

UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

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MEETING # 48

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MONDAY, JULY 14, 1997

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The meeting was held in the Grand Ballroom at the Holiday Inn Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, MD, at 8:30 a.m., Dr. John Kane, Acting Chairperson, presiding.

PRESENT:

Dr. John M. Kane, Chairperson
Rhonda Stover, Executive Secretary
Dr. Stephen R. Marder, Member
Dr. Carl Salzman, Member
Dr. Emile Risby, Member
Dr. Ming T. Tsuang, Member
Dr. Roberto A. Dominguez, Member
Dr. Barbara Geller, Member
Dr. Daniel E. Casey, Consultant
Dr. Carol A. Tamminga, Consultant
Dr. Pippa M. Simpson, Statistician
Mary Gomez Curll, Consumer Representative

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FDA REPRESENTATIVES PRESENT:

Dr. Paul Leber
Dr. Thomas Laughren
Dr. Greg Burkhart
Dr. Judith Racoosin

SPONSOR REPRESENTATIVES PRESENT:

Dr. Thomas Koestler, Novartis
Dr. Ravi Anand, Novartis
Dr. Noel Weiss, Novartis
Dr. Stanton Gerson, Novartis
Lawrence Hauptman, Novartis

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

(8:33 a.m.)

CHAIRPERSON KANE: Okay, I'd like to welcome everyone to the 48th Meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration. The topic today is proposals to reduce the frequency of required white blood cell count monitoring for Clozaril.

I'd first like to ask everyone at the table to introduce themselves. My name is John Kane. I'm from the Hillside Hospital and Albert Einstein School of Medicine in New York.

DR. SALZMAN: Carl Salzman, Harvard Medical School and Massachusetts Mental Health Center.

DR. RISBY: Emile Risby, Emory University, Atlanta.

DR. TSUANG: Ming Tsuang, Harvard University and Mass Mental Health Center.

DR. GELLER: Barbara Geller, Washington University in St. Louis.

DR. DOMINGUEZ: Roberto Dominguez from the University of Miami.

DR. TAMMINGA: Carl Tamminga from the University of Maryland.

MS. CURLL: Mary Curll, San Antonio

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1 College School of Nursing.

2 MS. STOVER: Rhonda Stover, FDA.

3 DR. MARDER: Stephen Marder, West Los
4 Angeles VA Medical Center in UCLA.

5 DR. SIMPSON: Pippa Simpson, Children's
6 Hospital of Michigan, Wayne State University.

7 DR. CASEY: Daniel Casey from the VA
8 Medical Center in Portland, Oregon and the Organ
9 Health Sciences University.

10 DR. LAUGHREN: Tom Laughren, FDA.

11 DR. LEBER: Paul Leber, FDA.

12 DR. BURKHART: Greg Burkhart, FDA.

13 CHAIRPERSON KANE: Thank you.

14 MS. STOVER: I will now read the conflict
15 of interest statement.

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

20 Based on the submitted agenda and
21 information provided by the participants, the Agency
22 has determined that all reported interests in firms
23 regulated by the Center for Drug Evaluation and
24 Research present no potential for a conflict of
25 interest at this meeting with the following

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1 exceptions.

2 We would like to disclose for the record
3 that Dr. Stephen Marder, as part of his federal duties
4 as an employee of the Department of Veterans Affairs,
5 is currently participating in a study involving
6 Clozapine. In addition, we would also like to
7 disclose that Dr. Kane recently served as a
8 participant in a one-day Clozaril board meeting.

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

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

19 CHAIRPERSON KANE: We now have time for
20 the open public hearing portion. No one signed up in
21 advance to speak. Is there anyone in the audience who
22 did come prepared to make some comments?

23 Yes? If you could identify yourself,
24 please?

25 MS. FITCH: My name is Carol Fitch and I

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1 am here to represent the National Alliance for the
2 Mentally Ill.

3 NAMI, as many of you know, is a non-profit
4 organization of families and people with severe mental
5 illnesses. Large numbers of our members have
6 psychotic disorders and many of them are now on
7 clozapine.

8 Oh, you should also know that Novartis
9 does, in fact, contribute unrestricted educational
10 grants to NAMI.

11 I've been asked to support this proposal
12 on behalf of NAMI. As many of you know, the blood
13 draw has become very difficult for many people.
14 Particularly after more than a year, the blood vessels
15 collapse and the incentive to continue on this very
16 fine medication dissipates as the difficulties of a
17 blood draw continue. We hope very much that the
18 proposal is accepted.

19 Thank you.

20 CHAIRPERSON KANE: Thanks very much.

21 I'd like to add that we did receive a
22 number of letters from physicians, from consumer
23 groups regarding this hearing as well. The letters
24 have been distributed to the Committee members. I'm
25 going to allude to one letter from Jean Smith Silver

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1 of Akron, Ohio, in which she requested to be made a
2 part of the meeting's record. This letter also has
3 been distributed to the members and will be included
4 in the record.

5 In her letter, Mrs. Silver stated that her
6 son has been treated with clozapine for over ten
7 years. Based on his difficult experiences with the
8 weekly blood tests, she proposed limiting testing to
9 no more than once-a-month, specifically in those
10 instances where clozapine has been used over an
11 extended time period with no traces of adverse
12 hematologic effects.

13 The other letters we received were quite
14 similar.

15 Now, I'll ask Dr. Laughren to make the FDA
16 introductory comments.

17 DR. LAUGHREN: Good morning and welcome to
18 the 48th meeting of this Committee.

19 As you know, Clozaril is available only
20 under a restrictive distribution system. This is
21 known as the "No Blood/No Drug" policy. This policy
22 was put in place at the time that Clozaril was
23 approved and this is the labeling language that
24 describes the policy. "Clozaril is available only
25 through a distribution system that ensures weekly

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1 white blood cell testing prior to delivery of the next
2 week's supply of medication."

3 Now, why was this system put in place? At
4 the time that we approved Clozaril, we believed that
5 Clozaril had a very high risk of agranulocytosis
6 compared not only to other antipsychotic drugs but to
7 other drugs on the market. Of course, agranulocytosis
8 is a serious event. It's potentially fatal. There is
9 no way to predict who might develop agranulocytosis.
10 At the time that we approved Clozaril, we believed
11 that weekly monitoring of white blood cells could
12 reduce the risk of agranulocytosis and death. And we
13 also believed at the time that routine labeling would
14 likely not accomplish the goal of weekly testing for
15 all patients. So, this was the basis for putting that
16 original system in place.

17 A reasonable question to ask is why was it
18 weekly monitoring? Now, the goal of any monitoring
19 here, of course, is to try and pick up cases early.
20 Both patients who are drifting downwards toward
21 agranulocytosis and to pick up any cases of
22 agranulocytosis before the patients become ill. So,
23 there's this obvious relationship between the
24 frequency of monitoring and the probability of early
25 detection. The more frequent you monitor, the more

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1 likely you will pick up cases early. Following that
2 logic, the ideal monitoring situation would be to
3 monitor continuously. Obviously, that's impossible.
4 So, a practical, but admittedly arbitrary compromise
5 was to monitor weekly. We felt, and the company felt,
6 that that was something that could be accomplished.
7 And so, that's the basis for the weekly monitoring.

8 Now, during the roughly eight years that
9 Clozaril has been available, what have we learned
10 about the risk of agranulocytosis under the system of
11 weekly monitoring? I think we've learned two
12 important things. First of all, we've learned a lot
13 more about the precise nature of the risk over time.
14 As you know from reading the materials, the risk of
15 agranulocytosis with Clozaril rises steeply during the
16 first two months. It peaks at about three months. It
17 falls equally dramatically to six months, and even
18 after six months, it continues to fall more gradually.
19 And we know this with much greater precision now than
20 at the time that Clozaril was approved. I mean, we
21 had some data to suggest that there might be a risk
22 interval, but we know this now with much greater
23 precision.

24 Secondly, I think what we've learned is
25 that the risk of dying in patients who develop

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1 agranulocytosis is about three percent.

2 So, basically, what we have, having had
3 this very extensive experience with Clozaril is a more
4 refined estimate of agranulocytosis. A reasonable
5 question to ask is how does this compare with what are
6 believed to be the risks for other marketed drugs?
7 I'm not going to address that. Dr. Racoosin from the
8 Division is going to talk about that later on in the
9 program.

10 I wanted to raise the issue because I
11 think it is a relevant question to ask. Again, if you
12 think back to one of the reasons why the system was
13 put in place in the first place is that we believed
14 that the risk of agran for Clozaril is much higher
15 than other drugs. So, it's reasonable to ask now that
16 we know the risk with much greater precision, how it
17 compares with what we believe to be the risks for
18 other drugs?

19 Now, what have been the apparent benefits
20 of having this "No Blood/No Drug" policy? First of
21 all, it appears that the risk of agranulocytosis has
22 declined compared to our pre-marketing estimates. It
23 also appears that the risk of dying, once you get
24 agran, has declined compared to our estimates. Now,
25 I say apparent benefits because one can't know with

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1 any certainty whether or not this has actually
2 happened because, again, we didn't know with any great
3 precision, what the estimates were pre-marketing
4 either for the risk of agran or the case fatality
5 rate. And the other thing that, of course, has
6 changed during the many years since Clozaril was first
7 used is the medical management of patients with agran
8 has changed. That, clearly, may also be a factor in
9 reducing the case fatality rate. But I think most
10 people who have been familiar with this story believe
11 that there probably has been a decline in both of
12 these.

13 Now, if the frequency of white blood cell
14 monitoring were to change, what would be the
15 consequences? Again, if you follow the logic of
16 monitoring and the fact that the more frequently you
17 monitor, the more likely you are to pick up cases
18 early, logic would tell you that as you decrease the
19 frequency of monitoring, you're going to be less
20 likely to pick up patients who are drifting downwards.
21 You would certainly expect that there would be some
22 increase in the incidence of agranulocytosis.

23 Is it possible to estimate that risk?
24 You're going to hear about that in the program. Dr.
25 Weiss from Novartis is going to talk about that, and

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1 Dr. Racoosin from the Division is going to comment on
2 the model and give some of her own thoughts about
3 that. So, I won't comment further on that model.

4 Now, what about the risk of dying of
5 agranulocytosis? Again, following the same logic, you
6 would expect as you move further away from continuous
7 monitoring, you would expect that you would not be
8 catching patients early enough to do anything and
9 there would be some increase in mortality. In this
10 case, there are so few deaths that it's not possible
11 to model deaths in the same way that agranulocytosis
12 was modeled. But certainly, there would be an
13 expectation that there would be some increase in
14 mortality as you move away from continuous monitoring.

15 What about the benefits of decreasing
16 monitoring? Certainly, one would expect that as you
17 make the system more convenient and less painful to
18 patients, they would be more willing to take the
19 medication. Similarly, you would expect that as you
20 reduce the costs associated with monitoring and the
21 complexity of the delivery system, the patients may
22 have greater access. This is hard to prove. This is
23 hard to quantify. Certainly this is the message that
24 we have overwhelmingly heard over the eight years that
25 Clozaril has been marketed.

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1 So, given our greater knowledge about the
2 precise risks of agranulocytosis under the system with
3 the monitoring, given what you will hear about the
4 risks of decreasing monitoring, considerations of
5 possible benefits of reducing monitoring and any other
6 thing that you want to throw into the mix, we have
7 several questions that we'd like you to consider.

8 These are the questions. First of all,
9 should the frequency of required white blood cell
10 monitoring be reduced at some time point after
11 initiation of therapy? If so, when? What reduced
12 frequency of required white blood cell monitoring
13 would be acceptable? Should required white blood cell
14 monitoring be stopped altogether at some time point?
15 If so, when? Thirdly, should the program be changed
16 overall? In other words, should it become voluntary
17 as is most advice in labeling regarding monitoring for
18 adverse events?

19 I want to draw your attention to one
20 slight change that I've made in the questions. I've
21 added the qualifier "required" white blood cell
22 monitoring in questions one and two. The reason I did
23 that is to draw a distinction between monitoring that
24 is in some way linked to the delivery system -- in
25 other words, the availability of drug -- and

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1 monitoring that may appear as a recommendation in
2 labeling. What I want to suggest is that there are
3 many possible options for changing the labeling for
4 this drug. Let me just give you a scenario. This is
5 not a recommendation. This is purely an example of
6 how this might work.

7 For example, supposing you felt that the
8 system, as it's in place now, is essential for the
9 first six months of treatment. In other words, no
10 blood/no drug, required mandatory monitoring for the
11 first six months. At that point, supposing you felt
12 that the required part of that system could be
13 abandoned. You could have labeling that included
14 mandatory monitoring for the first six months and then
15 moved to a voluntary recommendation for monitoring at
16 some frequency from that point forward. For example,
17 supposing you felt that every two weeks would be
18 sufficient. That could be a recommendation rather
19 than a requirement. The point that I'm making here is
20 that there's great flexibility in how we may try and
21 resolve this problem. There's a possibility of a
22 combination of required monitoring plus recommended
23 monitoring.

24 The other point that I want to make here
25 is that this is not the usual kind of question that we

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1 bring to this committee. Ordinarily, we come to the
2 committee with a drug that we're about to approve and
3 we want a specific vote on whether or not the drug
4 should be approved. This is a more complicated
5 situation. It's hard to formulate in advance, the
6 questions. It's difficult to know whether or not the
7 committee is going to even be able to reach a
8 consensus on this. What's most important to us is to
9 have a full discussion of all the issues, and if
10 possible, a sense of the committee about where we
11 should go with this.

12 One possibility would be to give us that
13 general sense and let us work out the details. In any
14 case, this is a very open discussion. You know, we're
15 open to whatever advice you can offer us. Thank you.

16 CHAIRPERSON KANE: Thanks, Dr. Laughren.

17 Next we have the sponsor's presentation,
18 a new drug -- by Dr. Thomas Koestler.

19 DR. KOESTLER: Dr. Kane, Dr. Leber,
20 members of the Advisory Panel, FDA and guests,
21 colleagues, good morning. I'm Tom Koestler. I'm head
22 of Regulatory Affairs for Novartis Pharmaceuticals
23 Corporation.

24 Novartis is pleased to have the
25 opportunity to come before you today to present data

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1 on the current system employed for the use and
2 monitoring of Clozaril tablets in patients with
3 treatment resistant schizophrenia.

4 Our agenda today is presented on this
5 slide and I will begin by giving a very brief
6 overview. I will be followed by Dr. Noel Weiss who is
7 the professor of epidemiology at the University of
8 Washington. Dr. Weiss will present to you a summary
9 of the risk analysis report, and he will provide for
10 you an analysis for different monitoring paradigms and
11 the projections that we might expect from that
12 analysis.

13 He will be followed by Dr. Ravi Anand. He
14 is our executive director in the Central Nervous
15 System Department at Novartis. Ravi Anand will give
16 you a clinical perspective on the data that you will
17 see here today.

18 Now, before proceeding into the overview,
19 I'd like to briefly introduce a number of consultants
20 that we have asked to join us here today to help
21 provide us with advice as we address the issues before
22 this committee. Let me begin by introducing Dr. David
23 Dunner. He's professor and vice chairman of the
24 Department of Psychiatry at the University of
25 Washington. We have Dr. Stan Gerson, who is the

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1 professor of medicine, Chief, Division of Hematology
2 and Oncology at Case Western Reserve University; Dr.
3 Gil Honigfeld, who is associate professor, Department
4 of Psychiatry at the Robert Wood Johnson Medical
5 School, University of Medicine & Dentistry of New
6 Jersey.

