion of the antibody, there were about 25
4 patients per group, and placebo was given for 5, 10, and 20
5 mg/kg.
6 It was an efficacy and safety study, but I will
7 show you the pharmacokinetic parameters, which were assessed
8 here, also to confirm the prior studies.
9 [Slide.]
10 As you can see on this slide, the Cmax in the area
11 under the curve showed a nice dose-response relationship and
12 increase with dose. As you would also expect, clearance and
13 volume of distribution, mean residence time, and terminal
14 half-life were not dependent on dose.
15 I would like to point here also to the fact that
16 the volume of this distribution is between 3 and 4 liters
17 for the antibody, which suggests that most of the antibody
18 is confined to the circulation.
19 Another important point here is that-the terminal
20 half-life is between 10 and 24 days, which is exactly the
21 half-life that you would expect for human IgG.
22 [Slide.]
23 To sum up my talk and to sum up the clinical
24 pharmacology, the pharmacokinetics of infliximab are
25 predictable. The pharmacodynamics suggest or indicate that

1 you need at least 1 mg/kg dose in order to neutralize in the
2 acute situation TNF that is induced by endotoxin challenge.
3 The pharmacokinetic assessment in patients with
4 Crohn's disease indicates that a dose of 5 mg/kg or more
5 maintains infliximab in circulation for at least four weeks,
6 and taken together, these considerations have led to the
7 selection of the 5 mg/kg dose or more for the subsequent
8 assessment of the efficacies in the T16 and the T20 trial.
9 Thank you.
10 MR. PAGE: Thank you, Professor van Deventer.
11 I will next introduce Dr. Thomas Schaible,
12 Director, Immunology Clinical Research, for Centocor, who
13 will present the clinical efficacy and safety data.
14 Efficacy and Safety
15 [Slide.]
16 DR. SCHAIBLE: Thank you, Martin.
17 Dr. Frank and members of the committee: In my
18 presentation this morning, I will begin by reviewing the
19 results for efficacy with infliximab.
20 [Slide.]
21 These data have come from a series of four
22 clinical trials conducted in the U.S. , Europe, and Canada,
23 including two open-label trials and two placebo-controlled,
24 randomized, double-blind trials. A total of 233 patients
25 with Crohn's disease were studied. All four trials have

1 been described in the briefing document. This morning I
2 will present results from the two controlled trials which
3 support the proposed indication.
4 [Slide.]
5 In these trials, the evaluation of Crohn's disease
6 encompassed clinical, endoscopic, and laboratory
7 measurements. Clinical signs and symptoms were measured
8 using the Crohn's Disease Activity Index, or CDAI, the
9 Inflammatory Bowel Disease Questionnaire, or IBDQ, the
10 number of open draining fistulas, and the patient's
11 assessment of their fistulas.
12 Endoscopic evaluation of mucosal inflammation
13 employed the Crohn's Disease Endoscopic Index of Severity,
14 or CDEIS. As a serum marker of inflammation, measurements
15 of C-reactive protein, or CRP, were determined.
16 [Slide.]
17 The CDAI was measured in all of the clinical
18 trials in patients with Crohn's disease. This is a
19 validated instrument that measures the signs and symptoms of
20 Crohn's disease and is widely used in Crohn's disease
21 delivery trials.
22 It consists of eight components and yields a
23 component score ranging from approximately zero to 600.
24 Scores below 150 indicate inactive disease or disease
25 remission, while scores of 150 or more indicate active

disease. A score of 300 or more corresponds to a patient status of poor condition as rated by a physician's evaluation in the original validation of the CDAI as published by Best, et al. in 1976.

[Slide.]

The components of the CDAI include the number of loose or liquid stools, the patient's assessment of abdominal pain and general well-being, extra-intestinal manifestations of the disease, such as fistulas, arthritis, fever, and uveitis, presence of an abdominal mass, use of antidiarrheal drugs, hematocrit, and body weight.

[Slide.]

The C0168T16 trial, or T16, provides data demonstrating the efficacy of infliximab to reduce the clinical signs and symptoms of Crohn's disease in patients with active disease.

[Slide.]

The T16 study was a multi-center, randomized, double-blind, placebo-controlled trial. The primary endpoint of a reduction in the signs and symptoms of Crohn's disease was evaluated in an initial treatment phase. In addition, the study had a retreatment phase, which evaluated secondary endpoints for maintenance of the initial treatment benefit.

[Slide.]

1 The target population included patients who had.
2 moderate to severe active Crohn's disease defined as a CDAI
3 between 220 and 400. Patients were to have had a disease
4 duration of at least six months.
5 The protocol also required that patients had
6 demonstrated an inadequate response to conventional
7 treatment for Crohn's disease. This was defined as one or
8 more of the following conditions: concurrent use of
9 corticosteroids, concurrent use or had failed treatment with
10 aminosalicylates, 6-mercaptopurine or 6-MP, and/or
11 azathioprine, or had failed treatment with methotrexate or
12 cyclosporine.
13 [Slide.]
14 The T16 study was conducted at 18 study centers in
15 the U.S., Europe, and Canada. Patients were randomly
16 assigned to treatment groups and study drug was distributed
17 to the study centers by an independent party.
18 Central laboratories were used, and data
19 management and analysis were performed by the sponsor,
20 Centocor.
21 All personnel at the study center with the
22 exception of the pharmacist preparing the study agent were
23 blinded to treatment assignment through the entire study.
24 The sponsor remained blinded until the databases for the
25 initial treatment phase and the retreatment phase were each

finalized.

[Slide.]

This slide shows a schematic diagram of the study design for the initial treatment phase. Patients received one of four treatments in the initial treatment phase - placebo, 5, 10, or 20 mg/kg of infliximab. These were administered as a two-hour intravenous infusion. Treatment was randomly assigned and stratified by study center and concurrent corticosteroid use.

The primary endpoint measurement, a predefined clinical response, which I will describe momentarily, was determined at 4 weeks. Patients not achieving the primary endpoint were eligible for an open-label treatment of 10 mg/kg at that time.

The patients demonstrated the clinical response at 8 weeks were eligible to enter the retreatment phase of the study beginning at 12 weeks. Patients not achieving a clinical response at 8 weeks received no additional treatment.

[Slide.]

Patients eligible for the retreatment phase were randomly assigned to receive either placebo or 10 mg/kg of infliximab every 8 weeks, for a total of four additional infusions . Patients were followed for efficacy and safety through 48 weeks.

1 [Slide.]

2 The prespecified primary endpoint in the trial was
3 defined as a clinical response at four weeks. A clinical
4 response was defined as 70 point or more decrease in the
5 CDAI not accompanied by an initiation of, or increase, in
6 medications for Crohn's disease or surgery for Crohn's
7 disease.

8 The 70 point decrease was selected because it
9 represents the difference between the minimum CDAI required
10 for study entry, 220, and the minimum CDAI indicating active
11 disease, 150.

12 In addition, this definition of clinical response
13 exceeds the 50 point change in the CDAI associated with a
14 categorical change in disease activity as determined in the
15 original validation of the CDAI.

16 [Slide.]

17 We based the statistical power and sample size of
18 the T16 trial on several considerations. For the primary
19 endpoint we assumed a 30 percent response rate" in placebo-
20 treated patients, 80 percent in the infliximab-treated group
21 with the highest response, and 55 percent in the other
22 infliximab groups.

23 We designed the trial to have 80 percent power to
24 detect a significant difference among groups with an alpha
25 0.05. Based on these considerations, a sample size of 25

1 patients in each of the four groups was required.

2 The primary efficacy analysis employed a Cochran-

3 Mantel-Haenszel chi-square test for general association. If

4 a significant treatment effect was observed, pairwise

5 comparisons of each infliximab group versus placebo were

6 performed using the same method. All reported p-values are

7 two-sided.

8 [Slide.]

9 Additional secondary analyses were prespecified

10 and included clinical response at each visit, clinical

11 remission at each visit, changes in health-related quality

12 of life, and laboratory and endoscopic response variables

13 including the IBDQ, CRP, and CDEIS.

14 [Slide.]

15 The secondary response variables included the

16 following. The IBDQ is a validated quality of life

17 instrument commonly employed in clinical trials in

18 inflammatory bowel disease. It comprises 32 questions over

19 four dimensional scores. These include bowel," systemic,

20 social, and emotional. Scores ranged from 32 to 224 with

21 higher scores indicating better quality of life.

22 CRP is an acute phase protein produced by the

23 liver and is a serum laboratory marker of inflammatory

24 activity. The CDEIS is the only validated method for

25 endoscopic evaluation of mucosal inflammation. It evaluates

1 segments of the intestine from the ileum to the rectum where
2 each segment is scored for the portion of the mucosal
3 surface having ulcers and other specific lesions. Scores
4 ranged from zero to 41 with lower scores being better.
5 [Slide.]
6 108 patients were enrolled in the T16 study
7 between June and October 1995 with between 25 and 28
8 patients randomly assigned to each group. Equal numbers of
9 men and women were enrolled. The median age was 37 years,
10 and all patients were white. No differences were observed
11 among treatment groups for demographic variables.
12 [Slide.]
13 The baseline disease characteristics of the study
14 population indicated that these patients had moderate to
15 severe disease activity. No differences were observed among
16 treatment groups for baseline disease characteristics
17 including disease duration, numbers of patients with
18 previous surgery, or the median CDAI, IBDQ, or CRP.
19 The one exception was involved intestinal area
20 where more placebo patients had disease limited to the
21 ileum.
22 [Slide.]
23 Over 90 percent of patients were receiving
24 concurrent medication for their Crohn's disease, 77 percent
25 of patients were receiving corticosteroids and/or the

1 immunomodulatory agents 6-MP or azathioprine at study entry.
2 Fifteen percent of patients were receiving aminosalicylates
3 alone at study entry, while 8 percent of patients were
4 receiving none of these medications because of previously
5 documented treatment failure on these therapies. No
6 differences were observed amongst the treatment groups for
7 concomitant medications.
8 [Slide.]
9 Here are the results for efficacy. To review, the
10 primary endpoint was a 70 point or greater decrease in the
11 CDAI at the four-week evaluation visit. Each of the three
12 infliximab treatment groups demonstrated a statistically
13 significant greater number of patients achieving the primary
14 endpoint compared to placebo.
15 The 5 mg/kg infliximab group demonstrated the
16 highest proportion of patients responding, 81 percent,
17 compared to the placebo response rate of 17 percent, with a
18 p-value for this comparison of less than 0.001.
19 Although response rates among the treatment groups
20 varied, we believe this represents a flat dose-response
21 relationship. Additional analyses in subsequent slides will
22 support this conclusion.
23 Because both placebo and infliximab treated
24 patients were receiving concurrent therapies for their
25 disease, the clinical benefit provided by infliximab

1 treatment represents a therapeutic benefit well beyond that
2 provided by currently available therapies.
3 [Slide.]
4 The extent of the clinical benefit provided by
5 infliximab was profound. Many of the responding patients
6 achieved clinical remission defined as a CDAI less than 150.
7 As was observed for the primary endpoint analysis, the 5
8 mg/kg infliximab group demonstrated the highest proportion
9 of patients achieving clinical remission, 48 percent
10 compared to 4 percent of placebo patients, with a p-value
11 less than 0.001.
12 [Slide.]
13 To obtain an overall estimate of the infliximab
14 treatment benefit, the results for clinical response and
15 clinical remission were combined for all three infliximab
16 treatment groups.
17 In this analysis, approximately two-thirds of the
18 infliximab-treated patients demonstrated a clinical response
19 and approximately one-third demonstrated clinical remission.
20 Comparison to placebo response rates demonstrate highly
21 significant p-values for both clinical response and clinical
22 remission.
23 [Slide.]
24 Infliximab treatment produced a rapid and profound
25 benefit lasting at least 8 to 12 weeks for all response

1 variables that were measured. Here, median results for the
2 CDAI at each evaluation visit through four weeks are shown
3 for all patients in the left panel.
4 Patients who demonstrated a clinical response at
5 four weeks continued to be followed through 12 weeks.
6 Results in these patients are shown in the right panel for
7 the infliximab treatment groups.
8 The data in the right panel are informative in
9 characterizing the degree and duration of clinical benefit
10 in patients who responded to infliximab treatment. For the
11 all patient analysis on the left, the CDAI for the placebo
12 group, shown by red circles, did not change through four
13 weeks .
14 In contrast, each of the three infliximab
15 treatment groups demonstrated a reduction in the CDAI at the
16 first evaluation visit at two weeks, and continued to
17 improve through four weeks.
18 In the infliximab patients demonstrating a
19 clinical response, shown on the right, the CDAI was reduced
20 to values associated with disease remission and was well
21 sustained through 12 weeks. The three doses were not
22 distinguishable for the degree of treatment benefit.
23 [Slide.]
24 Turning to another response variable, the IBDQ,
25 results following infliximab treatment also demonstrated a

1 definitive improvement. Because a 16-point change in the.
2 IBDQ is considered clinically meaningful, the increase of 40
3 to 70 points at four weeks for infliximab-treated patients
4 compared to 2 points for placebo-treated patients represents
5 a relevant and definitive benefit.
6 This improvement was consistently observed for all
7 four dimensions of the IBDQ - bowel, systemic, social, and
8 emotional, indicating a broad impact of infliximab treatment
9 on the patient's state of health.
10 As shown on the right, in patients demonstrating a
11 clinical response, the median IBDQ achieved values
12 associated with disease remission for at least 12 weeks
13 follow-up treatment. Again, no effective dose on the extent
14 of response was observed.
15 [Slide.]
16 Infliximab also produced a rapid reduction in CRP,
17 a serum inflammatory marker. The median CRP concentration
18 in placebo-treated patients, shown in red, demonstrated a
19 gradual increase over four weeks, whereas, the" median CRP
20 concentration rapidly decreased to well within the normal
21 range in all of the infliximab-treated groups.
22 The effects of infliximab treatment on this
23 objective measurement of antiinflammatory activity were
24 highly consistent with the antiinflammatory effects observed
25 for the CDAI and the IBDQ.

1 [Slide.]

2 The clinical improvement observed following
3 infliximab treatment was associated with a reduction in
4 mucosal inflammation. All European centers participating in
5 the T16 study were to perform ileocolonoscopy at baseline
6 and at four weeks. Twenty-seven patients had endoscopy
7 performed at both times and were evaluated for a disease
8 severity using the CDEIS method.

9 The infliximab treatment groups demonstrated an
10 approximate 60 percent reduction from baseline in the CDEIS
11 compared to a 25 percent reduction in the placebo treatment
12 groups.

13 [Slide.]

14 Unlike corticosteroids, changes in clinical
15 improvement with infliximab were directly associated with
16 changes in endoscopic improvement, as shown in this analysis
17 which plots the change in CDAI versus the corresponding
18 change in the CDEIS in individual patients.

19 This association is particularly important because
20 it demonstrates that the source of the patient's symptoms,
21 mucosal inflammation, is directly ameliorated by infliximab
22 treatment.

23 [Slide.]

24 To explore the consistency of the benefit of
25 infliximab, we performed additional analyses examining the

1 effect of treatment within subgroups of patients according
2 to demographic variables, disease characteristics, and
3 concurrent medications. These analyses were performed by
4 comparing the odds ratio for each of the patient subgroups.
5 [Slide.]
6 The odds ratio is the odds of an infliximab
7 patient achieving the primary endpoint divided by the odds
8 of a placebo-treated patient achieving the primary
9 endpoints. The odds ratio for each subgroup is shown by a
10 vertical bar and the 95 percent confidence intervals by the
11 horizonal lines extending from the bar. An odds ratio
12 greater than 1, indicated by the yellow line, corresponds to
13 observed treatment benefit with infliximab.
14 For reference, the dashed line indicates an odds
15 ratio of 10 on the logarithmic scale.
16 [Slide.]
17 The slide shows that for all patient subgroups
18 based on gender, age, and weight, and for patients enrolled
19 in North American or European centers, the odds ratios
20 approximated the odds ratio for all patients shown in orange
21 at the top. All subgroups have overlapping confidence
22 intervals and all have odds ratios greater than 1. This
23 analysis indicates the consistency of the treatment effect
24 in each of these subgroups.
25 In addition, examination of results for individual

1 centers indicated that 16 of 18 participating centers
2 reported a higher response in infliximab-treated patients
3 than in placebo-treated patients.
4 [Slide.]
5 This slide shows a similar analysis for baseline
6 disease characteristics including disease duration, involved
7 intestinal area, disease severity at the CDAI, and baseline
8 CRP concentration. Again, all had overlapping confidence
9 intervals greater than 1.
10 Importantly, benefit was uniformly observed in
11 patients who had disease limited to the ileum, limited to
12 the colon, or limited to both the ileum and colon. As
13 provided in your briefing document, consistent treatment
14 benefit was also observed in patient subgroups according to
15 previous resection, presence of fistulas, or extra
16 intestinal manifestations.
17 [Slide.]
18 Consistent treatment benefit was also observed
19 regardless of the concurrent medications that were received.
20 This included corticosteroids, 6-MP azathioprine,
21 aminosalicylates, and. antibiotics.
22 [Slide.]
23 Although the initial treatment benefit of
24 infliximab lasted 8 to 12 weeks in most patients, continuing
25 benefit beyond this time has not been well defined. The

retreatment extension of T16 was conducted to explore the longer term benefit of infliximab.

[Slide.]

This slide shows the results of the 73 patients who were eligible to enroll in the repeated treatment phase. The left side of the panel shows, in blue, the proportion of patients achieving the 70 point clinical response during the initial treatment phase.

The right side shows response rates for the repeated treatment phase according to infliximab treatment, in yellow, or placebo retreatment, in red. Arrows at the bottom of the panel indicate when infusions were given. In patients retreated with placebo, a gradual loss of clinical response was observed over several months. In patients retreated with infliximab, the clinical response present at the end of the retreatment phase was kept stable during the retreatment period.

[Slide.]

Similar results with retreatment were observed using the more stringent criterion clinical remission, as shown here. As mentioned earlier, a large multi-center, placebo-controlled, double-blind trial will begin this summer to evaluate retreatment regimens that can maintain the treatment benefit of infliximab for prolonged periods.

[Slide.]

1 In summary, the T16 study demonstrated that
2 infliximab rapidly reduced the size and symptoms of Crohn's
3 disease with two-thirds of patients demonstrating a
4 infinitive clinical response and one-third of patients
5 achieving clinical remission.
6 The observed clinical benefit was associated with
7 mucosal healing. The treatment benefit was consistent in
8 all patient subgroups defined by demographic variables,
9 baseline disease characteristics, and concurrent
10 dedications. A 5 mg/kg infusion was the lowest effective
11 dose and produced a high degree of benefit for all response
12 variables measured, and lasted at least 8 weeks.
13 [Slide.]
14 The second controlled trial in patients with
15 Crohn's disease was the T20 trial, a study in patients with
16 enterocutaneous fistulas as a complication of Crohn's
17 disease. We undertook this trial based on observations in
18 the T16 trial and the earlier open-label trials that patient
19 with draining enterocutaneous fistulas demonst"rated healing
20 of these fistulas with infliximab.
21 [Slide.]
22 The T20 trial was a multi-center, randomized,
23 double-blind, placebo-controlled trial including three
24 treatment groups, each using a three-dose infusion regimen
25 and an 18- to 26-week follow-up period. The T20 trial

.P-

1 represents the largest clinical trial of a therapeutic agent
2 ever conducted in patients with fistulizing Crohn's disease.
3 [Slide.]
4 The target population included patients who had
5 single or multiple enterocutaneous fistulas draining for at
6 least three months. Concurrent medications for Crohn's
7 disease were permitted, but had to represent a stable
8 therapeutic regimen by criteria specified in the study
9 protocol.
10 These medications included corticosteroids,
11 immunomodulatory agents specifically 6-MP, azathioprine, and
12 methotrexate, antibiotics, and aminosalicylates.
13 [Slide.]
14 The T20 study was conducted at 12 study centers in
15 the U.S. and Europe. As was the case for the study
16 organization of the T16 trial, patients were randomized and
17 study drug distributed by an independent party. Central
18 laboratories were used, and data management and data
19 analysis was performed by the sponsor.
20 [Slide.]
21 This slide shows a schematic diagram of the study
22 design. Patients were randomly assigned to one of three
23 treatment groups, stratified by study center, and whether
24 the patient had a single draining fistula or multiple
25 draining fistulas.

1 The three treatment groups were placebo, 5 or 10
2 g/kg infliximab, with each treatment given at weeks zero,
3 , and 6. The more frequent dosing regimen was used because
4 t was believed that fistulas would be more refractory to
5 reatment.
6 Patients were evaluated every four weeks through
7 'eek 18. patients who were still responding to treatment at
8 'eek 18 returned at weeks 22 and 26 for additional follow-up
9 evaluations.
10 [Slide.]
11 The prespecified primary endpoint was defined as a
12 50 percent or greater reduction in the number of open
13 fistulas for at least two consecutive evaluation visits or
14 approximately one month.
15 A fistula was considered closed when it was no
16 longer draining despite gentle compression. These criteria
17 had to be achieved without an initiation of, or increase in,
18 dedications for Crohn's disease or surgery for Crohn's
19 disease.
20 [Slide.]
21 Sample size was determined assuming the primary
22 endpoint would be achieved in 15 percent of patients in the
23 placebo group and in 55 percent of patients in one of the
24 infliximab groups.
25 The trial was designed to have 80 percent power to

1 detect a significant difference between placebo and one of
2 the infliximab groups with an alpha of 0.025. Given these
3 considerations, a sample size of 25 patients in each of the
4 three treatment groups was required.
5 The primary efficacy analysis was performed using
6 a Mantel-Haenszel chi-square test for linear association.
7 If a significant treatment effect was observed, pairwise
8 comparisons of each infliximab group to placebo were
9 performed using Fisher's exact test. Again, all reported p-
10 values were two-sided.
11 [Slide.]
12 Additional secondary analyses were prespecified
13 and included additional characterization of fistula closure,
14 including the number of patients who had a complete
15 response, that is no draining fistulas for two consecutive
16 visits, the onset of response, and the duration of the
17 response.
18 The patient's assessment of their fistulas was
19 also determined. In addition, the clinical improvement as
20 measured by the CDAI was determined over time.
21 [Slide.]
22 Ninety-four patients were enrolled between May and
23 October of 1996 with between 31 and 32 patients randomly
24 assigned to each treatment groups. Roughly equal numbers of
25 men and women were enrolled. The median age was 35 years,

1 91 percent of patients were white and 9 percent were black.
2 No differences were observed amongst treatment groups for
3 demographic variables.
4 [Slide.]
5 Baseline disease characteristics indicated the
6 mean duration of disease was 12 years. The majority of
7 patients had disease involving both the ileum and colon, 55
8 percent of patients had multiple draining fistulas, and 4s
9 percent had a single draining fistula. Ten percent of
10 patients had abdominal fistulas, while 90 percent had
11 perianal fistulas.
12 The median CDAI was 167. This lower value
13 indicates that although all of these patients had draining
14 fistulas, their overall disease activity was less than that
15 in the T16 trial. There were no differences amongst
16 treatment groups for baseline disease characteristics.
17 [Slide.]
18 Eighty-three percent of patients were receiving
19 concurrent medications for their Crohn's disease, 69 percent
20 of patients were receiving corticosteroids, 6-MP, or
21 azathioprine and/or antibiotics, while 14 percent were
22 receiving aminosalicylates alone, 17 percent of patients
23 were receiving none of these medications. Therefore, most
24 of the patients in the study population had draining
25 fistulas despite receiving conventional treatments for their

1 Crohn's disease. No differences were observed amongst the
2 treatment groups for concurrent medications.
3 [Slide.]
4 Here are the results for efficacy. Both
5 infliximab treatment groups demonstrated a statistically
6 significant greater number of patients achieving the primary
7 endpoint compared to placebo. No apparent dose-response
8 effect was observed between the 5 and 10 mg/kg infliximab
9 treatment groups.
10 The 5 mg/kg infliximab group demonstrated the
11 highest proportion of patients responding, 68 percent,
12 compared to the placebo response rates of 26 percent, with a
13 ?-value for this comparison of 0.002.
14 These findings represent the first time that a
15 statistically significant therapeutic benefit has been
16 demonstrated in the closure of draining fistulas.
17 [Slide.]
18 The highest ranked secondary analysis in the
19 analytical plan was the number of patients achieving a
20 complete response, that is, no draining fistulas for two
21 consecutive study visits. Consistent with the primary
22 endpoint analysis, both the 5 and 10 mg/kg treatment groups
23 demonstrated a statistically significant greater number of
24 patients achieving a complete response.
25 Again, the 5 mg/kg infliximab group demonstrated

the highest proportion of patients achieving a complete response, 55 percent, compared to the placebo response rate of 13 percent, with a p-value of 0.001.

[Slide.]

When combining the results from the two infliximab treatment groups, 62 percent of treated patients achieved the primary endpoint and 46 percent of patients achieved a complete response. As shown here, both of these findings were high statistically significant compared to the placebo group.

[Slide.]

Closure of draining fistulas by infliximab treatment was characterized by a rapid onset and a lasting benefit. The median onset of response was 14 days in both the 5 and 10 mg/kg treatment groups, corresponding to the first evaluation visit at two weeks. The median duration of the response in infliximab-treated patients was approximately three months.

[Slide.]

Photographs of each fistula at each evaluation visit were obtained. This slide shows multiple abdominal fistulas in a 50-year-old female patient with a previous resection. Abdominal fistulas, such as these, are not uncommon in patients following abdominal surgery.

This patient had five draining abdominal fistulas

at study entry. Most had been draining for more than one year. All of the draining fistulas had completely closed by the first evaluation visit at two weeks in response to the 5 mg/kg dose regimen.

The fistulas remained healed through the entire follow-up period. The next slide shows close-up photographs of this fistula.

[Slide.]

This close-up more clearly shows the rapid onset of fistula healing at two weeks and the continued benefit of treatment through 18 weeks.

[slide.]

This 42-year-old male patient had a single draining perianal fistula. He also received the 5 mg/kg dose regimen. The fistula demonstrated significant healing by the two-week evaluation visit, but still had slight drainage. The fistula stopped draining by the six-week evaluation visit and remained completely healed at 10 weeks, as shown here, and through the rest of the follow-up period.

[Slide.]

Results for the patient's assessment of their fistula activity were consistent with the results for the primary endpoint. The percentage of patients reporting that their fistulas were causing no problem are summarized over time here.

1 Approximately 30 to 40 percent of infliximab-
2 treated patients reported this response following treatment
3 compared to approximately 10 percent of placebo-treated
4 patients. This benefit was evident by the two-week
5 evaluation in the infliximab groups, but not in placebo, and
6 was still evident at the 18-week evaluation visit.
7 [Slide.]
8 An additional secondary measurement of efficacy
9 was the CDAI obtained at each study visit. Similar to all
10 of the other studies with infliximab in patients with
11 Crohn's disease, a rapid reduction in CDAI was observed
12 following treatment with either the 5 or 10 mg/kg dose
13 regimens of infliximab, but not following treatment with
14 placebo. The reduction in the CDAI lasted through the 18-
15 week evaluation visit.
16 [Slide.]
17 We employed the same odds ratio method as you saw
18 earlier to examine the consistency of infliximab treatment
19 in the closure of fistulas in similar subgroups of patients
20 as used in the T16 analysis.
21 [Slide.]
22 All subgroups based on gender, age, and weight
23 demonstrated consistent benefit. Similarly, the treatment
24 benefit was virtually identical in patients enrolled in U.S.
25 and European study centers. Again, no subset of centers

1 accounted for the overall observed treatment benefits.

2 [Slide.]

3 Here, we are showing the same analysis for

4 subgroups based on various baseline disease characteristics.

5 These include disease duration, involved intestinal area,

6 previous surgery, number of draining fistulas, and the CDAI

7 at study entry. Again, all of these subgroups demonstrated

8 a consistent benefit of infliximab treatment.

9 Of particular interest, similar benefit was

10 observed both in patients with a single draining fistula and

11 with multiple draining fistulas.

12 [Slide.]

13 Similar to what was observed in the T16 study,

14 concurrent medications for Crohn's disease did not affect

15 the benefit of infliximab in the closure of fistulas, as

16 shown here, for corticosteroids, 6-MP/azathioprine,

17 aminosalicylates, or antibiotics.

18 [Slide.]

19 In summary, infliximab rapidly closed draining

20 fistulas. Approximately, two-thirds of patients

21 demonstrated a 50 percent or greater reduction in the number

22 of draining fistulas, and approximately one-half

23 demonstrated closure of all draining fistulas.

24 Most of the patients in this trial had draining

25 fistulas despite receiving medication for Crohn's disease,

substantiating the unique treatment benefit provided by infliximab in these patients.

Infliximab had a consistent treatment benefit in all patient subgroups.

Finally, the 5 mg/kg dose regimen was the lowest effective dose and produced a high degree of benefit lasting at least three months".

[Slide.]

The safety data from the infliximab clinical trials demonstrate that the benefit of infliximab in reducing the signs and symptoms of Crohn's disease outweighs the risk of adverse events. This review will also include the most recent data from our ongoing long-term follow-up program.

[Slide.]