7 We also have Dr. Ken Rothman, who is
8 senior scientist, Epidemiology Resources, Inc. and he
9 is professor of public health at the Boston
10 University. He is also the editor of the journal,
11 Epidemiology. And finally, Dr. Weiss, who I've
12 already introduced. He will provide you the data
13 presentation on the risk analysis report.

14 Now, in this specific context of
15 monitoring frequency, patients currently receiving
16 Clozaril therapy, and in particular family members of
17 these patients, have indeed contacted Novartis about
18 a number of issues that they feel are important. In
19 particular, they have requested whether or not they
20 might be more eligible for a less frequent monitoring
21 requirement. We have heard that already from some
22 comments from Dr. Laughren and some comments that were
23 written into the committee.

24 Two prevailing themes have emerged. The
25 first is particularly on patients on long-term

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1 therapy. We heard the one example from a patient
2 that's been on therapy for ten years. The burden of
3 weekly needle sticks for venipuncture for blood
4 sampling can, in fact, result in a very difficult
5 situation and an inconvenience for these patients.
6 And in many cases, we see that there is an instance of
7 collapsed veins. In addition, attendant to this
8 inconvenience of the weekly monitoring is just the
9 burden to the families for coming to the physician's
10 office or to the clinic on a weekly basis.

11 As we proceed through the balance of our
12 presentations this morning, the next two speakers will
13 provide information and data in order to address the
14 following two issues. What are the risks of reducing
15 the frequency of white blood cell monitoring? And
16 conversely, what are the benefits of reducing the
17 frequency of white blood cell monitoring? In the
18 context of these two discussion points, our
19 presentations today will leave you with three
20 important considerations.

21 First, the risk of agranulocytosis and
22 death can be, and are indeed, quantifiable events.
23 And you will see the data presented shortly.
24 Conversely, the benefits of a reduced white blood cell
25 monitoring frequency, while we can readily articulate

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1 what some of these benefits are -- and Dr. Laughren
2 briefly alluded to this as well in his opening
3 comments -- these events are not quantifiable. And
4 then finally, there is always some risk of
5 agranulocytosis and death associated with Clozaril
6 therapy. You'll see that data presented as well.

7 For my concluding slide of this overview,
8 I thought it might be useful to mention briefly what
9 the current treatment monitoring system consists of.
10 The system consists of the physician or the
11 institution or clinic, a pharmacist, and the quality
12 assurance committee. The Clozaril National Register,
13 or the CNR as you're well aware of, as it is commonly
14 referred to, is unique. It is the only centralized
15 epidemiological database in the United States relied
16 upon to make scientific decisions regarding the safety
17 of a drug. You've already heard from the introductory
18 comments that Novartis has always employed a policy of
19 no blood or no drug to ensure patients' safety with
20 this therapy. We think that this registry is a
21 reliable registry. It's a comprehensive database and
22 it's a system that we believe works.

23 At this point, I'd like to now introduce
24 Dr. Weiss and Dr. Weiss will present a summary of the
25 risk analysis report comparing a variety of different

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1 monitoring paradigms.

2 DR. WEISS: Good morning.

3 Novartis has asked me to discuss with you
4 the occurrence of agranulocytosis in users of the drug
5 Clozaril. My presentation is going to be in two
6 parts. In the first, I'm going to talk about the
7 incidence of agranulocytosis and the mortality from
8 agranulocytosis as present in the US Clozaril National Registry
9 through the end of April of 1995. The focus of those
10 data is toward the identification of possible
11 subgroups of patients in whom the risk of agranulocytosis is
12 sufficiently low that one might plausibly consider a
13 reduction in the frequency of monitoring. And we're
14 going to then focus on the particular group that's
15 most promising, that is people who have used the drug
16 for a certain period of time, in whom the risk,
17 indeed, is quite a bit lower than in other Clozaril
18 users.

19 Given that information, then the second
20 part of the presentation will make some estimates
21 about what the occurrence of agranulocytosis might be if the
22 frequency of monitoring were to be reduced in such
23 long-term users of Clozaril.

24 Before I get started, with that, we'll
25 have to define a few terms just to make sure we're all

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1 starting from the same place. As has been described,
2 you don't go immediately from having a normal white
3 count to the state of agranulocytosis, but rather
4 there's a progression of various precursor conditions
5 leading to agran. The first would be something that's
6 termed moderate leukopenia, defined as having a total
7 white count of between 2000 and 3000 cells per cubic
8 millimeter of blood. Below the level of 2000, we get
9 to something called severe leukopenia.
10 Agranulocytosis is not defined on the basis of the
11 total white count, but rather with the total number of
12 neutrophils on the basis of the so-called ANC or
13 absolute neutrophil count. When that gets to be below
14 500 cells per cubic millimeter, then that's
15 agranulocytosis.

16 The monitoring system in the US that's
17 been present ever since the introduction of the drug
18 has required that in order to be started on Clozaril
19 therapy, one must have a total white count of greater
20 than 3,500 and that weekly monitoring be conducted
21 irrespective of duration of use. And in addition,
22 once the patient ceases the drug, four further weeks
23 of monitoring are done.

24 This slide now describes what happens if
25 the white count becomes abnormal. If it drops below

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1 3,500 or if there's a substantial drop no matter what
2 the absolute level, or if they're immature forms, not
3 only is a repeat white count done but a differential
4 count is done to determine the number of neutrophils
5 because that's going to be the indicator of
6 agranulocytosis. If the white count is only mildly
7 depressed between 3,000 and 3,500 -- not yet meeting
8 the criterion for moderate leukopenia -- and if the
9 neutrophil count is above 1,500, the drug is continued
10 but the frequency of monitoring is increased to twice
11 a week, and differential counts are done as well.

12 If the white count, however, falls below
13 3,000 or the neutrophil count falls below 1,500, then
14 therapy is interrupted and daily counts are done.
15 Now, depending on which direction things go, one of
16 two possibilities can ensue. The drug might be
17 discontinued permanently if the white count falls
18 below 2,000 or the neutrophil count falls below 1,000.
19 However, it is possible, starting at this level, to
20 resume therapy if the white count then rises above
21 3,000 and the neutrophil count arises above 1,500.
22 So, there are various strategies involved in trying to
23 minimize to monitor often, weekly, and to take action
24 to try and minimize -- agranulocytosis.

25 What I'm now going to start showing are

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1 the data from the US Clozaril National Registry, and
2 once again, these go through April of 1995. You'll
3 see in the next slide there, this represents some 400
4 agranulocytosis cases that have developed in the
5 Clozaril users during that period. This presents the
6 most relevant feature which is the pattern of risk in
7 relation to duration of therapy. As was mentioned
8 earlier, the risk rises very quickly during the first
9 several months of therapy, peaking at about three
10 months of therapy. The rate at this point is about 30
11 per 1,000 patient years.

12 However, later on during the first six
13 months, the risk begins to fall and then gradually
14 declines starting about -- the decline is more gradual
15 starting about six months and continuing on and out
16 through several years of use. Basically, this is as
17 much data as there is, up to around this point.

18 On the next slide, we'll try and put these
19 into numbers in a table. Here are the total of 406
20 cases of agran that have developed in the 160,000
21 person-years accrued by Clozaril users since the drug
22 was introduced through, again, 1995. That rate is
23 about two-and-a-half per 1,000 patient years. As you
24 can see, almost all of the -- not almost all, but the
25 large majority of the cases have occurred in the first

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1 six months of therapy: 340 of them for a rate of 8.6
2 per 1,000 patient years. You can see that the rates
3 decline, certainly from six to 11 months and possibly
4 thereafter, although the numbers are not large enough
5 to be sure that there's a further decline.

6 Note, however, that even out at 24 months
7 and beyond of therapy, that agran continues to develop
8 in persons taking Clozaril. Here are a total of 16
9 cases in the category of two years or longer to
10 correspond to this rate of .35 per 1,000 patient
11 years. And again, it has to be stressed that this
12 incidence is what has been occurring in the presence
13 of weekly monitoring, a program that was designed, in
14 part, to avert the incidence of agran by the rapid
15 detection of the precursors of agran that do develop.

16 In addition to the variation by duration
17 of therapy, there are other subgroups of patients that
18 ought to be at least explored for the possibility of
19 groups that are unusually low risk. We picked out two
20 that are in the database. One is gender; one is age.
21 The data have been split according to duration of
22 therapy because the first six months is such a high
23 risk period. During that first six months, we can see
24 that between men and women, the rates are not a whole
25 lot different. But that as you go from patients under

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1 40 to over 40, we do see an increase in the risk.
2 There's a several-fold increase both in men and in
3 women.

4 That same pattern, an increase with
5 increasing age, is also seen in persons over the age
6 -- sorry, who have taken the drug for more than six
7 months, here from .36 to .7, .39 to 1.1. Older people
8 do seem to have a higher risk when they use Clozaril,
9 but nonetheless, the absolute change here in the
10 persons who have used the drug for more than six
11 months is quite modest compared to the really
12 substantial difference in the people who have taken
13 the drug for the first six months and those who have
14 taken it for a longer period of time.

15 This slide focuses now on mortality from
16 agranulocytosis. It was mentioned earlier that a
17 total of three percent of all the agran cases in the
18 United States have died of their disease while there
19 were 402 cases and here are the 12 deaths that
20 occurred, corresponding to a rate of .07 per 1,000
21 person-years. All of the 12 deaths through that point
22 in time, April of '95, occurred in persons who had
23 used the drug for less than six months. And indeed,
24 all the deaths had occurred in persons who had used
25 the drug for less than three months. But the deaths

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1 occurred both in men and in women during the early
2 phase of the therapy and they occurred in both persons
3 under the age of 40 and over the age of 40. Although
4 once again, we see that the rates in those who are
5 older are higher than the rates than persons who are
6 younger. And once again, as I've reminded you before,
7 this is the mortality rate in the presence of a weekly
8 monitoring system which is in part designed to keep
9 the mortality rate as low as possible by rapid
10 identification of the development of agranulocytosis.

11 Let's summarize where we've been so far.
12 In terms of the observed incidence, it's far greater
13 in the first six months than thereafter, but new cases
14 do develop beyond two years. Incidence does go up
15 with increasing age. But in the group who have taken
16 the drug for six months or more, the absolute
17 difference across the age groups is kind of small.
18 And finally, in the presence of weekly monitoring, at
19 least through this point of April of '95, deaths had
20 not occurred in patients who had taken the drug for
21 six months or longer.

22 Now we'll go to the second part of the
23 presentation and ask what might happen if we decided
24 to try to reduce the monitoring in persons who are in
25 this lower risk category, specifically persons who

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1 have used the drug for six months or longer? I'll
2 kind of meander into the approach that we used because
3 there are some subtleties to it. What I'm going to
4 focus on now entirely are data from the patients who
5 have used Clozaril for six months or longer. So,
6 we're only focusing on that group and we're going to
7 talk about the occurrence of the precursor dyscrasias
8 starting with moderate leukopenia and we're going to
9 talk about what happens to those patients in terms of
10 their likelihood of developing agranulocytosis.

11 If we go to the registry, we can find that
12 in persons who have used Clozaril for six months or
13 longer, there were a total of 581 who developed
14 moderate leukopenia. Actually, that's a group who
15 either were found at the weekly monitoring to have a
16 white count that met the criteria for moderate
17 leukopenia, or they already had a white count that was
18 lower than the threshold for moderate leukopenia but
19 presumably, they got there by travelling through, so
20 to speak, the state of moderate leukopenia. And
21 that's called the 581.

22 Now, some of these 581, their blood count
23 was dropping so fast that the monitoring system missed
24 them. That is, by the time the weekly monitoring was
25 done, those persons had already gone from normal white

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1 count to a count that was below the threshold for
2 moderate leukopenia all the way to severe leukopenia.
3 These patients whose white count is dropping so fast,
4 it's no surprise that in them, the ultimate chance of
5 developing agranulocytosis was quite high. And
6 indeed, in 45.2 percent of those patients with rapidly
7 dropping white counts, rapidly enough that they were
8 missed by monitoring, did develop agranulocytosis.

9 In contrast, if a patient was detected as
10 having moderate leukopenia during weekly monitoring,
11 those patients once the drug was stopped -- of course
12 the drug was stopped in both groups -- if the drug was
13 stopped when the person was identified as having
14 moderate leukopenia, then only 6.7 went on still to
15 agran whereas 93.3 percent of them, that progression
16 of declining blood counts was arrested and they did
17 not develop agran.

18 The approach that we're going to take in
19 making projections of the occurrence of agran is to
20 assume that these percentages will probably hold, even
21 with the monitoring that's less frequent. That is
22 that if you can catch somebody, even with less
23 frequent monitoring, and still find them at the stage
24 of moderate leukopenia, that 6.7 percent of them will
25 go on to develop agran. Whereas a person who's missed

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1 by monitoring -- missed meaning they've already
2 dropped below the level of moderate leukopenia by the
3 time you identify their blood dyscrasia -- that about
4 45.2 percent of them will go on to develop agran.
5 That's kind of the foundation assumption in our
6 projections.

7 Well, let's turn to this next slide that
8 I'll go through somewhat slowly. I want to start out
9 by emphasizing that this is the Clozaril users who
10 have used the drug for six months or more -- and we're
11 only talking about them -- and of course, it's the US
12 weekly monitoring system. It turns out there are a
13 lot of people, 67,661 persons, who fall into this
14 category. So, there's a lot of data for us to base
15 our estimates on. It turned out that of these 67,000-
16 plus users, a total of 63 cases of agran occurred.
17 This chart is basically going to trace how do those 63
18 patients get there in terms of the development and
19 detection of moderate leukopenia.

20 Well, here's a familiar number, I hope,
21 581. That's the number of people, these Clozaril
22 users of six months duration or longer, who developed
23 moderate leukopenia. There are 581 of them. Of
24 these, some of them were actually detected at the
25 stage of moderate leukopenia, whereas others were

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1 detected when they passed through that stage and have
2 gone all the way to severe leukopenia. Let's take the
3 ones that were detected. It turns out that 550 of the
4 581 were actually caught while still at the stage of
5 moderate leukopenia and that's 94.7 percent of the
6 total group.

7 Of this 550 -- it's getting a little
8 blurry on the side here -- but it turns out that there
9 are 37 of those 550 who nonetheless went on to develop
10 agran, and that's that 6.7 percent figure we saw
11 before. So, this is the group that despite the
12 ability of the testing system, the monitoring system,
13 to pick up the case while still at the stage of
14 moderate leukopenia, nonetheless, agran developed in
15 37 or 6.7 percent of them. 93.3 percent agran was
16 averted.

17 In contrast, there are the patients whose
18 white counts were declining rapidly. By the time they
19 were found to have a blood dyscrasia, they were
20 already past the stage of moderate leukopenia. That's
21 going to go down this arm, and here's the 31 patients
22 of the 581 who fell into that category. It's a small
23 number of patients, but in them, the chances of
24 getting agran were much higher. Well, here it is:
25 45.2 percent that we saw on the previous slide;

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1 fourteen of the 31 developed agran. So, in terms of
2 the numbers of cases of agranulocytosis, we had 14
3 that arose this way through too late detection of
4 their blood dyscrasia. We had 37 who arose this way
5 that even with prompt detection of the blood dyscrasia
6 they, nonetheless, went on to develop agran despite
7 cessation of therapy. Fourteen plus 37, that's only
8 51 and we have a total of 63. So, we've got 12 other
9 cases to account for. How did they arise? Well, it's
10 a function of the monitoring system. The monitoring
11 system aims to detect low white cell counts. But
12 there are a few patients who meet the criteria for
13 agran -- that's a low neutrophil count -- even though
14 their total white count is still in the normal range.
15 So, these 12 patients are those who, despite having a
16 normal total white count -- which the total white
17 count was normal so it wouldn't be detected through
18 the monitoring system and no alert would arise.
19 Nonetheless, they met the criteria for agran. So,
20 it's a total of the 63 cases.

21 Now, what we're going to do in the
22 projections is to, again, assume that these
23 percentages of 45.2 percent of agran developing in
24 missed patients, 6.7 percent of caught patients
25 developing agran, that those are going to be the same.

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1 What's going to differ is as we reduce the frequency
2 of monitoring, the fraction of the patients who are
3 caught at the stage of moderate leukopenia is going to
4 decline. Specifically, that as we go to biweekly
5 monitoring, or monthly monitoring, or even less
6 frequent monitoring, that instead of catching 94.7
7 percent of patients at the stage of moderate
8 leukopenia, they were going to be catching a smaller
9 percentage. I'm going to show you some means of
10 estimating just what these percentages might be, as
11 the monitoring gets less and less frequent, we're
12 going to shift them from here all the over to here.
13 Okay?

14 As I go through the rest of the slides, if
15 there are any questions, I don't think you should
16 hesitate to interrupt me because it can be a little
17 bit complicated. But I'll continue on now.

18 What I'm going to talk about is how do we
19 go about estimating what those percentages would be --
20 percentages of caught patients, patients caught while
21 there still in moderate leukopenia, or caught not
22 until later. Just to get us started, what we did was
23 to look at the white count profiles, the white count
24 patterns over time, of every single one of those
25 patients who developed moderate leukopenia, all 581

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1 who developed it after six months of therapy. And
2 this is just one example of one of them.

3 Day zero means the initiation of Clozaril
4 therapy. They started out with a white count of
5 almost 8,000 and the count went along monitored weekly
6 all the way up through Days 180 or so at six months of
7 therapy. It turned out that just shortly after six
8 months of therapy, the patient started to have a
9 declining white count and finally met the criterion
10 for moderate leukopenia. Moderate leukopenia was
11 identified, the drug was stopped and the patient's
12 white count went up.

13 What we did for each such patient was to
14 define what's called the prodrome. The prodrome is
15 the period of declining white counts leading up to
16 moderate leukopenia. The onset of the prodrome is
17 defined as the last white count before the decline
18 allowing for a one, at most one, rise in the white
19 count during that period as long as that rise didn't
20 exceed the initial peak before the decline. And then
21 statistically, a slope was given to these observations
22 to project now what likely would have happened had the
23 monitoring not taken place.

24 Now, what we're going to do is show two
25 more now hypothetical slides illustrating cases that

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1 are both caught at the level of moderate leukopenia
2 and missed. Here's one such patient and now we start
3 with Day zero. Day zero in this slide and the next
4 one no longer refers to the day of starting Clozaril
5 therapy, but this is day zero of the prodrome. That
6 is the first day in which the white counts start to
7 decline. Imagine, if you will, that these two squares
8 are really at the same point because technically, the
9 hypothetical example -- if this one is higher than
10 this one, then we would label this as the start of the
11 prodrome. So, just in your mind, think that they're
12 probably the same. Then the slope is drawn like this.

13 This example now is for biweekly
14 monitoring. If biweekly monitoring had occurred,
15 there would be a count here, a count here. There
16 would be one here, one here, and this one wouldn't
17 occur. And so, the question is, once we go from this
18 one at biweekly visit number three to here, biweekly
19 visit number four, would the slope that we've observed
20 all the way up to that point -- where would this X
21 have landed? Would it have landed within the criteria
22 for moderate leukopenia which are these two dotted
23 lines? Or would it have landed below the threshold
24 for moderate leukopenia?

25 In this particular hypothetical patient,

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1 the slope is gradual enough, it's shallow enough, that
2 the X would land within the threshold for moderate
3 leukopenia. This is a patient that, even by weekly
4 monitoring, would project to have caught while they're
5 still at the stage of moderate leukopenia before they
6 had progressed to severe leukopenia. So, this would
7 be a patient who even during biweekly monitoring would
8 have been caught.

9 Contrast this with a second patient whose
10 declining white count was more rapid. They started
11 higher at 11,000 but the count fell rapidly. And if
12 you go now from visit three to visit four, biweekly
13 visit number three to biweekly visit number four, the
14 projected line would land this X outside the band
15 defining moderate leukopenia. Therefore, this
16 particular patient was deemed one that would have been
17 missed at moderate leukopenia had biweekly monitoring
18 rather than weekly monitoring been present.

19 Well, for every one of the 581 patients,
20 similar lines were drawn and all the statisticians and
21 artists who devised this scheme, all they did was
22 count up these X's. Did the X's fall here? Do they
23 fall here? They did this for biweekly monitoring.
24 They also did it for a policy of monthly monitoring,
25 and we'll show data for both types.

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1 Once these percentages of caught and
2 missed patients were determined, then it was time to
3 put these into the overall equation to come up with
4 some overall figures. So now, we're talking about --
5 remember these two categories of patients. There's
6 the caught patients. This is the not-caught or the
7 missed patients. And remember, if the patient is
8 caught, 6.7 percent -- it says percent progressing to
9 agran. It's really the proportion progressing to
10 agran. .067 or 6.7 percent of patients caught at
11 moderate leukopenia would likely develop
12 agranulocytosis. 45.2 percent of patients missed
13 would go on to develop agran. And now, we apply this
14 6.7 percent, or the 45.2 percent to the number of
15 patients that we estimate would be caught or would be
16 missed.

17 Now, this is a program -- this is a slide
18 for one particular policy. It's for biweekly
19 monitoring starting at six months of therapy. The
20 projections suggest that 424 of the 581 patients who
21 developed moderate leukopenia, or 73 percent, would be
22 caught at that stage. Instead of 95 or 96 percent
23 which was the percentage caught for weekly monitoring,
24 now the percentage is lower at 73 percent. And so,
25 it's 424 times that gives you an anticipated 28.4

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1 cases of agran developing in that category of patient.
2 71 patients would develop agran among those who were
3 not caught at moderate leukopenia. And remember that
4 old 12 is still with us. It's the 12 patients in whom
5 agran developed but moderate leukopenia did not.

6 When we add up these numbers and we get
7 111 cases. These 111 cases can be interpreted as if
8 in the cohort of Clozaril users in the United States
9 through April of '95, in them had a policy of biweekly
10 monitoring been present starting at six months of
11 treatment, we would estimate that a total of 111 agran
12 cases in them would have occurred. 111 versus what?

13 Well, let's go to this slide. It's a lot
14 of numbers, but some of them we've seen before.
15 Here's the 111. It's a program of biweekly monitoring
16 in the Clozaril cohort. That contrasts with the 63
17 observed cases. 63 observed in the presence of weekly
18 monitoring and we think because we missed some cases
19 while they were still at moderate leukopenia, that
20 there will be a higher incidence overall of agran in
21 biweekly monitoring, 111. For monthly monitoring you
22 have more cases at the early stages of blood
23 dyscrasia, so yet more will go on to agran, 181. And
24 finally, in the absence of monitoring, it's a higher
25 number still.

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1 Parenthetically, there was one additional
2 assumption made in this category where there was no
3 monitoring because in them, there was never an
4 opportunity to identify any of the intermediate
5 dyscrasias like moderate leukopenia. And so, the
6 estimated percentage of patients who silently develop
7 moderate leukopenia going on to agranulocytosis was
8 shifted upwards to 67 percent. That number is
9 arbitrary. It is the best estimate that our
10 hematologist, Dr. Gerson, but it is certainly only an
11 estimate. But of course, this number under no
12 monitoring is going to be higher than the numbers that
13 we see under the presence of monitoring.

14 Now, the rates of agranulocytosis that are
15 observed to occur under weekly monitoring -- here it's
16 .5 per 1,000 patient-years. Under biweekly
17 monitoring, the rate is almost double and the rates
18 would continue to be higher, we estimate, given less
19 frequent monitoring.

20 Now, what are the other numbers on this
21 slide? One could argue that while one strategy might
22 be to delay a reduction in monitoring -- don't do it
23 at six months, maybe do it at a year. Keep weekly
24 monitoring going for a year and only then reduce the
25 frequency. And so, what we've done is estimate what

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1 would it be like under a program of biweekly, monthly
2 or no monitoring starting at one year and two years
3 after the onset of therapy. These numbers are the
4 cumulative numbers predicted in the Clozaril cohort in
5 the United States starting at six months of therapy
6 and going on with a delayed onset of change in
7 monitoring frequency. So, these numbers are lower
8 than the 111, for example, because these patients
9 here, the 99, reflect patients who have had the weekly
10 monitoring that went on for a whole year rather than
11 just six months. So there, higher incidence would
12 only begin starting at one year rather than earlier.
13 Then we can see rates of agran that correspond to
14 these different strategies on the right-hand side.

15 The next slide is just like this one. The
16 only thing it does, it's going to subtract out the 63
17 cases in the presence of weekly monitoring from the
18 totals. So, it's going to give you the extra cases --
19 the extra cases that you can expect because we
20 switched from a program of weekly monitoring to a
21 program of less frequent monitoring or no monitoring.
22 So, specifically, this 48 -- this is the extra cases
23 from a program of biweekly monitoring starting at six
24 months of therapy. This 48 simply comes from the
25 total of 111 cases that we saw that we predict to

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1 occur in the presence of biweekly monitoring, minus
2 the 63 cases that we already know we get in the
3 presence of weekly monitoring. 111 minus 63 equals 48
4 and all the other numbers come in the same way. Here
5 are the extra rates, the added rates, associated with
6 each of these policies.

7 Well, it's time to move on to mortality
8 from agran, and yet more assumptions, more problems.
9 The mortality from agranulocytosis is influenced, of
10 course, not just by the incidence of agran, but also
11 by the case fatality. Among the cases with agran,
12 what fraction go on to die of it? There's a lot of
13 uncertainty, for good reason. There's a lot of
14 uncertainty regarding the percentage of agran patients
15 who had gone to die of the disease depending on the
16 frequency of monitoring.

17 One could take the three percent --
18 remember, in the total cohort of US Clozaril users,
19 there were 12 deaths in 402 agran patients, or three
20 percent. We could use that figure and, indeed, we
21 have used it for one set of estimates. You could
22 argue that, well, there were 63 agran cases that
23 occurred in Clozaril of more than six months'
24 duration. None of them died, zero percent. Why don't
25 we use the figure of zero percent case fatality?

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1 There are two reasons. One is that zero
2 out of 63 is statistically really quite compatible
3 with the true rate of three per 100, and it just isn't
4 a large enough denominator to securely say that the
5 true case fatality is zero. Second, it has to be
6 stressed again that this case fatality of three
7 percent is what was observed in the presence of weekly
8 monitoring. As monitoring becomes less frequent,
9 those cases of agranulocytosis that do occur will be
10 identified relatively later in their natural history
11 and could easily be associated with a poorer outcome,
12 a higher case fatality rate.

13 So, we think that zero is probably a bad
14 number. Three percent is not a bad one and so we give
15 some percentages for three percent, some data for the
16 three percent case fatality. And here's this other
17 one, 15 percent. We looked in the literature and
18 found that there was an experience with a drug-induced
19 agranulocytosis -- agranulocytosis due to Mianserin
20 therapy in which no monitoring of white counts was
21 done in patients using Mianserin. And in the
22 literature, you can find a series of 19 cases of agran
23 in Mianserin users. Three of them died, about 15
24 percent case fatality. You know, that's a plausible
25 figure also.

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1 Basically, as you can sense from my
2 waffling here, there's not a lot of security as to
3 what the true case fatality would be depending on the
4 frequency of monitoring. But by giving figures for
5 three percent and for 15 percent case fatality, I hope
6 to have bracketed, at least, what may be true.
7 Although my personal suspicion is, it's going to be in
8 the neighborhood of three percent.

9 Once we pick a case fatality, then the
10 rest of the numbers filed very quickly, specifically,
11 biweekly monitoring. Remember, we had in the Clozaril
12 cohort, 111 cases that we have projected to have
13 occurred. 111 times three percent is three deaths.
14 111 cases times 15 percent, if it's really that high,
15 would be 17 deaths and that's where these numbers come
16 from. The rest of the numbers would -- we would
17 correspondingly multiply the number of cases expected
18 under that monitoring strategy multiplied by the case
19 fatality.

20 If we look at the rates, we see over here
21 that the rates are as low as .02. The projected rates
22 are as low as .02 per 1,000 patient-years for a policy
23 of biweekly monitoring instituted at six months and
24 going on up to higher rates in the absence of
25 monitoring. Just to give some context -- if you don't

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1 like rates, but you like to think of numbers of
2 patients, in the United States right now, there are
3 very roughly 50,000 patients who are using Clozaril
4 and have done so for more than six months. I think
5 it's 57,000 or 53,000, but let's say over 50,000. If
6 this is the rate. .02 per 1,000 patient-years, we
7 simply multiply this by 50 to get the approximate
8 number of deaths that one might expect in the US
9 Clozaril users right now per year. If the program of
10 biweekly monitoring were instituted starting at six
11 months, it's not a difficult multiplication. 50 times
12 .02 would be about one. And so, if this monitoring
13 strategy were adopted biweekly at six months, our
14 projections are that about one death in the current
15 Clozaril user population would occur per year. This
16 is one of the low numbers on the slide, so lower
17 frequency of monitoring or no monitoring would give us
18 additional deaths. So, again, whether you like rates,
19 the rates are there. And if you want numbers,
20 hopefully, that's giving you some idea as well.

21 At last, the summary. I want to stress,
22 this only summarizes the last part and it only
23 stresses one point. But it's an important one. That
24 is that these are projections, projected occurrence of
25 agranulocytosis both incidence and mortality. They're

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1 projections because we have no direct data. In the
2 United States, the policy has been for weekly
3 monitoring and we don't have any experience in the
4 presence of less than weekly monitoring, so we have to
5 make educated guesses. These assumptions that we've
6 made are not going to be 100 percent accurate, and
7 therefore, these projections are not 100 percent
8 accurate. But I would argue that as you begin to
9 evaluate the risks and benefits associated with an
10 altered frequency of monitoring of patients using
11 Clozaril, that the projections that have been made are
12 very plausible ones and should give you some sense of
13 this most important risk of a reduced frequency of
14 white count monitoring.

15 Well, I'm through. The next speaker will
16 be Dr. Anand talking more about the clinical aspects
17 of this possible change in monitoring.

18 DR. ANAND: Good morning, ladies and
19 gentlemen.

20 Dr. Koestler, in his brief overview,
21 outlined some of the issues which we're here to
22 discuss today and I think Dr. Weiss gave you a review
23 of the data indicating what the impact of changes in
24 the monitoring would be. What I'd like to do very
25 briefly is talk about the clinical perspective, what

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1 these changes might translate into, and what are the
2 issues regarding patient care which this may impact
3 on.

4 From the time of introduction of Clozaril
5 in February 1990 to date, in the US and worldwide,
6 it's the only product which has been approved for the
7 treatment of therapy-resistant schizophrenia. What
8 I'm going to do is now talk about the efficacy of this
9 compound, its unique side effect profile of not being
10 associated with EPS or free of TD, but the fact that
11 patients who are treated with Clozaril seem to enjoy
12 unique benefits.