For purposes of reporting safety, we have combined the safety experience. in the 199 infliximab-treated patients in Crohn's disease trials, the 203 treated patients in rheumatoid arthritis trials, and the 51 treated patients in other studies.

We believe it is appropriate to combine these data because almost all of these patients had a disease involving an immune disorder, and were receiving similar types of antiinflammatory and immunomodulatory medications. Therefore, the safety database is based on 453 patients

1 treated with infliximab, 304 of whom have received multiple
2 infusions.
3 This database from completed trials was used to
4 determine the safety profile of infliximab that I will
5 present to you this morning.
6 [Slide.]
7 Additional experience from other completed trials
8 an ongoing blinded trials has also been used in our
9 assessment of safety. This includes two completed trials in
10 patients with sepsis in which 80 patients were treated with
11 infliximab. Safety data from these studies are not included
12 in the safety database because of the high morbidity and
13 mortality that occurs in these patients, however, data from
14 these trials were reassuring for safety in that a
15 nonsignificant trend for lower mortality was observed with
16 infliximab.
17 The additional safety experience also includes a
18 10-patient, open-label trial in patients with rheumatoid
19 arthritis that was completed since the BLA submission, and
20 the 428-patient trial in rheumatoid arthritis, currently in
21 progress, is still blinded, in which approximately 80
22 percent of patients have been randomized to receive
23 infliximab.
24 Finally, an NIH-sponsored trial conducted in AIDS
25 patients has treated 15 patients to date. This additional

1 safety experience has been incorporated in the assessment of
2 malignancies that will be presented by Dr. Roger Cohen
3 shortly.
4 [Slide.]
5 Analysis of the safety database has shown that
6 infliximab is well tolerated at all doses. Most adverse
7 events are mild to moderate in severity. Changes in
8 laboratory and vital sign measurements, when they occurred,
9 were mild and transient, and major safety events occurred
10 infrequently, were manageable and without sequelae.
11 [Slide.]
12 A consideration in assessing safety is that
13 differences were observed between placebo and infliximab-
14 treated patients for the duration of on-study follow up.
15 This occurred because placebo patients dropped out earlier
16 or crossed over to infliximab treatment.
17 Infliximab-treated patients were followed on study
18 nearly twice as long as placebo-treated patients, 22 weeks
19 versus 12 weeks. Therefore, in the presentation of safety
20 data, results will be shown for all safety events regardless
21 of the duration of on-study follow up and also using a
22 common follow-up period.
23 [Slide.]
24 This slide tabulates the adverse events that were
25 reported in 5 percent or more of infliximab-treated

1 patients. Corresponding adverse event rates for placebo-.
2 treated patients are also shown. Seventy-six percent of
3 infliximab-treated patients had at least one adverse event
4 compared to 57 percent of placebo-treated patients, an
5 absolute difference of about 20 percent.
6 As shown here, the most frequently occurring
7 adverse events were reported in both placebo and infliximab-
8 treated patients.
9 [Slide.]
10 The frequency of adverse events over comparable
11 follow-up periods for placebo and infliximab groups was
12 analyzed in the two control trials in Crohn's disease.
13 Comparable follow-up periods were for four weeks following
14 the infusion in the T16 study and through 18 weeks in the
15 T20 study.
16 In each study, the absolute differences for the
17 excess of infliximab-treated patients having adverse events
18 was about 10 percent. This compares to the 20 percent
19 difference when the longer follow up in infliximab-treated
20 patients is included.
21 [Slide.]
22 Serious and reasonably-related adverse events are
23 shown here. A reasonably related event was one judged by
24 the investigator as possibly, probably, or definitely
25 related to study treatment. 4.4 percent of infliximab-

1 treated patients and 1.8 percent of placebo-treated patients
2 had serious, reasonably related adverse events. Such events
3 reported by more than one infliximab-treated patient were
4 pneumonia in four patients, fever in four patients, dyspnea
5 in three patients, and rashes in two patients.
6 Each of these events was manageable and without
7 long-term sequelae.
8 [Slide.]
9 Infusion reactions and antibody responses have
10 been reported for biological agents including monoclinal
11 antibodies which may be of particular concern for
12 retreatment of these agents. Therefore, we examined our
13 experience for adverse events following infliximab
14 retreatment, as well as the occurrence of infusion reactions
15 and the development of human antichimeric antibodies against
16 infliximab or HACAS.
17 [Slide.]
18 This slide characterizes our current experience
19 with retreatment. In the 304 patients retreated with
20 infliximab, the median number of infusions received was 3.
21 The median duration between the first and last infusion of
22 infliximab was 12 weeks, and the median cumulative dosage
23 given was 20 mg/kg.
24 In Crohn's disease trials, the median cumulative
25 dosage was 30 mg/kg.

1 [Slide.]

2 Shown here are the percentage of Crohn's disease
3 patients having an adverse event according to the number of
4 infliximab infusions received. No trend for a higher
5 incidence of adverse events with multiple infusions was
6 observed.

7 [Slide.]

8 In assessing infusion reactions, we selected a
9 conservative definition for these events, that is, any
10 adverse event that occurred during the infusion or within
11 the two-hour observation period following the infusion.
12 Across all trials, using this broad definition, 16 percent
13 of infliximab-treated patients had an infusion reaction
14 compared to 6.5 percent of placebo-treated patients.

15 In the two controlled Crohn's disease trials, 16
16 percent of infliximab-treated patients had infusion
17 reactions compared to 11 percent of placebo-treated
18 patients. As suggested by the placebo rates for infusion
19 reactions, and as summarize in your briefing document, many
20 of these events were mild and nonspecific in nature.

21 [Slide.]

22 To assess more significant infusion reactions, the
23 number of serious infusion reactions was tabulated. Four
24 serious infusion reactions occurred out of 1,207 infliximab
25 infusions administered. Three of these occurred in patients

1 with Crohn's disease and one in a patient with rheumatoid.
2 arthritis. The drowsiness that occurred in the rheumatoid
3 arthritis patient was actually mild, resulting from
4 antihistamine administration for a rash, and the patient
5 stayed in the clinical research unit for a few hours longer.
6 By definition, this became a serious adverse event.
7 The three events in Crohn's disease patients all
8 had cardiopulmonary symptoms, and each occurred on the
9 second infusion of infliximab. Each of these events was
10 manageable either by discontinuation of the infusion and/or
11 with medications. Each resolved within two hours and
12 without any sequelae.
13 [Slide.]
14 One potential consequence of administration of any
15 protein is the development of antibodies against that
16 protein. Antibodies against infliximab or HACA developed in
17 18 Crohn's disease patients. No patients were positive for
18 HACA at study entry.
19 HACA responses were generally low titer, 16 of 18
20 Crohn's patients had HACA responses with a titer less than
21 or equal to 1 to 40. Two patients developed HACA prior to a
22 retreatment with infliximab. One patient had a serious
23 infusion reaction upon retreatment, and received in further
24 infliximab. The other patient received all four additional
25 infusions that were scheduled safely and with continued

1 efficacy

2 [Slide.]

3 Another consideration in assessing the safety of
4 infliximab is to recognize that the nature of the population
5 of patients with these diseases and their management place
6 these patients at higher risk for having adverse
7 experiences. These patients had long-standing disease with
8 a history of high inflammatory activity, and many received
9 chronic treatment with immunomodulatory therapies. As such,
10 it is possible that these populations may have increases in
11 infections, autoimmune disorders, malignancy, and mortality.
12 I will review with you our data for patients with
13 infections, autoantibodies, and autoimmune disorders, and
14 mortality. Dr. Roger Cohen will then review our experience
15 in patients who have had malignant conditions.

16 [Slide.]

17 Infections occurring in 1 percent or more of
18 infliximab-treated patients are shown here. These were
19 identified by examination of the adverse event" database for
20 reported infections or constellations of symptoms for which
21 antibiotics were given.

22 Twenty-one percent of infliximab-treated patients
23 had an infection compared to 11 percent of placebo-treated
24 patients, an absolute difference of 10 percent. Again, it
25 is important to note that average weeks of follow up was

1 nearly twice as long in the infliximab group.

2 [Slide.]

3 Because of this longer follow up, we evaluated the
4 number of placebo and infliximab-treated patients with an
5 infection requiring antibiotic treatment for comparable
6 periods of follow up in the T16 and T20 studies. AI-I
7 absolute 3 percent increase in infections occurred in
8 patients receiving infliximab in the T16 study, and no
9 increase was observed in the T20 study.

10 [Slide.]

11 Serious infections, that is, infections that
12 usually required hospitalization, occurred in 2.4 percent of
13 infliximab-treated patients and 1.8 percent of placebo-
14 treated patients.

15 Each of the infections are shown here.
16 Infliximab-treated patients with infections have responded
17 well to antibiotic therapy. Four additional serious
18 infections occurred, but did not meet our definition for
19 inclusion because antibiotic treatment was not' documented,
20 nor was instituted within one week of infection. These
21 infections were reported in briefing documents provided to
22 you by the sponsor and FDA.

23 [Slide.]

24 To examine the potential for development of
25 autoimmune disorders, the 202 patients in the T16 and T20

1 clinical trials, and the 222 patients participating in
2 rheumatoid arthritis trials, were tested for the presence of
3 auto-antibodies. Nine percent of infliximab-treated
4 patients developed anti-double-stranded DNA antibodies.
5 These occurred at low concentrations and were transient.
6 They often normalized while patients were still on study.
7 Because anti-double-stranded DNA antibodies are
8 characteristic for systemic lupus erythematosus, or SLE, we
9 further evaluated laboratory measurements and clinical
10 findings in these patients. No other antibodies
11 characteristic for SLE were observed. All patients were
12 negative for anti-RNP, anti-Sin, anti-Ro, and anti-La.
13 In SLE, hypocomplementemia often occurs. All of
14 the infliximab-treated patients positive for anti-double-
15 stranded DNA had normal complement concentrations. In SLE,
16 major end-organ effects are characteristic, specifically
17 renal or CNS complications.
18 In infliximab-treated patients, no major organ
19 damage was observed.
20 [Slide.]
21 Two infliximab-treated patients while on study
22 developed a lupus-like syndrome - one Crohn's disease
23 patient with's migratory arthritis and one rheumatoid
24 arthritis patient with a pleuropericarditis . Neither
25 patient had any renal or CNS symptoms. Both patients were

1 medically managed with a course of steroids with
2 complications.
3 The clinical and laboratory features in both of
4 these patients are more consistent with a drug-induced lupus
5 syndrome than SLE.
6 [Slide.]
7 Importantly, in our long-term follow-up program,
8 which I will summarize in a moment, no autoimmune disorders
9 other than the patient's underlying disease have been
10 reported.
11 [Slide.]
12 Our long-term follow-up program follows all
13 patients in clinical trials through three years following
14 their last infusion for the occurrence of death, malignancy,
15 and autoimmune disorders.
16 Some patients had events reported after three
17 years . These are not included in the tabulation of events
18 reported here.
19 Ninety-three percent of infliximab-treated
20 patients have had follow up obtained in this ongoing
21 program. Most of the patients, 83 percent, have now had
22 follow up obtained for one year or longer after their last
23 treatment. This follow-up program has provided 773 total
24 patient years of follow up in infliximab-treated patients.
25 Because many placebo patients crossed over to

1 infliximab treatment, only 68 patient years of follow Up are
2 available for placebo patients, too few to perform any
3 meaningful analyses.
4 [Slide.]
5 No patients died while they were on study. Nine
6 deaths have been reported during the three-year, long-term
7 follow-up period. Of the nine patients who died, two had
8 Crohn's disease and seven had rheumatoid arthritis. Causes
9 of death included cardiovascular disease, malignancy or its
10 treatment, infection, and immunosuppressive therapy.
11 Three additional patient deaths were reported to
12 Centocor beyond the three-year follow-up period. Thes e
13 three deaths were reported to FDA, and include a Crohn's
14 disease patient who died of cardiovascular disease four
15 years after infliximab treatment, and two deaths in
16 rheumatoid arthritis patients, one patient who died of
17 preexisting coronary artery disease a little more than three
18 years after treatment, and one patient who died of gastric
19 cancer more than three and a half years after treatment.
20 In addition, one AIDS patient who participated in
21 a non-Centocor, NIH-sponsored trial died of lymphoma. This
22 case will be discussed by Dr. Cohen.
23 The observed mortality over the course of long-
24 term follow up following infliximab treatment is within the
25 expected incidence when compared to a cohort of 3, 500

1 patients with rheumatoid arthritis published by Wolfe, et,
2 al., in 1994.
3 Nevertheless, we had all deaths reviewed in detail
4 by the investigators and expert consultants including
5 examination of medical records and autopsy reports. The
6 conclusion of this review was that all deaths occurred as
7 part of the natural history of the patient's underlying
8 disease or its treatment.
9 [Slide.]
10 To summarize the safety data presented so far,
11 infliximab was well tolerated at all doses studied, either
12 given as a single infusion or multiple infusions. Major
13 safety events occurred infrequently, were manageable by
14 medication or discontinuation of infusion, and were without
15 sequelae. Mortality was within the expected incidence.
16 MR. PAGE: Thank you, Dr. Schaible.
17 May I next introduce Dr. Roger Cohen.
18 DR. FRANK: I am sorry to interrupt, but I think
19 that we all need a break for 15 minutes. We will be back
20 here at 25 after, please.
21 [Recess.]
22 MR. PAGE: I would like to introduce our next
23 presenter, Dr. Roger Cohen. Dr. Cohen is Director of the
24 Cancer Center Clinical Trials at the University of Virginia.
25 He will provide an evaluation of the lymphoproliferative

1 disorders observed in the longer term follow up of the
2 infliximab trials.
3 Safety Perspective
4 DR. COHEN: Thank you, Mr. Page, Dr. Frank,
5 nembers of the committee, ladies and gentlemen.
6 [Slide.]
7 Approximately, 804 patients participated in the
8 non-sepsis infliximab clinical trials, 199 with Crohn's
9 disease and approximately 555 with rheumatoid arthritis, and
10 together they account for nearly 1,000 patient years of
11 follow up.
12 Among the 804 patients, there have been a total of
13 3 patients with solid tumors and 6 patients with various
14 lymphoproliferative disorders over a three-year follow-up
15 period that was defined prospectively in the various
16 studies.
17 The solid tumors reported during the three-year
18 follow-up period are described on the next slide.
19 [Slide.]
20 The sponsor did not include two solid tumors, one
21 gastric, one colon, that occurred more than three and a half
22 years after treatment, after the prospectively defined
23 follow-up period. The sponsor feels that the long time
24 interval and the less comprehensive data collection on these
25 patients makes those latter two events very difficult to

1 interpret.

2 Each of the solid tumors on this slide arose in

3 the setting of a preexisting, premalignant condition. The

4 first is a patient actually not mentioned in your FDA

5 documents who presented with a pathological clavicle

6 fracture and widespread bone metastases one week after

7 receiving infliximab. The pathology was consistent with a

8 primary breast tumor.

9 The second is a patient with a history of basal

10 cell cancer who developed a Clark's Level II melanoma in a

11 preexisting pigmented lesion that was under surveillance.

12 This was removed, and the patient is well and free of

13 melanoma.

14 The last cancer arose in a nodular thyroid,

15 another premalignant condition. The cancer arose in a

16 nodule that had been under surveillance prior to infliximab

17 treatment. The thyroid was partially removed and the

18 patient is alive and free of cancer.

19 [Slide.]

20 Among the lymphatic cancers, there were 4

21 lymphomas, 1 Hodgkin's disease, and 1 myeloma. All of these

22 cancers arose in patients with advance disease of long

23 duration, and in each case patients had received prior

24 immunosuppressive therapy with prednisone, methotrexate, or

25 azathioprine, and in some instances, all three.

1 There was no relationship to infliximab dose or.
2 duration of treatment. The time elapsed between the last
3 infliximab infusion and the detection of lymphoproliferative
4 disease varied. As you will see shortly, in two instances,
5 it was relatively short, 3 and 6 1/2 months, while in others
6 it was quite long, 17 and 18 months. In any case, there was
7 no clear pattern.
8 The lymphomas are summarized in the next slide and
9 each case is also described in your briefing documents.
10 [Slide.]
11 There was a single case of lymphoma in a patient
12 with Crohn's disease. He had a long history of Crohn's
13 disease and had received prednisone and azathioprine, the
14 latter since 1989. He had pre-study lymphopenia secondary
15 to azathioprine of sufficient severity that he was initially
16 not eligible for the study. He developed a high grade
17 intravascular B-cell lymphoma and a gastric polyp 8 months
18 after infliximab treatment. The pathologist felt that this
19 was not consistent with a gastric maltoma.
20 The next three cases occurred in patients with
21 severe long-standing rheumatoid arthritis, the first of
22 these in a patient with rheumatoid arthritis for 16 years
23 who had received azathioprine, methotrexate, and prednisone.
24 Importantly, this patient had a 12-year history of
25 lymphadenopathy including enlargement of supraclavicular

1 nodes which had been biopsied in the past. This patient
2 also had enlarged axillary nodes at baseline and developed a
3 high grade B-cell lymphoma in axillary and cervical nodes 18
4 months after treatment.
5 The second case of lymphoma was in a patient with
6 long-standing rheumatoid arthritis treated with
7 methotrexate. He had long-standing splenomegaly pre-study
8 and six a half months after treatment, he developed a
9 Hodgkin's disease with mixed cellularity in an axillary
10 node.
11 The third lymphoma arose in a woman with a 37-year
12 history of rheumatoid arthritis who had received
13 methotrexate continuously for 15 years. She developed an
14 intermediate grade lymphoma of bone marrow and
15 retroperitoneal nodes. This particular patient is in the
16 rheumatoid arthritis trial in progress that has been
17 described, is still blinded, and we do not know if she
18 received the study drug or not.
19 A single case of myeloma was observed in a 59-
20 year-old woman with rheumatoid arthritis for seven years,
21 also treated with methotrexate and azathioprine, and her
22 myeloma developed 17 months after her last infliximab
23 treatment.
24 Finally, investigators at the National Cancer
25 Institute observed a single case of lymphoma in an AIDS

1 patient with a CD4 count of 25, and AIDS patients are well
2 known to be at exceptionally high risk of developing
3 lymphoma.
4 As a general rule, patients with rheumatoid
5 arthritis do not develop CNS lymphomas, and the sponsor's
6 experience is similar in that none of the lymphomas has
7 involved the central nervous system.
8 It is important to note further that none of the
9 patients had low lymphocyte counts as the result of
10 infliximab treatment. Most of the patients were positive
11 for Epstein-Barr virus, but more detailed information on EBV
12 status is not available.
13 I will first discuss lymphoma in Crohn's disease
14 and then discuss lymphoma risk in rheumatoid arthritis,
15 [Slide.]
16 Lymphoma in Crohn's disease is rare. What this
17 slide does is summarize some of the cohorts that have been
18 published in manuscripts or abstract form and some of them
19 are quite recent from the AGA meetings of two weeks ago.
20 They range in size from 34 to 1,655, in each,
21 there have been anywhere from zero to four cases observed
22 over periods ranging from a few months up to 50 years.
23 In some of the studies, the investigators have
24 gone ahead and calculated standardized incident ratios and
25 shown that they are higher than background for the general

1 public, but in each instance, the small numbers in each
2 series mean that the confidence intervals do not exclude the
3 value of 1, and the very small numbers in all of the series
4 make any association with Crohn's disease and lymphoma
5 difficult to establish with any degree of certainty.
6 [Slide.]
7 There are many more data on lymphoma risk in
8 rheumatoid arthritis patients, and the association between
9 lymphoma and rheumatoid arthritis is cited by many
10 authorities and is based upon numerous cohort and case
11 control studies published over a 25-year period.
12 The current consensus from literature review is
13 that patients with rheumatoid arthritis have at least a two-
14 to threefold increase in lymphoma risk. This could even be
15 higher. These risk estimates were observed before the
16 emerging use of agents, such as methotrexate and
17 azathioprine in the management of that disease, and as a
18 result, those observations suggest that lymphoma is part of
19 the natural history of the disease.
20 The debate right now focuses on the precise
21 magnitude of risk and risk factors for lymphoma development,
22 especially medical therapy such as azathioprine and
23 methotrexate.
24 The association with rheumatoid arthritis appears
25 to be strongest for lymphoma, including low and high grade

1 disease, the associations with multiple myeloma and AML are
2 much weaker, and in each instance, the pathogenesis remains
3 unclear.
4 [Slide.]
5 This slide summarizes some of the largest
6 published cohort studies. It does not attempt to be
7 comprehensive, only representative. The studies are
8 arranged chronologically from to top to bottom. Some of the
9 cohorts are from a particular hospital, region or clinic.
10 Others, such as the Nordic studies, reflect national
11 population data. In each case, the investigators have
12 calculated standardized incidence ratios for lymphoma and
13 other diseases, and adjusted those ratios for sex, age,
14 calendar year, and type of cancer.
15 What the studies show with one exception is a
16 consistent increase in lymphoma risk especially for the
17 larger studies from Finland, Sweden, and Denmark, the
18 relative risk for lymphoma development lies somewhere
19 between 2 and 3.
20 It is also important to note in the next to the
21 last column that the incidence of all cancers is not
22 increased in any of the studies. This is a very general
23 observation across cohort studies of rheumatoid arthritis
24 and suggests that there is something unique about this
25 population and its risk for developing lymphoma.

1 [Slide.]

2 A number of investigators have attempted to
3 elucidate those clinical features of rheumatoid arthritis
4 that may be associated with lymphoma, and several case
5 control studies have indicated that duration of disease and
6 severity of disease appear to be related to the risk of
7 developing lymphoma in rheumatoid arthritis.

a A recent analysis suggests just how high the risk
9 night be in patients with severe disease, thus, Baecklund
10 and Ekbom performed a nested case-controlled study on a
11 subset of the patients in the Swedish cohort that was
12 presented to you in the preceding slide, and they show that
13 the odds ratio for developing lymphoma could be as high as
14 26 for patients with high compared to low inflammatory
15 activity.

16 Treatment with various medical therapies may be an
17 additional risk factor as shown in the next slide.

18 [Slide.]

19 Two recent studies are cited here. Each of these
20 examined the possible effects of contemporary broad spectrum
21 mmunosuppressive therapy on the lymphoma risk. For the
22 ost part, these studies, and similar studies, have looked
23 t the effects of methotrexate and azathioprine.

24 Jones and coworkers, in a matched cohort study
25 ublished in the British Journal of Rheumatology, compared

1 unique population of patients in Wichita, Kansas, who were
2 not exposed to drugs such as azathioprine, to patients in
3 the United Kingdom who were exposed, and calculated and
4 observed relative risk of neoplasms of the immune system, a
5 broad category of 6, for the exposed population.
6 Similarly, Williams and coworkers, in a study
7 published in the Journal of Clinical Rheumatology, performed
8 a similar type of matched case control study using the
9 ARAMIS database in North American registry, and similar to
10 Jones and coworkers, observed an elevated odds ratio for
11 lymphoma of 5 for azathioprine and 1.7 for methotrexate.
12 There appears to be general agreement that
13 treatment with agents, such as azathioprine, raises the
14 lymphoma risk in rheumatoid arthritis, just as it does in
15 the solid organ transplant setting. The exact magnitude of
16 this effect is being debated, but most studies are
17 consistent with at least a twofold additional increase in
18 risk superimposed upon an already high background rate.
19 It should be noted very carefully, though, that
20 the confidence intervals for all of these risk estimates are
21 fairly high.
22 [Slide.]
23 Taken together, the available published and
24 republished data suggest that a relationship between
25 infliximab therapy and the development of lymphoma is

1 unlikely for the following reasons.

2 Lymphoma in Crohn's disease is rare, most series
3 show no or very few cases. The sponsor observed a single
4 case in a very immunocompromised patient.

5 Next, lymphoma is part of the natural history of
6 rheumatoid arthritis, and rheumatoid arthritis patients, in
7 the sponsor's study, were at high risk for lymphoma, they
8 had long duration of disease, severe inflammation, and
9 invariably, had been exposed to immunosuppressive therapies.

10 [Slide.]

11 Lymphomas appeared in patients who had received in
12 the past, or concurrently broad spectrum immunosuppressives,
13 such as azathioprine and methotrexate. Lymphomas did not
14 occur in patients without exposure to those agents.

15 The lymphomas were mainly nodal and they did not
16 involve the central nervous system. This observation may be
17 helpful given the predilection of the classic
18 immunesuppression-induced lymphoproliferative disorders to
19 involve the CNS and to predominate in extranodal sites.

20 As noted before, there appears to be no
21 relationship to infliximab dose or duration of exposure, and
22 finally, the number of cases seen during the infliximab
23 studies and the three-year follow-up period is in the ranges
24 that have been observed in similar cohorts of subjects in
25 various European and U.S. studies.

1 Thank you very much.

2 MR. PAGE: Thank you, Dr. Cohen.

3 May I now introduce Dr. Daniel Present, Clinical

4 Professor of Medicine at the Mt. Sinai Medical School in New

5 York, an institution with a long association with Crohn's

6 disease. Dr. Present with present a practicing clinician's

7 perspective on the use of infliximab in Crohn's disease.

8 Clinical Perspective

9 DR. PRESENT: Thank you. Dr. Frank, members of

10 the committee, visitors: I would like to introduce myself

11 and tell you why I am here.

12 I have been an academic practicing

13 gastroenterologist for 32 years. I have always been

14 involved with inflammatory bowel disease since my fellowship

15 at Mr. Sinai, and as you are well aware, Mt. Sinai is not

16 only a center for excellence, but is the home of Crohn's

17 disease. My mentors have included multiple inflammatory

18 bowel disease experts, such as Henry Janowitz and Arthur

19 Autses.

20 I was privileged to be the first researcher to be

21 given a grant from what is now known as the Crohn's and

22 Colitis Foundation, looking at the efficacy and toxicity of

23 6-mercaptopurine, an immunosuppressive agent in Crohn's

24 disease. I have been participating in multiple control

25 trials in Crohn's disease, most recently budesonide and

1 intravenous azathioprine, and I was helpful in designing an
2 immunosuppressive study in ulcerative colitis using
3 cyclosporine.
4 The reason I am here, however, is somewhat
5 different. I am here as a clinician. I have seen in my
6 career well over 2,000 patients with inflammatory bowel
7 disease, and I currently take care of approximately 40
8 patients a week with this disorder. I am on the firing line
9 taking care of patients.
10 I have been involved with the infliximab studies
11 almost since the inception, have been a principal
12 investigator in the T16 and T20 study, and my goal today is
13 to tell you in a short period of time what the impact of
14 approval of this drug would mean to Crohn's patients.
15 You have heard today Crohn's disease is not
16 curable, it is a disease of a lifetime most commonly
17 affecting young people, children, adolescents, and young
18 adults, and having, as you have heard, a significant impact
19 on quality of life, and it can interfere with 'social inter-
20 reactions, affect marriages, child-bearing, and sexual
21 enjoyment.
22 This disease, and especially fistulization, can be
23 mild, but it can be very severe and have a great effect on
24 the patient. This includes items, such as body image, a
25 patient's concept of how they look, curtailment of

1 activities, which can be especially devastating.

2 However, even more basic, you heard of someone who

3 can't even eat lunch, is being able to sit. Many patients

4 with severe fistulization have difficulty in sitting either

5 at school or at work. It can produce significant pain.

6 About 6 percent of all patients become addicted to pain

7 medications, often because of fistula and requiring

8 narcotics, and as you have heard, this disease can produce

9 and result in permanent ostomies.

10 So, how do we treat Crohn's disease? As was

11 mentioned, there has been only one drug thus far that has

12 been approved by the FDA for the treatment of Crohn's

13 disease, and that is corticosteroids . The response of this

14 drug in the studies that we have been, national cooperative

15 study, was 60 percent response to the drug with a 30 percent

16 response to placebo. You can do better with steroids by

17 giving higher doses, but when you use higher doses, you now

18 run into a major problem.

19 [Slide.]

20 This is the side effects of corticosteroids, and

21 if you look at them, you can see some rather simple but some

22 quite severe, hypertension, et cetera, and what is happening

23 now, with the advent of ability to test bone density, we are

24 finding out that high percentages of patients who have

25 received steroids have developed significant osteoporosis.

1 [Slide.]

2 And it goes on. The side effects of

3 corticosteroids take up two pages in our studies.

4 I had planned at this point to show you several

5 examples of patients of mine who were in the study and who

6 improved, but I think because of time factors, I would like

7 to show you just one patient which demonstrates the efficacy

8 both in the T16 and the T20 study.

9 I would like to show you what this drug can do for

10 our patients.

11 [Slide.]

12 This is a 21-year-old female patient who had a

13 two-year history of Crohn's disease. It involved both the

14 small bowel and the large bowel. She had developed perianal

15 fistula, which had been draining for one to two years. She

16 had had at least three or four local surgical procedures in

17 the rectal area, replacement of setons to prevent abscess

18 formation and keep the drainage open.

19 She had received a standard array of" what we are

20 using nowadays, mesalamine, 5 ASA drugs, antibiotics,

21 netronidazole, and had received an immunosuppressive agent.

22 This patient had failed to heal.

23 A consultation was arranged at my office, and the

24 patient's parents came. The patient did not show up in the

25 office. Why? Because the parents felt that if she were not

1 capable of entry into the study, this would be too difficult
2 for her to make this trip to New York, and when I told them
3 that I thought she would be a candidate, she came to the
4 office and stood through the entire consultation, she could
5 not sit down at all. This patient was taking six to eight
6 Percocet daily, had been unable to function in her last
7 years of school, and could not work.
8 If one looks at this patient, as you heard
9 originally, the Crohn's Disease Activity Index is over 300,
10 and that indicates a severely ill patient. If you look at
11 the various aspects of this, this patient was different than
12 most of our patients in that her major problem was fistula,
13 so she was not having a lot of diarrhea, but remember she
14 was taking narcotic painkillers which diminished the amount
15 of bowel movements.
16 She has severe abdominal pain and her well-being
17 was severely impaired. She did have fistulization. As yOU
18 can see, she was somewhat anemic. Well, what happened to
19 the patient? We were-blinded, but she was infused with the
20 study drug. I was called 48 hours later. The patient said
21 for the first time I can sit, and within approximately 7 to
22 10 days, she had discontinued narcotics, and you see from
23 the response rate at 2 weeks what happened to the Crohn's
24 Disease Activity Index with a marked decrease, and at 6
25 weeks, going into remission.

1 Now, there are a lot of subjective improvements
2 here, significantly, but there are also objective
3 improvements with ultimate healing of the fistula, increase
4 in body weight, and improvement in her hematocrit, and these
5 are quite objective.
6 Could you put on the slide of her perianal area,
7 please .
8 [Slide.]
9 This is how the patient looked on coming to the
10 office, and that day had a large ulceration which had been
11 demonstrated to be connected by a fistula. At two weeks,
12 you can see healing improvement. Interestingly, her pain
13 went away before. At 10 weeks, and finally, at 14 weeks at
14 significant and dramatic improvement, and at that time,
15 despite the skin looking open, there was no drainage with
16 finger pressure.
17 From whatever point of view you look at it,
18 especially quality of life, this patient was dramatically
19 improved. She is back to work. Since the study has been
20 completed, she has not received any more drugs. She has
21 relapsed slightly, but if you ask her, it is about 80 to 90
22 percent improved over her prior state.
23 [Slide.]
24 so, simply, in concluding from a clinician's point
25 of view, this is a chronic, incurable disease. It

1 unfortunately occurs predominantly in younger people. The
2 treatment is challenging. You have heard stories today.
3 Each patient is somewhat different and challenges all the
4 time.
5 Our conventional drug therapy at this time has
6 significant shortcomings both for efficacy and, in steroids
7 case, for toxicity. There is a significant clinical need
8 for new treatment, especially the [trianboy] steroid
9 toxicity. This drug infliximab has demonstrated a rapid and
10 consistent efficacy and, in my experience, significant
11 toxicity, and in my opinion, I believe that this drug is
12 really a breakthrough and that it has demonstrated a
13 significant impact on patient's quality of life.
14 I think that this drug deserves the consideration
15 of this panel for approval for Crohn's patients.
16 Thank you very much.
17 MR. PAGE: Thank you, Dr. Present.
18 To finalize our presentations, Dr. Schaible will
19 summarize what you have heard this morning.
20 Conclusions
21 DR. SCHAIBLE: Thank you.
22 [Slide.]
23 To conclude our presentation, we believe that the
24 following indication for infliximab is supported by the data
25 provided in your briefing document and presented to you this

1 morning.

2 Infliximab is indicated for patients with active

3 Crohn's disease for the reduction of symptoms and signs

4 including enterocutaneous fistulas.

5 [Slide.]

6 Based on the two controlled clinical trials in

7 patients with active Crohn's disease, the recommended dose

8 for reducing symptoms and signs in patients with fistulas is

9 5 mg/kg. The recommended dose for patients with

10 enterocutaneous fistulas is also 5 mg/kg followed with

11 additional 6 mg/kg doses administered at 2 and 6 weeks after

12 the first infusion.

13 [Slide.]

14 As you have seen in patients with active Crohn's

15 disease, as measured by the CDAI, about two-thirds of

16 infliximab patients demonstrated a definite clinical

17 response to treatment, and about one-third achieved clinical

18 remission.

19 [Slide.]

20 In patients with active Crohn's disease with

21 draining enterocutaneous fistulas, infliximab treatment

22 closed at least 50 percent of draining fistulas in about

23 two-thirds of patients, and closed all draining fistulas in

24 about one-half of patients.

25 [Slide.]

1 Reductions in clinical disease activity using a,
2 validated and broadly accepted index, the CDAI, were
3 observed in both controlled clinical trials. This occurred
4 in all infliximab treatment groups with a rapid onset of
5 action being apparent by the first post-treatment evaluation
6 at 2 weeks.
7 These reductions occurred in patients with a broad
8 range of disease activity, as measured by the CDAI. This
9 included patients with moderate to severe disease activity,
10 as shown on the left for the T16 study, and patients with
11 less overall disease activity as shown in the right, for the
12 T20 study.
13 [Slide.]
14 These reductions in disease activity produced by
15 infliximab are relevant in that no reduction in the CDAI was
16 observed in the placebo-treated patients.
17 [Slide.]
18 The treatment benefit of infliximab was highly
19 consistent . As you just saw from measurements" of the CDAI,
20 consistent benefit was observed across clinical trials.
21 This was true for all measurements of disease activity
22 including clinical, quality of life, laboratory, and
23 endoscopic measurements.
24 The benefit of infliximab treatment was not
25 restricted to any particular subgroup of patients, but was

1 uniformly observed in subgroups of patients according to
2 demographic characteristics, disease characteristics, and
3 concomitant medications.
4 [Slide.]
5 To summarize safety, infliximab was well tolerated
6 at all doses. Major safety events occurred infrequently,
7 were manageable by medication of discontinuation of the
8 infusion, and were without sequelae.
9 Malignancies occurred infrequently and, as
10 reviewed by Dr. Cohen, were unlikely related to infliximab.
11 No dose-relationship was observed and they occurred in
12 patients with elevated risk given the duration and severity
13 of disease and medication history.
14 [Slide.]
15 To conclude, the treatment benefit of infliximab
16 was characterized by a rapid onset of effect, high response
17 rates, and a high degree of benefit for all outcome
18 measurements.
19 This treatment benefit was obtained in patients
20 with active disease despite conventional therapies,
21 including corticosteroids and immunomodulatory agents.
22 Therefore, infliximab treatment of patients with
23 active Crohn's disease has a favorable benefit-risk profile.
24 Major safety events were infrequent and were manageable. On
25 the other hands, the benefit of infliximab was compelling,

1 consistent, and clinically relevant.

2 Thank you.

3 MR. PAGE: That does conclude our presentations.

4 We thank everybody for their careful attention this morning,

5 and our presenters and consultants will be happy to respond

6 to any questions you may have.

7 DR. FRANK: Thank you very much, Mr. Page.

8 I would like to call on panel members now who have

9 questions regarding the data or specific issues.

10 Dr. Laine.

11 Questions from the Committee

12 DR. LAINE: Just a couple of very concrete

13 questions before we get into more interesting things. Dr.

14 Schaible, on the T16 study, it had been stated that I

15 thought 220 CDAI was the requirement, but it looked like you

16 had patients with less than 220 on your baseline demographic

17 slide.

18 DR. SCHAIBLE: Right. I think there was one

19 patient who was at 215.

20 DR. LAINE: There seemed to be a couple more, I

21 mean I don't know how many, but more than one.

22 DR. SCHAIBLE: One of the explanations for that is

23 that the calculation of the CDAI was done at the study

24 center for determination of the patient's eligibility. Once

25 that data was collected, came in-house, and was clean, it

1 could sometimes change very modestly, and that could explain
2 some small variations in the CDAI.
3 DR. LAINE: So there were a small number? Do you
4 know how many people were less than 220 or not too many?
5 DR. SCHAIBLE: It was very few. I would say it
6 was probably one or two, and they were below -- it was like
7 215, it was by five points or so.
8 DR. LAINE: Just another small, concrete question.
9 On your clinical remission, the T16 was about 50 percent
10 versus 25 and 25 in the two higher doses Ninety-five
11 percent confidence intervals are helpful in these small
12 numbers a lot of times.
13 Can you tell me if there was overlap of 95 percent
14 confidence intervals between the 5 and the 10 and the 20
15 clinical remissions?
16 DR. SCHAIBLE: Yes, there was.
17 DR. LAINE: Okay.
18 DR. FRANK: Yes, Dr. Elashoff.
19 DR. ELASHOFF: I would like to ask a question, a
20 two-part question, having to do with comparing efficacy
21 across the two trials".
22 Have you got results for the T20 trial using the
23 primary efficacy measure for the T16 trial at greater than
24 70-point decrease in CDAI?
25 DR. SCHAIBLE: Yes . That was actually one of the

1 secondary analyses that was specified in the trial. In
2 order to do that analyses, we identified those patients who
3 were enrolled in T20, who had a CDAI at entry of greater
4 than 220.
5 I think we can try to put that table up. If I
6 could have the study report, I can actually provide you some
7 numbers .
8 [Slide.]
9 This is going to be very difficult to see. I
10 apologize for that. We don't have the back-up slide for
11 this. But of the placebo patients, 9 patients had a CDAI
12 greater than 22o. Again, the overall patient population had
13 lower overall disease activity. If we look at the combined
14 cA2 treatment groups, 21 patients had a CDAI greater than
15 220.
16 If we then looked at the number of patients who
17 achieved a 70-point decrease over time in the CDAI group, it
18 was 61.9 percent at two weeks, 70 percent at six weeks, 63.2
19 percent at 10 weeks, 57.9 percent at 14 weeks," and 45
20 percent at 18 weeks.
21 DR. ELASHOFF: Can we just have the four-week,
22 which would correspond to the other one for the placebo and
23 the overall --
24 DR. SCHAIBLE: There was no four-week visit in the
25 study. I can give you the six-week number, if you want

1 that.

2 DR. ELASHOFF: Okay.

3 DR. SCHAIBLE: That was 70 percent in the cA2

4 treatment groups combined.

5 DR. ELASHOFF: What for placebo?

6 DR. SCHAIBLE: At that point, 3 of 7 placebo

7 patients achieved a response, for 43 percent, but that was

8 the only -- at evaluation visit thereafter, the placebo

9 response rate was reduced to about 15 percent, so at that

10 time point, 3 patients.

11 DR. ELASHOFF: As a second question, in terms of

12 the issue of how much change you expect at different

13 baselines and thinking tomorrow as to possible other primary

14 efficacy definitions, do you have a plot of four weeks CDAI

15 versus baseline CDAI separately for the placebo and the

16 treated patients?

17 DR. SCHAIBLE: The median CDAI?

18 DR. ELASHOFF: No, individual scatter plots,

19 individual results.

20 DR. SCHAIBLE: We don't have an individual scatter

21 plot, no.

22 DR. ELASHOFF: If that could be produced, that

23 would be helpful for tomorrow's discussion.

24 DR. SCHAIBLE: Okay. We will have that programmed

25 and available for tomorrow.

1 DR. FRANK : Yes, Dr. Steinberg.

2 DR. STEINBERG: I have several questions. Do we
3 know the long-term effect or the consequence of having
4 double-stranded anti-DNA, which appears in something like 10
5 percent of the patients, what one could expect from that as
6 time goes on?

7 DR. SCHAIBLE: I might ask Professor Smolen to
8 respond, who is one of our consultants here today.
9 Professor Smolen, as some of you may know, is a
10 rheumatologist and an expert in autoimmune disorders, as
11 well as autoantibody measurements and their interpretation.

12 DR. SMOLEN: So, the question is, if I understand
13 correctly, what the frequency of about 9 percent of anti-
14 double-stranded DNA in Crohn's disease patients may mean in
15 the long term?

16 DR. STEINBERG: Yes .

17 DR. SMOLEN: In principle, we have to view this
18 from several aspects. One aspect is that these antibodies
19 were at very low concentration, and they did not persist, so
20 the assumption is that they were primarily of the IgM type
21 and of low affinity, and to my recollection, at least in my
22 lab, all those ANA-positive patients in sera did not have
23 anti-double-stranded DNA positivity on Crithidia lucilia,
24 which would pick up high avidity antibodies in particular
25 and directed only to double-stranded DNA.

1 so, that is one of the aspects. Low concentration
2 and transient, did not persist over time, which does not
3 appear that these are primarily pathogenic.
4 Speaking of pathogenicity, we have two types of
5 lupus, again principally. One is drug-induced lupus, the
6 other type is conventional, classical idiopathic systemic
7 lupus erythematosus. The Crohn's disease patients that were
8 shown as having lupus-like syndrome would not qualify
9 according to the American College of Rheumatology criteria
10 to be a systemic lupus erythematosus. Also, this patient by
11 Crithidia lucilia did not have antibodies to the double-
12 stranded DNA by Grithidia lucilia, and again, this patient
13 had relatively low titer. I think the highest titer was 46,
14 and we, in caring for a number of lupus patients, would
15 regard a significant titer from 50. So, that is the
16 aspects. Does that answer your question?
17 DR. STEINBERG: So, you do not expect any of these
18 patients to develop lupus as time goes on?
19 DR. SMOLEN: Well, obviously, we cannot predict
20 this, but it is not very likely, but I should say that other
21 drugs used for the treatment of Crohn's disease and
22 ulcerative colitis, such as sulfasalazine, can induce
23 nanifest systemic lupus erythematosus, and there was a
24 recent survey from Sweden, for example, where 11 patients
25 with systemic lupus erythematosus and high titer anti-

1 double-stranded DNA antibodies were shown, and three of them
2 had inflammatory bowel disease.
3 Now, none of the patients treated with infliximab
4 up to now, and particularly not the patient with Crohn's
5 disease, had any evidence of major organ involvement, no CNS
6 involvement, no involvement of the kidney, not even
7 leukocytopenia, not even thrombocytopenia, which most of the
8 patients on sulfasalazine in lupus had.
9 So there may definitely some possibility for
10 patients with several types of chronic immune disorders to
11 develop other immune disorders with therapy, but I think
12 that we can say that for the time being, there is evidence
13 that the patients seen with lupus-like syndrome qualify more
14 for drug-induced lupus syndrome rather than for systemic
15 lupus erythematosus.
16 DR. SCHAIBLE: I would add to Professor Smolen's
17 comments that I mentioned this in my presentation -- it
18 wasn't on the slide -- but in our three-year follow-up
19 program, we specifically asked questions whether autoimmune
20 disorders have developed in patients, and in that three-year
21 follow-up program, we have not had a single report of
22 autoimmune disorder other than the patient's underlying
23 disease.
24 DR. LAINE: Did they still have autoantibodies?
25 DR. SCHAIBLE: They were not measured at that

1 time. They were measured typically through 12 to 26 weeks
2 after their last infusion.
3 DR. SMOLEN: Most of the patients, at least Up to
4 12 weeks after the end, had dropped their autoantibodies
5 either into negative or into much lower frequencies, which
6 were very low, such as 8 or 12 or 10 units.
7 DR. SIMON: Could I just make an extension of that
8 question, because could you comment on those patients that
9 were retreated, were any of those patients who had developed
10 positive serologies being antinuclear antibody or anti-
11 double-stranded antibodies, were any of those retreated, and
12 what happened to those titers?
13 DR. SCHAIBLE: We have not done that analysis, but
14 certainly patients -- given that we have 9 percent of the
15 patients, those patients would have to be retreated, but in
16 looking at those results, nothing has come out that was
17 apparent to us in terms of exacerbating the anti-double-
18 stranded DNA.
19 DR. SIMON: So, just as an extension for that,
20 therefore, we really don't know, because it has not been
21 looked at, given this is not a curative agent, it would
22 likely imply that some of the patients would traditionally
23 be repeatedly receiving therapy over time. We don't know
24 the implications of recurrent therapy associated with
25 conversion, just positive serology.

1 DR. SCHAIBLE: Right. But even with patients who
2 have been repeated multiply, as Professor Smolen indicated,
3 double-stranded DNA antibodies are still at low
4 concentrations.
5 DR. SIMON: But we don't know.
6 DR. STEINBERG: Since your indications do not say
7 this, where do you see this new drug fitting into the
8 armamentarium that we now use? Is this a drug that -- shall
9 we wait on this until later?
10 DR. FRANK: Let's wait on that one until later.
11 Dr. Surawicz.
12 DR. SURAWICZ: I would like to say that I thought
13 the presentations this morning were extraordinarily clear,
14 as was all of the briefing material. I have a few questions
15 about the infusion reaction and what you postulate the
16 pathogenesis might be and whether -- 1 don't remember from
17 the slide -- whether it would be more likely to occur in
18 older rather than younger, and the possible mechanism of the
19 cardiovascular symptoms?
20 DR. SCHAIBLE: We had three infusion reactions,
21 and two consisted of hypertension with some chest tightness,
22 and then in the other, 'with" no hypertension but some chest
23 tightness. In each of these reactions, with discontinuation
24 of the infusion, they resolved fairly quickly. So, to the
25 extent that that speaks to a possible mechanism of action,

1 they were very dependent on the infusion rate.

2 We have seen many other infusion reactions be very

3 responsive to even slowing down of the infusion.

4 DR. SURAWICZ : Were they all in older people who

5 might have underlying cardiovascular disease, or did they

6 occur in younger people, as well?

7 DR. SCHAIBLE: I don't have those data available

8 to me right now. We could look those up and get back to

9 you .

10 DR. WEISMAN: I am Harlan Weisman. I am also a

11 member of the Clinical Research Group at Centocor. In terms

12 of the infusion reactions, to answer your question a little

13 more directly, there was not any age-related factor to make

14 it more predictable or not, however, it was not surprising

15 to us early on. In fact, infusion reactions following the

16 infusion of large protein, such as monoclinal antibodies,

17 are fairly typical and have been responsive to

18 interventions, such as changing the infusion rates, and so

19 forth, as well as formulation changes.

20 That is something that we were extremely

21 interested in. It turns out that most of the infusion

22 reactions seen, that were reported by Dr. Schaible, occurred

23 early on in the development of the product.

24 We have subsequently changed the formulation of

25 the product to a lyophilized formulation for a number of

1 factors, one of which was to get a better formulation, a
2 more stable formulation of the protein product that might
3 have the potential of avoiding infusion reactions, and in
4 fact that is the case.
5 In the T20 study which employed the lyophilized
6 formulation, there is actually a dramatic lowering of
7 infusion reactions and in fact there is very little
8 difference. I think it is an actually identical rate of
9 infusion reactions between the placebo group and the
10 treatment group, and there are no serious infusion
11 reactions .
12 In the ongoing trial we are blinded, but we do
13 have serious adverse event reporting made to us, and there
14 have been no reports of serious infusion reaction in those
15 trials .
16 To some extent it appeared to be large protein
17 related phenomenon that is common reported, for example,
18 with products such as IVIG, and was highly responsive to a
19 change in the formulation of the product, which was very
20 gratifying.
21 DR. FRANK : Any other questions? Yes .
22 DR. STEINBERG: Are there any other observations
23 on other extraintestinal manifestations of Crohn's besides
24 fistulas that have come out of these studies?
25 DR. SCHAIBLE: We have seen about 20 percent

1 reductions in the number of patients reporting arthritis or
2 arthralgia, similar sorts of reductions with uveitis
3 compared to no changes seen in placebo patients. So, it
4 appears to be about 20 or 30 percent reductions with
5 treatment and no reduction in placebo
6 DR. SURAWICZ: Any patients with pyoderma?
7 DR. SCHAIBLE: We had a few patients with -- I
8 think one or two patients with pyoderma in which that
9 resolved with treatment, but not large numbers of patients.
10 DR. SIMON: Could you tell me a little bit more
11 about the clinical pharmacology part of the presentation?
12 You demonstrated that there was a dose response to a fall in
13 TNF alpha levels that were measurable. After therapy, were
14 any patients studied to determine if there was a rebound
15 event with much higher levels of TNF alpha after therapy was
16 accomplished, and was that correlated at all with
17 nonresponders or responders?
18 DR. SCHAIBLE: No, we did not measure any TNF
19 alpha levels in our patients, and as Professor"van Deventer
20 has indicated, serum concentrations of TNF alpha are not
21 associated with disease activity.
22 DR. SIMON: Okay. That is number one. Number
23 two, I was struck by -- and, you know, I am a country
24 rheumatologist, so I don't use the CDAI as evidence of
25 active disease or not -- and I was 'struck by a plateau event

1 where your numbers go below 150 and don't go below 100. Do
2 we not see numbers that go down to zero in patients who
3 respond to therapeutic success?
4 DR. SCHAIBLE: You will see patients, in fact, the
5 case that Dr. Present showed, that it went down into the 80
6 or 90 range. We have seen a few patients who actually had a
7 negative CDAI result, because they have gained body weight
8 and all their other symptoms have disappeared. So, it can
9 go below.
10 DR. SIMON: But that was not common in this
11 particular therapeutic intervention.
12 DR. SCHAIBLE: No, but again I think the question
13 is what is the relevance of disease activity below 150. In
14 the validation of the original CDAI, 150 was set because it
15 was associated with a physician's evaluation of significant
16 disease activity.
17 DR. SIMON: So, I can understand this a little bit
18 more. so, therefore, when it is below 150, there really
19 isn't a lot of clinical indication of active disease or
20 relevance to what the patient may complain about how active
21 the disease is when it is measured below 150?
22 DR. SCHAIBLE: I might ask Dr. Feagan to comment
23 on that because he has done a lot of work looking at CDAI
24 relative to other measurements of disease activity, such as
25 the IBDQ. I think he can answer that better.

1 DR. FEAGAN: Well, traditionally, the CDAI,
2 although it's a continuous variable, has been dichotomized
3 into remission or non-remission at the 150 cut point. So,
4 the question you have raised, what is the relevance of
5 scores below 150 is an interesting one in which there are
6 not a lot of data.
7 We do have cross-sectional data, though, in which
8 comparative correlations have been made between patient
9 global ratings and IVDQ scores, which is a well-validated
10 response, a reliable measure of quality of life, and in that
11 case, we do see that the correlation extends below 150.
12 So, my sense of things is that there is continuing
13 value to decreasing the CDAI score to some degree below 150.
14 Where that benefit stops is I think unknown.
15 DR. SIMON: So, there is value to going below 150,
16 and we have measured the fact there seems to be plateau
17 event . If one then carried out much longer trials with much
18 larger numbers of patients, would we be seeing some other
19 issues come out that are just not being evidenced because of
20 the small numbers that we are dealing with over time? Is
21 that possible?
22 DR. FEAGAN: I am not I fully understand your
23 question. I think what you are saying is that if you are
24 losing information potentially by dichotomizing the outcome,
25 I think that is probably true.

1 DR. SIMON: Okay.

2 DR. FRANK: Yes. Dr. Miller.

3 DR. MILLER: I would like to comment on what Dr.
4 Simon said about the TNF levels. It would have been nice to
5 use TNF levels potentially in the stool or actually when you
6 biopsied, when you did endoscopies to look at whether you
7 see an effect. Scientifically, that might help, and that
8 wasn't done.

9 DR. SCHAIBLE: Actually, Professor Rutgeerts is
10 here today. He has done immunohistology in mucosal biopsy
11 samples, staining for the presence of TNF. Perhaps he may
12 wish to comment on those studies.

13 DR. RUTGEERTS: In the subset of patients studied
14 at OUr University, our pathologist, professor Geboes, did
15 immunohistochemical stainings for a number of inflammatory
16 mediators, also including TNF alpha, ICAM-1, and others, and
17 indeed after four weeks there is a dramatic drop in the
18 presence of TNF alpha in the tissue.

19 This parallels endoscopic healing and improvement
20 also of infiltration with mononuclear cells in the tissue.

21 DR. MILLER: Thank you. The second thing, TNF
22 does have effects on Epstein-Barr virus, not real strong
23 effects, but it does have effects on Epstein-Barr virus
24 application. Are there any experimental models that have
25 looked at the blockade of TNF and growth of

1 Lymphoproliferative diseases?

2 DR. SCHAIBLE: I think I will ask Dr. Roger Cohen

3 to handle that one.

4 DR. COHEN: There are many reports in the

5 literature and unfortunately, many of them are

6 contradictory, but some of the more recent data, including

7 data published two weeks ago in Blood, would suggest that

8 TNF promotes the growth, for example, of hairy cell leukemia

9 cells, TNF promotes the growth of CLL cells in culture, and

10 in fact in lymphoma patients, at least in France, in Bertran

11 Coffier's group, TNF alpha by itself is an independent first

12 prognostic feature inpatients with high-grade lymphoma, and

13 this is in addition to the standard international risk

14 indices.

15 so, there are considerable data indicating that

16 TNF may in fact promote tumor growth rather than being

17 involved in the more traditional surveillance or prevention

18 of tumor growth. I hope that answers some of your question.

19 DR. MILLER: Actually, the blockade," when you are

20 talking about a secondary lymphoproliferative syndrome, like

21 if you inhibit T cells in experimental animals, you can

22 increase Epstein-Barr'related lymphoproliferative diseases.

23 Is there any evidence that if you blockade TNF, you can do

24 the same in an Epstein-Barr mediated model of

25 lymphoproliferative disease?

1 DR. COHEN: None that I am immediately aware of.

2 DR. MILLER: One last question about infectious

3 complications. All the adverse events, there were no p-

4 values given in any of the slides. What was statistically

5 significant and what was not?

6 DR. SCHAIBLE: We did not perform statistical

7 analyses on the safety adverse events.

8 DR. MILLER: I didn't see that in the FDA packet

9 either.

10 DR. WEISS: We did specifically perform tests for

11 significance of the differences. We just looked at the

12 comparisons of the differences.

13 DR. MILLER: One further question. Did you look

14 at the incidence of anemia or improvements in anemia in

15 patients treated with the antibody versus not? A lot of the

16 anemia associated with Crohn's disease is one of the things

17 that has been postulated to influence both on inhibition of

18 erythropoietin production, as well as inhibition of

19 erythropoiesis if TNF, so I was wondering as a" surrogate

20 marker, whether you have had any improvements in anemia with

21 blockade of TNF.

22 DR. SCHAIBLE: Well, hematocrit is actually one of

23 the components of the CDAI, and as Dr. Present has shown

24 you, there are patients who will show definite increases in

25 their hematocrit. When we look at this on a population

1 basis, there was not a clear trend in the entire population
2 for an increase in hematocrit, but you do see that. You
3 certainly see that in individual patients.
4 DR. MILLER: Thank you.
5 DR. FRANK: Dr. Simon.
6 DR. SIMON: Could you just further expand the
7 issue about the infection rates, and there were four cases
8 of pneumonia. Did those patients have defined bacterial
9 pneumonia, viral pneumonia, or what do we know about those
10 patients?
11 DR. SCHAIBLE: I would ask our chief medical
12 officer at Centocor, Dr. Richard McCloskey, who is an
13 infectious disease specialist, and who has reviewed each of
14 these cases in detail, to answer that question.
15 DR. McCLOSKEY: The brief answer is no, these
16 patients were not bacteriologically documented.
17 DR. SIMON: Thank you.
18 DR. FRANK : Dr. Tremaine.
19 DR. TREMAINE: I am curious about the patients who
20 had failed aminosalicylates only in the T16 trial. You
21 showed us the data, the subanalysis for patients who had
22 been on immunosalicylates. What about those who had been
23 only on immunosalicylates, if you take those out of the
24 analysis, is there still a significant difference in the T16
25 trial?

1 DR. SCHAIBLE: We have not done that analysis, but
2 as we indicated in the medication slide, only 15 percent of
3 the patients were on aminosalicylates alone, so to the
4 extent that there may have been any differential response
5 there, I would predict it would not contribute much to the
6 overall treatment benefit observed because of the small
7 number of patients who were actually on immunosalicylates
8 alone. But the answer to your question is we have not done
9 that analysis.
10 DR. FRANK: Mr. Getz.
11 MR. GETZ: All the trials were done on people that
12 were already taking a significant amount of other drugs. Do
13 you have any feeling whether this infliximab would be able
14 to replace some of these drugs, or do you think it would be
15 taken in conjunction with the existing drugs?
16 DR. SCHAIBLE: Perhaps I would ask one of our IVD
17 specialists. I would like to ask Dr. Stephan Targan from
18 Cedar Sinai to answer that question. We have little
19 experience with that in our clinical trials, and in terms of
20 our longer term clinical development plan, that is one of
21 the things that we will be addressing in particular, whether
22 patients can go off steroids who are on steroids if they are
23 on infliximab treatment.
24 DR. TARGAN: I think that is a good question. I
25 think the direct answer is we don't have any data. If there

1 to come out whether this would be used initially, it would
2 certainly be on those patients that were in these trials,
3 which were very severe, somewhat resistant to other
4 medications . In the long term, we may develop information
5 that other kinds of patients may benefit and be treated just
6 as well.
7 DR. FRANK: Are there any other questions from the
8 panel? Yes .
9 DR. BERARDI: I have two questions that involve
10 the safety issues. With regard to using this drug and the
11 fact that you are doing additional long-term follow-up study
12 to collect safety data, I was wondering if you have any
13 information or plan to gather any data on potential drug
14 interactions with this particular agent, and in addition to
15 that, the second part of it is are there any patients with
16 any disease states that would require a dosage adjustment
17 either upward or downward?
18 DR. SCHAIBLE: Currently, in our long-term follow-
19 up, we are specifically collecting data on maj"or safety
20 events, such as malignancy," death. As those occur and are
21 reported to us, we then go back and collect additional
22 information on those patients, so that developing database
23 will enable us over time to determine whether there are any
24 drug-drug interactions for some of these significant events
25 that occur.