13 Approximately two-thirds of the patients
14 who are treated with Clozaril long-term experience
15 very significant clinical benefit. In one-third of
16 these patients, approximately one-third, it has been
17 noted that many of these patients are able to resume
18 normal lives, go back to having jobs, continue to
19 function in the community. In another one-third of
20 patients, there are modest clinical benefits, but
21 still, these patients are able to live in the
22 community.

23 What is important about Clozaril is that
24 unlike many other drugs which have association with
25 hematologic adverse events, Clozaril patients continue

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1 treatment long-term. This is not a drug which is used
2 for three months or for six months, but for years and
3 years. Although it is difficult for us to say that
4 these patients are treated for life-long, the current
5 data set seems to indicate that if possible, these
6 patients will continue to be treated for very long
7 periods of time.

8 However, the use of Clozaril is also
9 associated with some key issues. In the US database,
10 up to May 1st, 1997, there have been 153,000 patients
11 in whom treatment of Clozaril was associated. Out of
12 these 153,000 patients, to date, more than 2,400
13 patients have had to discontinue therapy because of
14 hematologic adverse events. Despite the weekly
15 monitoring which greatly attenuates the number of
16 patients who progress on to agranulocytosis, 476
17 patients were diagnosed with agranulocytosis. Despite
18 the early identification and the aggressive treatment
19 which was instituted, tragically 19 patients died
20 because of complications associated with
21 agranulocytosis.

22 I think Dr. Laughren and Dr. Weiss have
23 already mentioned about the outcomes of agran, so I
24 won't go into any great detail. Of course, as we all
25 know, not only is this a potentially life threatening

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1 disorder, but also causes severe disruption. For
2 patients who are doing well in the community, there is
3 now the need for hospitalization. More than the need
4 for hospitalization is the fact that patients have to
5 go into isolation. And we're talking here about
6 reverse isolation where patients have to be protected
7 also from their physicians and nurses who were giving
8 them treatment. For anybody, this would be a scary
9 scenario. However, for a schizophrenic patient, this
10 is doubly so. I think our trust of the Clozaril
11 monitoring system has been to ensure that patients can
12 be prevented from getting to this potentially life-
13 threatening situation.

14 The Clozaril monitoring system has put a
15 lot of stress on identifying patients who are at risk
16 and taking steps to ensure that these patients are not
17 exposed to undue risk. The Clozaril National Registry
18 contains data on all patients who have been treated
19 with Clozaril to date. In this registry, and I think
20 as you have heard during Dr. Weiss' presentation, we
21 have put a lot of stress on certain hematologic cutoff
22 points. For patients whose WBC counts are less than
23 3,000, as Dr. Weiss indicated, we need to follow them
24 very carefully.

25 What are the reasons for this? Patients

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1 whose counts went below 3,000 but did not go below
2 2,000 are termed retreatable. However, data has shown
3 that in these patients whose counts went below 3,000
4 or stayed above 2,000, once treatment was interrupted,
5 the counts normalize. Patients are put back on
6 Clozaril. Their risk for experiencing agranulocytosis
7 is four times as high as the rest of the Clozaril
8 treated patients. I may also mention, for those
9 patients whose counts have gone below 2,000, the risk
10 for experiencing agranulocytosis is forty-fold as
11 high.

12 In our data set, 50 percent of the
13 patients whose counts go below 2,000 go on to develop
14 agranulocytosis. As -- remarked earlier,
15 agranulocytosis is a potentially life threatening
16 disorder and the case fatality rate for Clozaril,
17 despite the weekly monitoring, is about three percent.
18 But data, as has been discussed before, suggest that
19 it may go as high as 15 percent as with Mianserin,
20 although the literature talks about some other
21 compounds where it may be as high as 40 percent.

22 In the Clozaril National Registry, there
23 are two sets of databases which are referred to in the
24 slide. In this registry, there is a data set which we
25 call a rechallengeable database and a non-

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1 rechallengeable database. The rechallengeable
2 database refers to those patients whose counts went
3 below 3,000 but stayed above 2,000. What we mean by
4 this is that if treatment is interrupted in these
5 patients and the count recovers to go above 3,500,
6 these patients are retreatable and they can continue
7 to enjoy the benefits of treatment with Clozaril.
8 However, there are 1,559 patients who have been termed
9 non-rechallengeable. In these patients, it has been
10 determined that because their WBC count has gone below
11 2,000, these patients should never be rechallenged
12 with Clozaril as the risk for agran is considered too
13 high.

14 The Clozaril National Registry, at the
15 present moment, is the only mechanism which is
16 existing to ensure that these patients who are at such
17 high risk for agran will not be re-exposed to
18 Clozaril. When a physician sends in information for
19 a new patient whose data are sent in, the Clozaril
20 National Registry tries to identify if such patient
21 has received treatment before. It is very clear to
22 physicians and patients, those who are termed non-
23 rechallengeable should never be treated with Clozaril
24 again.

25 However, patients who have been on

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1 Clozaril and have enjoyed the benefits are very driven
2 to try to obtain treatment with Clozaril. We have
3 identified at least 12 patients who attempted
4 rechallenge by going to a different physician even
5 though they had been declared non-rechallengeable. In
6 the absence of the Clozaril National Registry, such
7 cases will not be caught and those patients who are at
8 this high-risk for agranulocytosis might be re-
9 exposed.

10 We have been discussing here today a
11 little bit about the long-term risk of
12 agranulocytosis. As stated before, treatment with
13 Clozaril is going to continue for very long periods of
14 time. Therefore, it is important to determine whether
15 the risk for agran with Clozaril is reduced over time
16 or is eliminated over time. Based on the data which
17 is contained in the Novartis Clozaril National
18 Registry -- and we have sufficient data up to three-
19 and-a-half years -- the data indicate that the risk
20 for agran continues for at least three years, 3.5
21 years after starting treatment just as is indicated,
22 after 3.5 years, there is no additional risk. We can
23 not be complacent about that. The reason is that at
24 this point, we only have about 7,000-odd patients for
25 whom we have data. Based on the computed risk for

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1 agran, those numbers would be too insufficient to draw
2 a clear conclusion that the risk does not exist after
3 three-and-a-half years after treatment.

4 In trying to determine the risk for other
5 antipsychotics, we are at a disadvantage. It is only
6 the Clozaril database which is comprehensive enough
7 and large enough to make an accurate determination of
8 the risk for agran. For no other antipsychotic could
9 we determine a database which points to this risk.

10 There may be some unique features
11 associated with Clozaril treatment. Clozaril appears
12 to be the only antipsychotic that we could find which
13 still has cases of agran emerge later into treatment.
14 For Haldol, we could not find any cases of agran in
15 the literature. For Chlorpromazine, we could not
16 determine substantiated cases of agran occurring later
17 in therapy. So Clozaril, for that reason, appears to
18 be different from other antipsychotics.

19 We've talked about the risk of agran with
20 Clozaril and therefore, it behooves us to discuss the
21 issue, whether this is different than seen in the
22 population or the other treatments. In the general
23 population, there are very scanty data to indicate
24 what the background risk of agran is. The
25 International Study for Agranulocytosis and Aplastic

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1 Anemia indicates a case rate of .034 to .047 cases per
2 1,000 person-years. In schizophrenia, we could not
3 find any definitive estimate of what the background
4 risk for agran would be in the general schizophrenia
5 population. Furthermore, although it could be
6 speculated that treatment-resistant patients might be
7 at higher risk for agran, there are no data which
8 could substantiate this.

9 Risks with other psychotropic drugs have
10 been mentioned. Carbamazepine, the rate is mentioned
11 as .05 cases per 1,000 person-years. Again, they're
12 very scanty data and no data indicating a continued
13 risk over time. For Mianserin, the antidepressant
14 which is not on the market in the United States but is
15 available elsewhere, the rate was .57 to .74 cases per
16 1,000 patients. And for Chlorpromazine, based upon
17 the international study, the rate is estimated at .004
18 to 6.8 per 1,000 patients. Again, I would stress
19 those data are not as comprehensively collected, are
20 not as reliable. And again, most of the cases of
21 Chlorpromazine seem to occur early in therapy where
22 they also seem to be associated with dose and are not
23 seen later in therapy. So, again, Clozaril appears to
24 be associated with a risk which is different from
25 other psychotropic drugs.

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1 Now with Clozaril, the risk for agran is
2 well documented. However, we seem to be in a somewhat
3 lucky situation, and I mean that seriously. Lucky
4 because we have been able to identify a strategy for
5 dealing with this risk. The thrust of the Clozaril
6 monitoring effort has been that by the institution of
7 frequent monitoring, rigorous enforcement of the
8 rules, ensuring the no blood/no drug policy, we have
9 been able to reduce the number of patients who
10 progress to the stage of severe leukopenia and
11 consequently, agranulocytosis. Without the procedure,
12 many more patients would experience agranulocytosis.
13 I think as I've mentioned before, the case fatality
14 rate there is three percent. It could also be higher
15 if it did not have this policy in place.

16 So therefore, even though there's a well
17 documented risk for agran with Clozaril, there is also
18 a well substantiated strategy for dealing with this
19 risk which appears to have worked. The long-term
20 treatment with Clozaril, from the data that have been
21 shown, clearly indicate that there's a need to
22 continue monitoring long-term. I'll address this
23 issue in a sec.

24 Presently today, we are considering three
25 kinds of changes: a reduction in the frequency of

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1 monitoring, elimination of the monitoring after a
2 certain amount of time, and perhaps elimination of the
3 Registry. And as Dr. Laughren said, he's modified the
4 question to consider whether they should become
5 voluntary after some period of time or should remain
6 with the current system.

7 However, before we go on to the merits of
8 this, what are the potential benefits? As has been
9 stressed before, the benefits could be that there
10 might be an increase in the number of patients who
11 might receive Clozaril; a reduction in the number of
12 patients who are discontinuing currently because of
13 inconvenience; and that fewer patients may experience
14 difficulty with venipuncture. Let us take the first
15 point.

16 Clozaril is indicated and will continue to
17 be indicated, that it is restricted for the use of
18 patients with therapy-resistant schizophrenia. We do
19 not expect that any reduction in the monitoring
20 frequency or its elimination at some time point will
21 greatly increase the number of patients who will be
22 prescribed this therapy. Furthermore, the initial
23 difficulties in getting on to Clozaril therapy. That
24 the fact that at least for six months, or for one
25 year, there is a need for monitoring. We believe

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1 there is enough of an impediment that is not greatly
2 going to increase the number of patients who are
3 prescribed Clozaril.

4 This, of course, is an issue, that many
5 patients do discontinue treatment with Clozaril
6 because of the weekly blood draw, the inconvenience of
7 having to go to the clinic. This needs to be
8 evaluated seriously. Based on the data that we have
9 in the Clozaril National Registry, more than half of
10 the patients who discontinue treatment with Clozaril
11 due to reasons of -- non-compliance, inconvenience,
12 this happens during the first six months of therapy.
13 Therefore, a reduction after six months or one year,
14 again, would not greatly reduce those numbers.

15 This is, of course, correct that there are
16 many patients -- and as was so eloquently stated by
17 Dr. Kane in reading out the letter -- in whom there is
18 significant difficulty with venipuncture. Patients'
19 veins collapse or close. I think for this patient
20 population, we perhaps need to consider whether there
21 could be alternative strategies in which we may be
22 able to collect the same information without having to
23 go through venipuncture. A policy where probably some
24 adjustment of the procedure involving pin pricks, et
25 cetera, might be evaluated. I may mention that

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1 Novartis is currently working on this strategy.

2 However, looking at the possible impact of
3 the reduction in monitoring frequency, I think Dr.
4 Weiss has gone through a lot of data with you. If we
5 were to look at the data from the April 1995 database
6 to see what the impact of reduction in the monitoring
7 frequency would be, the data clearly indicate that if
8 we were to move to a biweekly monitoring frequency, we
9 would have at least 48 additional cases. If you were
10 to just change this to no monitoring, after the end of
11 six months of therapy, this would be 338 additional
12 cases. Similarly, after one year or after two years,
13 the number of cases who would experience agran after
14 biweekly or after no monitoring would increase
15 substantially. I do not need to emphasize that
16 increased incidence of agran will also translate into
17 increased fatalities.

18 We have briefly touched on the issue of
19 the fall in the incidence of agranulocytosis and other
20 hematologic events after six months. However, I think
21 we need to put it in perspective that there is no
22 magic of wall dividing six months of therapy from
23 later in treatment. The data from the US database of
24 approximately 67,000 patients indicates that after six
25 months of therapy, 581 cases of moderate leukopenia,

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1 67 of severe leukopenia, and 66 cases of agran were
2 reported after six months of therapy. After 12
3 months, there's still about 378 cases of moderate
4 leukopenia, 39 of severe leukopenia, and 39 of
5 agranulocytosis. Even after two years of therapy,
6 there are more that 150 patients who experienced
7 moderate leukopenia, 13 with severe leukopenia and
8 agranulocytosis. These data and the 12 month data are
9 based upon approximately 55,000 patients and the 24 on
10 35,000 patients.

11 These data, based upon a very robust data
12 set, clearly indicate that as long as you are
13 continuing treatment with Clozaril, there will be a
14 risk for hematologic adverse events and therefore
15 implies the need for monitoring.

16 I have not talked much about the Clozaril
17 National Registry. However, I think there are some
18 points which we need to keep in mind. The success of
19 the Clozaril monitoring system is contingent upon the
20 role played with the Clozaril National Registry and
21 its rechallengeable database. The Clozaril National
22 Registry and its enforcing mechanisms is what makes
23 the current system work. These are the mechanisms by
24 which physicians can be advised to discontinue
25 treatment. I think Dr. Laughren alluded to the fact

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1 that perhaps we could consider a voluntary mechanism
2 after six months. I would like to remind you that
3 during our clinical trial database in which we did not
4 have a mandatory system, compliance with the reporting
5 requirements was less. It was about 70 to 80 percent.
6 Using the mandatory system which we have currently in
7 place, compliance is 99 percent. Clearly, if we were
8 to go to a more voluntary system, the strict and rigid
9 enforcement of the rules would suffer.

10 In summary, the data that we have shown to
11 you indicate that some frequency of monitoring, even
12 during long-term treatment, needs to be maintained
13 because there is always some risk of agranulocytosis
14 associated with the use of Clozaril and there's always
15 some risk of deaths. The Clozaril National Registry
16 must be maintained. We need to have a mandatory
17 mechanism to enforce the rule of no blood/no drug. We
18 also need to make sure that patients who are
19 considered non-rechallengeable and who are at very
20 significant risk for experiencing potentially life
21 threatening hematologic events do not get re-exposed.

22 Ladies and gentlemen, we have here with
23 Clozaril, a drug which has been shown to work. It
24 works in long-term treatment. With the help of the
25 FDA, the system which was put in place of monitoring

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1 patients' safety has been shown to work. We ask for
2 your due consideration of these results as you
3 continue to review the suggestions.

4 Thank you.

5 CHAIRPERSON KANE: Thanks very much, Dr.
6 Anand.

7 The sponsor's presentation are open for
8 questions now. Do any of the committee members have
9 questions?

10 Dr. Casey?

11 DR. CASEY: I have some questions for Dr.
12 Anand and for Dr. Weiss. Do we have a preference in
13 which we want to have the speakers address these?

14 Dr. Anand volunteers.

15 The first question about the 12 patients
16 that sought rechallenge through a bit of the nefarious
17 approach of doctor shopping. What actually happened
18 to those people? Did some get rechallenged? How many
19 did you detect and prevent from rechallenge?

20 DR. ANAND: These 12 patients who sought
21 rechallenge were identified in the Clozaril National
22 Registry as patients who had earlier received
23 treatment with Clozaril and had been deemed as non-
24 rechallengeable. None of these 12 were allowed
25 treatment.