1 In terms of subgroups of patients where the dose
2 nay be adjusted, we have evaluated our clinical pharmacology
3 data or pharmacokinetic data by a number of factors
4 including concurrent medications, and have not shown
5 differences in pharmacokinetic parameters by other drugs
6 being received.
7 DR. BERARDI: Thank you.
8 DR. FRANK: Any other questions? I have a couple
9 questions. I understand that you did not measure TNF alpha
10 in the stool in any of the studies, is that correct?
11 DR. SCHAIBLE: That is correct.
12 DR. FRANK: In your chimp studies, how long were
13 the chimpanzees studied after their infusions, and were they
14 looked at for any of the potential adverse effects?
15 DR. SCHAIBLE: Those animals were followed for six
16 weeks following their treatment with infliximab.
17 DR. FRANK: Can we look at them longer term? They
18 nust, hopefully, still be around.
19 DR. SCHAIBLE: I am sure they still are around,
20 but we don't have data on them beyond six weeks. Doing
21 studies in chimpanzees is not -- it is must easier to do
22 studies in humans than it is in chimpanzees, unfortunately.
23 DR. FRANK: The fistulas, you specified that they
24 had to be closed at each of two visits. Did that assume
25 that they were closed for the entire month between those

1 visits?

2 DR. SCHAIBLE: The assumption was made that the

3 fistula was closed during the interval between the two

4 visits.

5 DR. FRANK: The cancers that occurred more than

6 three years after the infusions, were any of those in

7 Crohn's patients and what type of cancer were they?

8 DR. SCHAIBLE: Dr. Cohen will answer that.

9 DR. COHEN: They were in rheumatoid arthritis

10 patients. One was gastric, one was colon.

11 DR. FRANK: There were only two?

12 DR. COHEN: Yes, that occurred at that 41- and 44-

13 month follow-up dates, more than three years.

14 DR. FRANK: You said that the patients in the T16

15 study were stratified by corticosteroid use. I wasn't quite

16 sure how that happened. How did you do that?

17 DR. SCHAIBLE: That uses a method called an

18 adaptive stratified design which assigns patients randomly

19 to treatment groups, assuring that equal proportions of

20 patients in each treatment group are either not receiving

21 steroids or receiving steroids, so it is a mechanism to

22 balance the treatment groups for whether steroids were being

23 received or not received.

24 DR. FRANK: Finally, you only looked at the

25 endoscopic appearance and biopsies in the European studies.

1 How come? How come you didn't look at it in the whole
2 series?
3 DR. SCHAIBLE: Because it was much easier to get
4 those procedures done in Europe. There are issues related
5 to cost and acceptability by the patients, but that was the
6 reason. These are cheaper, practical reasons.
7 DR. FRANK: If there are no further questions, we
8 will break for lunch and be back at 1:45 exactly, please.
9 [Whereupon, at 12:45 p.m., the proceedings were
10 recessed, to be resumed at 1:45 p.m.]

1 AFTERNOON PROCEEDINGS

2 [1:45 p.m.]

3 DR. FRANK: Let's get started. I would like to

4 call the meeting to order again for the afternoon session.

5 I will call on the first member of the FDA to

6 speak, Kurt Brorson from the Division of Monoclinal

7 Antibodies .

8 FDA Presentation

9 DR. BRORSON: Good afternoon. My name is Kurt

10 Brorson and I am the Chair of the infliximab BLA Committee.

11 I will be giving a brief introduction for the FDA

12 perspective on infliximab.

13 [Slide.]

14 The infliximab BLA has been reviewed thoroughly by

15 a panel of experts within the agency that represent a wide

16 range of expertise.

17 [Slide.]

18 Infliximab, as you have already heard this

19 morning, is a chimeric IgG1:kappa anti-TNF monoclonal

20 antibody. It has a Ka of 10^{10} molar and is produced in

21 mammalian cell culture by a cell substrate transected with

22 an expression construct containing murine variable and human

23 constant region genes.

24 [Slide.]

25 A brief note about the manufacturing. Infliximab

1 is produced using standard biotechnology manufacturing at,
2 Centocor BV in Leiden, The Netherlands.
3 The cell bank safety characterization has been
4 completed. It is produced by perfusion fermentation and
5 purified by several chromatography steps. There are
6 specific virus inactivation of safety steps in the
7 manufacturing process.
8 Infliximab will be marketed as a sterile
9 lyophilized dosage form containing 100 mg of the antibody
10 per vial.
11 I should note that there are some outstanding
12 manufacturing issues, however, CBER is working with the firm
13 to resolve them.
14 With that, I would like to introduce Barbara
15 Matthews who was the clinical reviewer for the infliximab
16 BLA .
17 [Slide.]
18 DR. MATTHEWS: I now have the pleasure of
19 presenting the clinical review of Centocor's license
20 application for chimeric (human) monoclinal antibody, or cA2
21 -- which is how I will refer to it for my presentation -- to
22 tumor necrosis factor for the therapeutic agent for Crohn's
23 disease.
24 [Slide.]
25 To give you a brief run-through of my

1 presentation, I will first provide you a brief background.
2 summary for cA2, followed by a summary of the efficacy
3 review which will focus primarily on the clinical trials T16
4 and T20, and followed by a summary of safety review.
5 [Slide.]
6 CA2 has been evaluated in the clinic for four
7 indications: sepsis, ulcerative colitis, rheumatoid
8 arthritis, and, of course, Crohn's disease. The sponsor has
9 conducted two, Phase II trials in the area of sepsis and
10 evaluated 113 patients. No therapeutic efficacy was noted
11 and there is no ongoing development for this indication.
12 In addition, a Phase II trial was conducted in 11
13 patients with ulcerative colitis, and again no efficacy was
14 detected, and there is no ongoing development for this
15 indication.
16 In the area of rheumatoid arthritis, however,
17 there is active, ongoing development for this indication.
18 The sponsor has conducted one, Phase I trial, and three,
19 Phase II trials between the years of 1992 and 1996, and as
20 they have mentioned this morning, there is an ongoing Phase
21 III trial.
22 Then, of course, there is Crohn's disease, which
23 is the reason why we are here today.
24 [Slide.]
25 On May 15th, the sponsor notified us that they are

1 changing their prior indication which was provided to you. in
2 your briefing document, from two indications, one for the
3 treatment of active Crohn's disease with chronic retreatment
4 and for healing of enterocutaneous fistula to infliximab is
5 for the treatment of patients with active Crohn's disease
6 for the reduction of signs and symptoms including closure of
7 draining enterocutaneous fistula.
8 [Slide.]
9 The recommended dose for retreatment for reduction
10 in signs and symptoms was withdrawn, and the modified dose
11 recommendation is the recommended dose for reducing signs
12 and symptoms in patients without fistula is 5 mg/kg. The
13 recommended dose for patients with enterocutaneous fistula
14 is also 5 mg/kg followed with addition 5 mg/kg doses to be
15 administered at weeks 2 and 6 following the first infusion.
16 [Slide.]
17 There have been four clinical trials conducted
18 that evaluated the treatment of cA2 for Crohn's disease.
19 There were two, open-label trials, T08 and T11, that were
20 conducted between 1993 to the end of 1994. T16, which is
21 one of the focuses of our discussions, was conducted at 13
22 sites in the United States and 5 sites in Europe between
23 June 1995 and March of 1996. T20 is another placebo-
24 controlled trial used to support the application, and this
25 was conducted at 7 sites in the United States, 5 sites in

1 Europe, and it was conducted between May and October of
2 1996.
3 In total, there have been 199 patients with
4 Crohn's disease who have been treated with cA2 among these
5 four trials.
6 [Slide.]
7 The open-label trial T08 evaluated two doses in 10
8 patients, and it was conducted at a single center. Nine out
9 of these 10 patients were evaluated for an endoscopic
10 endpoint. These patients had baseline endoscopy followed by
11 an endoscopy at week 4 and week 8. In 9 out of the 10
12 patients that were evaluated, all of them showed some
13 response at week 4, and a majority continued to show
14 response at week 8, although the response was diminishing.
15 T11 was a dose-ranging study in 21 patients
16 evaluating 1, 5, 10, and 20 mg/kg cA2. In addition to the
17 pharmacokinetic analysis that was presented this morning,
18 the other endpoint that was evaluated was a drop in the CDAI
19 score of greater than or equal to the 70 point's from
20 baseline.
21 There was no dose effect seen, but because of an
22 effect that was seen on the CDAI score, the sponsor went on
23 to design T16.
24 [Slide.]
25 This is a placebo-controlled trial evaluating

1 anti-TNF antibody, or cA2, in the treatment of patients with
2 active Crohn's disease.
3 [Slide.]
4 The major eligibility for this trial were the
5 patients had to have moderate to severe Crohn's disease as
6 defined by a CDAI score between 220 and 400. In addition,
7 they had to have disease that was showing no improvement on
8 their medications for Crohn's, and they also had to be on
9 stable doses of therapy for Crohn's and on no current
10 methotrexate or cyclosporine for three months prior to
11 enrollment.
12 [Slide.]
13 Now, T16 is elegant, but it is also slightly
14 complicated, and I think it is worthwhile going through this
15 a little bit. Patients were randomized at week zero to
16 receive one of four doses of blinded drug, either placebo or
17 5, 10, 20 mg/kg of cA2.
18 They were then evaluated for the primary endpoint
19 for a response at week 4, and this was defined as a greater
20 than or equal to decrease from baseline of 70 points without
21 a change in medications for Crohn's disease, nor for the
22 need for surgery related to the Crohn's disease.
23 Now, patients who responded at week 4 continued on
24 the top time line, and those who continued to respond were
25 again evaluated at week 8. Again, the response was by

1 definition of a greater than or equal to a decrease in CDAI
2 score of 70 points from baseline.
3 Patients who were in response at week 8 were then
4 eligible to enter a retreatment phase which started at week
5 12, and they were then rerandomized to blinded drug, with
6 cA2 or placebo, to be administered at weeks 12, 20, 28, and
7 36. Of course, patients who did not respond discontinued
8 the clinical trial.
9 Now, to return to the primary endpoint at week 4,
10 patients who did not respond were then offered open-label,
11 10 mg/kg cA2, and their time line was reset to zero. They
12 were then evaluated for a response at their week 8, and
13 again, this is in comparison to their baseline CDAI score
14 back at the original week zero.
15 If they were in response, they were eligible to be
16 rerandomized to either cA2 or placebo in the retreatment
17 phase of the clinical trial. In case you are lost, don't
18 worry. We are going to go through this again as I discuss
19 the various parts of the trial.
20 [Slide.]
21 The treatment groups were relatively small. There
22 were 25 patients randomized to placebo, 27 randomized to 5
23 mg/kg of cA2, and 28 patients randomized each to 10 and 20
24 mg/kg cA2. The treatment groups were balanced according to
25 patient characteristics. I would just like to point out

1 what was pointed out this morning, the patients did have
2 moderate to severe disease as defined by the CDAI score.
3 These patients had high 200 to low 300.
4 [Slide.]
5 The prospectively designed primary endpoint was a
6 decrease of CDAI score from baseline of more than or equal
7 to 70 points, and was analyzed by the chi-square test. As
8 you can see, a greater proportion of patients who were
9 treated with cA2 responded by the study endpoint compare to
10 placebo.
11 [Slide.]
12 Now, a reduction in CDAI score by greater than 100
13 points was not prospectively defined in the clinical trial,
14 but it is a more stringent endpoint and one that is used by
15 other drug developers for medications for the treatment of
16 Crohn's disease. Again, as you can see, patients who were
17 treated with cA2, a higher proportion of these patients
18 responded by this definition greater than 100 points
19 decrease compared to those treated with placebo.
20 [Slide.]
21 As you have been informed this morning, a CDAI
22 score less than 150 is used in clinical trials to assess
23 remission, and again the proportion of patients who achieved
24 remission by the CDAI score is higher when treated with cA2
25 compared to placebo.

1 [Slide.]

2 Now , this slide shows the maintenance of clinical
3 response out to week 12, and just to reiterate, the
4 definition of the primary endpoint was a response greater or
5 equal to a CDAI score less than 70, not 100. This was after
6 a single dose.

7 Now, patients who were in response at week 4 were
8 again evaluated at week 8 and then at week 12, and as you
9 can see, the proportion of patients in response out to week
10 12 is greater than placebo, the white bar, however, there is
11 a gradual decrease in the proportion of patients who
12 continued to respond..

13 [Slide.]

14 Now we are entering into the open-label part of
15 the clinical trial. These are patients who were assessed at
16 week 4 and did not have a response by CDAI score or had to
17 have a change in their medication or need for surgery.
18 These patients were then given open-label cA2.

19 [Slide.]

20 There were 25 patients randomized initially to
21 blinded, placebo therapy, and 19 of these patients failed to
22 respond and were given open-label 10 mg/kg of cA2, and of
23 these 19, 11 responded, for an overall response proportion
24 of 58 percent. This response rate is similar to those
25 patients who received cA2 as their initial blinded therapy.

[Slide.]

Now we are entering into the retreatment phase of T16, and these are patients who were assessed for a response by CDAI score back at week zero for a response at week 8, and you can consider this as an independent trial, which is shown schematically on the next slide.

[Slide.]

In essence, patients were assessed for a response at week 8 either to a single infusion of blinded therapy, placebo or cA2, or to cA2 or placebo plus an open-label dose of cA2, and keep in mind that initial dose of cA2 could be anywhere from 5, 10, or 20 mg.

Now, patients who were in response at week 8 were then eligible to be enrolled in the retreatment phase, which started at their week 12, and patients were randomized either to 10 mg/kg of cA2 or placebo to be administered at weeks 12, 20, 28, and 36.

There were 73 patients enrolled in the retreatment phase of T16; 36 of these patients were randomized to placebo and 37 patients were randomized to cA2. Of the 73 patients, 4 were nonresponders at week 8, and" in addition, there were 3 patients who were in response at week 8, but they were not rerandomized.

Now , as you may note, there is a 4-week interval from the time that patients were assessed for eligibility

1 until the time they entered the retreatment phase and were
2 again treated with cA2.
3 [Slide.]
4 This slide shows the number of patients entering
5 the retreatment phase who were in response by CDAI score
6 only at week 8 and then also at week 12. There were 70
7 patients in response by CDAI score at week 8, and of these,
8 15 patients lost their response by week 12.
9 [Slide.]
10 Data from the retreatment phase of T16 was
11 considered a secondary endpoint, and no clear analysis was
12 prospectively defined since T16 was designed as a Phase II
13 clinical trial. In one of the FDA's analysis of the
14 retreatment phase, we looked at the number of patients in
15 response only by their CDAI score, that is, a greater than
16 or equal to 70 point decrease from their baseline CDAI score
17 between weeks 12 and 44. Thus, the maximum number of weeks
18 that a patient was monitored for this response was 32.
19 As you recall, blinded drug was given at weeks 12,
20 20, 28, and 36. Patients were evaluated at monthly
21 intervals out to week 48, but we stopped the analysis at
22 week 44 since this would have been the time that a fifth
23 dose, if it were in the trial, would have been administered.
24 [Slide.]
25 This slide depicts the clinical course of patients

1 through that 12 to 44-week period of the retreatment phase.
2 Of the 36 patients randomized to placebo, 17 had a CDAI
3 score recorded at each monthly visit. Of the 19 patients
4 for whom there is an incomplete score, that is, the score
5 was not recorded each. four-week period, 16 experienced loss
6 of efficacy, 2 withdrew, 1 because of a voluntary
7 withdrawal, and another due to noncompliance, and for 1
8 patient there is a missing data point.
9 Of the 37 patients randomized to cA2, 18 had a
10 score recorded at each monthly visit. Of the 19 patients
11 without a CDAI score recorded at each clinic visit, 6
12 experienced loss of efficacy, 6 experienced an adverse
13 event, and there are 7 patients for whom there is a missing
14 data point.
15 [slide.]
16 Now, for patients for whom there is a CDAI score
17 recorded at each monthly visit, 11 of the 36 patients
18 randomized to placebo remained in response, and again, this
19 is just by the CDAI score alone, not by a change in
20 medication or need for surgery.
21 Of these 11 patients, 5 were in remission. Of the
22 37 patients randomized to cA2, 14 patients remained in
23 response during the 32-week period by CDAI score, and 6 of
24 these patients were actually in remission.
25 [Slide.]

1 so, in conclusion, the results from T16 indicate
2 that treatment with cA2 reduces the CDAI score at 4 weeks by
3 greater than or equal to 70 points from their entry at
4 baseline. The proportion of patients responding by week 12
5 decreases suggesting the need for additional treatment.
6 Additional data for retreatment was needed, and a
7 Phase III clinical trial has been proposed. This trial I
8 will refer to as T21, and I will mention it briefly at the
9 conclusion of my presentation.
10 [slide.]
11 The second pivotal trial in support of the use of
12 cA2 for the treatment of patients with Crohn's disease is a
13 clinical trial T20, and this is a placebo-controlled trial
14 evaluating cA2 in patients with enterocutaneous fistulae who
15 had this as a complication for their Crohn's disease.
16 [Slide.]
17 The major eligibility criteria for this trial was
18 that patients had to have Crohn's disease of more than 3
19 months duration. In addition, they had to have single or
20 multiple distinct draining fistulae that greater than 3
21 months duration and must be maintained on stable medication
22 for their Crohn's disease.
23 [Slide.]
24 The clinical trial design for T20 is much simpler
25 compared to that of T16. Patients were randomized either to

1 placebo 5 mg or 10 mg/kg of cA2, and it was administered
2 intravenously at weeks zero, 2, and 6.
3 [Slide.]
4 Prior to the commencement of T20, the definition
5 of closure was changed from visual closure to absence of
6 drainage from fistula with gentle compression. So, the
7 endpoint was a greater than or equal to 50 percent reduction
8 in the number of draining fistulas for at least 2
9 consecutive visits. As you heard this morning, these visits
10 had to be one month apart, and drainage was assessed by
11 gentle compression.
12 The fistula to be assessed had to be older than 3
13 months, but a new fistula that occurred during the study
14 could be assessed, and if patients had multiple fistulas,
15 the same fistula were not required to remain closed on
16 consecutive visits.
17 Now, T20 did not specify that radiological tests
18 needed to be done to assess healing of fistula. There was
19 an amendment that encouraged MRIs, and these were done at
20 some of the European sites, however, the results have not
21 been reviewed completely by the sponsor nor by the FDA.
22 [Slide.]
23 The study period for T20 was 18 weeks, and all
24 patients were evaluated at weeks zero, 2, 6, 10, 14, and 18.
25 In addition, as you have heard, patients who were in

1 response by the study definition at week 18 were again
2 evaluated at weeks 22 and 26.
3 [Slide.]
4 The cohorts for T20 were balanced by their
5 clinical characteristics. In contrast to T16, where the
6 median CDAI score was in the high 200s to low 300s, patients
7 enrolled into T20 had an overall lower median CDAI score
8 anywhere from 160 to the low 200s.
9 [Slide.]
10 The cohorts were also balanced by the distribution
11 of patients with 1 or multiple, that is, greater than 1
12 fistula. The major of patients had perianal fistula, but
13 there were approximately an overall 10 percent of the
14 patients had abdominal fistula, and there were no patients
15 who had both perianal and abdominal fistula at study entry.
16 [Slide.]
17 Now, patients who consented had photographs taken
18 at each clinic visit to record their response to treatment,
19 and these photographs. were reviewed by two clinical
20 reviewers at the agency, myself and Dr. Brian Harvey.
21 As you could see and heard from this morning's
22 presentation, some of these patients had fairly dramatic
23 responses to cA2, and this was also apparent on our review
24 of the photographs. However, this does raise some concerns
25 with regard to the potential for unmasking by the clinical

1 investigators.

2 These photographs were used to help corroborate
3 the endpoints. However, use of these photographs were
4 difficult because of the need for gentle compression as
5 defined by the endpoint. In addition, we thought that
6 perivaginal fistulas could be difficult to assess for
7 drainage because of the natural drainage that occurs in this
8 anatomical site.

9 Regardless of these difficulties or questions, we
10 accepted the investigator's assessment for the vast majority
11 of the photographs that we reviewed. However, there were 4
12 patients who we felt needed to be reconsidered after review
13 of the photographs. Three of these patients had no apparent
14 baseline fistula on review of the photographs. Two of these
15 patients had been randomized to the 5 mg/kg cohort, and one
16 patient had been randomized to 10 mg/kg. We deleted these
17 patients from our analyses.

18 In addition, there was one patient how had an
19 extremely large fistula at baseline, and the patient showed
20 a dramatic response to treatment with cA2, but there was no
21 apparent closure on the photographs that were recorded as
22 closed for the two visits in the line listing, and we
23 reclassified this patient as a nonresponder.

24 [Slide.]

25 Because of these changes in the database, there

1 were 31 patients randomized to placebo, 29 patients
2 randomized to the 5 mg/kg group, and 31 patients evaluated
3 in the 10 mg/kg group.
4 The prospectively defined statistical endpoint was
5 an analysis of the overall treatment effect using the chi-
6 square test. The proportion of patients treated with cA2
7 and who had a greater than or equal to 50 percent reduction
8 in the number of their draining fistulas was higher compared
9 to patients treated with placebo.
10 [Slide.]
11 As I pointed out, the distribution among the
12 cohorts for patients who had 1 or multiple fistulae was
13 even, and this slide shows that for patients who had either
14 a single or multiple fistulae, the proportion of patients
15 treated with cA2 and who had a response by study definition
16 was greater compared to placebo, but it is interesting when
17 you look at the data, because for patients with multiple
18 fistulae there appeared to be what I would call an all or
19 none effect. That is, the patients who responded tended to
20 do so by the study definition at greater than or equal to 50
21 percent reduction in the number of their draining fistula.
22 There was only one patient in each cohort who had
23 a partial response, and by that I mean instead of 3 out of
24 6, 2 out of 6 had their fistula closed.
25 [Slide.]

1 In addition, the proportion of patients with
2 multiple fistulae who closed all their fistulae were
3 actually fairly similar between treatment arms. Four out of
4 7 patients in the placebo arm had multiple fistulae who
5 closed all of them compared to 7 out of 10 and 7 out of 15
6 in the two cA2 cohorts.
7 [Slide.]
8 Patients who responded at week 18 were also
9 followed for a clinical evaluation at week 22 and week 26,
10 This graphs shows the durability of response in those
11 patients who responded at week 18.
12 As you can see, the proportion of persons who were
13 in response by study definition at week 18, and treated with
14 cA2, were higher than those patients treated with placebo.
15 However, by week 22, this effect is more of a plateau, and
16 again, this was followed out to week 26.
17 [Slide.]
18 Now, clinical trial T20 wasn't designed to
19 evaluate the effects of cA2 on the healing of fistula, that
20 is, on the internal aspect of the canal, and the plateauing
21 effect that I showed you on the previous slide suggests that
22 there may have been none with the dose regimen that was
23 evaluated.
24 In addition, patients treated with cA2 developed
25 new fistula within the 26-week study period, with 5 or 9 of

1 these patients developing new fistula before week 18.

2 [Slide.]

3 Also of note was the development of abscesses in 7

4 out of 63 of the patients treated with cA2, and it is

5 interesting to note that 6 of these 7 patients were

6 responders by study definition, and 1 patient was a partial

7 responder. Actually, if I recall correctly, he did have 2

8 out of 6 of his fistulae closed.

9 As far as we could tell from the data that was

10 submitted, abscesses occurred in the area of the fistula.

11 [Slide.]

12 In conclusion, the clinical data from T20 indicate

13 that treatment with cA2 reduces the number of draining

14 fistulae by greater than or equal to 50 percent. However,

15 it appears that with discontinuation of treatment with cA2,

16 the response is lost. Again, this suggests that perhaps

17 retreatment may be needed.

18 The data also suggest that complete healing of the

19 fistula may not occur. Patients did develop new fistula and

20 in addition, there were the development of abscesses.

21 [Slide.]

22 We now turn to the safety review. The primary

23 safety concerns with treatment with cA2 are: deaths,

24 malignancies, serious infections, infusion reactions, and

25 the formation of antibodies.

1 The clinical trials T16 and T20 are relatively
2 small, and the proportion of patients who were treated with
3 cA2 are much higher than those patients treated with just
4 placebo. In fact, for T16, of the 108 patients who were
5 enrolled, there is only 3 patients who never received a dose
6 of cA2.
7 Now, in order to address the concerns of deaths,
8 malignancies, and serious infections, the review draws upon
9 the follow-up safety data that the sponsor described this
10 morning. The review of the infusion reactions and the
11 formation of antibodies draws upon the clinical data that
12 was generated during the conduct of all clinical trials
13 evaluating cA2 except those evaluating sepsis, as the
14 sponsor also did, and this was because of the complexity of
15 discerning what is an adverse event due to drug or due to
16 the underlying condition of the patients with severe sepsis.
17 [Slide.]
18 This table gives you some idea of the size of the
19 follow-up safety database. The data has been collected for
20 up to 36 months following conclusion of the study period.
21 During this time, patients have not been treated with cA2.
22 Of the 202 patients who have Crohn's disease and
23 were treated with cA2, 37 percent received a single dose,
24 and the remainder had received multiple doses. Of the 214
25 patients with rheumatoid arthritis who were treated with

1 cA2 , 15 percent had received a single dose, and the
2 remainder had received multiple doses.
3 What I would like to point out is the
4 disproportionate number of patients in both of these
5 protocol types who were treated with cA2 compared to
6 placebo, also the follow-up safety data is quite good.
7 About 90 percent of the patients have had some sort of
8 follow-up data collected.
9 [Slide.]
10 The length of follow up for patients who were
11 enrolled into the Crohn's protocols and the rheumatoid
12 arthritis protocols differ. The patients with rheumatoid
13 arthritis are shown in the blue, and the patients with
14 Crohn's are shown in the red.
15 The majority of the patients enrolled into the
16 rheumatoid arthritis protocols -- and this is independent of
17 the ongoing Phase III trial naturally -- have concluded,
18 well, they have completed 6 months, and the majority are now
19 into the second and third year of follow up.
20 In contrast, the majority of the patients who have
21 been enrolled into the Crohn's protocols are now entering or
22 completing the first year.
23 [Slide.]
24 My review of the deaths also include patients who
25 were reported beyond that 36-month period which the sponsor

1 has also described. There were no deaths that occurred
2 during the study periods for any of the trials. Since the
3 conclusion, there have been 13 deaths, 3 patients with
4 Crohn's disease and 9 patients with rheumatoid arthritis,
5 and in addition, there is 1 patient who received cA2 under a
6 National Institutes of Health protocol, and that patient has
7 also died.
8 I should point out that 2 of these deaths occurred
9 after the 36-month period. I should also point out that
10 although all the deaths have occurred in patients treated
11 with cA2, there is a disproportionate number of patients who
12 were treated with cA2 compared to the 61 patients treated
13 with placebo.
14 [Slide.]
15 To make it simple, the causes of death can be
16 categorized into three: cardiac, malignancy, and pulmonary.
17 There are 5 cardiac-related deaths. One occurred in a
18 patient with Crohn's, and 4 occurred in patients with
19 rheumatoid arthritis. Two out of the 5 of these patients
20 were female.
21 One was a 26-year-old woman with Crohn's disease
22 who experienced a sudden myocardial infarction 44 months
23 after a single dose of 10 mg/kg infusion of cA2. It is
24 interesting to note that she did have a severe infection
25 with CMV associated with bacterial sepsis and vasculitis.

1 The other female was a 43-year-old woman with a
2 history of rheumatoid arthritis who experienced a cardiac
3 arrest 16 months after a dose of 20 mg and 10 mg/kg of cA2.
4 There were five malignancy-related deaths. One
5 occurred in a patient with Crohn's disease, 3 occurred in
6 patients with rheumatoid arthritis, and 1 in a patient with
7 HIV/AIDS. Four of these were lymphoma related and 1 was a
8 gastric adenocarcinoma. Again, some of these are reported
9 after the 36-month follow-up period that the sponsor
10 described this morning.
11 There were 3 pulmonary-related deaths. One
12 occurred in a patient with Crohn's and 2 occurred in
13 patients with rheumatoid arthritis. The cause in one case
14 was not specific, no organism was identified as the cause of
15 the pneumonitis, and 1 patient had pneumocystis carinii, and
16 the other patient had Staph aureus.
17 [Slide.]
18 There were 9 cases of malignancy, again in
19 patients treated with cA2, but again I would like to remind
20 you that there were 462 patients who have been treated with
21 cA2 compared to only 61 treated with placebo.
22 Two of these malignancies occurred in a patient
23 with Crohn's disease, 6 occurred in patients with rheumatoid
24 arthritis, and again, the last outstanding one was the
25 patient with HIV/AIDS.

1 [Slide.]

2 The types of malignancies were the 4 lymphomas and
3 the 1 gastric carcinoma that was already mentioned. In
4 addition, there was 1 patient with colonic carcinoma, 1
5 multiple myeloma, a malignant melanoma, and 1 patient with
6 Crohn's disease who developed thyroid carcinoma, but has a
7 history of Graves disease. Yes, I did forget. There was 1
8 patient who had breast cancer.

9 [Slide.]

10 The third safety concern are the occurrence of
11 serious infections. The serious infections in this analysis
12 include those who were reported as serious by the
13 investigator whether or not antibiotic therapy was recorded.

14 The majority of serious infections occurred during
15 the study period. In fact, there is only one serious
16 infection that was reported after the conclusion of the
17 study period, in the follow-up safety database that I have
18 described.

19 The incidence of serious infection were greater in
20 patients treated with' cA2 compared to placebo. There were
21 15 patients treated with cA2 compared to 2 patients treated
22 with placebo.

23 [Slide.]

24 The two serious, infections in placebo were
25 paravesicular abscess that occurred in a patient with

1 Crohn's disease that was discovered at the time of
2 resection, and the second one was an incidence of olecranon
3 bursitis, but associated with sepsis in a patient with
4 rheumatoid arthritis.
5 [Slide.]
6 Of the serious infections reported in patients
7 treated with cA2, there are 5 suspected cases of pneumonia,
8 2 cases of cellulitis, and 1 case each of an infected
9 central venous catheter infection, symptoms of infection
10 associated with a patient with B-cell lymphoma, but no
11 distinct pathogen was identified, a case of Salmonella
12 specie sepsis, cholecystitis,endophthalmitis,postsurgical
13 sepsis, bronchitis, furunculosis associated with 2
14 abscesses.
15 The 5 cases of pneumonia are of note. In none of
16 the cases was an organism actually identified or reported,
17 and this raises some question whether or not these were true
18 inflammatory reactions to a specific pathogen as opposed to
19 a reaction to treatment with cA2.
20 [Slide.]
21 The review of infusion reactions incorporates the
22 safety data from all the clinical trials except sepsis. The
23 incidence of infusion reactions were higher in patients
24 treated with cA2 compared to placebo. There were 72
25 patients treated with cA2 out of 453, compared to 9 out of

1 139 patients treated with placebo.

2 The majority of infusion reactions were not

3 serious. The common infusion reaction for patients with

4 Crohn's disease are headache, nausea, dizziness, flushing,

5 chest pain, hypertension, abdominal pain.

6 There were 4 serious infusion reactions, which hav

7 already been mentioned, and they all occurred in patients

8 treated with cA2. Three, as the sponsor has discussed,

9 occurred in patients enrolled into the Crohn's protocol

10 T16, , and 1 was a patient treated in the rheumatoid

11 arthritis protocol T9.

12 I should point out that the 3 serious infections

13 reported in T16 were all cardiopulmonary in nature, and the

14 patients ranged between the age of 35 and 48. The 1 patient

15 who had a serious reaction in T9 was, as the sponsor

16 described, a case of continued nonresponsiveness after an

17 infusion which may be attributed to an antihistamine.

18 There were 9 discontinuations due to infusion

19 reactions. Three of them were the serious reactions that

20 occurred in T16, 6 occurred in other protocols.

21 [Slide.]

22 Review of the data suggests that infusion

23 reactions may be more likely with the second infusion. Of

24 all the patients who received cA2, 7 percent had some form

25 of an infusion reaction, and this is in contrast to patients

1 who received a second infusion, which 10 percent of these
2 patients had some sort of infusion reaction.
3 It is interesting to note that all 4 of the
4 serious reactions that were reported occurred with the
5 second infusion.
6 [Slide.]
7 In addition, there may be an association between
8 the occurrence of infusion reactions in patients who had
9 HACA, and HACA is the human antichimeric antibody, and this
10 conformed because cA2 contains the variable region of the
11 mouse antibody and it can act as a neoantigen.
12 Of the 80 patients who had HACA, 29, or 36
13 percent, experienced some sort of an infusion reaction, and
14 this is in comparison to 203 patients without HACA and 22 of
15 these patients experience an infusion reaction.
16 Also of note is that 3 of the 4 serious infusion
17 reactions occurred in patients with HACA.
18 [Slide.]
19 We now turn to the last safety concern, which is
20 the formation of antibodies, and these include human
21 antichimeric antibody and the development of the
22 autoantibodies ANA or antinuclear antibody, an antibody
23 against double-stranded DNA.
24 [Slide.]
25 The presence of cA2 in the serum interferes with

1 the assay for the human antichimeric antibody. Of the 402
2 patients evaluated, 283 could be assayed for HACA, which is
3 70 percent of the patients.
4 There appears to be a lower incidence of HACA
5 formation in patients enrolled into Crohn's protocols
6 compared to patients enrolled into the rheumatoid arthritis
7 protocols. That is, 18 out of 133 of patients in the
8 Crohn's protocol or 13 percent, compared ot 42 percent of
9 those enrolled in the rheumatoid arthritis protocols.
10 [Slide.]
11 In addition -- and I thought this was kind of
12 interesting -- the development of HACA appears to be
13 associated with the use of immunosuppressants at baseline,
14 and this seems to be more apparent in patients with Crohn's
15 disease in contrast to patients with rheumatoid arthritis.
16 Patients with rheumatoid arthritis are shown in the bright
17 blue bar, and the Crohn's enrollees are shown in the red
18 bar, but the numbers are very small.
19 Of the 35 patients who received no
20 immunosuppressants, 8, or 23 percent, developed HACA, and
21 this is in contrast to 10 out of 99, or 10 percent of the
22 patients who received any immunosuppressants.
23 It is also interesting to note that again the
24 numbers are very small that of patients treated with
25 immunosuppressants other than steroids, for example,

1 azathioprine and 6-mercaptopurine, none of the 25 patients
2 developed HACA.
3 [Slide.]
4 Now, although some patients changed their ANA
5 status from baseline at study entry to negative, there was
6 an overall net increase in the development of ANA or ANA
7 seropositivity in patients treated with cA2. There were 85
8 out of 357, or 24 percent, of the patients who were ANA
9 positive at baseline, and there were 36 percent who were
10 positive at the last evaluation.
11 The development of seropositivity to ANA was
12 similar between patients enrolled into the Crohn's and
13 rheumatoid arthritis protocols.
14 [Slide.]
15 No patient randomized to placebo became positive
16 to anti-double-stranded DNA antibody. Thirty-three patients
17 who were treated with cA2 did become positive at some point
18 during therapy, and 13, or approximately 4 percent, were
19 positive at their last visit. Again, the rates of
20 seropositivity for anti-double-stranded DNA were similar for
21 patients enrolled into the Crohn's and rheumatoid arthritis
22 protocols.
23 [Slide.]
24 There does seem to be some association between the
25 use of immunosuppressants and the development of anti-

1 double-stranded DNA. Patients who were on
2 immunosuppressants at baseline tended to develop anti-
3 double-stranded DNA antibody less frequently than those who
4 were not, and the effect appeared to be slightly more
5 prominent in the patients enrolled into the Crohn's trials,
6 where 3.5 percent of the patients who were on any
7 immunosuppressant developed antibody to double-stranded DNA
8 compared to 21 percent who were not on any immunosuppressant
9 agent.
10 [Slide.]
11 In addition, patients who were positive for ANA at
12 baseline tended to have an increased chance of developing
13 antibody against double-stranded DNA, and the rates differ
14 slightly between patients with Crohn's disease and
15 rheumatoid arthritis, where 7 percent of the patients
16 without ANA, compared to 16 percent of the patients with
17 ANA, developed antibody against double-stranded DNA, and so
18 you can almost say it is two times the risk.
19 This is in contrast to the patients with
20 rheumatoid arthritis where 5 percent of the patients without
21 ANA developed antibody against double-stranded DNA compared
22 to approximately 20 percent of the patients who were ANA
23 positive at baseline.
24 [Slide.]
25 As you know, we have already discussed a little

1 bit this morning the presence of antibody against double-,
2 stranded DNA can be a characteristic of systemic lupus
3 erythematosus, and this was reported in two patients, one
4 patient enrolled into the rheumatoid arthritis protocol, an
5 the second, a patient with Crohn's disease.
6 [Slide.]
7 In summary of the safety review, the limited
8 exposure history and the limited number of patients in the
9 safety database, and in addition, the flip-flopping, the
10 variability in the exposure history of some of these
11 patients make it very difficult to adequately assess the
12 safety database.
13 There does appear to be an association between
14 serious infections, infusion reactions and perhaps the
15 development of antibodies. The association between
16 malignancy and treatment with cA2 cannot be ruled out from
17 the data that we have.
18 [Slide.]
19 As I have mentioned and as the sponsor has
20 mentioned briefly this morning, there is under discussion
21 with the agency a Phase III trial whose objective is to
22 generate some efficacy and safety data of the treatment of
23 the patients with chronic to severe Crohn's disease on a
24 chronic basis with cA2.
25 To briefly reiterate the study design, patients

1 will be randomized to placebo or 5 mg/kg of cA2. The dose
2 regimen does differ from that used in T16. Patients will
3 receive blinded therapy at week zero, 2, and 6 in a fashion
4 similar to that used in the enterocutaneous fistula clinical
5 trial T20.
6 Patients will then enter a retreatment phase at
7 week 14. Patients who start the trial on placebo will
8 continue to receive placebo for the 54-week study period,
9 and patients will be receiving study drug during the
10 retreatment period every 8 weeks for the 54-week study
11 period.
12 The patients who were randomized to cA2 will
13 continue on cA2 on an every 8-week dosing schedule again out
14 Eor 54 weeks.
15 [Slide.]
16 Because patients who are randomized to placebo
17 will continue to be on placebo for that approximately year-
18 long study, we are hopeful that data generated from this
19 clinical trial allows some better comparison of the safety
20 data.
21 Lastly, I would like to acknowledge Dr. Terry
22 Neeman for her statistical review and her assistance in
23 generating these slides, and in addition, on behalf of the
24 FDA review committee, I would like to acknowledge the
25 patients and thank you for participating in the clinical

1

2 Thank you.

3 DR. FRANK: Thank you, Dr. Matthews.

4 I will now open the floor to the panel to ask

5 questions to either the sponsor or the FDA.

6 Loren.

7 Questions for the Committee

8 DR. LAINE: I have a million questions, but maybe

9 just a couple of general ones first, one to the sponsor and

10 one to you.

11 The data you presented clearly does seem to

12 indicate it works in the short term. We don't have evidence

13 of long-term retreatment benefit at this time, so I assume

14 if this was approved, it would be approved for acute short-

15 term therapy.

16 So, the first question I guess for the sponsors

17 and your IBD expert you can bring out there, let's just

18 assume for a minute, as we have to in evidence-based

19 medicine a regulatory issue that this works short term at 4,

20 5, 6 months, the patients are back where they started in a

21 sense, because it is only used one time in the short term.

22 Is it worth giving this therapy if you have two

23 months of doing very well, but then that is the end of it?

24 And can you achieve that with other antiinflammatory agents,

25 as well? Let's use steroids as an example. That would be

1 the first question.

2 DR. MATTHEWS: That is one of our questions

3 actually.

4 DR. WEISS: This is a formal question after all

5 the discussion that we are going to pose to the committee,

6 but if people want to respond now, that is okay, too.

7 DR. LAINE: Along the lines, if this was approved

8 for a short term -- and this may be one of your questions,

9 too -- but if this is approved for the short term, the ICH

10 guidelines that you gave to us are talking about long term,

11 six months. Certainly, when a drug is approved, it can be

12 used for long term, but if this was approved for just a

13 short term use, does one have to go by those ICH guidelines,

14 and if they do, then, they haven't met that, if they don't,

15 then they have.

16 DR. SIEGEL: Guidelines are just that, guidelines,

17 so when you say does one have to go by guidelines, well,

18 they are used to provide guidance to sponsors, so that when

19 they develop products, and they are internationally

20 harmonized on a worldwide basis, they don't come into

21 surprises when they are told in one region to do this, and

22 then another region has a different standard.

23 They are intended for chronic therapy, however, I

24 think there are a number of biological which have the

25 potential for longer term immunomodulation after single

1 doses, and we look at those numbers, but we also look at
2 many factors as are recognized in that guideline in terms of
3 deciding what is an adequate safety database, but there is
4 no absolute number that has to be achieved.
5 DR. LAINE: So, you are saying the guideline is
6 really not all that strongly adhered to by the agency in
7 general?
8 DR. SIEGEL: No, I am not saying that, I am not
9 saying that at all.
10 DR. LAINE: Well, we need to one way or the other.
11 DR. SIEGEL: The guideline is not a requirement,
12 it's a guideline to industry to suggest how much safety data
13 we think is sufficient, but obviously, the amount of safety
14 data that are sufficient will depend on many other factors,
15 such as the biology of the drug, what is known about related
16 drugs, what is known about the disease, the amount of
17 benefit, what is the sufficient safety data for a serious
18 illness may be different for a vaccine going into healthy
19 individuals, and so forth.
20 So, they are guidelines, and they are followed,
21 but they are not rules, they are guidelines.
22 DR. LAINE: And the chronicity of the therapy?
23 DR. SIEGEL: Yes.
24 DR. LAINE: Do you want to wait to discuss that
25 other question until later?

1 DR. WEISMAN: Let me reintroduce myself. I am
2 Harlan Weisman, and Martin Page, who was actually serving
3 our moderator role, had to leave suddenly, but for a very
4 good reason. His daughter is graduating from medical school
5 today, so he ran up to the graduation ceremonies. So, I
6 will fill in for Martin for now.
7 Just to answer the question shortly, we agree with
8 the statement that you made, that the indication that we are
9 seeking today is for the treatment of active Crohn's disease
10 for signs and symptoms, and we also agree that there are a
11 number of questions remaining regarding the long-term
12 maintenance therapy potential of this agent.
13 We believe that the results from the T16 trial are
14 certainly promising and suggesting the possibility of a
15 long-term maintenance effect, and we also believe that the
16 results of both T20 and T16 are promising in showing that
17 even a short course of therapy benefits at least some
18 patients over a long period of time.
19 Having said that, though, I think the real
20 question is how are doctors going to use it. I will ask Dr.
21 Steph Targan to address that. This is something that a
22 group of our consultants have discussed, and I think Steph
23 can summarize those.
24 DR. TARGAN: As I think I said this morning, and
25 will reiterate, I think if this were approved, that you have

1 to understand that the majority of this has been in very
2 sick patients who have not responded to any therapies, many
3 of them at wit's end.
4 I think the way it will be used is acutely to get
5 these people into response and some of them into remission.
6 I think we are going to learn some more information from
7 these trials that are ongoing, some of our patients that
8 have been treated before, to see what the retreatment is
9 going to be like and what the needs are going to be, but I
10 think in our experience, there are some patients that
11 respond an enormous longer period of time for us, these
12 patients that haven't responded, some of them up to 9 months
13 up to a year, that have been very sick for years prior to
14 this .
15 so, I think we are going to learn from that, but I
16 think the way we will use it initially will be what we have
17 seen here, which is for very resistant fistulous patients,
18 as well as other patients who have not responded, who are
19 still very sick, from other medications, and then learn how
20 we are going to use it repetitively or in the future.
21 DR. LAINE: I mean obviously, there are a number
22 of questions, I mean can you achieve that with another
23 antiinflammatory, in other words, as well as high-dose
24 steroids really bumping that up, I mean there are a
25 hodgepodge of patients, and the second, do you have

1 information on steroids' sparing effects during the
2 treatment --
3 DR. TARGAN: We looked at the specifics of steroid
4 sparing effects. These were at least 20 mg on many of these
5 trials.
6 DR. LAINE: Did steroids decrease with the amount
7 of steroids used, did the amount of agents decrease that
8 were used during the 8 or 16 or 24 weeks?
9 DR. WEISMAN: One statement I was going to make,
10 there is anecdotal experience, and certainly there is a
11 suggestion that is a possibility, but that is another goal
12 of the next clinical trial. I think there are a number of
13 interesting questions about this drug and how it will fit in
14 eventually into the armamentarium.
15 Right now we have identified a clear-cut use,
16 which is fairly discrete, and there is still a number of
17 open questions including steroid sparing. When we asked our
18 consultants, as well as other gastroenterologists, what do
19 they want in patients, one of the things is to get off
20 steroids. We don't have that data. We don't have that data
21 in any definitive fashion.
22 We have actually had extensive discussions with
23 FDA in terms of trial design, as well as our investigators,
24 to determine how does one actually demonstrate a steroid-
25 sparing effect over time, and what is sufficient

1 information.

2 I think one of the things we are looking forward

3 with, quite frankly, is what this committee indicates to us

4 in the way of guidelines on how to study this prospectively.

5 We are very eager to pursue that question. I think anything

6 we said today should be assumed to be anecdotal evidence,

7 and I wouldn't want to put a lot of weight onto it.

8 DR. FRANK: You have a number of centers actively

9 participating at the moment in the studies you have

10 described. You have also I believe have other centers that

11 are going to be participating?

12 DR. WEISMAN: Yes. Certainly the new trial for

13 maintenance therapy will be a more expansive trial. It will

14 be a larger trial. Right now we are anticipating this to be

15 several hundred more patients over the long term with an

16 endpoint -- again, we are in discussions -- but the way we

17 currently contemplate with the contingency of what we see

18 tomorrow it that probably the endpoint will be about a year

19 in duration, so there will be a greater number" of centers.

20 The other thing I wanted to comment on, though,

21 one trial that none of us have mentioned, that has been

22 finalized with our investigators, is now at the agency under

23 review, is a trial for extended use.

24 We have a number of patients that have already

25 gotten the drug that actually fit the circumstance that you

1 asked about, which is what do you do with a patient that has
2 gotten infliximab 6 months later and had recurrence of their
3 acute or they have reactivity of their disease, what is the
4 story there.
5 We have some information from T16, but we are
6 instituting a trial, is about ready to go. I know the
7 investigators are eager to get that going, to say, okay, we
8 are going to allow retreatment of patients that have already
9 gotten the drug in either the T16 or T20 trial. That we
10 think will also be helpful over the near term in answering
11 some of these questions as we wait for the completion of the
12 larger, one-year trial.
13 DR. LAINE: In terms of other data that you may
14 not have, do you have any information about subgroups or
15 subsets that did respond, for instance, this idea of 25
16 percent of people have the microsatellite TNF haplotype, do
17 those people tend to respond or not respond, are there any
18 other baseline laboratory data or treatment data that help
19 you decide who or who isn't going to respond, and define a
20 subset of people to treat?
21 DR. WEISMAN: In a formal clinical trial sense, we
22 don't know the answer to that question. It is a fascinating
23 question, it is one that we have been eager to explore. It
24 is one that some of our investigators have spent a lot of
25 time exploring. Centocor does not know the answer to that.

1 1 think it is an important question.

2 Again, Steph, you may want to comment about that,

3 because that has been one of your personal interests.

4 DR. TARGAN: Yes, I think in certainly preliminary

5 looks , there may well be some markers or genetic alleles

6 that may relate to response or non-response. They really

7 haven't in a major second look or a formal trial been looked

8 at, so the answer to your question, I think we are in avid

9 investigation of that ongoing to see if, in fact, that will

10 hold up, but it may, in fact, be possible. At this stage,

11 we couldn't say yea or nay one way or the other.

12 DR. WEISMAN: The interesting aspect of just that

13 question, about two-thirds of patients respond to Crohn's

14 disease, about two-thirds of patients respond in rheumatoid

15 arthritis, it is very similar data. Although we would agree

16 that the small ulcerative colitis trial did not show

17 overwhelming evidence of efficacy, about one-third of

18 patients seemed to respond in that trial even given the

19 small numbers.

20 It may be that, you know, we are talking about

21 disease that were described clinically on the words of

22 hospitals, such as Mt. Sinai Hospital, it may be that

23 ultimately, we will find a molecular basis that allows us a

24 clearer definition.

25 DR. FRANK: Dr. Miller.

1 DR. MILLER: Based on what you were just saying.
2 about the fact that this was used in patients who are
3 heavily treated, why was the indication changed to take out
4 the words patients who had failed or who had been treated,
5 because I think what you have shown is that in this group of
6 patients, as you said, the answer about how it can be used
7 in other patients is wide open, but the wording was changed.
8 DR. WEISMAN: The wording was changed at the
9 suggestion of consultants who examined our initial
10 application and also in discussions with the Food and Drug
11 administration, as well as among ourselves, and we felt that
12 active Crohn's disease was something that we could define,
13 and had clearly defined in the protocols, and clearly
14 defined the patients.
15 The issue of refractoriness or what defines
16 treatment resistance, I think is one of the questions posed
17 for tomorrow. It is one that had less certainty about it
18 and one that people felt less comfortable about, and that is
19 why we went with the suggested rewording. It seemed to have
20 a greater comfort and definition around it.
21 DR. MILLER: But based on the wording that is
22 listed now, it is being approved for any stage, I mean any
23 diagnosis of active Crohn's disease whether the patient has
24 been treated with anything else.
25 My question is do you have data that supports

1 being able to go for that indication as compared to the
2 indication that was studied in the trials?
3 DR. WEISMAN: Well, I think the data that is in
4 the trials supports the indication that is being proposed.
5 DR. LAINE: A lot of your enterocutaneous did not
6 have active disease, so in a sense, that labeling isn't
7 exactly correct since your median was 160, so your
8 enterocutaneous fistula patient, on the other hand, often
9 did not meet your criteria of active disease.
10 DR. WEISMAN: I will ask some of our experts to
11 respond to that, but I think it was a different measurement
12 of activity of disease. One measurement of activity of
13 disease was sort of a pancolitis, ileitis measured by a CDAI
14 score, which is very good at doing that.
15 Another measurement of activity of disease are
16 these awful fistulae, which is clearly active disease. You
17 heard that and saw that in the pictures.
18 Maybe Dan or any one of the other people who are
19 experts at this might want to comment on whether fistulous
20 disease is active disease.
21 DR. PRESENT: You heard the Crohn's disease
22 Activity Index indicates how sick you are. You can have a
23 Crohn's Disease Activity Index of 20 just with fistula and
24 be pretty sick.
25 DR. LAINE: Then, you are having two different

1 definitions. It seems for your trials you defined activity
2 as a certain thing. It is really a semantic issue for the
3 labeling.
4 DR. WEISMAN: I think what we said -- the labeling
5 was actually worded to take into account exactly what you
6 are saying. It is patients with active Crohn's disease for
7 the control of symptoms and signs including enterocutaneous
8 fistula.
9 DR. PRESENT: Crohn's disease is probably about
10 six or seven different diseases in how it behaves. Whether
11 it will turn out to be that way genetically, we don't know.
12 For example, some people can be totally disabled, with the
13 extraintestinal manifestations, arthritis or pyoderma, and
14 still not be sick from the bowel point of view, so that is
15 why we said in our slides that there are a different variety
16 of people, and you have to individualize each patient. I
17 think this indication covers most of the people we are going
18 to see, but each one is different.
19 DR. FRANK: Dr. Simon.
20 DR. SIMON: Could the FDA help me understand more
21 about the abscess formation and the implications of such?
22 If the indication is going to be for healing of fistulae,
23 and a subset of those patients will heal superficially their
24 fistulae, who won't heal their infections within the
25 fistulae, it seems that we are really addressing only one

1 aspect of the fistula, and it seems that this has not been
2 significantly addressed by the sponsor, and I was wondering
3 if you could review again one more time the exact
4 implication of the number of patients with this kind of
5 problem, and indeed, should we as a panel consider this as
6 an issue that would preclude approval based on not having
7 enough patients based on the database just being too small
8 to give us a ramification of what it would really mean in
9 the real world?
10 DR. WEISS: Before I have Dr. Matthews just
11 address your specific question, we do have a question for
12 the committee in the FDA questions with respect to
13 terminology because you need to think about the issue of
14 closure, loss of drainage, and healing, and I think they all
15 mean different things, and you asked a specific question
16 about healing, and I think that really goes to the question
17 about the actual data that we have on hand.
18 DR. MATTHEWS: Right, and if you noted, the
19 indication is for the treatment of draining enterocutaneous
20 fistula without saying exactly what is being treated in
21 terms of what the clinical response should be.
22 When I used the word healing in my presentation, I
23 neant that the fistula healed completely, that is, the tract
24 from the gastrointestinal tract to the enterocutaneous exit
25 was healed. I recognize that closure had different

1 meanings.

2 When I was reviewing the clinical data and I asked

3 people what they thought by closure, people thought of

4 fistula being there and then not there, and yet I also

5 recognize that closure could mean absence of drainage, so as

6 Dr. Weiss has mentioned, that still needs to be discussed.

7 The reason why I presented that data was for two

8 reasons. First of all, the safety review is an overall

9 safety database that consists of all patients treated with

10 cA2, and when you look at the overall safety database, the

11 development of abscesses is basically lost because the

12 percentages to down, so I think it is a distinct safety

13 concern for patients who are treated with cA2 and have

14 enterocutaneous fistula.

15 If you ask me what I really think, I have to say

16 that the way I visualize it is that you have stoppage of

17 drainage from an infectious disease perspective, if you have

18 a hole in the gut, and bacteria want to get out, and they

19 can't get out, then, they develop an abscess, and that's the

20 way the body reacts to bacteria when they are in the wrong

21 place. So, I think it is something that should be noted. I

22 don't know exactly what significance to make of it.

23 DR. SIMON: I was wondering if we could just

24 expand that for one more second, because there are lumpers

25 and splitters, and I am having a hard time with this lumping

1 and splitting business.

2 ICH guidelines don't make it clear to me -- maybe

3 they are clear to you -- as to what the patient is that is

4 being assessed. We have two different diseases being

5 lumped together here for therapeutic intervention, which may

6 or may not have different safety implications based on the

7 underlying disease.

8 It is pretty simple because the fistulae don't

9 happen in RA, and they do happen in Crohn's, and we have

10 just seen them disappearing in the whole data set based on

11 the percentages. Yet, if we just take patients with Crohn's

12 disease, and we would require 600 patients or 300 patients

13 just with Crohn's disease for ICH guidelines, then, that

14 data might become much clearer.

15 It seems to me that although we had this

16 discussion before that guidelines aren't rules, on the other

17 hand, if we don't really apply the rule, we are not going to

18 get the data to understand the implications of the safety

19 issue, because if we mix too many different kinds of

20 diseases, we won't get a clear understanding of this drug's

21 effect in this particular disease as related to safety. Is

22 that not right?

23 DR. MATTHEWS: That is partly right. I think your

24 issue of saying lumpers and' splitters, though, that is one

25 of the questions that we have for the committee, that is,

1 how close are these patient populations in terms of the
2 treatment effect that you see in T16 will substantiate the
3 response that is seen in T20, are they just continuations of
4 a similar disease process, you know, that is the nature of
5 that question.
6 DR. WEISMAN: I would like to respond or have
7 Centocor respond to a couple of the points that you raise.
8 The first one is the abscess one, and I will come
9 back to that, and Dr.. Schaible will go to that, but let's
10 just talk about lumping and splitting. What we are talking
11 about -- and we have to remember this here -- is that we are
12 not talking about treatment for the common cold, we are
13 talking about an orphan drug application for a serious
14 disease that affects a very small part of the U.S.-based
15 population.
16 Now, let's talk about the safety concerns which I
17 am not going to minimize. We agree with every comment made
18 by the FDA, and I think we actually agree on how to analyze
19 it and have presented it concordantly. SO, I don't want to
20 downplay the concerns. But how do you acquire it?
21 We are talking about relatively rare events.
22 Whatever the incidence of lymphoma is in these diseases,
23 whether it's Crohn's or RA, I think the one thing we can say
24 is that whether it's in our database or in another database,
25 it is a relatively rare event.