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1 DR. CASEY: I imagine there are some who
2 have been rechallenged even though the recommendation
3 is not to rechallenge. Do you have experience about
4 what happened to those people?

5 DR. ANAND: I don't think we have the data
6 here to reflect those -- as far as we know, patients
7 who are considered non-rechallengeable by the registry
8 would not be allowed to be rechallenged. We have here
9 -- people give you more precise detail if you're going
10 to need this information at a later stage.

11 DR. CASEY: It's something I would be
12 interested in knowing because it gets to the larger
13 issue that we need to discuss which is the faults
14 positive level of information that we're working with
15 or without. We've had a lot of information, but we
16 also want to know how much of that would be
17 potentially leading to denial of treatment
18 unnecessarily.

19 DR. ANAND: There are cases in whom the
20 blood test would indicate that they are non-
21 rechallengeable. In this case, the physician
22 approaches his or her hematologist and frequently the
23 hematologist will approach the registry and he will
24 have a consultative hematologist review each case for
25 its own merits. There are some cases in which

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1 physicians will make out the case that the values are
2 because of another treatment having been given. There
3 are some cases in which it has been found that we may
4 need to change our decision. But in those cases where
5 patients have been determined non-rechallengeable
6 because the white count went below 2,000, in the
7 absence of other factors, we would not allow treatment
8 to initiated.

9 DR. CASEY: There's the lure around that
10 there are some people who have been rechallenged even
11 though they were not supposed to be, and that all of
12 those people redeveloped agran and some people
13 redeveloped it sooner. Do you have data to say
14 whether that is really lower and not true, or that
15 there are some documented cases of that fact?

16 DR. ANAND: I think in the absence of very
17 specific questions from you of which patients those
18 were, we would not be able to answer that. To the
19 best of our knowledge, patients deemed non-
20 rechallengeable have not been allowed to be re-exposed
21 to Clozaril treatment.

22 DR. CASEY: Okay. I'll consider that we
23 haven't answered that.

24 Could I go on to --

25 CHAIRPERSON KANE: While Dr. Anand is at

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1 the microphone, why don't we see if there are other
2 questions.

3 Carol?

4 DR. TAMMINGA: Yes, I had a question that
5 was really following on your questions, Dr. Casey.
6 How do you identify these non-rechallengeable
7 patients?

8 DR. ANAND: They are based upon -- are you
9 saying in what patient characteristics?

10 DR. TAMMINGA: No, how do you know you
11 have the same person?

12 DR. ANAND: There are patient identifiers
13 in the Clozaril National Registry: the date of birth,
14 the social security number, and so on, the treating
15 physician identifier.

16 CHAIRPERSON KANE: Dan?

17 DR. CASEY: Another question. You
18 mentioned that you have 7,000 patients in greater than
19 three-and-a-half years of treatment. This is
20 insufficient to give you the numerator and denominator
21 you like to adequately power an estimate. What number
22 of patients would you need for three-and-a-half, or
23 two or some years of treatment where you could
24 adequately power an estimate where you would be able
25 to detect Clozapine induced agran versus the

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1 idiopathic or spontaneously occurring rate in society?
2 I guess that's a statistical analysis and that there
3 could be some number determined for some degree of
4 exposure.

5 DR. ANAND: Why don't I defer the question
6 and get the information from a statistician as to what
7 the denominative would be that they would be
8 comfortable with? I'll get back to you.

9 DR. CASEY: Okay.

10 And the last question I have was, do you
11 have an estimate of the percent of patients with
12 diagnoses other than treatment resistant schizophrenia
13 that are getting treated with Clozapine? Because part
14 of the issue is focusing on treatment resistance
15 schizophrenia and the benefit risk ratio there, but
16 there are potentially other clinical considerations to
17 put in mind.

18 DR. ANAND: Of course, the biggest
19 category would be the neoleptic intolerant patient who
20 may not be therapy resistant and they've gone in. I
21 think it's a very small percentage, probably about ten
22 percent -- less than ten percent.

23 DR. CASEY: How about the Parkinsonian
24 patients due to the levodopa induced psychosis?

25 DR. ANAND: I don't think we have any

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1 accurate data on those patients.

2 DR. SALZMAN: Or bipolar patients.

3 DR. CASEY: Or bipolar.

4 DR. ANAND: Again, I think those are a
5 very small percentage of patients. We would not have
6 exact numbers on the percentage of patients in the
7 database.

8 DR. CASEY: Shouldn't those diagnoses be
9 listed in the CNR when the information comes in?

10 DR. ANAND: No. The CNR does not record
11 the diagnosis.

12 DR. CASEY: Okay.

13 CHAIRPERSON KANE: Dr. Simpson?

14 DR. SIMPSON: This sort of follows on to
15 some of the issues Dr. Casey raised. You have a table
16 where you talk about the hematologic of ANC associated
17 with Clozaril over time and you have greater than six
18 months, greater than 12 months, and greater than 24
19 months. But you also stated before that people who
20 had had a hematologic event were more likely to have
21 another one. How many in the greater than 12 months
22 and greater than 24 months are repeats?

23 DR. ANAND: I would have to defer the
24 answer to that to get back to you, for an accurate
25 answer.

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1 DR. SIMPSON: Okay, thanks.

2 CHAIRPERSON KANE: Ravi, if I could also
3 ask you, in your presentation, you alluded to the fact
4 that the majority of patients who appear to have
5 discontinued Clozapine because of concerns about the
6 weekly monitoring occurred in the first six months.
7 Do you have any specific data as to what those numbers
8 are and how many people discontinue after six months?

9 DR. ANAND: Yes. I think we have data
10 that approximately of the 70,000-plus patients who
11 have discontinued, approximately 37,000 are within the
12 first six months.

13 CHAIRPERSON KANE: But do we know among
14 those who discontinued, how many discontinued because
15 of their difficulty with the blood monitoring?

16 DR. ANAND: No. Unfortunately, the
17 registry records reasons for discontinuation as non-
18 compliance and other, or just simply lost to follow-
19 up. The patients who have difficulty for either
20 venipuncture or do not come back, they're recaptured
21 in the category of non-compliance. It does not make
22 it down any further.

23 CHAIRPERSON KANE: Are there any other
24 databases that might be available to help answer that?

25 DR. ANAND: I think in the Clozaril

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1 National Registry, we don't have any database which
2 will break it down any further.

3 CHAIRPERSON KANE: Yes. Okay.

4 Dr. Marder?

5 DR. MARDER: I'm not sure if you're best
6 suited to answer this, or whether it's the hematology
7 consultant, but the issue of my answering as a way to
8 estimate the mortality rate for individuals who
9 develop agranulocytosis without monitoring, I'm
10 interested in are there -- how similar is that
11 agranulocytosis and are there other -- if monitoring
12 were less frequent, would there be other prodromes,
13 clinical prodromes that would be useful for lowering
14 mortality?

15 DR. ANAND: That definitely is a question
16 now for the psychiatrist, so I'd defer to Dr. Gerson.

17 DR. GERSON: Yes, thank you.

18 Let me, if I could, go back -- I'll answer
19 that question first and then I'll go back to the
20 previous question about the rechallenge issue.

21 The 15 percent in the Mianserin case is
22 actually useful because it was an unmonitored
23 situation. And so, the presentation in all those
24 instances was of symptomatic agranulocytosis. In
25 fact, some used the term agranulocytosis to mean

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1 symptomatic, whereas in this case, it's always used as
2 an ANC count of less than 500.

3 It's very clear in a variety of other
4 settings that patients who present with symptoms
5 related to agranulocytosis almost always fever have a
6 higher morbidity as well as mortality than those who
7 present simply with a neutropenia in the absence of
8 the symptoms. Now that database for pure drug
9 associated agranulocytosis is hard to come by in
10 larger studies and is typically anecdotal. It
11 certainly exists in very large studies for the
12 anticipated symptomatic agranulocytosis, i.e., the
13 febrile neutropenia that is associated with
14 chemotherapy administration.

15 Now, admittedly in that setting, there are
16 co-morbid conditions, the underlying suppression
17 perhaps and the underlying tumor of most of those
18 individuals, but certainly there are other instances:
19 renal transplants, people receiving immunosuppression
20 for rheumatoid arthritis, in which there is an
21 understanding and expectation of the possibility of
22 neutropenia in presentation of febrile neutropenia.

23 If you look in large antibiotic studies
24 comparing antibiotic regimen A with B, those mortality
25 rates since 1990 have ranged between five and 30 or 40

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1 percent. But a reasonable number in those antibiotic
2 studies is, in fact, on the order of five to ten
3 percent. But even in those settings, that's a
4 monitored situation. In the febrile neutropenia
5 associated with agranulocytosis, it's again between
6 five and 15 percent. So, if you now extrapolate to a
7 totally unmonitored situation, I'm comfortable with
8 the range of between five and 15 percent, perhaps on
9 the order of 15 percent as it was in my answer. So,
10 I think that's actually a pretty reasonable number.

11 CHAIRPERSON KANE: If I could just follow
12 up on that, I think part of Dr. Marder's question also
13 was the -- that's seen with my answer, would you
14 characterize that as very similar in nature to that
15 seen with Clozapine?

16 DR. GERSON: The duration of those
17 neutropenic episodes -- again, it's a small sample set
18 -- was fairly similar, on the order of -- if I
19 remember correctly, seven to 14 days which, in the
20 absence of GCSF, again, the absence of monitoring is
21 fairly similar here.

22 Unfortunately, once one presents with
23 febrile neutropenia, the mortality rate is less
24 associated with the ultimate duration of that by
25 intervention as it is with morbidity at presentation.

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1 So, it's the severity of the presentation which
2 predicts mortality, not the expected duration. But
3 it's fair to say that if somebody with -- thinking
4 back now to the earlier data with Clozaril that if one
5 presented with febrile neutropenia, there was a much
6 higher mortality rate than if one presented simply
7 with neutropenia. That mortality rate was really
8 quite high. I think in excess of 40 percent.

9 CHAIRPERSON KANE: While you're at the
10 microphone, it appears, although it's difficult
11 because the content intervals are broad, that the
12 fatality rate in those patients developing
13 agranulocytosis after six months may be lower than
14 among those patients developing it before six months.
15 Given the different theories as to the possible
16 etiology of this particular type of agranulocytosis,
17 do you make anything out of that? Is it possible that
18 people who take longer to develop this response have
19 a different form of the disorder?

20 DR. GERSON: That's actually a very good
21 question. If you look in the data that was presented
22 to you, at the rate of decline in the neutrophil
23 counts, early and late, before and after six months,
24 it's remarkably similar. So that, it's not easy from
25 that data to argue that there's actually a difference

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1 in the prodrome before and after six months.

2 So, my sense is that, in fact, that
3 population is a small number of cases. And there
4 hasn't been mortality, but there certainly has been
5 morbidity associated with it. So, I'm not comfortable
6 arguing that there's a difference in the onset. I
7 think that I've certainly reviewed a goodly number of
8 these cases and the precipitous drop cases, which is
9 a quarter or so of all cases, certainly appear to
10 happen early. But again, that may be an incidence
11 driven phenomena, not a proportion driven phenomena.

12 CHAIRPERSON KANE: Now, I understand that
13 from the standpoint of the prodrome that there's no
14 difference between the early occurring and late
15 occurring cases. Might there be any potential
16 differences though in terms of etiology? If we think
17 that this is partially immune, mediated, for example,
18 would that have any implications?

19 DR. GERSON: Once drug is stopped, the
20 recovery period seems to be independent of the
21 duration of prior treatment. So, I don't think that
22 there's a reason to believe that the effect on the
23 marrow, when at presentation of agranulocytosis leads
24 to any difference in a co-morbidity or time to
25 recovery. I think one has to consider them to be

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1 really, quite identical early and late cases.

2 I wonder if I could go back and just
3 comment briefly about my own admittedly skewed
4 appreciation of the rechallenged cases. Because, of
5 course, nobody calls me if they're doing well, but I
6 do get lots of phone calls from physicians directly,
7 or probably even numbers through Novartis with a
8 question of "what do I do with this case?" There are
9 a couple of key exceptions to the -- or one key
10 exception to the rule, and that is the chemotherapy
11 patients.

12 There's a large enough database not
13 surprisingly. There are a number of people with
14 cancer who have been now co-treated. And those
15 individuals are picked up because in the course of
16 their cancer treatment if they, of course, develop
17 agranulocytosis from their chemotherapy -- and there
18 is now a review process to allow rechallenge in that
19 setting. It's fairly clear that those people do not
20 have a -- there's not an exacerbation of the
21 probability of Clozapine-associated agranulocytosis if
22 someone is on chemotherapy. So, that is one instance
23 in which rechallenge has been allowed.

24 I have received a number of phone calls
25 that are outside the CNR rechallenge request from

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1 physicians asking whether or not the person really can
2 be rechallenged because of some extenuating
3 circumstance. For the most part, those extenuating
4 circumstances really don't add up and the patient
5 really, in my mind, shouldn't be rechallenged. There
6 have been a couple of instances in which the specifics
7 were such that a drug with an associated
8 agranulocytosis was started the week or two before and
9 agranulocytosis developed. But that's really a quite
10 rare phenomena.

11 But I would say that I've received many
12 more phone calls than the 12 from physicians
13 attempting to rechallenge. My own sense would be that
14 if there wasn't a system, that those folks would
15 probably go ahead and rechallenge as the expert local
16 hematologist.

17 CHAIRPERSON KANE: I guess before Dr.
18 Leber asks a question, I have one more question.

19 We've been looking at data that's been
20 collected since 1990 and we're trying to make
21 projections now going forward from 1997. Could you
22 comment on what impact changes in the management of
23 agranulocytosis have had over the period since 1990
24 and what implications you might see for mortality
25 rates going forward?

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1 DR. GERSON: Sure. I think that's really
2 a very good question.

3 As you know, there isn't a requirement for
4 a protocol for treatment once agranulocytosis is
5 developed, but it's fairly common -- I would say
6 probably maybe in two-thirds of cases or so -- that
7 patients would be administered growth factors and the
8 third generation, fourth generation antibiotics to
9 support them through a neutropenic episode. Most
10 hospitals now, as opposed to even seven years ago,
11 have very good neutropenic precaution policies in
12 place that weren't in place before and I think that
13 awareness has contributed to the three percent
14 incidence. It's really very hard to find studies with
15 less than the three percent incidence of death
16 associated with neutropenia or febrile neutropenia.
17 That's a really very low number, and not at all a high
18 number.

19 However, the use of growth factors has
20 recently come into question. In a recent New England
21 Journal article, in chemotherapy-associated growth
22 factor use, it really queried whether or not it had
23 any benefit at all. It shortened neutropenic episodes
24 by a day or two, maybe shortened fever by a day or
25 two. It had absolutely no impact on overall morbidity

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1 or mortality.

2 I would take issue with that result in the
3 Clozapine population because our data clearly showed
4 that if you administer GCSF, you shorten the duration
5 of neutropenia not by a day or two, but by five to
6 seven days which is a significant time period. There,
7 of course, hasn't been a huge randomized study, but
8 there certainly is data bouncing around, again
9 reaffirming, that with the use of GCSF, you shorten
10 the duration to perhaps five to seven days with a
11 median of about six to seven days which is what we
12 reported initially back in '92. So that I would be a
13 strong advocate for the very early use in
14 agranulocytosis of growth factor support, and of
15 course, use of broad spectrum antibiotics.

16 So, I think that has contributed -- I
17 don't see anything on the horizon that's going to
18 alter that. I think we're where we are now. I don't
19 see new drugs or new cytokines coming along which
20 would alter that.

21 CHAIRPERSON KANE: Dr. Leber?

22 DR. LEBER: Yes, this is really a
23 hematological question and it requires a guess because
24 you couldn't know this empirically. We make the
25 assumption that if you initiate a stoppage of therapy

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1 when someone needs some critical value, that the
2 consequent benign course is a result of stopping
3 therapy. What you really want to know is how often
4 stopping makes a difference? In order to know that,
5 you would have had to expose individuals continually
6 to Clozaril to see what their course would have been.
7 Of course, we didn't do that.

8 I just wonder, is there any literature
9 independent of this that talks about spontaneous
10 recovery at various levels of the nadir of the white
11 count? In fact, is it even conceivable that you could
12 recover from a chemical agran, that is in terms of
13 absolute neutrophil count being lower than 500 on a
14 single measurement and then coming back?

15 DR. GERSON: With this medication, there
16 are individuals with mild neutropenia who will bounce
17 along, who will have the drug stopped and restarted,
18 stopped and restarted, and will never go on to severe
19 neutropenia or agranulocytosis. That group is within
20 the 55 or so percent who really are sort of immune, if
21 you will. They clearly have a drug effect, moderate
22 leukopenia or leukopenia but don't go on to
23 agranulocytosis.

24 There are other drugs in which you can
25 sort of watch people on prolonged course of therapy

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1 and they'll meander around the moderate leukopenia
2 level and not have an agranulocytosis event. But with
3 Clozapine -- Clozapine is clearly different -- and
4 there are a good proportion of those individuals who
5 will go on. How to bracket the real proportion which,
6 if unmonitored, would go on is very difficult. I
7 think that the best estimates are those that Dr. Weiss
8 gave us from the proportions that we've seen. And
9 again, without doing the study, it's going to be very
10 hard to tell.

11 DR. LEBER: One reason that I was
12 interested in this is that in the surveillance in New
13 Zealand from Mianserin, if it is in fact clinical
14 agran, the number of cases of actual agran could be
15 much larger and therefore, the case fatality rate
16 would drop for reason of expanded denominator. I
17 mean, I'm not really challenging the absurd, or even
18 suggesting it -- I mean, we knew I guess in Finland,
19 there was a 70 percent case fatality rate in '74. So,
20 clearly, monitoring has some advantage, logically.

21 But I just wonder if there is any other
22 situation in which one could say something else
23 accounts for recovery short of stopping drugs?

24 DR. GERSON: It is actually pretty
25 impressive that of the agranulocytosis cases with

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1 Clozapine, you can really look hard to find early
2 recoverers so that a very sizeable proportion -- in
3 excess of 80, maybe even 90 percent -- of folks who
4 develop the criteria of agranulocytosis go through
5 this really delayed recovery period. So, it really
6 isn't the case that there are individuals who sort of
7 randomly drop and then bounce back up. And that,
8 again, is something that is seen with other drugs, but
9 not seen, to my knowledge, with this drug.

10 CHAIRPERSON KANE: Dr. Tsuang?

11 DR. TSUANG: I have epidemiological
12 questions as a whole. In terms of risk factors,
13 already been indicated that the age using -- point of
14 40 seems to be important. Are there any other
15 important risk factors when the data has been analyzed
16 for agranulocytosis? -- talking about the ethnic
17 group. Any other important factors, particularly
18 generic risk factors? Anything which we can do to
19 really identify those risk factors? That is one.

20 And while we are talking about the risk
21 factors, epidemiologically, is it possible to estimate
22 the risk benefit ratio from the available data to
23 assume the benefit which has already been indicated
24 and the risk has already been -- could we roughly
25 estimate the risk benefit ratio?

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1 Anyone can elaborate in these areas
2 because it's very important. Comparing with other
3 medication, is there any unique features for Clozapine
4 that impress us that current systems should be
5 continued with the assessment of benefit risk ratio?
6 That is probably what I'm asking.

7 DR. ANAND: Let me ask the question. Are
8 you saying what are the benefits of Clozaril therapy
9 which would outweigh the risks associated with agran?
10 If that is the question, then the answer would be that
11 based upon the control trial data, approximately 35
12 percent of Clozaril patients would be considered
13 responder to the likely specified criteria and I think
14 the risk for agran would be about one to two percent.
15 So, that is a very broad definition of this benefit.
16 I'm sure Dr. Leber has some other definition in mind.

17 DR. LEBER: I wish I did.

18 DR. TSUANG: You see, that is the only
19 very crude assessment. I am talking about
20 epidemiologically, to the population who needs the
21 treatment, in terms of their benefit. Can you assess
22 it from the patients' -- consumers' point of view and
23 the financial and the administrative burden? Those
24 kinds of things versus the risk of preventing
25 occurrence of the agranulocytosis and the mortality.

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1 That is probably what I am talking about.
2 Epidemiologically, could we find a way to estimate
3 that?

4 CHAIRPERSON KANE: I think there was a
5 paper in the archives by Zhang which attempted to do
6 that.

7 DR. ANAND: Yes.

8 CHAIRPERSON KANE: Ravi?

9 DR. ANAND: There are about actually three
10 papers: the cost benefit study, the studies which
11 have looked at the cost associated with the Clozaril
12 therapy and how this helps in saving money. It also
13 estimates the cost of treating agran. In all those
14 studies, there's a very conclusive benefit shown for
15 treatment with Clozaril. I think there's a Zine
16 paper, there's a Ravicki paper. There's a Melzer cost
17 effectiveness study. I think those are the kind of
18 data that are actually referenced in your briefing
19 blurb pointing out the benefits of treatment.

20 CHAIRPERSON KANE: I think the question
21 relates more though to the risk benefit analysis of
22 the WBC monitoring. I think the Zhang paper in the
23 archives of '96 suggested that beyond six months, the
24 cost effectiveness was changed.

25 DR. TSUANG: Yes. Probably, this is the

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1 somewhat academic question. The reason I asked about
2 the risk of developing agranulocytosis, is there any
3 way of detecting this at the time of the first visit?
4 Is there any way to estimate the risk so that this
5 could be preventable?

6 DR. ANAND: At the present moment, based
7 on all the data, there is no way of identifying
8 whether a patient is going to experience agran before
9 starting Clozaril treatment. There were some
10 anecdotal studies indicating that the risk for agran
11 was higher in individuals than Ashkenazy origin.
12 However, subsequent studies could not confirm that
13 increased risk. Other than those, I'm not aware of
14 any systematic data to address that issue.

15 DR. TSUANG: Is it possible to analyze the
16 current available data so that epidemiologically, we
17 can estimate what are the risk factors?

18 DR. ANAND: I think we have our consultant
19 statistician here.

20 DR. HAUPTMAN: My name is Lawrence
21 Hauptman. I'm a statistician who works for Novartis.

22 The data in the Clozaril National Registry
23 that we saw today is not comprehensive in terms of a
24 lot of the epidemiological aspects that one would wish
25 to investigate, like ethnicity or other aspects. What

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1 we showed you, we did only for age and gender because
2 those bits of information are collected
3 comprehensively. For other things, it was just not
4 set up in order to comprehensively collect other
5 epidemiological data.

6 Another thing you mentioned in your
7 opening remarks is that the risks seemed to go up at
8 40. Of course, when you present data like this, you
9 have to make a cut somewhere. There was nothing magic
10 about 40. If we made it 45, if we made it 50, the
11 same kind of picture would ensue. There wasn't any
12 dramatic age level where the risks jumped
13 precipitously. I don't think we need to show them
14 unless you want them.

15 We do have a slide to show the risks in
16 five year intervals, I think. The picture is sort of
17 a gradual increasing risk over that time rate, but it
18 does flip-flop around and I don't think from that
19 slide there's anything that jumps out at you that this
20 is a magic age where there is a dramatic difference.

21 CHAIRPERSON KANE: Dr. Casey?

22 DR. CASEY: Some questions to the team
23 that presented. It gets to the issue of what's the
24 noise in the system? I'm trying to understand who was
25 in the database. Were the 581 people defined as

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1 people who had moderate or greater leukopenia, people
2 that you then followed for sure and know whether they
3 did or did not develop agran? Compare that to how
4 many people might have gotten into the moderate
5 leukopenia group, got dropped because the doctors or
6 patients got concerned, and then you do or do not know
7 what happened to those people in the going forward
8 basis. So, what is the size of the unknown in that
9 population?

10 I'm trying to define the definitions of
11 who got into your 581 analysis and who's not in it,
12 and what we don't know about who's not in it?

13 DR. ANAND: I think the 581 are those who
14 met the criteria for moderate leukopenia. I think
15 your second part of your question is were these
16 followed up to see how many progressed on and how many
17 actually stopped treatment at that point and
18 therefore, can not be counted? Is that what your
19 question is, sir?

20 DR. CASEY: That's a good starting place.

21 DR. ANAND: Let me get back to you again
22 on that pretty good question because we will have to
23 count the patients to see how many dropped out at that
24 time point.

25 DR. CASEY: But to clarify the definition

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1 of your 581, those are all the people that met
2 moderate or greater leukopenia --

3 DR. ANAND: Right.

4 DR. CASEY: -- and were discontinued?

5 DR. ANAND: Yes, who were followed.
6 Moderate leukopenia patients have interruption of
7 treatment once -- if their values go back above, then
8 they can be retreated.

9 DR. CASEY: And they would be in this data
10 set?

11 DR. ANAND: They would be in this data
12 set.

13 DR. CASEY: Okay.

14 DR. SALZMAN: And the denominator for that
15 581 is the 67,661? 581 out of --

16 DR. ANAND: Yes, right -- 67,000-plus is
17 the 581.

18 DR. SALZMAN: So, help me out a little
19 bit. It seems to me that's an extraordinarily small
20 number and the number gets smaller as you follow these
21 people along. So that, we're actually talking about
22 an extremely small number, few number of people who
23 are getting Clozapine after six months have really
24 entered into a risk range. The calculation seems like
25 it's about .008 percent, or something like that.

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1 I think I'm making a mistake, if you could
2 help me out with it because the number is confusing.
3 It seems very small --

4 DR. WEISS: The numbers you're citing are
5 correct. It's 581 patients of the 67,000-plus who
6 used Clozaril for six months or longer developed
7 moderate leukopenia or worse.

8 DR. SALZMAN: Right.

9 DR. WEISS: The numbers, it's true, get
10 smaller. The numerator gets smaller at one year and
11 two years, but of course, the denominator shrinks as
12 well. But the rates are what the rates are. They
13 were presented earlier and I know you have them in the
14 materials in front of you. Whether those numbers --
15 rates are small or not small is, I guess, to some
16 extent, in the eye of the beholder. But they are what
17 they are, as best we can estimate.

18 DR. SALZMAN: Well, the reason I'm asking
19 the question is because in clinical life, it's not the
20 agranulocytosis that's the major event. It's the
21 leukopenia because that's the critical identification
22 point. If the number of people -- not the rate, but
23 the number of people who develop moderate leukopenia
24 is so small, then it seems to me that continuing to
25 monitor that closely really doesn't make a lot of

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1 sense.

2 DR. WEISS: The idea of screening for
3 disease in apparently healthy individuals is one that
4 is not unique to this situation. As you know, we
5 screen for cervical cancer and other things where the
6 large majority of people in whom screening is done do
7 not have the condition. Ultimately, one has to assess
8 whether the benefit that a few individuals will obtain
9 from this is worth the overall cost that is borne by
10 the entire group. It's a balancing of those two
11 things.

12 DR. SALZMAN: Okay, last question then.
13 Could you remind me of the numbers for the first six
14 months? Here, the ratio is the 581 over 67,661. What
15 would that ratio be for the first six months so we can
16 see what the change has been?

17 DR. WEISS: Do you know the number who
18 developed moderate leukopenia in the first six months?
19 I don't know that number in my head.

20 It would certainly be much larger. The
21 agranulocytosis numbers are in roughly -- 957, I'm
22 told.

23 DR. SALZMAN: Over?

24 DR. WEISS: Right -- and the denominator
25 -- it's on one of the slides.

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1 DR. CASEY: 153,000-plus?

2 DR. WEISS: No. There were --

3 DR. ANAND: 96,000.

4 CHAIRPERSON KANE: Dr. Tamminga?

5 DR. TAMMINGA: All of the data -- the age
6 effect in the briefing books that we had was really,
7 seemed to me, a relatively permanent effect. All the
8 data that you presented today, the bulk of you
9 presented was data without the age, in fact, taken
10 into account.

11 Left with what I've read in the briefing
12 book, I would think that a good proportion of the
13 cases that you reported today of the agranulocytosis
14 and the leukopenia was probably in the over 40 or in
15 the elderly folks. But I'd just like you to make some
16 statement about how important you think the age effect
17 was. I'm sure we'll hear more about it for the rest
18 of the morning, but it seems like the age effect is
19 really -- the elderly are really a very, very
20 prominent risk.

21 DR. WEISS: Let's take a look at the
22 numbers and we'll have something specific to talk
23 about. These are the incidence rates by age. The
24 point that I was trying to make -- let's see if this
25 magical thing goes all the way up there. Here it is.

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1 You're certainly right that even beyond
2 six months, whether it's in men or in women, males or
3 females, that the persons over the age of 40 have
4 several times the rate of persons under the age of 40.
5 As was pointed out, it's not that there's anything
6 magical about 40, it's that the rate generally tends
7 to go up with increasing age.

8 The reason that we haven't given a lot of
9 attention in the rest of the presentation to these age
10 differences is that the absolute magnitude of this
11 difference is like a half or one case per 1,000
12 person-years which is dwarfed by the difference in the
13 six months and beyond, as opposed to the first six
14 months where now we're talking about a difference of
15 three, five, seven, ten per 1,000 person-years. This
16 going from the first four numbers to the bottom four
17 numbers. So, it's not that age isn't probably of some
18 importance, but its absolute magnitude is not very
19 great in the critical period, critical for our
20 discussion now which is in the period six months and
21 beyond.

22 DR. SALZMAN: Can I just follow that up?

23 There are at least three publications in
24 the elderly, including one of our own. By elderly
25 now, over 65. In all cases, the agran rate went way,

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1 way up, particularly in the older females. I'm
2 wondering if there are any cumulative data from
3 Novartis about over 65-year-olds because that is a
4 group for whom we might have use for this drug.

5 DR. WEISS: These are detail data for the
6 occurrence of agranulocytosis by age. If we focus on
7 the elderly groups down here -- here are the rates --
8 we note that the denominator, in terms of person-
9 years, is somewhat small. But the actual number of
10 cases are not that small and we can we rates of four,
11 five, and ten. While those are generally higher than
12 the rates that we see in middle-aged adults, it's not
13 drastically higher.

14 DR. TAMMINGA: I can't see how you can say
15 that 6.9 is not drastically higher than .91. Am I
16 reading this wrong?

17 DR. WEISS: Well, I'm contrasting the
18 elderly from 65 on with middle-aged -- so I'd say 45
19 to 65, where we're seeing rates of four, five, and
20 ten. Here, it's six, seven, six, three, two. I mean,
21 it's higher, but it's not drastically higher.
22 Obviously, when you get down to the pediatric
23 population, the rates there are different, but I
24 didn't think that was the question.

25 DR. TAMMINGA: Well, through the 30s and

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1 40s, the rates are like one-and-a-half or two, and
2 then you get up to the elderly and the rates are
3 between seven and ten. That's really quite a bit
4 different.