1 We are dealing with event rates of anywhere from
2 about half a percent to 1.5 percent, to say absolutely worst
3 case, 2 percent, and if we are talking about mortality,
4 abscesses, or lymphoma, we are talking about rare events, so
5 how do you determine that, how do we get satisfaction on a
6 point estimate on those numbers, how many patients do you
7 need? You need a lot, you need thousands to really refine
8 that, to not only know what it is in our database, but to
9 understand that relative to what is available in other
10 databases.
11 To put this into perspective, the two clinical
12 trials you have seen today are the largest randomized
13 clinical trials that have ever been conducted in Crohn's
14 disease. Is that good? No, I am not saying that is good,
15 it's a fact. This is a rare disease that is devastating.
16 So, the dilemma that we all face is how do we
17 acquire the data while making potentially very useful
18 therapy, because the efficacy isn't in question here I don't
19 think yet. How do we make this available while we are
20 acquiring in a very responsible manner from our standpoint
21 as sponsor, to your standpoint as the advisors to the FDA,
22 and people who are going to using that. That is the
23 question before us, but doing more clinical trials, let's
24 say we did another clinical trial of 100 or 200 or 300
25 patients, you would not get the information in a way that

1 would be satisfactory to YOU, because the point estimates
2 are so small, and the confidence intervals are so wide.
3 So, the thing that we really need to discuss is
4 how does one adequately get this type of information and
5 over time refine the information, so that prescribing
6 physicians over time get more confidence on what the risks
7 really are and how do patients make those judgments with
8 their doctor.
9 I wanted to address that first, but the issue of
10 abscess, I don't want to dispute you, Barbara, because you
11 are an infectious disease expert, and you know far more
12 about it than I do, but I do want to go over at least our
13 analysis of that data. Tom has that.
14 DR. SCHAIBLE: We reviewed these cases as well,
15 and there were 7 patients. All of these patients had
16 perianal fistulas, and all of these patients had a history
17 of abscess. What I would like to do is ask Professor
18 Rutgeerts to just make a few comments on the occurrence of
19 abscess and put this into some kind of context' in terms of
20 managing patients with perianal disease.
21 DR. RUTGEERTS: I think that fistula and abscess
22 are really the same manifestation of a complication of
23 Crohn's disease. You can call it perianal disease. So, the
24 abscess that occurs in patients who have closed their
25 fistula and who were treated with cA2, is, in fact, a

1 relapse of perianal disease, and whether the fistula opens
2 again or whether they develop an abscess is the same
3 manifestation of relapse of perianal disease.
4 DR. FRANK: Perhaps you can minimize that
5 occurrence of the abscess. A surgeon, when he gets a
6 fistula, and treat it locally and with antibiotics, actually
7 probes the fistula to keep it open, so that it heals from
8 the inside out and doesn't form an abscess.
9 I was a little concerned that no attempt was made
10 to document complete healing of these fistulae, and I am
11 sure you can do it at a much cheaper rate than getting MRIs
12 in all these people, because we do, and perhaps youcantry
13 to minimize the development of subsequent abscesses at the
14 site of fistulae in some way.
15 DR. RUTGEERTS: I think that, in fact, you are
16 right in the sense of the fistulae always originate
17 internally at anal glands, so when the fistula recurs, you
18 always keep this inflammation going. It is only when you
19 remove, in fact, the initiator of the inflammation that the
20 fistula will be cured permanently.
21 But , in fact, in these patients, if you have a
22 relapse of this fistula, maybe with reinfusion of cA2, you
23 could keep the fistula closed and closed for a longer time.
24 I agree that radiological assessment may be useful, and in a
25 number of patients there were MRIs performed, but it is very

1 difficult to analyze MRIs because if it is difficult also to
2 differentiate between scars of fistula and also active
3 fistulas. This is the situation right now, I think.
4 DR. FRANK : Dr. Miller.
5 DR. MILLER : If people had an abscess, does that
6 by definition mean they cannot be a responder, could they be
7 included in the responder, because the hole closes, and the
8 abscess does not make them not be a responder?
9 DR. WEISS: These patients were considered
10 responders. Abscess was not considered as part of the
11 definition.
12 DR. MILLER: So, somebody who closed the hole and
13 developed an abscess was considered a responder.
14 DR. RUTGEERTS: I think they were considered a
15 complication.
16 DR. MILLER: In this data we say 100 percent
17 response.
18 DR. MATTHEWS: You are right. Six of those 7
19 patients were responders by study definition, and 1 of the
20 patients was a partial responder. They had a few of their
21 multiple fistulas stop draining.
22 DR. RUTGEERTS: But all these abscesses occurred
23 late in the follow up, so they represent relapse of perianal
24 disease.
25 DR. WEISMAN: I think it is important to put it

1 into context. Number one, the patients who were responders
2 responded early. The usual response rate was by the first
3 visit, which was at 2 weeks. The abscesses, when they
4 occurred -- and there were some -- there weren't that many,
5 and they occurred late, and the numbers we are talking about
6 are fairly small, and there isn't a lot of definition about
7 whether there is really a difference between the three
8 groups.
9 DR. SIMON: But it is also important because you
10 are using two different terms. Is it a complication or is
11 it a relapse? That is a very different issue. Is this
12 disease that is breaking through from the monoclinal
13 antibody effect or is this because you have closed the
14 drainage port and you then accumulate pus behind that, and
15 thus, it is a complication of superficially affecting
16 healing without actually addressing the deep issue, and I am
17 still confused about that.
18 DR. WEISMAN: The question is whether it even
19 natters to the patient which one of those it is. The
20 question is how often does it occur and what happens to most
21 of the patients. The reality is that this doesn't happen
22 that often. It happens both in placebo patients and treated
23 patients. It happened in a small number of patients late.
24 It happens at a time when recurrences may be occurring, it
25 happens at a time when new fistula may occur, it happens at

1 a time when new abscesses may be occurring. The causality
2 that is being speculated about is exactly that, it is
3 speculation, and the numbers are fairly small.
4 Again, I don't want to downplay the occurrence
5 rates. I do think it is important emphasize that the net
6 benefit was great. Whether or not this was recurrence of
7 disease or something that may have been a part of the
8 treatment of the disease is something that is relegated I
9 think to speculation at this point.
10 DR. RUTGEERTS: I think that it is relapse because
11 they occur late. If it was only superficial closure of the
12 fistula, this abscess would occur within days after
13 superficial closure, but this does not happen. It does
14 happen after a longer time period.
15 DR. FRANK: Dr. Surawicz, you have questions?
16 DR. SURAWICZ: Yes. Dr. Matthews, your
17 presentation was really clear and I enjoyed it very much.
18 About the issue of malignancies, I guess I would like to
19 know what you think is the bottom line. I understand how
20 complicated it is because it is such a broad group of
21 patients with immunosuppressive therapy and a wide range of
22 age and risk and premalignant conditions.
23 What is your bottom line degree of concern?
24 DR. MATTHEWS: I hate to be this truthful, but to
25 answer you truthfully, I really don't know, and I don't

1 think we will know with the safety database that we have,
2 because these patients, the safety database incorporates the
3 patients with rheumatoid arthritis, and as Dr. Cohen has
4 pointed out, there is an association between a higher
5 incidence of lymphoma in these patients.
6 In addition, the numbers are relatively small.
7 so, I am kind of frustrated by not knowing, but I can't see
8 that there is no association, just like I can't say there is
9 an association, but I think it is something that patients
10 and physicians should be aware of, of our concern regarding
11 this.
12 DR. SURAWICZ: What would be your recommendations
13 for how to best collect data in the future to answer this?
14 DR. MATTHEWS: I compliment the sponsor, Centocor,
15 on doing what they are doing because many sponsors don't do
16 that. They are obtaining the follow-up data on patients who
17 have been enrolled. Again, they have obtained data on 90
18 percent of these patients. So, I think at this point that
19 is the best that we can do.
20 DR. SIEGEL: The issue of getting adequate data on
21 the possibility of changes in the incidence of events
22 occurring as a background in the population, which is true
23 of the issue of abscesses, as well as the issues of
24 malignancies, and particularly on the rare events, is a
25 rather complicated and difficult one, and that really gets

1 to what I was trying to say about the guidelines.

2 The reason that they are guidelines is that, as I

3 pointed out in the guidelines, sometimes the background

4 incidence of a disease will make it more important to get

5 more patients if you need to know an answer, sometimes the

6 small amount of efficacy may make it more important to get

7 more information if we need to know the answer.

8 There are many factors that need to be weighed -

9 is there enough benefit, what is the size of the effect, how

10 possible is it to get the data, how possible is it to get

11 the data postmarketing versus premarketing.

12 That is why I emphasized the fact that these are

13 guidelines.

14 I want to return briefly to the gist of that

15 question. The number most relevant in that document are not

16 the numbers of 6 or 1 year treatment because we are not

17 being proposed to have chronicity of treatment here, but the

18 numbers you look at of around 1,500 of people exposed to a

19 drug all together.

20 Those exposures, when the document was negotiated,

21 I am quite sure were intended to reflect exposures in any of

22 a variety of diseases an a variety of regimens, but, of

23 course, it is hard to make hard and fast rules. Some of the

24 information available in some diseases may be highly

25 relevant, and some may not be.

1 We made a determination, for example, here that
2 most of the data in sepsis was very difficult to look at
3 when you have 30 percent of the patients dying in the
4 placebo arm in a disease and high incidence of kidney
5 failure, liver failure, CNS problems, and so forth. It is
6 very hard to determine against that background anything
7 about drug toxicities.
8 The rheumatoid arthritis data we feel are
9 relevant, but some of the issues regarding lymphoma risk,
10 certainly the issues regarding abscess formation may limit
11 its relevance in some areas.
12 so, I think the bottom line is that -- and the
13 reason I am emphasizing that these are guidelines is that we
14 need to make a clinical judgment, and as you see through our
15 questions, we are asking for your assistance in making that
16 judgment.
17 There is not a black and white answer. There is
18 less known any of us would like to know about whether or not
19 this drug increases the risks of any of a number of things
20 and how much. The data are limited. The disease is an
21 orphan disease in which it is not uncommon to have rather
22 limited data, and it is one in which there is background
23 problems in which it is not uncommon to have limited data.
24 The question boils down to an assessment of the
25 magnitude of the benefit. Those risks can be communicated

1 through labeling and through physicians to patients, and the
2 unknowns can be communicated, but what I was trying to
3 emphasize was we don't have a document here that says there
4 is rule you have to get 500 more patients. We don't know
5 that 500 more patients will answer these questions.
6 I would think regarding that malignancy question,
7 in fact, that it depends on how much of a risk you want to
8 rule out, but if you want to make sure that there is not a 1
9 percent increase in malignancy, we could figure out the
10 number of patients that would need to be studied and how
11 long they need to be followed, but I suspect it is a rather
12 large number, and it is not the sort of thing you will find
13 with uncontrolled trials very easily.
14 You can see what has happened after decades of
15 experience with drugs more commonly in use. There is very
16 limited and somewhat conflicting data. So, that is where we
17 are.
18 DR. FRANK: Dr. Tremaine, did you have any
19 comments?
20 DR. TREMAINE: Yes, with regard to the issue of
21 lymphoma, my colleague, Ed Loftus, had plannedtobehere
22 today, but unfortunately was unable to be here, he was
23 referenced as one of the studies looking at the relative
24 risk of lymphoma. He has looked at our Olmsted County,
25 Minnesota data, which is the only population database in the

1 U.S. to look at true incidence and prevalence rates in a
2 total population.
3 Unfortunately, with 230 some-odd patients in our
4 study, the numbers of, patients were rather small to come to
5 any strong conclusions, but the bottom line was that we
6 didn't find any convincing association between inflammatory
7 bowel disease and a risk of lymphoma, but the power of the
8 study was not great, and I think as has been mentioned
9 before, we can't have any firm conclusion from that.
10 I would like to ask a question also. Dr.
11 Matthews, I also enjoyed your presentation. You mentioned
12 that the response rate was nearly identical in the
13 retreatment of patients who had failed the first time around
14 in the T16 study.
15 I wondered if in your analysis, you found anything
16 common among those patients who seemed to respond the second
17 time around, who had failed to respond the first time.
18 DR. MATTHEWS: Well, we didn't. We looked. I
19 looked at sometimes the dose exposure prior, because if you
20 recall, patients had so many different dosing exposures
21 before, but the numbers got too small, because there were
22 only I believe 14 or 13 patients responding, and the numbers
23 just got too small. That was the frustrating part about the
24 analysis in that retreatment phase.
25 DR. TREMAINE: If I could ask the sponsor also, as

1 a clinician who treats patients with Crohn's disease, and
2 knowing that patients who have failed the first time around
3 may be very well respond with retreatment, in the
4 recommendations for doses for those without fistulas, it is
5 mentioned that a patient be treated with a 5 mg/kg dose, but
6 if a patient fails, then what ? Would retreatment be
7 appropriate at the 2- or 6-week mark as with the fistula
8 patients or should we wait 4 or 8 or 12 weeks, or what would
9 be the guideline there?
10 DR. WEISMAN: That is a great question. The way I
11 would anticipate that being answered is in the clinical
12 pharmacology section of the labeling, would be a description
13 of exactly what you just said. The indication would read
14 exactly as we said. The dosing instructions would be left
15 alone. But we would indicate in the pharmacology section
16 what the clinical trial results were and what the findings
17 were and let clinicians, along with their patients, make
18 judgment realizing that the chance of response is the
19 greatest the first time around.
20 Just to correct one thing that you said. The
21 open-label phase of that trial, the response rate that was
22 identical were among the placebo patients who didn't
23 respond. That was 65 percent or something like that. It
24 was almost identical to the patients that received cA2 the
25 first time.

1 The response rate among the cA2 patients, the
2 infliximab patients, who did not respond the first time was
3 lower, but not zero. It was about 35 percent. So, there is
4 a response rate, but it is lower. In fact, that knowledge,
5 for example, because we felt that fistulizing disease was
6 much more severe than active disease without fistula, was
7 one reason why we went for the 026 there, because we felt
8 that you might need that extra boost of therapy in that
9 situation.
10 DR. FRANK: Dr. Elashoff.
11 DR. ELASHOFF: I believe I heard someone say that
12 there had been a change in the formulation of the dosing
13 between the T16 and the T20 trial. Should we be concerned
14 about whether the results in the T16 trial really apply to
15 the newer formulation?
16 DR. WEISMAN: No, you shouldn't be because -- and
17 I think this was addressed very briefly in the presentation
18 by CBER, the first presentation -- is that all of our
19 product goes through extensive testing to ensure its
20 bioactivity, and the bioactivity release assays ensure the
21 equivalence of the product.
22 So, what we went from was a liquid formulation to
23 a lyophilized formulation, but the final product in the vial
24 in terms of bioactivity is identical by the release assays,
25 and I think that has met the satisfaction of the FDA.

1 DR. FRANK : Yes, Dr. Miller.

2 DR. MILLER: Can I get the FDA's perspective on
3 the question I asked before, about the broadness of the
4 indication based on the data that we have here? They said
5 it was discussed with you, but for the members of the
6 committee and the guests who are going to help advise about
7 the way the indication is written, can you give your
8 opinion.

9 DR. WEISS: We actually have this advisory
10 committee meeting because that is actually very much one of
11 the questions, as a matter of fact, that is Question 3 to
12 the committee is do the data support an indication, and if
13 so, do they support a broad indication or a more limited
14 indication. We can I guess give our opinions, but we really
15 want to hear your expert opinion on what you believe the
16 data support.

17 DR. SIEGEL: It should be noted that many diseases
18 where there are many approved drugs, there are accepted
19 indications, and in some we have worked on and have
20 developed, and have finalized guidances that say these are
21 the type of indications you can get and what you need to do
22 to get those indications, and, you know, whether studying
23 data from severe patients should apply to less severely
24 affected patients, chronic use, short-term use, fistulae,
25 other things, are all questions that are appropriate to

1 address in considering what is the right indication.

2 I think that we do not have preexisting guidance,

3 and we don't have preexisting really much in the way of

4 preexisting -- well, there is this manuscript that was

5 referred to, but that is not a formal FDA guidance document,

6 and we do not have any preexisting track record in terms of

7 drugs approved for different indications in Crohn's disease,

8 so in some sense, the decisions we make about this product

9 are not only -- I mean these questions about what are the

10 indications are not only pertinent in terms of what these

11 data support, but in terms of setting a precedent for how do

12 you categorize this disease, how broadly can you generalize

13 from the patients that are treated to other patients, or how

14 sharply should you narrow from the patients that are treated

15 to subsets of those patients.

16 DR. WEISMAN: Dr. Miller, one point I should have

17 made earlier is that one of the reasons for the definition

18 that was used, the duration that a patient had to have

19 Crohn's disease, as well as the fact that the patients were

20 on therapies, was to indicate and clearly define, so it

21 wouldn't be a question that these were Crohn's disease

22 patients with active disease.

23 In a sense, it was an artifact of defining the

24 patient population in a convincing manner, so that it would

25 be clear that we truly were dealing with active Crohn's

1 disease of a serious nature, whereas, if we had had it
2 basically anyone who walks in the door can get it, it would
3 have been really unclear as to who the patient population
4 was.
5 DR. MILLER: I understand that. I am not
6 questioning it from an efficacy endpoint. You have to be
7 very strict to be able to evaluate the efficacy of any
8 product. My concern more is the opposite, it is from the
9 safety. When we have" a limited number of patients, and then
10 you would try and generalize it, not from an efficacy
11 standpoint, but from a safety standpoint, I think the
12 question, as an oncologist, the question about malignancy I
13 think is not as concerning as the number of patients is very
14 small, that there was one case of lymphoma in Crohn's
15 disease, I don't think is what is concerning.
16 My concern more is the instance of early
17 infections and taking a patient population who may be
18 already at risk and then adding something that we know
19 modulates one of the body's immune mechanisms.' Now, maybe
20 we are modulating a lot less with this molecule than with
21 steroids, which blasts the entire immune system, but I think
22 that is the question that has to be resolved in clinical
23 trials. That is my concern, more safety.
24 DR. van DEVENTER: I think your point is well
25 taken, but I think you have to keep in mind that all the

1 other drugs actually that we are using in these patients
2 now, like steroids, 6-MP, cyclosporine, and so on, are all
3 associated with a substantial risk of infection. In fact,
4 in the case of 6-MP, it is like 7 1/2 percent in that order.
5 We know that steroids is associated with increased
6 infection, and so on.
7 In that respect, the infection risk in the study
8 of 4 percent is actually not very much. It is a low risk of
9 infection when compared to the other immunomodulator agents
10 that we are using in these patients.
11 DR. COHEN: Dr. Miller, as an oncologist, I also
12 share your concern about early effects, late effects,
13 unknown effects, and a lot of other things that can happen
14 to patients. I just wanted to share with you what has
15 happened to the immune capabilities of patients in the
16 clinical trials.
17 In the Crohn's studies themselves, there were no
18 effects in placebo or in infliximab-treated patients on any
19 of the T, B, and non-B/non-T cell subsets that" can be
20 enumerated. The numbers of patients were small, ranging
21 from about 4 in the placebo to about 10 in the treated
22 patients.
23 In rheumatoid arthritis, the ability of cells from
24 patients to respond to recall antigens and mitogens was
25 examined in 6 patient in an infliximab trial in the United

1 Kingdom, and without exception the response rates to those
2 recall antigens and mitogens increased rather than decreased
3 following treatment.
4 DR. SIMON: I would just like to comment as a
5 rheumatologist that I find that a discussion about the
6 immune effects of this particular agent as defined by how it
7 was just defined of somewhat actually not totally
8 straightforward, since we know that there are anti-DNA
9 antibodies that were made in some patients here, so there is
10 clearly an immune effect.
11 Because we don't understand it doesn't mean it may
12 not be important, and what came out again over and over
13 again is how small the population was that was studied, and
14 therefore, that is now being used as an excuse to try to
15 make the suggestion that we can't understand it because of
16 the small numbers, and thus it may not be important, on the
17 other hand, it may well have come out as a much more
18 important observation had the numbers been larger of
19 patients observed.
20 In addition, that kind of event, we can speculate
21 may not be important on repeated retreatment, but we do not
22 know that information, and because you only make a low
23 avidity antibody on one treatment or two treatment cycles
24 does not mean that at two years or three years or 15 years
25 of therapy, that that low avidity antibody may not become a

more important event.

Therefore, there is something immunologically going on here. Whether it is truly indicative of an important toxic event has yet to be shown.

DR. FRANK: I think that the sponsor wants to respond, but it is my impression you are going to be following these antibodies in the new trials, as well, right?

DR. WEISMAN: That's right.

DR. FRANK: The other thing is can you extend follow up where there are questionable issues in the new trials to more than a year in some cases?

DR. WEISMAN: All patients enrolled in our trials have a minimum of three-year follow up, and the consent forms make it very clear that the patients are consenting for a minimum of three-year, long-term follow up. When we have additional data available, as was reported by both us and the FDA, we report even longer term data.

DR. FRIES: I just wanted to make a clinical epidemiologist observation that perhaps you will find reassuring in the area of these serious side effects. There is a question of what your unit of comparison is, and here, through most of the analyses, it has been people, it has been prevalence, it has been percentage of individuals, and what we like to do in our studies of toxicity, particularly

1 when you are looking at infections or neoplasia, and so
2 forth, is to look at person years of exposure, so that you
3 are actually looking at a denominator which takes into
4 account the different periods of observation on the
5 different drugs.
6 When we corrected the serious infections, for
7 example, and you saw the slides just giving you the raw
8 data, when we corrected those for the 7-fold difference in
9 terms of years of exposure and the 4-fold difference in the
10 differences, it actually came out that there were fewer
11 infections in the exposed group. So, the prevalence way is
12 in a sense more conservative, but I would argue that the
13 first years of experience is relevant here and also relevant
14 when we get into the issues of the lymphomas because it
15 makes things look better.
16 DR. FRANK: We are going to take a break now for
17 just 10 minutes, please. Let's all get back, and then we
18 have specific questions to discuss and then to vote upon.
19 [Recess.]
20 Open Committee Discussion and Recommendations
21 DR. FRANK: There are a series of questions that
22 the FDA would like the panel to address. The first couple
23 of questions are for discussion and then the third question,
24 the last part of it will be for voting.
25 I will read the questions for the record.

1 The first question deals with endpoints. Study
2 T16. We have been asked to discuss the adequacy of the
3 primary endpoint, that is, the reduction in the CDAI by 70
4 points at week 4 in patients with moderate to severe Crohn's
5 disease.
6 Is there anyone on the panel that would like to
7 open the discussion on that? Dr. Tremaine.
8 DR. TREMAINE: Yes, I would be happy to. I think
9 that that endpoint in itself is not very compelling in that
10 we see that there were a number of ill patients in the study
11 with CDAIs of 300 or more. I am not sure it makes a
12 difference to a patient's quality of life to go from a high
13 CDAI of over 300 to 70 points less than that.
14 However, the fact that this was not the only
15 endpoint, some of the secondary endpoints that I find more
16 compelling, such as remission, also were positive, so I
17 think when you take it in the context of all the findings of
18 the study, that this is satisfactory.
19 DR. FRANK: Dr. Elashoff.
20 DR. ELASHOFF: As a statistician, I much prefer
21 looking at data that is collected as continuous data, as
22 continuous data, rather than making some arbitrary yes/no
23 categorization, and I think that is something that needs to
24 be discussed in more detail tomorrow. But it is a
25 reasonable endpoint, it was the one defined on a primary

1 basis, and as was just mentioned, a variety of other
2 secondary endpoints and redefinitions of it when you go to
3 100 points or whatever, seem to come out much the same.
4 So, from a statistical point of view, once you
5 have decided to look at CDAI, it seems that this endpoint is
6 as representative as other endpoints with CDAI.
7 DR. FRANK: In terms of the statistics, would it
8 be more valuable to question the duration of response rather
9 than asking about response at week 4, whether there is a
10 one-month, two-month, three-month response?
11 DR. ELASHOFF: In some respects, the answer would
12 be yes, you would really like to look at duration of
13 response. Looking at it only every month is difficult from
14 a statistical point of view because then it is very chopped
15 and also you have issues of, especially in these trials,
16 losing patients to other arms, and that sort of issue, which
17 makes it harder to look at.
18 So, I think that is an approach one would like to
19 take. It doesn't work awfully well with these particular
20 trials.
21 DR. FRANK: Any other comments?
22 The second part of that question is on Study T20.
23 The FDA would like us to discuss the adequacy of the primary
24 endpoint, that is, loss of drainage, in patients with
25 fistulizing Crohn's disease.

1 Can improvement in the number of draining fistulae
2 support a claim that cA2 closes enterocutaneous fistulae? I
3 think we have discussed that quite a bit.
4 Yes, Dr. Berardi.
5 DR. BERARDI: I guess in that regard I need some
6 clarification, because I am looking at three documents. I
7 am looking at something that was sent to me originally, that
8 talks about closing enterocutaneous fistula, and then I am
9 looking at what Barbara Matthews presented, and then one of
10 her slides she talks about infliximab is for the treatment
11 of patients with active Crohn's disease for the reduction of
12 signs and symptoms including closure of draining
13 enterocutaneous fistula, and then I am looking at Centocor's
14 slide here.
15 It talks about infliximab is indicated for the
16 treatment of patients with active Crohn's disease for the
17 reduction of symptoms and signs including enterocutaneous
18 fistula, but there is not word there that says anything to
19 do with closure. I am look at this document here that was
20 presented.
21 so, I guess I am questioning what are we looking
22 at, are we looking at closure, drainage, just signs and
23 symptoms including enterocutaneous fistula?
24 DR. WEISS: I just also want to clarify, if I can,
25 that over the course of really the last month, there has

1 been some change in terms of a proposed indication statement
2 that has come to us from Centocor, and these questions I
3 think are not in real-time because they reflect the initial
4 proposal from the company, which was as an indication to
5 close enterocutaneous fistula, and the trial was designed to
6 assess cA2's effects on closure. That may be little bit of
7 a moot issue now, as you are pointing out, with some of the
8 changes, but I think it is still worth discussing.
9 DR. LAINE: I would just say I would give
10 indications for what was actually studied in the study, and
11 I would want to change some of the wording of the
12 indication, but I would think closure of draining fistula
13 is, in a sense, what happened. They were no longer
14 draining. So, I would actually use that wording perhaps,
15 and I think that would be fine with that wording.
16 I probably would alter the proposed labeling,
17 which we can go into now or later, but anyway I would just
18 use closing of draining fistula probably.
19 DR. FRANK: Any other comments?
20 Is the pathophysiology of fistulae sufficiently
21 similar such that response in one location, that is,
22 perianal, can be extrapolated to other locations, for
23 example, an abdominal fistula?
24 I will allow the sponsors to make some comments
25 perhaps at the end of this series of questions, the

1 endpoints one, and then we will go on to the safety ones,
2 but I would like to go through the whole series first.
3 Do I have any comments, any discussion on the
4 fistulae? Dr. Tremaine.
5 DR. TREMAINE: I don't think we know enough about
6 the pathophysiology of fistulas to make a distinction
7 between the development of a fistula one place compared to
8 the other. I don't think we can differentiate the two.
9 DR. SURAWICZ: I agree. I don't think we really
10 understand why Crohn's disease causes fistulas. We do at
11 the pathologic level with transmural disease. But perhaps
12 they are different because the perianal disease will often
13 respond to antibiotic therapy, such metronidazole, and to my
14 know, the enterocutaneous ones don't, so they might be
15 different, but I don't think we understand the
16 pathophysiology or the pathogenesis of either of them.
17 I am not sure that understanding that would have
18 any real relevance in this case, however.
19 DR. WEISS: What we want to make certain from the
20 committee is that if this is approved, an indication would
21 address fistula in general, and not necessarily the
22 splitting between different types of fistula.
23 DR. LAINE: There are only about 9 or 10 percent
24 of non-perianal fistula, is that right?
25 DR. WEISS: Yes.

1 DR. LAINE: I don't remember, what were those
2 numbers in that 10 percent? I know it was too small
3 probably.
4 DR. MATTHEWS: This is Dr. Terry Neeman who did
5 the statistical review for this application from the agency.
6 DR. LAINE: so, 4, 3, and 2 in the different
7 treatment groups, or 4 in the placebo?
8 DR. NEEMAN: There were 4 in the 5 group, 2 in the
9 placebo, and 3 in the 10 group.
10 DR. LAINE: I shouldn't ask this, but how did
11 those 7 do?
12 DR. NEEMAN: Well, the 2 patients in the placebo
13 group, there was no improvement in either of those patients,
14 and one of them developed another fistula. There was
15 improvement in the 4 patients in the 5 group, and also some
16 improvement among the 10, so there was evidence.
17 DR. LAINE: In a very small number, I know, very
18 small.
19 DR. FRANK: In my experience clinically, perianal
20 fistulizing disease is the primary fistulizing disease in
21 Crohn's disease, where you see the abdominal, the
22 enterocutaneous fistulas on the abdominal wall is in the
23 patients who had surgery usually.
24 Next . Please discuss the significance of new
25 fistulae and/or abscess formation in some patients in the

1 cA2 treatment group vis-a-vis the pathophysiologic processes
2 involved in fistula formation and closure.
3 Again, I think we did discuss that in rather a bit
4 of detail. I don't think we need to go into the recurrence
5 versus complication issue again. I think that timing really
6 is important in deciding whether that is a complication or a
7 recurrence, and perhaps the answer to some of that will come
8 in the multiple-dose study that is being initiated.
9 Any other comments about that?
10 DR. WEISS: Your comment is that the multidose T21
11 trial is not specifically for people with fistulizing
12 disease, is that correct, Harlan?
13 DR. WEISMAN: It is not exclusively patients with
14 fistulizing Crohn's disease, but they are included among the
15 patient population, so basically, the long-term maintenance
16 trial will include both patient populations that were
17 included in T16 and T20.
18 DR. FRANK: Finally, please discuss the importance
19 of radiologic assessments to evaluate an effect on fistula
20 healing.
21 DR. SURAWICZ: We don't really use them very much
22 clinically.
23 DR. TREMAINE: I would agree. I think that the
24 clinical assessment of patient's symptoms are often more
25 important than the radiologic appearance. Sometimes it is

1 obvious to the patient and the doctor that there is a
2 fistula. A woman with a rectovaginal fistula passing stool
3 or gas through the vagina knows there is a fistula there,
4 and sometimes it can't be documented on an x-ray, so I don't
5 think that is critical to have a picture of it.
6 DR. LAINE: I would say it would be real
7 interesting to do in future studies, just mechanistically,
8 but I would agree that clinically, I don't think it is
9 really mandatory as long as you have good follow up on the
10 patients for recurrences and complications.
11 DR. FRANK: I think the question of rectovaginal
12 fistula, by the way, the woman really can tell when there is
13 a fistula versus normal secretions. They complain very
14 bitterly when they have a fistula and when it goes away,
15 they know it immediately. I think that is probably one of
16 the easiest to tell.
17 Would the sponsors like to comment at all on any
18 of these issues that we have talked about?
19 Then, we will go on to the discussion of questions
20 of safety.
21 Of the 233 patients enrolled in the four clinical
22 trials evaluating cA2 treatment for Crohn's disease, 199
23 received at least one dose of cA2; 100 of the 199 received
24 repeated doses of either 5 or 10 mg of cA2, that is, 37
25 patients enrolled in T16 and 63 patients enrolled in T20.

1 Because of clinical trial designs and rerandomization
2 schemes, the number of patients with Crohn's disease who
3 received placebo are disproportionately lower than those who
4 received cA2 to the extent that adequate comparison between
5 the treatment groups is difficult.
6 The committee is asked to discuss the adequacy of
7 the safety database in terms of numbers of subjects exposed
8 to the agent, duration of follow up, and in the adverse
9 events observed, for example, infections, malignancies,
10 cardiovascular events and lupus-related events.
11 Any discussion? Dr. Laine.
12 DR. LAINE: It is obviously inadequate. I am not
13 saying it's a problem, it is obviously inadequate in the
14 best of all possible worlds I think we have already
15 discussed that in great detail. I mean these are all low
16 incidence, as was stated by the sponsor, they are low
17 incidence, so I mean it is inadequate. The question is what
18 we do with that inadequacy.
19 DR. FRANK: I think that long-term follow up is
20 going to be very important for all of these issues. I think
21 that even in the case of malignancy, longer than 3 years may
22 be required for some of this, and time will tell.
23 Dr. Simon.
24 DR. SIMON: I would just like to throw in an
25 observation that we have from the Arthritis Advisory

1 Committee that the creation of databases that one then
2 'follows over a period of time to try to answer events that
3 are so small in occurrence that you begin to actually have a
4 decreasing series of returns when one tries to create a
5 registry or some kind of long-term observational study.
6 so, although it sounds attractive that one might
7 be able to follow patients over time, and find an answer
8 particularly about malignancy, I am actually much more
9 concerned about the immunologic problems, but I think that
10 it may not be doable because, in fact, it just may not be
11 enough patients that this would happen in, and under those
12 circumstances, there are plenty of drugs that are on the
13 market, drugs as opposed to biologics, which actually do
14 have malignancy associated with their use, and they have
15 been approved, and I think that is much more of a labeling
16 issue.
17 I am not entirely sure we will find out some of
18 those answers in these observational studies. I am
19 concerned, however, that from a size point of view, that I
20 don't understand the incidence of immunologic event and the
21 importance of that event, and I am not sure that we have to
22 depend upon long-term observational studies to understand
23 that better, and I don't know, if we had had a larger safety
24 database, that we wouldn't have that answer in the
25 circumstance.

1 There was a measurable significant incidence of
2 anti-DNA antibodies, and there were several episodes of
3 lupus-like disease. If that database was larger, it may
4 well have been more common.
5 I would like to make the observation that the
6 conversion to significant antinuclear antibodies we talk
7 about much more frequently, and we think that that may or
8 may not be more important, but usually we think about anti-
9 DNA antibodies as being more important an observation and
10 event that seems to be more conserved in the human body. It
11 is harder to make that conversion take place it appears,
12 even in true lupus, it is uncommon. In drug-induced lupus,
13 it is extremely uncommon.
14 So, the fact that people are converting with anti-
15 DNA antibodies, I don't think can be explained by the
16 observations that we have here.
17 DR. FRANK: What do you suggest?
18 DR. SIMON: I would just like to have had a larger
19 safety database to begin with, and I think that if we had,
20 in fact, had this meeting after the next study was done and
21 accomplished, we may have actually had that larger database,
22 and it may have been a specious issue based on the larger
23 database. It is just an issue that is standing out there
24 and I don't just think there are enough patients that have
25 received this product to be able to answer the question.

1 DR. FRANK : The next item for discussion is: In
2 addition to long-term follow up of patients who had been on
3 the initial studies of cA2, what other data, for example,
4 specific tests of immunologic function, formal drug
5 interaction studies, should be gathered to strengthen the
6 safety information? Note that if approved, this information
7 could be requested as part of the postmarketing commitments.
8 Comments? Dr. Steinberg. I haven't heard from
9 you for a while. What do you think?
10 DR. STEINBERG: Not being an immunologist, I don't
11 really know how to respond to this other than monitoring the
12 things that are being monitored already, specifically, these
13 anti-double-stranded DNA. So, I will leave it at that.
14 DR. FRANK: In other words, gather the same data
15 on a larger number of patients, as Dr. Simon has suggested.
16 Yes, Dr. Miller.
17 DR. MILLER: Just a question of what does this
18 committee feel about requesting data using this antibody
19 compared to other standard treatments, especially if this is
20 approved with a broad indication, such as azathioprine. I
21 mean the safety information is going both ways. It could
22 clearly show that this drug is maybe safer than some of the
23 other treatments that are used for Crohn's disease. How do
24 you feel about that?
25 DR. FRANK: I am not sure of the question.

1 DR. MILLER: When you are talking about other
2 data, it is not just other data about this drug compared
3 with placebo, but the question about this drug compared to
4 other drugs that are more standard of care, if there is one,
5 for the treatment of Crohn's disease. It may be, in fact,
6 safer than those other drugs, but unless we actually compare
7 them, since this population is so heterogeneous, how will
8 you know that?
9 DR. FRANK: That is a good question. One of the
10 problems that we have in the treatment of Crohn's disease,
11 and one of the reasons we don't have a clear idea of the
12 best treatment for Crohn's disease is because these other
13 drugs just sort of arrived and never did have good
14 randomized, double-blind trials evaluating their efficacy in
15 different populations with inflammatory bowel disease. We
16 are stuck with that because those drugs are out there on the
17 market, and no one has required it.
18 I think that we have to thank Centocor for
19 engaging in trials and working hard over this drug, and I am
20 sure that the other drugs that come down the line after it
21 will be hopefully following some of the guidelines that come
22 out of this meeting.
23 DR. LAINE: It is not a safety issue, but there
24 are a lot of studies that would be interesting. The problem
25 is the relatively small number of patients and the amount of

1 money they want to spend doing this.

2 The other issue is if you can induce somebody, so

3 to speak, into remission with this, and then follow up with

4 one of the standard agents, it would also be a very

5 important question if you give this, and you give

6 methotrexate or 6-MP, is that better -- I mean those are

7 studies that do not relate to safety, but I think would be

8 very interesting to have the sponsor consider in the future,

9 as well. It is a problem of how to prioritize those

10 treatment studies.

11 DR. FRANK: Certainly, the patients who got

12 infliximab plus an immunomodulating agent seemed to have

13 Less incidence of the antibodies than the patients who were

14 not on the immunomodulatory agents in addition.

15 That is something that could be measured quite

16 clearly.

17 DR. TREMAINE: With regard to safety studies, in

18 the transplant literature, patients who have been on

19 immunosuppressives, who have developed lymphomas, often have

20 had EBV virus in the tissue. The sponsor mentioned that EB

21 virus was found in serology, but not examined further. I

22 would think if any other lymphomas are identified that an

23 exam for tissue presence of EB virus would be critical to

24 help us sort out is it the drug or background risk from the

25 disease.

1 DR. FRANK : Does someone want to respond to that?

2 DR. McCLOSKEY: We have tissues from three of

3 those patients. We will be doing mRNA and BCL2 surrogates

4 for EB virus.

5 DR. MILLER: But also the lymphomas associated

6 with rheumatoid arthritis often can often be EB-positive

7 without having to call into effect that this antibody has an

8 affect, so that is going to be difficult to determine. You

9 can compare it to the general incidence where the EBV

10 association is lower, but not with any immunologic

11 nechanism. There are immunologic mechanisms, in fact, that

12 are often EBV-positive.

13 DR. FRANK: Dr. Miller, do you have any

14 Suggestions about further evaluating infections?

15 DR. MILLER: I just think in any study, future

16 studies, that infectious complications early on be collected

17 during the treatment courses, the way it is done today, but

18 Larger populations to compare.

19 DR. FRANK: Any other comments? Would anyone from

20 the company like to discuss -- also, 1 think that one of the

21 things that I noted was the fact that although when you took

22 individual adverse effects, there wasn't a whole lot of

23 incidence, but if you added up all the upper respiratory

24 infections, they got pretty high, didn't they?

25 DR. WEISMAN: Yes. That is a good point. Number

1 one, I guess I would say that as a general comment, we
2 concur with what the committee members said are the relevant
3 concerns and the relevant needs for information and the
4 relevant open questions, and we are certainly committed to
5 moving forward on answering those, both in the clinical
6 trials, as well as the ongoing safety surveillance that we
7 have been discussing.
8 In terms of what Dr. Simon said, you know, we
9 agree if this was rheumatoid arthritis, and it was chronic
10 disease in a situation in which there are adequate
11 therapies, where this" may be" an improvement, you would want
12 that larger database, and we believe that so much that are,
13 in fact, doing that in rheumatoid arthritis. The fact is we
14 are here today for Crohn's disease and this indication with
15 the database we have.
16 In rheumatoid arthritis we are now conducting a
17 clinical trial that is almost over and has over 420 patients
18 in it. A lot of the questions that you raise, that you said
19 you were concerned about, are being collected in that trial,
20 as well as in the ongoing planned Crohn's trials.
21 In terms of the upper respiratory tract
22 infections, we really believe that is a reflection of the
23 longer follow up in the trial for the patients on infliximab
24 relative to placebo, and when you can correct for that
25 Length of follow up, you actually an evening out of the

1 upper respiratory tract infection rate. The fact is that.
2 over time, people start getting colds, and if you only
3 follow people for 12 weeks, you are less likely to see a
4 cold than you are if you follow them for 24 weeks.
5 DR. FRANK: The next issue is on net clinical
6 benefit. First, on Study T16. Patients enrolled into T16
7 responded at 4 weeks to a single IV infusion of cA2, but the
8 proportion of patients responding over the subsequent 8 week
9 period gradually diminished suggesting the need for
10 continued dosing to maintain clinical response. Another
11 clinical trial, T21, is proposed to evaluate the safety and
12 efficacy of cA2 for chronic treatment of patients with
13 noderate to severe Crohn's disease. Results from this
14 clinical trial will provide additional safety data in
15 accordance with the ICH Guidance on the Extent of Population
16 Exposure.
17 We are asked to discuss the clinical utility of
18 administering a single dose of cA2 to improve the signs and
19 symptoms of moderate to severe Crohn's disease' when response
20 diminishes with time and data are limited for retreatment.
21 Would anyone like to take that? Dr. Laine.
22 DR. LAINE: That is just what I had said earlier.
23 I think. I think the data are quite good in my mind that it
24 works acutely. I think at this point we have to assume we
25 don't have data about whether it works long term. It may or

1 may not. So, my issue was just for the committee to discuss
2 is if we approve something and assume it works for two
3 months really well, and then it goes away and doesn't work
4 long term follow up, is that still worth approving for the
5 benefit patients get for two months or three months.
6 That was the question I was raising. I would be
7 interested in other people's views of that.
8 DR. FRANK: Dr. Tremaine.
9 DR. TREMAINE: If we look at the current available
10 therapy, most commonly it is steroids. It is the same
11 situation. It works acutely; but not chronically. So, for
12 the patient who is ravaged by side effects from steroids,
13 even if it is just a tradeoff for something else that works
14 acutely, and they get away from those side effects, that
15 could be a benefit.
16 DR. LAINE: I am not against that. The only
17 difference may be that at this point, we can't say -- I am
18 not saying it doesn't -- but we can't say that it works when
19 we retreat. I am not saying it doesn't, but we don't have
20 those data.
21 With steroids, we- do know that it generally will
22 work if you retreat acutely. I am not saying it maintains
23 remission, but at six months later -- Dr. Rutgeerts
24 disagrees -- but I mean I think if someone has recurrence a
25 year later, we can retreat with steroids. We don't know

1 that is the case with this drug although it may well be.

2 DR. STEINBERG: Could we have perhaps some of the

3 Crohn's experts who have dealt with this drug comment on

4 this, because they have vast experience, someone like Dr.

5 Present perhaps? Where would this drug fit in?

6 DR. PRESENT: The comment that if you retreat with

7 steroids it works is not true, and that the more often you

8 use steroids, the less effective they become, and

9 approximately 40 percent of patients will become refractory

10 and fixed on steroids without any benefit will have to

11 remain on them.

12 Where does this drug belong? I think we have seen

13 from the studies it belongs in patients who have failed to

14 respond to other medications and are chronically active

15 despite that, so I think the T16 study demonstrates that.

16 We do not have any drugs that statistically heal fistulas,

17 steroids do not. Immunosuppressant drugs have shown some

18 response, but you are dealing with a significant toxicity

19 with cyclosporine, or azathioprine, so that I think for

20 patients with fistulization, there is no question but there

21 is an indication for this drug.

22 The long-term issue remains to be seen. Whether

23 other drugs, as we have mentioned, will then take over,

24 treating and putting someone into a remission is different

25 than maintaining the remission, as we found out with these

1 diseases, so that you may be able to have a drug that will
2 not put someone in a remission, but may help to maintain a
3 remission, and I am hopeful -- we don't have the data which
4 I hope we will have long term -- is that if one can induce a
5 remission with the infliximab, then, perhaps some of the
6 other drugs that have been ineffective will then be able to
7 maintain the remission, but we have to see that data.
8 DR. FRANK: I think that one of the possibilities
9 that I see is that we know that drugs like azathioprine take
10 a good six weeks to show any benefit, and if we can get some
11 acute response in the. patient who is very active and very
12 sick, and give them a chance to respond to the drugs like
13 Imuran, that might be a real benefit also.
14 I think just from a well-being point of view
15 sometimes it is a big help, too. It helps with their
16 nutrition and other things to catch up.
17 Mr. Getz.
18 MR. GETZ: Speaking as a Crohn's patient myself, I
19 think any of us would grab at that opportunity" to even have
20 two months, go from an acute phase to a remission state,
21 take our chances from there, but certainly I don't think you
22 would find any Crohn's patient who would say no, I don't
23 want to do that, whatever the risks are, whatever the future
24 may bring in two months time, I think we would all take that
25 opportunity and chance.

1 DR. LAINE: My sense is that. I am not trying to
2 be overly negative. I guess I am saying if we look at -- I
3 am not saying I wouldn't use it either -- but I guess all I
4 am saying is if we really look at the data we have, and we
5 assume that four or five months down the line, you are the
6 same as you were, and there is no evidence that anything
7 else is going to make you any better, certainly, if you add
8 methotrexate or add 6-MP, and you can maintain that
9 remission, it would be wonderful.
10 I guess what I am asking is if you knew six months
11 from now, that was it, and you never were going to get
12 benefit again, and you got this two months once in your
13 life, and I guess that is the question I am asking, is that
14 clearly going to be worthwhile to you especially when you
15 have some safety issues that you really still have
16 unresolved.
17 MR. GETZ: The question of safety issues arises,
18 as many people mentioned, with just about everything we
19 take. Every drug that all of us take has enormous safety
20 issues . My sense of this is that it is no less unsafe than
21 any of the other things that I and other people take, so I
22 guess that really wouldn't be an issue for me and most other
23 Crohn's patients I believe.
24 I am in the fortunate position of not being as
25 sick as the people that you heard this morning, but I am

1 sure that they would be more than willing to take that risk
2 and worry about two months when two months comes.
3 DR. SIMON: Madam Chairman, can I ask just a point
4 of information that I am still confused about? Does TNF
5 alpha levels in the tissue, do they come back up six months
6 after therapy is ended? Do we know that data?
7 DR. van DEVENTER: We don't know that. We know
8 actually that the TNF levels, as well as the TNF production
9 from cells isolated from the mucosa goes down, but we
10 haven't done follow-up studies, "and I think you have to
11 remember what that takes, because you have to go back in the
12 patient, do a colonoscopy for a couple of times.
13 Most repetitive colonoscopies that we have done
14 was at 4 and 8 weeks. We haven't done later colonoscopies.
15 DR. SIMON: The reason I asked that question is
16 related to, in fact, what you just said. Again, at the risk
17 of being labeled here as the most negative person, I take
18 care of patients with rheumatoid arthritis. We had a drug
19 that was touted as being a spectacular drug, that made a lot
20 of patients better who were very sick.
21 All of us have had experience with these patients
22 then going on to having a new disease caused by the drug,
23 not lymphoma, but another autoimmune disease. The dilemma
24 is that this is a biologic therapy. I don't hear enough
25 data that tells me what happens long term with this biologic

1 therapy.

2 If I give this to you, I might actually change the

3 way you biologically respond, in the one hand, in a very

4 positive way with the disease, that may be very short-lived

5 after one single dose, but on the other hand, it may have a

6 very long-term biologic effect that we don't understand.

7 We cannot 'think about biologic therapies in the

8 same way we think about drugs. We don't even have tools to

9 evaluate, in fact, what happens under the circumstances of

10 their use. All we have is observation, and there has not

11 yet been enough observation to even know what might happen

12 under these circumstances.

13 I don't mean to maximize the safety issue, but I

14 don't also want to maximize the efficacy issue here. It has

15 limited efficacy from what I can see. It is useful in one

16 circumstance, and we don't know the durability of the

17 response. I am a little concerned about that, and we face

18 this issue about response and whether or not TNF comes up or

19 doesn't come up, and in other circumstances, with many, many

20 other drugs -- excuse me -- biologics that we have actually

21 looked at in the past, and we don't understand the ef-fects

22 of those either.

23 As a result, I am just not sure that we understand

24 all the issues.

25 DR. van DEVENTER: Maybe I can add to that, that

1 actually we do know a lot more immunologically from the
2 antibody than has been shown today, and all the data that we
3 have indicate that the immune system goes back to the normal
4 state. That is, if we look at the TNF production and
5 production of other cytokines in the mucosa, it returns to
6 norms 1. If we look at the distribution of T cells within
7 the circulation, actually, it normalizes.
8 If we look at T cell function, T cell function is
9 suppressed by chronic TNF exposure, and again it normalizes.
10 So, from all we know from the immunological data that we
11 have, from the mucosal immune system and from the systemic
12 immune system, everything we observe it towards
13 normalization, not some nonspecific activation or anything
14 like that.
15 DR. SMOLEN: Maybe I can add to that. One aspect
16 of adding to that, lupus in our hand is a disease in which
17 TNF alpha is high and correlates with disease activity, so
18 this actually came as a surprise, and I am not surprised
19 that these patients come back to normal and that we don't
20 see any individual that has long-term sequelae with respect
21 to autoimmune disease after years of being treated with the
22 antibody. In two patients that had lupus-like syndrome that
23 I, after really thoroughly going through, do not classify as
24 systemic lupus erythematosus, they came back to normal, just
25 like any other conventional drug-induced lupus that does not

1 continue going into systemic lupus, which some of the drugs
2 like T-penicillamine and sulfasalazine, which is also being
3 used in this disease, actually do.
4 So, I think that you raise an important issue, but
5 I believe that with the data that are available, we already
6 can tell that this issue is overemphasized at the present
7 time. That does not mean that one should not control these
8 patients. It does not mean that maybe these patients should
9 be taken off and not repeated once they have anti-DNA
10 antibodies, since we know that anti-DNA antibodies come back
11 to normal once you stop the drug anyhow.
12 So, I don't think that there is a major issue in
13 that respect, and I am pretty confident that there is not.
14 We have, I don't know, hundreds of patient years
15 observations in the meantime, and there is not a single case
16 of lupus-like syndrome continuing, so I am really confident.
17 DR. FRANK: Any other comments?
18 Next, the Study T20. Results from Study T20
19 indicated that the number of draining fistulas was
20 significantly different between patients treated with three
21 doses of cA2 at weeks 0, 2, and 6, and those treated with
22 placebo. After completion of the three doses, response was
23 gradually lost, suggesting the need for continued therapy,
24 but no data are available for longer dosing in this patient
25 population.

1 We are asked to discuss the clinical utility of.
2 administering the proposed three dose regimen of cA2 to
3 reduce the number of draining fistulae in patients with
4 fistulizing Crohn's disease when the response is gradually
5 lost and no data are available on retreatment.
6 Dr. Elashoff.
7 DR. ELASHOFF: I just wanted to comment that,
8 strictly speaking, the way it is stated here is not the way
9 the primary response was defined. Although they are closely
10 related, it is not exactly how it was defined in the study.
11 DR. FRANK: Dr. Laine.
12 DR. LAINE: I was just going to say that the
13 discussion is really the same for this as the previous one
14 in my mind. I was just going to ask the sponsors that it
15 seems that most of the people who responded, looking at what
16 little information is there, but I would be interested in
17 more information, responded with the first dose, and I know
18 it was an empiric decision to use three doses.
19 Do you have further plans to evaluate that,
20 because it seemed interesting. It looked like there wasn't
21 much more response beyond, but maybe you have better data.
22 I think there was really very little data presented in this
23 book .
24 DR. WEISMAN: Dr. Laine, I think the best answer
25 to that is the comment you made before. A lot of what is

1 happening out of these clinical trials is raising a lot of
2 interesting secondary questions and hypotheses, and you made
3 the comment earlier to that point and said we are going to
4 have to prioritize which one of these is the first -- one of
5 the questions that has come up actually in the design of the
6 trial we are planning, T21, is should we examine that
7 question, should we examine the integral question, you know,
8 how often, should we examine the dosing question, because
9 you don't want to ask too many questions in the clinical
10 trial .
11 I think it is an interesting question. We don't
12 have the answer. The best comment I can give you is the
13 data that we have today indicates that the dosing regimen
14 that we used in the trial was effective, and I think I have
15 to let it stand at that.
16 DR. LAINE: I just wondered, do you have the
17 proportion that increased from, let's say, you know, week 2
18 to week 4 to week 6? You have the chart in here about the
19 patient's assessment, and it looked like the best two
20 responses were achieved right off the bat at week 2 and
21 didn't really go up at all. I don't know if there is other
22 data that isn't presented here.
23 DR. SCHAIBLE: Again, the median time of onset was
24 two weeks, so at least half of the patients who responded
25 had responded by the two-week evaluation. So, it is

1 slightly less than half of the patients who then will have
2 an onset of response after that initial two weeks.
3 DR. FRANK: Are you going to be looking at
4 retreatment of these people because it looked like almost
5 universally they were losing their effect after 18 weeks?
6 Do they then get additional injections?
7 DR. WEISMAN: Again, we are going to answer that
8 in two ways. One is the randomized, placebo-controlled
9 trial, which will include this patient population. The
10 other one is the extended treatment trial that will have
11 patients eligible from T20, the fistula trial, to come back
12 if they are having recurrence of their disease and they
13 participated in the trial, they will be eligible for
14 retreatment, and we will try to get preliminary evidence
15 from that retreatment trial.
16 DR. TREMAINE: May I address that also?
17 DR. FRANK: Yes.
18 DR. TREMAINE: I am not comfortable we have enough
19 data to make strong decisions about dosing here. We heard
20 that another third of patients who were retreated in the T16
21 trial will respond who didn't respond the first time, so it
22 took two doses actually in the non-fistula group, and then
23 some of the patients in the fistula group respond after one
24 or two doses.
25 If we think of Crohn's disease in general with

1 fistulas as one part of that, I am not sure we can split
2 these so conclusively that this group needs three doses, and
3 that group needs one dose. I think the strongest message I
4 can take is that these patients seemed to respond, and some
5 respond with more doses than others.
6 With regard to the proposed indication, the first
7 part, 5 mg/kg dose is indicated, and I am not sure we can go
8 much further than that.
9 DR. FRANK: Any comments?
10 DR. LAINE: My view would just be we are get into
11 labeling next, you just have to go with what the studies
12 did, and just have to do labeling with that even though it
13 may turn out that really three is the wrong number. I would
14 just say if that worked, that is what you would have to do
15 even that may not turn out to be the right dose in the long
16 term is how I would approach it.
17 DR. FRANK: Any additional comments?
18 The next part of the question we are asked to vote
19 on. The patients enrolled in T16 and T20 were evaluated for
20 an effect on two different clinical endpoints, reduction in
21 signs and symptoms and closure of fistulae.
22 Given the heterogeneous nature of Crohn's disease,
23 do the safety and efficacy results from these two trials
24 evaluating cA2 cross-substantiate a claim for the treatment
25 of patients with Crohn's disease?

1 In other words, do we think that we have enough
2 evidence here that patients can be treated for the initial
3 acute therapy?
4 DR. SIMON: Regardless of their manifestation?
5 DR. LAINE: No, one was activity, one was
6 enterocutaneous fistula.
7 DR. SIMON: But that is the question, only with
8 fistulae or with any manifestation of Crohn's disease?
9 DR. LAINE: The broad indication under (a) I
10 think.
11 DR. WEISS: I think it might be helpful to
12 consider the first question is, in your opinion, do you
13 think these data support an indication. I guess that is the
14 first question to vote. And then if you think it supports
15 an indication, we would like your advice on whether it
16 supports something somewhat broad as the sponsors proposed
17 or --.
18 DR. LAINE: I would think you would want to define
19 first rather than second. Rather than say it is an
20 indication, I would think you would want -- if you do think
21 it needs to be split, then you would want to define that
22 before on whether -- 1 think personally, as I said earlier,
23 would actually favor a more strict definition, and one
24 reason is I think that the trials were different. One was
25 activity, looking at people with CDAS over 300, one was

1 people with fairly mild '[CD activity," and enterocutaneous
2 fistula, although colloquially, it depends on how you use
3 active. If you use "active" in a colloquial sense, yes,
4 they have active Crohn's disease, but as Dr. Present
5 mentioned, you know, steroids work for flares of active
6 Crohn's disease, but they don't work for enterocutaneous
7 fistula. They may be different. I personally would not
8 lump them, but I would probably do both, and actually say
9 one dose for the active, and one dose for the
10 enterocutaneous fistula.
11 DR. SIEGEL: Let me just say, as I am sure you
12 know, under 3.c., which we are discussing, and 3.c.i., we
13 ask about the specific indications, and I will go on record
14 as saying we want your advice as to whether there should be
15 an indication of which one, but don't have a strong feeling
16 as to which order to address those questions, and we will
17 leave it to the committee and Chair if you would rather --
18 are you suggesting you would rather vote specifically on
19 fistulae separately before voting on whether there should be
20 any indication, is that what you are saying?
21 DR. LAINE: My point is if you don't know whether
22 you are going to break it or split it, how can you vote on
23 an indication -- 1 mean break it or combine it. It would
24 seem to me you need to define what you are voting on first
25 is all I guess I am saying.

DR. WEISS: I am very happy for you to pose a question that you are comfortable with, if the committee agrees to that, and then we can vote on that question and then the subsequent question. That's fine.

DR. SIEGEL: The intent of the way the question is worded, if that is what you are asking, would be that if you bought that it should be approved for any sort of indication, you would vote yes on 3.c. That is the intent if that is the question. Then, on 3.c.i., try to specify what that ought to be.

DR. FRANK: Can we vote on the first part of it? I would like to have a vote on the broad issue of do we think the drug has some clinical efficacy and should be approved for some indication.

All those in favor?

DR. SIMON: You are appending the word "some" to that, "some" efficacy, and that should be approved for some indication.

DR. FRANK: Yes.

Sidney Getz?

MR. GETZ: Yes.

DR. FRANK: Rosemary Berardi?

DR. BERARDI: Yes.

DR. FRANK: Janet Elashoff?

DR. ELASHOFF: Yes.

DR. FRANK: William Steinberg?

DR. STEINBERG: Yes.

DR. FRANK: Chris Surawicz?

DR. SURAWICZ: Yes.

DR. FRANK: Loren Laine?

DR. LAINE: Yes.

DR. FRANK: William Tremaine?

DR. TREMAINE: I am not voting.

DR. FRANK: Oh, you are not a voter. Sorry. Lee Simon?

DR. SIMON: Yes.

DR. FRANK: Dr. Miller?

DR. MILLER: Yes.

DR. FRANK: I believe that is unanimous.

Now we decide on the broad versus more limited indication. The broad indication would be for use for the signs and symptoms of a patient with acute Crohn's disease, active Crohn's disease including enterocutaneous fistulae, and if not, then a more limited indication either for signs and symptoms or specifically for fistulizing disease, or, Dr. Laine, would you like to specify how you would like to divide it?