5 DR. WEISS: Well, again, I was
6 specifically contrasting the 65 and older. That was
7 the question. It starts with five, 5.4. If you look
8 at the two age groups before that, getting towards my
9 age, for example, you're in rates that are not much
10 different. But I agree, at the younger stages, the
11 rates are lower.

12 DR. SALZMAN: Yes. But in actual clinical
13 practice, when you get to the 70 to 75 year olds,
14 those numbers are consonant with the published
15 experience and our own experience and it is a
16 substantial difference. It makes a very big
17 difference, actually.

18 CHAIRPERSON KANE: Dr. Casey?

19 DR. CASEY: Could I suggest, while we're
20 on this, when it becomes time to present the
21 information to the medical community, since age is a
22 continuous variable rather than a dichotomous one
23 where we get old at 40 -- which there are no old
24 people in this room -- that you present this type of
25 information that actually informs the practitioner by

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1 age group, how they could assess the information
2 rather than just by above or below 40.

3 The other question I was going to ask is,
4 if you know what happened to those n of 12 where they
5 met the criteria for agran, but not moderate or severe
6 leukopenia, didn't the course of those people turn out
7 to be different than the course of the people that you
8 had more opportunity to follow the trajectory of their
9 illness? Does that give us any information about the
10 value of the signal or not the signal in detecting
11 agran in monitoring? I guess, did those, say, 12
12 occur between six months and one year, or are we still
13 going out in two years and three-and-a-half years?

14 DR. ANAND: Again, we'll have to get back
15 to you on the specifics of those 12 cases.

16 CHAIRPERSON KANE: Dr. Geller?

17 DR. GELLER: When you're looking up those
18 12 cases, if we also could have their age and gender?

19 DR. ANAND: Sure.

20 CHAIRPERSON KANE: Ms. Curll?

21 MS. CURLL: Yes, I have two questions.
22 One is that I noticed in the early discussion that you
23 said that 70,000, approximately, were discontinued
24 because of non-compliance. I'm wondering how the cost
25 of the lab is being reimbursed by many of the patients

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1 and whether this could have been a problem in the
2 environment of third party and HMOs? And whether they
3 are reimbursing patients, or is this something that
4 they have to take on themselves, financial burden?

5 DR. ANAND: I'm sorry. I don't think we
6 have the information on that.

7 MS. CURLL: Because that may be
8 significant.

9 Secondly, if the registry were to
10 continue, could the program be reconfigured to include
11 the database for ethnicity for diagnosis as well as
12 reimbursement?

13 DR. ANAND: I think all of these
14 suggestions, we'll take them up and discuss how this
15 could be --

16 MS. CURLL: Because it may be significant
17 for the patient, for the individual and family. Thank
18 you.

19 CHAIRPERSON KANE: Dr. Risby and then Dr.
20 Tsuang.

21 DR. RISBY: Yes. It's my understanding
22 that Clozapine is used in some countries where there
23 is no monitoring system, such as China. Number one,
24 is that true? If so, is there any data on the death
25 rates in those patients?

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1 DR. ANAND: In all the countries of the
2 world where Novartis has marketed Clozaril, we have a
3 monitoring requirement. There's a recommendation for
4 monitoring, frequent monitoring, and the same
5 guidelines hold. That there are certain cutoff values
6 which are established for hematologic scores and
7 physicians are asked to respect those values.

8 Regarding China, Novartis does not have
9 the -- on the market. The use in China is through
10 other companies, Chinese local companies. We have no
11 information on the rates for agran in that population.

12 CHAIRPERSON KANE: Dr. Tsuang?

13 DR. TSUANG: Again, I'd like to come back
14 to the prediction of risk factors, in particular, to
15 epidemiologists and the -- statistician. The data now
16 you have available, can that be subject to a Cox
17 regression model? And to have the age and sex and the
18 diagnosis, probably there is none. I'm just talking
19 about this is a very important thing for this type of
20 work to be carried out. And then the age of onset and
21 what kind of other medication the patient is
22 receiving. And there are many clinical costs; many
23 clinical variables which can be included. And to
24 estimate the significant -- and to estimate the risk
25 factors which are significant in terms of developing

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1 agranulocytosis.

2 Can someone elaborate that for me from
3 your data analysis?

4 MR. HAUPTMAN: Yes, we have done Cox
5 regression analysis. But again, as I alluded to
6 earlier, we did it only for age and sex because those
7 were the only data which were comprehensive. Sex was
8 not statistically significant and age was. That's why
9 I said in looking at it, if we showed you the
10 histograms of the rates by five year groups, you will
11 see the risk, where with the few blips, essentially
12 increasing over age.

13 So, age is statistically significant from
14 the Cox regression analysis. Sex isn't. As far as I
15 know, the other kinds of information one would want to
16 include were just not collected comprehensively in the
17 database.

18 DR. TSUANG: For instance, response to
19 treatment, outcome and the clinical course. There are
20 many clinical variables which can be included in your
21 regression analysis. Those seem to be quite obvious.

22 CHAIRPERSON KANE: Dr. Laughren?

23 DR. LAUGHREN: I think there's always a
24 temptation when you hear about a huge cohort of
25 patients, to think of it as a research study. But in

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1 fairness, you know, this was a program that was set in
2 place as a way of marketing a drug safely to patients.
3 It's not a study per se. I think one can try and do
4 what one can with the data available, but this is not
5 a study.

6 DR. SALZMAN: Yes, but if you're trying to
7 figure out who are the likely people to develop this,
8 there may be data in-house right now to help, at least
9 partial analysis --

10 DR. ANAND: The Clozaril National Registry
11 will not have information on the diagnosis and
12 outcomes. It will only accept for discontinuation.

13 CHAIRPERSON KANE: Dr. Simpson?

14 DR. SIMPSON: I merely had a question for
15 the statistician. When you said you modeled the data,
16 did you model the time until the first event, given
17 that you had some repeats? Or how did you do it? Did
18 you do a multiple occurrence analysis?

19 DR. HAUPTMAN: I don't think we have any
20 multiple occurrences of agran. They were all analyses
21 of time to first event.

22 DR. SIMPSON: Okay, what about for
23 leukopenia?

24 DR. HAUPTMAN: Those were also analyses of
25 time to first event. I don't know off-hand, but --

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1 DR. SIMPSON: Is there an age effect on
2 that too?

3 DR. HAUPTMAN: Yes. What I said about age
4 and sex held true for both agranulocytosis, moderate
5 leukopenia and severe leukopenia. No severe gender
6 effect, but there is a significant increasing risk
7 with increasing age.

8 CHAIRPERSON KANE: Dr. Tamminga?

9 DR. TAMMINGA: Yes, I have one more
10 question for Dr. Anand. This isn't about the material
11 that you presented today, but it's about the material
12 in the briefing book.

13 You presented some incidence figures for
14 agranulocytosis, I believe, in the UK although the
15 criteria were different. It just seemed to me that
16 from glancing at those data, that the incidence was
17 significantly higher there. But I wanted to know
18 whether, in actual fact, it is higher? If it is
19 higher in the UK, what's your explanation of it or how
20 do you see it?

21 DR. ANAND: Well, first of all, the UK
22 database isn't as large as the US database so I think
23 -- we don't think it's robust enough to make any
24 comparisons. The cumulative incidence does appear to
25 be higher. At this point, we see no reasons to expect

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1 that the drug is behaving differently in the UK
2 compared to the US population. That would be our take
3 on the data at this point.

4 DR. SIMPSON: And you've done all these
5 same kind of age and sex analyses of the UK data and
6 they pretty much parallel what you see in the --

7 DR. ANAND: I think the data which Dr.
8 Hauptman was referring to and which is in your
9 briefing book is based on the UK data also, and you
10 see the same effect for age.

11 CHAIRPERSON KANE: Dr. Dominguez?

12 DR. DOMINGUEZ: There were 12 deaths
13 between 1990 and 1995. There were seven additional
14 deaths, it appears, between 1995 and 1997. and yet,
15 we hear of perhaps better medical management of these
16 patients. So, perhaps could you work backwards for me
17 on the rates that has been observed in the last two
18 years. Are there any surprises in the rates of
19 moderate leukopenia or agranulocytosis in the last
20 three years that did not appear in the first five
21 years?

22 DR. ANAND: I think the rates are very
23 consistent. The only additional finding is that one
24 of the deaths occurred after eight months after
25 therapy. As remarked before, most of the deaths, all

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1 the 12 deaths which had occurred, in the pre-'95
2 database were before six months of therapy, generally
3 around the third month of therapy. This was a late
4 death which occurred in the US. And there also have
5 been deaths outside the US which have occurred after
6 six months of therapy.

7 CHAIRPERSON KANE: Dr. Simpson?

8 DR. SIMPSON: I was just coming back to a
9 point you made about the fact that some of the other
10 psychotropics didn't have evidence of agranulocytosis
11 after about six months. So, how strong is that
12 evidence? Or how weak?

13 DR. ANAND: Very weak. Very weak data.
14 Basically, it's anecdotal data. The only so-called
15 definite study is the international study which also
16 does not have very systematic data collection. That's
17 why --

18 DR. SIMPSON: So, it could have occurred?
19 It could have occurred.

20 DR. ANAND: It could have occurred. We do
21 not have any data.

22 CHAIRPERSON KANE: Any other questions for
23 the sponsors?

24 Dr. Casey?

25 DR. CASEY: Dr. Anand, could you review

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1 again, the basis of your recommendations for
2 maintaining the Clozaril National Registry?

3 DR. ANAND: Yes. I think the Clozaril
4 National History is the repository of all of the WBC
5 information, also the patient identifiers. It
6 contains information on the non-rechallengeable
7 patients. These are the patients we are concerned
8 about because they should not be re-exposed.

9 There are other functions of the Clozaril
10 National Registry. On an average, we get about 600 to
11 700 phone calls a week from physicians. Schizophrenic
12 patients appear to move. They go to a new physician.
13 The physician wants to find out their previous WBC
14 data. It's only through the Clozaril National
15 Registry, at the present moment, that this information
16 is given out.

17 The Clozaril National Registry and its
18 enforcement mechanisms, the quality assurance
19 mechanism looks at different treatment systems to see
20 whether they're compliant or not. Those which are not
21 compliant are immediately informed that they are not
22 being compliant and what steps they need to take.

23 So, there's an enforcement mechanism,
24 there's a quality assurance mechanism. All of these
25 work quite hand-in-hand to ensure safety of patients

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1 on Clozaril.

2 DR. CASEY: Could I review for my own
3 sense of knowing the numbers that you are saying you
4 have no evidence about any patients who were
5 rechallenged once they developed agran. So, we have
6 no actual experience to say it's a good thing to
7 protect a patient from rechallenging? It may be
8 something with face validity, but we do not know
9 whether protecting somebody from rechallenge is a good
10 thing or not a good thing from what you're saying?

11 DR. ANAND: Right. As we said, we do know
12 that 12 patients were non-rechallengeable who did
13 attempt to get back on Clozaril therapy. We do know
14 that non-rechallengeable patients have 44 higher risks
15 for agran. We do know that non-rechallengeable
16 patients, patients whose values have gone below 2,000,
17 have 50 percent higher risk for developing agran.

18 Based on that and the fact that patients
19 with agran ultimately do have a small but finite risk
20 for death serves this role in reducing the risk to
21 this patient population.

22 DR. CASEY: I understand the incremental
23 risk that you describe. But I also want to be clear
24 about whether we do or do not know that we are
25 potentially denying somebody access to treatment which

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1 may be a very effective -- the only treatment for them
2 on the basis of them having agran and us believing
3 that it is a bad thing to allow them to get re-
4 exposed. But we don't have the data.

5 DR. ANAND: Well, I think the consultant
6 hematologist's opinion, I think, may be more
7 important, whether we should be allowing patients
8 exposure to Clozaril in the hope that they get better,
9 but do not experience agran if they've been declared
10 non-rechallengeable.

11 DR. GERSON: And we do have a database on
12 risk that says that the patient who has moderate
13 leukopenia which recovers has four times the risk of
14 going on to agranulocytosis. So, we have a, you know,
15 quantifiable increase in risk if you meet the first
16 point.

17 There are data on patients who have
18 developed agranulocytosis who have then been
19 rechallenged. Now that isn't recent data because the
20 CNR has been quite adamant and vociferous in its
21 defense of its own policy in not allowing rechallenge.
22 So, that data actually goes back and covers my brain
23 here, back to the early '90s in which there were
24 between six -- my memory is actually 10 to 12 patients
25 who were rechallenged. And in fact, those individuals

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1 went on to develop agranulocytosis and went on to
2 develop over the shorter interval. Some of that is
3 US; some of that is non-US. Some of that actually was
4 patients during the study period, pre-marketing, who
5 were then rechallenged.

6 And there are anecdotal cases in which a
7 plea was made and a "we'll do it carefully" mode was
8 done and I was involved with a couple of those cases
9 from afar. But my appreciation is that those with
10 documented agranulocytosis who were rechallenged
11 redeveloped agranulocytosis.

12 DR. CASEY: And that gets to the lure
13 issue that I was bringing up earlier that there's
14 information out there, quote/unquote, that people have
15 been rechallenged and the vast majority, or all of
16 them, have reexperienced agran.

17 Is that your general understanding of how
18 it has gone?

19 DR. GERSON: Yes.

20 DR. SALZMAN: Dr. Gerson, you said that if
21 there's a leukopenia, there's a four-fold increase in
22 risk. Is there a time frame for that? Over what
23 period would that increased risk be?

24 DR. GERSON: That's actually a very good
25 question. I think it's a contaminated answer because

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1 there is a quite broad range, and that's just from my
2 own personal knowledge, of the delay and rechallenge.
3 So that, some people may go off and come back on six
4 months or a year later. Others would go off for a
5 week and come back on as soon as their counts
6 recovered. So, I don't know quite how to interpret.

7 However, my sense is that from the start
8 rechallenged point to agranulocytosis is a relatively
9 short period of time. But that, again, has to do with
10 the incidence that peaks out in the first six or 12
11 weeks.

12 CHAIRPERSON KANE: Dr. Laughren?

13 DR. LAUGHREN: I had a couple of questions
14 for Dr. Anand.

15 In one of your slides, you mentioned that
16 elimination of the National Registry is one of the
17 changes under consideration. That was not one of the
18 issues that we put on the agenda. I just want to go
19 over a little bit with you what your meaning is here.
20 Certainly, it's possible, even if at some point the
21 program were to become voluntary, to still maintain a
22 registry and have, you know, physicians voluntarily
23 report. It seems to me that probably the major
24 advantage that the registry has is that it identifies
25 patients who perhaps shouldn't be rechallenged. And

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1 it would still, it would seem to me, be possible to
2 maintain that register even though -- voluntary at
3 some point.

4 Can you comment on your company's
5 intentions in that regard?

6 DR. ANAND: Yes. I think we agree with
7 you totally that the Clozaril National Registry
8 through its rechallengeable database, that serves a
9 very valuable purpose of protecting those patients who
10 never should be rechallenged.

11 If you're going to consider the option of
12 voluntary reporting, we believe that compliance with
13 voluntary reporting will not be as good. Some data
14 indicating to that, we point towards a clinical trial
15 database where, even though we believe that clinical
16 trials are done in a very rigorous way, the compliance
17 with the reporting was far lower. It's about less
18 than 80 percent. Compliance with the Clozaril
19 National Registry in the current form with its
20 mandatory reporting is over 99 percent. So, there's
21 a significant fall in compliance if you were to go to
22 voluntary reporting. That's what concerns us.