DR. LAINE: I personally would break it especially because the doses were different, the study populations were different. I would be willing to approve for both

1 indications, but I wouldn't put it in that one big
2 hodgepodge.
3 I probably would once again just state what the
4 study studied, and make the issue that people with active
5 Crohn's disease. I personally would not feel comfortable
6 having a very broad indication of anybody with Crohn's
7 disease, because I would think the utility of this drug
8 would be again in that subset of populations that we, as
9 clinicians, take care of who have severe disease, who have
10 not responded or on high-dose steroids, and need to be
11 treated.
12 so, I would want to have some wording to make it
13 more restrictive, but" given that, I would approve it for
14 active disease in the 5 mg dose, and then as a separate, I
15 would say the closure of draining fistula at the zero, 2, 4,
16 6, whatever it is.
17 DR. FRANK: Dr. Miller.
18 DR. MILLER: May I suggest that if we are talking
19 about limiting, consider actually what they put in the
20 initial indication, which was to reduce signs and symptoms
21 of patients with moderate to severe disease activity in whom
22 conventional therapies are not adequate, and then, number
23 two, close enterocutaneous fistula, because that actually
24 responds to what the initial protocol actually is.
25 so, I would recommend that if we are voting on

1 broad versus limited, that to me at least, this wording fits
2 my concerns.
3 DR. FRANK: Dr. Weiss.
4 DR. WEISS: I was just going to ask the sponsor,
5 what Dr. Laine said, would you propose putting in more
6 specifics in the indication to the moderate to severe, which
7 is in this one, and those who have failed therapy, Dr.
8 Miller already actually addressed that.
9 DR. LAINE: Yes.
10 DR. WEISS: If that is what people ask, we could
11 actually modify this, you know, take that into consideration
12 as you vote.
13 DR. LAINE: I think the old one, as she stated,
14 except for the absence of the word drainage, and the second
15 one was probably pretty reasonable.
16 DR. STEINBERG: The way you have that worded over
17 there, you say moderate to severe or those who have failed
18 therapy, whereas, the studies mostly have looked at people
19 how have not responded to therapy.
20 In other words, should the wording really have --
21 forget the moderate to severe who haven't been treated,
22 those who have been treated, but who haven't responded to
23 treatment, because that is really what the studies have
24 showed us.
25 DR. SIEGEL: That is a question worth considering.

1 There are certain things we always generalize. You know, we
2 probably aren't going to put in your creatinine has to be
3 above or below something, there are others that we don't.
4 I suppose what I would wonder or ask back about
5 that question is if the study was done in people who failed
6 to respond to other therapies, you might want to put that in
7 the indication, and I would think that decision would depend
8 on (a) is there any reason to believe it wouldn't work if
9 used before other therapies, or (b) are there other reasons
10 why you might not want to use it as a first-line therapy.
11 Many new drugs come in as second-line therapies,
12 and we don't indicate them first-line because we don't have
13 enough safety data or they are not safe enough or they are
14 not as good as alternative, so it is not uncommon to label
15 things for disease refractory to other therapy, but not
16 routine either.
17 I wonder if anyone would care to comment on those
18 issues.
19 DR. LAINE: I would agree with Dr. Steinberg. I
20 would use both personally, moderate and severe, and some
21 sort of indication of failure. I have a problem with
22 failure of conventional therapy, if somebody is on steroids
23 and you can't lower the dose, that is not a failure of
24 conventional therapy, nevertheless, it would be perhaps an
25 indication.

1 So, we would have to think somehow about wording
2 it in a slightly different way perhaps, but I would be of
3 the opinion that it would be not my first-line therapy, and
4 I would not want to use it in mild Crohn's disease
5 especially right now when we don't know about the long-term
6 efficacy and we still have some questions about safety that
7 we need to have resolved.
8 I think we would only want to use it in people who
9 are really problematic. When we get more information, you
10 night want to change that and make it much more liberal.
11 DR. FRANK: But you don't want to require that
12 patients already be tried on all the immunosuppressives, I
13 lope, failure to respond to methotrexate and Imuran --
14 DR. LAINE: I don't think you want to get that
15 specific.
16 DR. SIMON: Why did you say that?
17 DR. FRANK: Because I am not sure that that ought
18 to be a requirement. I don't know that those agents are so
19 much safer.
20 DR. SIMON: But we don't know that.
21 DR. FRANK: But we know we gets lots of problems
22 with the others in some cases.
23 DR. SIMON: That is because they are used over
24 long periods of time. This is one dose. They fail. We may
25 have to use this over long periods of time for those

patients, and we don't know what the safety issues will be in those patients. Unless we have head to head with methotrexate or other drugs, it is attractive to say that, out that is speculative. We don't know that.

DR. STEINBERG: Wouldn't you agree that we are at the point now that we should discourage this drug as a first-line drug?

DR. SIMON: Right.

DR. STEINBERG: And we should have the indications tate that in some way, that this is not your first-line rug at this point.

DR. SURAWICZ: It wasn't studied as a first-line rug.

DR. STEINBERG: But the way the wording is right ow, it can be construed to be used as a first-line drug.

DR. SIMON: Right.

DR. STEINBERG: And that is really not as it has en designed, nor as I think clinicians would want to use I think we ought to have that somehow written into the dications.

DR. SURAWICZ: I think that is going to be very fficult because what are your first-line drugs. They uld be anything from sulfasalazine or 5-ASA product, all e way to a one-year trial of azathioprine or 6-MP or closporine or whatever.

1 I think it is going to be impossible to mandate
2 that.
3 DR. STEINBERG: I don't think we should specify
4 what those first-line drugs are, but just because there is a
5 hodgepodge, but just say this is not a first-line drug.
6 DR. SIMON: Or alternative, do you want to say
7 failure of conventional therapy?
8 DR. SURAWICZ: Whatever that is.
9 DR. STEINBERG: Whatever that is.
10 DR. SIMON: All of what we just talked about.
11 DR. MILLER: One of the things you want to be able
12 to do is to make it so the clinicians have a decision point.
13 The way they put it, "conventional therapies are
14 inadequate, " leaves the clinicians some leeway. There may
15 be some patients who steroids are completely contraindicated
16 in, but by the intent of saying think about it before you
17 use it, use it under certain situations, you have sort of
18 given the clinicians -- and also from a reimbursement
19 standpoint -- you are giving them some leeway to say this is
20 why I say this is inadequate, my patient needs it, as
21 compared to saying you have to fail this, this, and this.
22 I think as long as we give the intent that this is
23 not you standard first-line therapy at this point, even
24 though it may be at some future time that the studies will
25 show that this will be better than what you used the first

1 time.

2 At this point, I think, number one, you need to

3 give the clinicians some leeway, but also give the idea that

4 use it when you really need. to. I like the other way it is

5 written.

6 DR. SURAWICZ: I think it is a good point, and I

7 think the term "conventional" is more realistic, more

8 helpful to me as a physician than "first line."

9 DR. LAINE: I think that wording is very good.

10 So, moderate to severe in whom patients with moderate to

11 severe Crohn's disease in whom conventional therapy is

12 considered inadequate?

13 DR. MILLER: Right, and close enterocutaneous

14 fistula --

15 DR. LAINE: That would be the first one I would

16 do, and then the second one would closure of draining

17 fistula.

18 DR. FRANK: So, the first question we are going to

19 vote on is indication for moderate to severe Crohn's disease

20 which has failed conventional therapy.

21 DR. LAINE: No, in whom conventional therapy is

22 inadequate. I think there is a difference. That is an

23 important point because it is not failed --

24 DR. FRANK: Right, in whom conventional therapy

25 has been inadequate.

1 DR. ELASHOFF: Is instead of has been, is
2 inadequate?
3 DR. LAINE: That's fine, yes. In whom
4 conventional therapy is.
5 DR. FRANK: In whom conventional therapies are.
6 DR. LAINE: That is fine.
7 DR. FRANK: Mr. Getz.
8 MR. GETZ: Yes.
9 DR. FRANK: Dr. Berardi?
10 DR. BERARDI: Yes.
11 DR. FRANK: Dr. Elashoff?
12 DR. ELASHOFF: Yes .
13 DR. FRANK: Dr. Steinberg?
14 DR. STEINBERG: Yes.
15 DR. FRANK: Dr. Surawicz?
16 DR. SURAWICZ: Yes.
17 DR. FRANK: Dr. Laine?
18 DR. LAINE: Yes.
19 DR. FRANK: Dr. Simon?
20 DR. SIMON: Yes.
21 DR. FRANK: Dr. Miller?
22 DR. MILLER: Yes.
23 DR. FRANK: Thank you.
24 The drug is indicated for use in closure of
25 terocutaneous fistulae.

1 DR. LAINE: Draining.

2 DR. FRANK: Closure of draining enterocutaneous

3 fistulae.

4 DR. SURAWICZ: Could I ask for clarification

5 because when I hear the term enterocutaneous, I don't think

6 of perianal disease. I think of the abdominal wall. If I

7 was reading that as a gastroenterologist, I would be

8 confused and I would think that it meant that it wasn't for

9 perianal disease, and I am wondering just say fistulizing

10 Crohn's disease or something like that would be a little bit

11 more clear.

12 DR. STEINBERG: Except so many of those fistulas

13 are entero-entero fistulas for which we would not be using

14 this.

15 DR. SURAWICZ: You might.

16 DR. STEINBERG: Perhaps we ought to say

17 enterocutaneous and perianal or whatever.

18 DR. SURAWICZ: I think if you just say fistula, it

19 is a little bit easier, because there are so many different

20 fistulas, they go in so many different directions, every

21 time you say this fistula or that fistula, then, you have

22 left out five other fistulas, so why not say fistulas. I

23 propose that. What do you think?

24 DR. LAINE: Or cutaneous fistula?

25 DR. FRANK: I think we need to leave the rest up

1 to the clinicians. I would like to take a vote on an
2 indication for use in fistulizing Crohn's disease.
3 DR. STEINBERG: Without specifying where the
4 fistula --
5 DR. FRANK: Without specifying.
6 MR. GETZ: Yes.
7 DR. BERARDI: Yes.
8 DR. FRANK: Dr. Elashoff?
9 DR. ELASHOFF: I guess I have a little bit of a
10 problem because I am not at all sure about what that might
11 include that wasn't included in the trial, simply because of
12 lack of knowledge.
13 DR. FRANK: I think the only thing that wasn't
14 evaluated was enteroenteric fistulae because they had
15 rectovaginal fistulae, they had abdominal fistulae.
16 DR. LAINE: Was that vaginal or perivaginal?
17 DR. FRANK: Does the sponsor know about that?
18 Where were the fistulae?
19 DR. LAINE: Were they internal or external?
20 DR. SCHAIBLE: Our review of the data indicated
21 there were three rectovaginal, the remainder were
22 perivaginal.
23 DR. ELASHOFF: I guess my vote is the kinds that
24 were covered in the trial I certainly would say yes on. I
25 am a little reluctant to say something that might include a

1 whole lot that weren't, and it is simply I am not familiar
2 with the language, so I guess I will leave it at that.
3 DR. SIEGEL: If we were to indicate perhaps
4 language like patients with draining fistulae, that would
5 presumably not include enteroenteric fistulae and cover
6 those, whether perianal or enterovaginal. So, we could
7 refer to drainage of fistulae, that might solve this
8 problem, but I wonder, part of the way the question was
9 asked, one of the things we were wondering about was part of
10 another question, is would the indications say something
11 about closure or given that the endpoint was stopping
12 drainage, is that the same thing, ought that to be in the
13 indication. I am not sure I have a clear feeling for what
14 this committee feels.
15 DR. FRANK: Ideally, we would like closure, but I
16 am not sure that is always possible.
17 DR. LAINE: What I thought earlier was because
18 when something is draining and it stops draining on
19 pressure, as long as you say closure of draining fistula, it
20 really is closed for all intents and purposes, if you are
21 unable to express anything out of it. So, I would be
22 willing to say if it was draining, and it is not draining
23 now, I would be willing to use the word closure of draining
24 fistula. Would other GI people agree?
25 DR. TREMAINE: As a non-voter, I would like to

1 just also express concern. We haven't mentioned
2 enterovesical. It is not an uncommon problem, and there is
3 no way to address enterovesical fistulas here. I think the
4 concept of draining to externally needs to be a modification
5 to this to capture what has been looked at experimentally.
6 DR. STEINBERG: You would want the wording to
7 specify exactly which fistulae have been closed.
8 DR. TREMAINE: I think the initial proposal for
9 enterocutaneous fistula, I think the concept of cutaneous
10 fistula is something that is draining to the outside should
11 be maintained. If enterocutaneous is confusing, then, maybe
12 just change it to cutaneous fistula or draining cutaneous
13 fistula.
14 DR. SURAWICZ: How about just draining, because if
15 it wasn't draining on the outside, you wouldn't know.
16 DR. FRANK: Well, you do know in cases of
17 enterovesical .
18 DR. LAINE: What is wrong with draining cutaneous
19 fistula? That is what I said, too. They are skin, they are
20 draining. I mean that is what was studied except for those
21 rectovaginal, which probably wouldn't really fit the
22 protocol study anyway.
23 DR. STEINBERG: But the word cutaneous doesn't
24 need to be there.
25 DR. SURAWICZ: No, I would take that out.

1 DR. STEINBERG: Because there are vaginal ones.

2 DR. LAINE: There were three vaginal, but the

3 study wasn't actually designed to -- was it designed to

4 include vaginal?

5 DR. WEISMAN: Yes.

6 DR. LAINE: So, is perianal and rectovaginal?

7 Interesting.

8 DR. WEISS: One question. The study specifically

9 asked for you had to have the fistula for at least three

10 months, and we got into this discussion when we lumped the

11 indication together when we talked about people with active

12 disease, and people who had sort of an acute episode, their

13 signs and symptoms -- actually, the word "acute" was in one

14 of the proposed indications, and the fact that the fistula

15 itself were more chronic, I guess, they had been there like

16 three months.

17 I am just asking you a question, is that an issue?

18 DR. WEISMAN: The technical reason for that is

19 these patients were permitted to be on therapy, and what you

20 wanted to avoid was a patient, for example, on azathioprine

21 or methotrexate, who didn't have an adequate trial of

22 therapy to show that they weren't closing from some other

23 reason. By its very nature, this is not a common disease,

24 all those patients were very precious, and we wanted to make

25 sure we were answering the question clearly.

1 think there was actually some concern on the sponsor's part, and I remember talking to Dr. Present and others, were we asking too much of the drug to close chronic fistula, but in retrospect, it certainly worked out.

DR. LAINE: Are you asking if you want to have the word chronic draining fistula, is that what you are asking?

DR. WEISS: Is that something that is of importance in terms of indication for people with fistulizing disease, some aspect that you have had to have it for a period of time?

DR. LAINE: Again, I am not sure people would start the drug just if somebody had had a fistula for just a few days anyway. It is not unreasonable since that was studied to put the word chronic in. That is what they studied. I don't think it would bother anybody to have chronic in there.

DR. SURAWICZ: It just adds more confusion and ambiguity. I would try to make it as clear as possible. I think I would leave it out. I think fistulas are a chronic problem. I don't think of that as you get an acute fistula and then it goes away. You get a fistula because you have a chronic process going on at that time, so I would tend to leave it out.

DR. FRANK: We are voting on closure of draining fistulas in Crohn's disease patients.

1 DR. SIEGEL: Maybe I can help out here. I think
2 we have a strong sense of this committee thinks there should
3 be an indication and a separate indication for fistula, and
4 we have heard from you about how to word -- I don't think we
5 necessarily need a vote on precise wording. I think we have
6 received the guidance we need unless you feel like you would
7 like to.
8 DR. FRANK: Taking into account the issues that we
9 have discussed in Question 2 on safety, what type of warning
10 should be included in the label to address the unknown
11 safety concerns? Dr. Simon. This is a discussion question.
12 Seriously, what should we add?
13 DR. SIMON: I think that we should say what we now
14 know, that things can happen. So, we know that you can
15 develop and anti-DNA antibody. You can develop an
16 antinuclear antibody. You can develop a lupus-like
17 syndrome. We have observed certain things. The incidence
18 of lymphoma needs to be identified. I don't think there is
19 anything wrong in identifying data when you have the data.
20 The problem, the down side of that, it is
21 uninterpretable in certain ways. We don't know the
22 importance of it. Again, we have left other things up to
23 the clinician. Perhaps we should leave that up to the
24 clinician, as well, weighing the risks and benefits. That
25 is what they do when they use glucocorticoids.

1 We know that glucocorticoids work in certain
2 diseases, short term and long term, and with that comes a
3 lot of baggage. Everybody talks about it. We don't write
4 them up as much any longer, and perhaps we should do the
5 similar thing here, list what the toxicities are and with
6 the caveat that we do not understand the ramifications of a
7 positive anti-DNA, and write down how long they last, if
8 they were nine months and they disappeared, so they were
9 anti-DNA-positive for, nine months. That is what I suggest
10 we do.
11 DR. FRANK: Dr. Miller.
12 DR. MILLER: I agree especially given the fact
13 that we have already limited the use or recommendation for
14 limitation of the use for patients who have moderate to
15 severe disease, inadequate response to other therapies, and
16 you could list them, but I wouldn't put big warnings on it
17 because the data speaks for itself, and as long in
18 appropriate clinical situations, the clinician should be
19 able to make that determination.
20 DR. FRANK: But I think the label should
21 definitely include the issue of infections and autoimmunity,
22 antibodies, and I would like to add not just lymphomas, but
23 also malignancies, period, need to be evaluated.
24 DR. SIMON: That's fine. I also wouldn't put a
25 big black box around it. That is not appropriate. We don't

1 know the ramifications of it.

2 DR. STEINBERG: How would you put it, there is a

3 fear of malignancy? I mean how you put this makes all the

4 difference in the world.

5 DR. FRANK: The way it was presented here, in

6 succinct form. The data that we have, the cases that we

7 have, and we don't know the primary disease versus the

8 therapy.

9 DR. LAINE: I was just going to say, just for the

10 committee's consideration, since we don't know the long-term

11 effects, I was wondering whether we should have a sentence

12 or about the fact that the benefits or the efficacy of

13 repeated treatments are unknown at this time. I think it is

14 worth physicians knowing that at this time we only know it

15 works in the acute short term, and it may or may not in the

16 future. What do the agency or other people think about

17 that?

18 DR. SIMON: I agree with that, but, Loren, I think

19 if you are going to say that, you also need to say we don't

20 know the toxic effects of being treated long term, as well.

21 DR. FRANK: I would like to urge the company not

22 to let down on these studies that you are proposing. I

23 think they are going to be critical, and I would not, if the

24 drug is approved for acute use, give up and let it go as it

25 is. I think it would be very important to get the long-term

1 usage with multiple doses.

2 There is one other issue that we have been asked

3 to look at. I think it will be discussed again tomorrow,

4 but I would at least like to read the issue and see if

5 anyone on the panel today has any comments, and that is

6 dealing with pediatric populations and study in pediatric

7 populations .

8 All completed studies with cA2 to date, for

9 Crohn's as well as for other indications, have been limited

10 to adults, although I gather that a few children have been

11 treated either compassionately or otherwise. I believe the

12 first patient who was treated was, what, 12 or 14, something

13 like that.

14 Regulations governing labeling for pediatric use

15 permit extrapolation of efficacy from adult data to

16 pediatric populations provided the course of the disease and

17 the drug's effects are similar. Other data, including

18 pharmacokinetic and safety data, would normally be required.

19 Provided sufficient PK data were collected in

20 pediatric patients to determine a dose and schedule or cA2

21 and safety assessments indicate no new or increased safety

22 concerns (other than described in the studies conducted in

23 adults) is it appropriate to extrapolate efficacy for cA2 as

24 determined from adult studies to pediatric populations?

25 How do we feel about that? Dr. Simon.

1 DR. SIMON: I actually think that the pediatric,
2 rule and its application to the issue of biologics to
3 children as it relates to development in areas that we don't
4 understand, we don't understand how this drug is really
5 working in adults, let alone children, and there may be
6 issues in children that are particularly unique.
7 So, although the statement that you made was
8 really related more to efficacy in children, and that there
9 would have to be safety issues raised in children, I think
10 that they are inextricable from each other, and there may be
11 unique ways that biologics behave in little people than they
12 do in big people, and I think we have to learn that.
13 DR. FRANK : Dr. van Deventer?
14 DR. van DEVENTER: Of course, I agree with that,
15 but the very first patient that was treated with infliximab
16 was a child, and she immediately started growing, and the
17 point is the indication in children is orphan drug
18 indication, and there will never be enough children with
19 Crohn's disease to do an adequate trial, and I" think that
20 should be kept in consideration, as well. There never will
21 be an adequate Crohn's disease in infliximab pediatric
22 trials, because there are simply not so many children.
23 The other point is that these children that have
24 Crohn's disease are not very small children. Usually, they
25 are children from age 8 up, they are not infants. I can't

1 imagine for very small children or infants there would be a
2 difference, but we are talking about children 8 years and
3 up. I believe that is most of the children with Crohn's
4 disease. So, I think those are considerations.
5 DR. STEINBERG: Can I ask you a question before
6 you sit down. Should any restrictions be placed on the age,
7 the minimum age from your standpoint?
8 DR. van DEVENTER: At this point, from a patient's
9 perspective, I know that there are very dramatic children
10 that are with very dramatic Crohn's disease, and I think
11 they deserve the same orphan indication for the drug as do
12 adults. If you do not grant the orphan indication based on
13 the data that there are now, I think it will take a long,
14 long time before that indication will be there.
15 DR. FRANK: Dr. Simon.
16 DR. SIMON: I would like it to be clear that I am
17 compassionate as the next guy. My problem is, is that I
18 don't know what the role of TNF alpha is in bone
19 development. I know if it's important in epiphyseal
20 closure. I don't know if it has anything to do with growth
21 in certain ways. The fact that one child responded by
22 growing based on therapeutic intervention, I am not exactly
23 sure that is extrapolatable in other children and to large
24 populations of children.
25 I recognize that it is difficult in rare diseases,

1 but I also would urge us to consider the fact that biologic
2 therapy is different than drug therapy, and there may be
3 significant ramifications that at least our trial needs to
4 be done in children of some size -- these were pretty small
5 trials -- for us to understand what the significant issues
6 are in the treatment of children with this particular
7 intervention.
8 DR. FRANK: Dr. Present.
9 DR. PRESENT: The pediatricians will tell us that
10 Crohn's disease in children is much more severe, more rapid
11 onset, more fulminating and lead to surgery more quickly.
12 It has taken them -- we did our 6-mercaptopurine report in
13 1980, and it wasn't until, as Sander just said, until 1998
14 that the first study was complete looking at 6-MP in
15 children, and it works equally as well.
16 I agree with you there is a lot of unknowns, but
17 most of our adolescents respond to the same drugs we are
18 using in our adults, and certainly I have experience from 13
19 on up, and they respond in a similar way. I can't speak for
20 children under that age, but I think it is an important
21 consideration that pediatricians need to be able to study
22 these patients.
23 DR. STEINBERG: So, Dan, you would place no
24 restrictions if you had your druthers on age?
25 DR. PRESENT: I would certainly let adolescents be

1 treated with this. I am hard put to say anything below that
2 because I don't treat children below that, but all
3 adolescents responded exactly the same way I have seen to
4 adults.
5 DR. STEINBERG: Should there be a restriction to
6 have from adults on up?
7 DR. PRESENT: I would allow adolescents.
8 DR. FRANK: We have a pediatric gastroenterologist
9 coming tomorrow that might lend some information on this.
10 DR. LAINE: Are there not rules about this,
11 though , I mean it is not up to us just to say we are going
12 to let 12- or 14-year-olds, is it?
13 DR. SIEGEL: The question you are answering is not
14 the one we asked, and, Dr. Simon, I guess I am a little
15 confused about the remark you made regarding safety and
16 efficacy and being concerned about both, because the
17 examples you gave are about safety.
18 The question as worded presumes that there ought
19 to be specific safety studies in children. One of the most
20 important ones would be studies of growth, to the extent
21 obviously that it is feasible to get those data, those data
22 should be gotten, and it presumes there ought to be
23 pharmacokinetic studies.
24 As to efficacy studies, it is pretty hard for most
25 [rugs, and I would suggest this one, as well, to get

1 efficacy other than from controlled clinical trials, and
2 what we face then in pediatric disease, in diseases such as
3 this, that affect both pediatric and adult populations, is
4 if we have efficacy in adult populations, to ask for safety
5 and PK data in children, and then to extrapolate efficacy,
6 or whether we believe" that the biology of the disease and of
7 the drug are such that efficacy may also be different in
8 children.
9 In fact, is that what your comment was, that you
10 have that concern about efficacy, as well?
11 DR. SIMON: I don't know how to perform a safety
12 trial without an efficacy component to it. That is my
13 concern. That is why I linked the two together.
14 If you don't use enough of the drug to make it
15 work, and you have no side effects, so what?
16 DR. SIEGEL: We do" open-label safety trials, and,
17 sure, you get some response rate data if you want to call
18 that efficacy data.
19 DR. SIMON: It has to be designed so that you know
20 that you have an efficacious dose of the drug that is going
21 to make a difference, and under those circumstances, that
22 that is the dose range you are going to be in to get your
23 safety data.
24 DR. LAINE: My understanding was after an adult
25 study like this, I mean you are not going to be writing --

1 the labeling is not going to include kids anyway, is that
2 not correct, so it is a non-issue?
3 DR. WEISS: Well, what we have been trying to do
4 is to obtain data, such as pharmacokinetic and some open-
5 label data, and actually, the newest pediatric proposals are
6 not final rules yet at the agency, and we will be discussing
7 more of that tomorrow, are actually going to now require
8 that at the time of a marketing application, at the time
9 that we are sitting here like this, we have in hand some
10 pediatric data. It may have to be controlled efficacy
11 trials, it may be open-label data showing safety, PK, and
12 response rate, but we are going to have to have some type of
13 data in hand.
14 The first part of the question we are throwing to
15 the committee right now is, is this a disease that is
16 expected to be similar enough in adults and children, and
17 you would have some reason to think that the drug's effects
18 would be similar, so that one can extrapolate the efficacy
19 and therefore maybe have a smaller, more limited type of
20 studies in hand.
21 We don't have anything right now in hand, but
22 oftentimes when we have information, such as pharmacokinetic
23 data, so that we can recommend a dose, and we know the
24 safety profile, we will not restrict the indication or we
25 restrict it to whatever age range may be appropriate, like

1 down to 12 year olds or adolescents or whatever, and provide
2 what information we have on a label.
3 DR. LAINE: But that is in the future, not now in
4 the case, is that right or not right?
5 DR. WEISS: In this case, we do not have pediatric
6 information yet, so I guess the question to the committee
7 would be given what we have, which is no pediatric data,
8 would we want to basically with this indication say this is
9 indicated for adults age whatever or just say it is
10 indicated for adults with enterocutaneous fistulas, you
11 know, moderate to severe disease, and some of our
12 indications are specific for adult, some are silent and just
13 say indicated for patients with these symptoms.
14 DR. FRANK: I would like to ask the panel how they
15 would feel about recommending this for pediatric population
16 until we have the data, the safety data from multiple doses
17 in the ongoing trials, how do you feel about that? Are you
18 happy with it now? Dr. Tremaine.
19 DR. TREMAINE: I would personally favor not
20 restricting it. I think we don't have any strong reason to
21 restrict it. I think we currently use the same medications
22 to treat children that we use to treat adults with active
23 disease. I think without any data to convince us that there
24 is a difference, that there is no good reason to restrict
25 it.

1 DR. LAINE: I probably would use it again in the
2 very seriously ill child who had failed other therapy. I
3 don't think I would not use it. Just like you said, we use
4 other drugs anyway, so I think clinically we would use it,
5 but frankly, I am not sure it matters what is in the label
6 because we do that anyway.
7 DR. TREMAINE: But it matters to the child in
8 terms of reimbursement whether or not this is going to get
9 covered.
10 DR. MILLER: I don't think we should limit, and we
11 should ask for the bumped PK data, but I don't think it
12 should be limited since we have already said you have to
13 have moderate to severe disease.
14 DR. SURAWICZ: I agree with what has been stated.
15 I wouldn't limit it. I think that pediatric
16 gastroenterologists really are the experts, and I would like
17 to have their input, but I would suspect that they would
18 like to have the freedom to be able to use something in
19 desperately ill children whom they are treating and that
20 they probably are twice as cautious about use of medications
21 because they are treating children, so I wouldn't be too
22 concerned.
23 DR. STEINBERG: I agree.
24 DR. WEISS: Is there a lower age that anybody
25 would -- or not at all, not even mention anything like that.

1 DR. FRANK : I don't think we can.

2 DR. WEISS: We will follow this up tomorrow when

3 we have some more discussion on pediatrics.

4 DR. FRANK: I think the pediatric

5 gastroenterologists will know better about the ages, I mean

6 because certainly the most frequent age are the adolescent

7 and the pre-adolescent.

8 Joan has asked me to just clarify our

9 recommendation for the use of the drug in moderate to severe

10 Crohn's disease and to specify short-term use because we

11 have not gotten the data for multiple doses.

12 DR. LAINE: That is what I was going to ask.

13 Where it says 5 mg, are we just going to say just what the

14 study says, one-time 5 mg dose or 3 time in the

15 nterocutaneous, are you just going to do exactly what --

16 DR. SIEGEL: I presume so.

17 DR. FRANK: I would like to thank the panel very

18 uch and the sponsor for their very lucid presentation and

19 ur audience.

20 The meeting is adjourned.

21 [Whereupon, at 5:04 p.m., the proceedings were

22 ecessed to be resumed at 9:00 a.m., Friday, May 29, 1998.]

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C E R T I F I C A T E

I, ALICE TOIGO, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

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