23 CHAIRPERSON KANE: Dr. Leber?

24 DR. LEBER: We may be drifting a little
25 bit off what I think we want to get from the

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1 committee. I think the specific solutions to this
2 problem are something that await a lot of
3 deliberation.

4 What we wanted to get from the committee
5 today is a sense of how valuable a mandated system of
6 no blood/no drug is, how long it should be in place?
7 Whether there's ever a point in time when it's
8 reasonable to consider alternatives -- not the
9 specifics of the alternatives, but whether the concept
10 is worth addressing? I think we're trying to get it
11 from a group of experts who represent knowledgeable
12 people familiar with the management of schizophrenia.
13 The details are something I'm not sure we even have a
14 good sense of ourselves yet or could give you an
15 answer legally or any other way.

16 So, I think we really want to get out of
17 the committee just how valuable? And I take the point
18 raised earlier that it would be nice to be able to do
19 this in terms of benefit risk. Unfortunately, our
20 measures of benefit are extremely hard to come by and
21 extremely arguable. So, I think you're going to have
22 to do with what you have, formed sort of very loosely
23 and non-quantitatively. But I think what we want to
24 get from all of you is how important and valuable this
25 is, and how long should it stay in place, or should it

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1 stay in place at all?

2 CHAIRPERSON KANE: Okay, thank you for
3 that.

4 I think we'll take a 15 minute break now
5 and then come back with the Division overview.

6 (Whereupon, off the record at 10:55 a.m.,
7 until 11:18 a.m.)

8 CHAIRPERSON KANE: The Division overview
9 will be presented by Dr. Racoosin.

10 DR. RACOOSIN: The clinical development
11 program of Clozapine identified agranulocytosis as a
12 serious adverse event associated with the use of the
13 drug. FDA approved labeling required that the drug
14 only be available through a distribution system that
15 ensured weekly white blood cell monitoring, the so-
16 called no blood/no drug rule that you've heard so much
17 about.

18 Data on white blood cell counts and agran
19 occurrence have been collected by the Clozaril
20 National Registry. Previous analyses of this database
21 have identified that the incidence of agran decreases
22 substantially after six months from the first drug
23 exposure.

24 Because of the significant decline in
25 agran risk after six months of use, we're asking your

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1 opinion on the following questions:

2 (1) Should the frequency of white blood
3 cell monitoring be reduced at some time point after
4 initiation of therapy? And if so, when and what
5 reduced frequency of mandatory white blood cell
6 monitoring would be acceptable?

7 (2) Should the mandatory white blood cell
8 monitoring stop altogether at some point? If so,
9 when?

10 (3) Finally, should the program be
11 changed overall? For example, should it become
12 voluntary, as is most advice in labeling regarding
13 monitoring for adverse events?

14 In order to build a framework for thinking
15 about these questions, I'm going to be reviewing the
16 following topics:

17 (1) The background agran rate in the
18 general population.

19 (2) Agran rates observed with other
20 drugs.

21 (3) Our analysis of the agran rates from
22 the Clozaril National Registry data.

23 (4) And the discussion of the hematologic
24 risk analysis you heard earlier.

25 Several studies have been done to try and

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1 estimate the incidence of agran in the general
2 population. One of the earliest studies was done by
3 Bottiger and Westerholm in Sweden. They did a medical
4 record review of all patients discharged from the
5 hospital with a diagnosis of a blood dyscrasia in the
6 Uppsala health care region in Sweden between 1964 and
7 1968. They defined agran as less than 180 neutrophils
8 per cubic millimeter and they found an all-cause agran
9 rate of 12.8 cases per million persons per year.

10 The most comprehensive study of agran
11 incidence was the International Agran and Aplastic
12 Anemia Study. The eight study sites were followed
13 prospectively for the occurrence of agran cases over
14 a predefined period of time. The population of the
15 study site city was used as the denominator for the
16 agran rate. Case control methodology was then used to
17 identify associations between specific drugs and drug
18 classes.

19 There were eight study sites in Europe and
20 Israel. They defined agran as less than 500
21 neutrophils per cubic millimeter. And the patient
22 also had to have symptoms such as fever, chills, or a
23 sore throat. The overall rate of agran was 4.7 cases
24 per million persons per year. Among the eight study
25 sites, the agran rate ranged from 1.7 to seven cases

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1 per million persons per year. There was an extension
2 of this study involving three sites: one of the
3 previous Swedish sites and two new US sites. They
4 came up with an agran rate of 3.4 cases per million
5 persons per year.

6 A more recent study to estimate the agran
7 rate in the US was done by Strom. They studied
8 Medicaid billing databases in Minnesota, Michigan and
9 Florida to estimate agran incidence, excluding
10 recurrent or chronic neutropenia. The case
11 identification was based on hospital discharge
12 diagnosis of agran with medical record verification.
13 Their definition was less than 500 neutrophils per mm³
14 and their incidence rate was 7.2 cases per million
15 persons per year. Over the three states, there was a
16 range from 2.3 to 15.4 cases per million persons per
17 year.

18 Despite differences in the approaches used
19 to estimate the agran rate and different populations
20 studied, the background agran rate in the general
21 population appears to fall in the range of five to ten
22 cases per million persons per year.

23 The more pertinent question is, what is
24 the background rate of agran in the schizophrenic
25 population? Unfortunately, there's no published data

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1 on this topic that's accessible at least through a
2 men-line search. Due to chronic exposure to
3 medications in this population, however, the
4 background rate of agran in the schizophrenic
5 population may be higher than that in the general
6 population.

7 We wanted to identify other drugs that are
8 considered to have a significant association with
9 agran. I searched the CD Rom version of the
10 Physician's Desk Reference to identify drugs that had
11 agran in the warning section of the labeling. These
12 are the five drugs that have a boxed warning in the
13 labeling for agran. This group of drugs has agran in
14 the warning section of the labeling, but does not have
15 a boxed warning. The information in the labeling
16 describing the specific risk for agran very
17 substantially from drug-to-drug, as does the criteria
18 used to define agran. I'm going to describe the agran
19 risk for a few drugs for which there is enough data to
20 make a reliable estimate.

21 First, let me define a few of my terms.
22 When I refer to a risk, I'm referring to the number of
23 cases per the number of people exposed. And when I
24 refer to a rate, I'm referring to the number of cases
25 per the amount of exposure time.

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1 The most pertinent comparison would be to
2 look at agran rates with other drugs used to treat
3 schizophrenia. Phenothiazines have been long
4 considered to cause agran. However, the data
5 describing this is somewhat inconsistent. Most of the
6 data comes from case series that were done in the
7 1950s and 1960s. In these series, the agran risk
8 varies widely from as low as .004 cases up to 6.8
9 cases per 1,000 persons. In the International Agran
10 and Aplastic Anemia Study, they looked at the
11 association of phenothiazines with agran and they
12 found that phenothiazine use did not differ
13 significantly between cases and controls. However,
14 overall in that study, phenothiazine use was not very
15 great.

16 Ticlopidine is an anti-platelet drug used
17 to treat TIA patients. Ticlopidine-associated agran
18 is well described in the labeling. The data comes
19 from the clinical trials. They defined agran as less
20 than 450 neutrophils per mm³ and neutropenia as 450 to
21 1,200 neutrophils per mm³. They had 17 cases of agran
22 amongst 2,048 patients leading to a risk of eight
23 cases per 1,000 persons. The risk for neutropenia was
24 16 cases per 1,000 persons. In the labeling, the
25 recommended white blood cell monitoring is every two

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1 weeks CBCs for the first three months of therapy.

2 Sulfasalazine is an anti-inflammatory drug
3 used to treat rheumatoid arthritis and inflammatory
4 bowel disease. The data on agran associated with this
5 drug is based on two post-marketing surveillance
6 studies. In both studies, agran was defined as less
7 than 500 neutrophils per mm³. The first study was
8 done in the Swedish Adverse Drug Reactions Advisory
9 Committee. They calculated the risk of agran using
10 the number of cases reported over a denominator
11 estimate of persons at risk, which they based on an
12 average daily dose calculated from pharmacy records.
13 They came up with a risk of .6 cases per 1,000
14 persons. From a figure in their paper, I was able to
15 estimate person-years of exposure from the
16 distribution of the estimated length of drug use in
17 34,500 patients. I came up with a rate of three cases
18 per 1,000 person-years.

19 The second study was done in the United
20 Kingdom's General Practice Research Database. Data
21 was submitted by primary care physicians to a
22 centralized database. They came up with the risk of
23 .7 cases per 1,000 persons. From a table in the paper
24 that described total number of prescriptions filled,
25 I estimated person-years for the whole cohort and came

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1 up with a rate of three cases per 1,000 person-years.
2 On the sulfasalazine labeling, the recommended white
3 blood cell monitoring just refers to "CBCs should be
4 done frequently."

5 Now I'm going to discuss our reanalysis of
6 the agran rates from the Clozaril National Registry
7 data. This is a slide from the sponsor showing how
8 they broke down the duration of therapy. They looked
9 at the first two years broken down into six month
10 periods, and then combined the last 3.25 years of
11 registry data into one strata greater than 24 months.

12 We wanted to determine whether the agran
13 rate continued to fall in that last 3.25 year period.
14 So, what we did was to break down the entire 5.25 year
15 period by six month intervals and look at the rates
16 for each of those intervals. Then we combined them
17 into four new strata: 0 to 6 months, 6 months to 2
18 years, 2 years to 3.5 years, and 3.5 to 5.25 years.
19 As you saw before, the peak rate is in the first six
20 months, around 8.6 cases per 1,000 person years. Then
21 it continues to fall through the rest of the follow-up
22 period to .7 in that next year-and-a-half, and then to
23 .4 and down to .2.

24 You can see graphically, again, the peak
25 in the first six month risk period and then the

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1 subsequent fall. But because it's hard to see what
2 happens here as it gets close to zero, you'll see on
3 the next graph that I've expanded the Y axis here just
4 to go from zero to one. So, you can see how the rate
5 falls out into this period. Now, it's unclear whether
6 this fall is real. It's unclear because, as was
7 mentioned earlier, the use out here is much less than
8 it was earlier.

9 Dr. Weiss described for you projections of
10 the agran rates that might be expected under
11 alternative monitoring schedules implemented at
12 different times. I'm going to highlight a few issues
13 raised by the risk analysis method and present an
14 alternative scenario.

15 First, the start of the prodrome is hard
16 to define reliably making the results of the risk
17 analysis sensitive to the criteria used to define the
18 prodrome length. Also, projections were based on the
19 assumption that the time to moderate leukopenia would
20 not change with the change in the monitoring system.
21 This is an intestable assumption.

22 Given these assumptions, let's look at the
23 projections again. This slide depicts the percentage
24 of patients who would be detected in moderate
25 leukopenia, observed under weekly monitoring, and then

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1 projected for biweekly, monthly, or no monitoring. It
2 also shows the projected number of agran cases in each
3 of these monitoring schedules. The worst case
4 scenario would be with a switch to no monitoring after
5 six months of weekly monitoring, leading to a
6 projected number of agran cases of 401.

7 This graph is based on Table E which Dr.
8 Weiss presented with the rates of agran that would be
9 projected under biweekly, monthly and no monitoring
10 implemented at six months, one year or two years. And
11 again, this graph refers to the upper 95 percent
12 confidence limit which we calculated so that we could
13 try and see well, what would be the absolute worst
14 case within this model. We see 3.6 cases per 1,000
15 person-years would be the upper limit.

16 The sponsor has suggested that the
17 projections are conservative estimates and could be
18 higher. We suggest that you consider the alternative
19 scenario here. Assume that the 581 patients who
20 develop moderate or severe leukopenia all progress to
21 agran. You can see that the projected agran rate
22 under the alternative scenario is about 30 percent
23 higher than that suggested by Novartis. However,
24 they're still within the same order of magnitude.
25 Now, 5.2 would be the worst case scenario, cases per

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1 1,000 person-years.

2 To summarize, I wanted to show you again
3 how the agran rates observed in the Clozaril National
4 Registry compare with other drugs marketed in this
5 country. In the first six months, there were 8.6
6 cases per 1,000 person-years with Clozapine, and then
7 .6 for the subsequent six month to 5¼ year period.
8 The risk observed with ticlopidine was eight cases per
9 1,000 persons. Unfortunately, we can't calculate the
10 rate per 1,000 person-years because we don't know the
11 exposure time for that cohort. However, what we do
12 know is that those cases of agran were seen within the
13 first three months of therapy and therefore, if one
14 followed 1,000 patients for a year, you would have
15 1,000 person-years. This would be, at the least,
16 eight cases per 1,000 person-years. But we know that
17 they weren't followed -- or these cases didn't develop
18 over a full year. It was really in the first three to
19 four months of therapy. So, it's likely that the rate
20 per 1,000 person-years would be higher. And then
21 finally, in the two post-marketing surveillance
22 studies, the rate of agran observed with sulfasalazine
23 was three cases per 1,000 person-years.

24 As we've seen, the incidence of Clozapine-
25 associated agran peaks in the first six months

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1 following first exposure, and then declines 40-fold
2 over the subsequent five years. Novartis has
3 suggested that a change to no monitoring after six
4 weeks of weekly monitoring, the incidence rate of
5 agran would increase over six-fold from .52 to 3.3
6 cases of agran per 1,000 person-years. Alternatively,
7 we presented a scenario where all patients who
8 developed either moderate or severe leukopenia ended
9 up progressing to agran leading to an agran rate that
10 could be as high as five cases per 1,000 person-years.

11 Under either of these scenarios, the
12 incidence of agran is still within the range observed
13 with other marketed drugs in the United States that do
14 not require a mandatory white blood cell monitoring.
15 Thank you.

16 CHAIRPERSON KANE: Any questions for Dr.
17 Racoosin?

18 Carol?

19 DR. TAMMINGA: Yes, I had a question for
20 you.

21 DR. RACOOSIN: Sure.

22 DR. TAMMINGA: When you went through the
23 drugs with the box warning for agran and just for a
24 warning for agran in the labeling, is there a
25 specified criteria that requires a box and a specified

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1 criteria that requires a warning?

2 DR. RACOOSIN: I may need a little help
3 with this, but there's no specific criteria, as far as
4 I know. I believe it's up to --

5 Let me let Dr. Leber answer this.

6 DR. LEBER: Well, the labeling
7 requirements of drugs are published in the Code of
8 Federal Regulations, but they're guidance. A certain
9 amount of judgment goes into the specifics of the case
10 where experts decide what the level of warning has to
11 be. And as you already know, they're consistency
12 across product line won't be found because individual
13 experts in different field reach different
14 conclusions.

15 CHAIRPERSON KANE: Dan?

16 DR. CASEY: We are most familiar with the
17 drug of carbamazepine in psychiatry of the items you
18 listed that have recognized risk out there. You did
19 not present data on that compound and I'm presuming
20 because we don't have the data from either spontaneous
21 reporting systems with its --

22 DR. RACOOSIN: Right. The best --

23 DR. CASEY: -- recognized limitations, or
24 other data sets.

25 DR. RACOOSIN: The best data we have on

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1 carbamazepine comes from the International Agran and
2 Aplastic Anemia study. In that study, again, it was
3 a case control study, so what they came up with was a
4 relative risk. And the relative risk that they saw
5 associating agran with carbamazepine was about ten
6 times that compared to the control group. So, the
7 relative risk was ten.

8 And if you look at the background agran
9 rate in that study which was five cases per million
10 person-years and you multiply it by ten because the
11 relative risk was ten times more than in the general
12 population of cases, then you can come up with a rate
13 of about five cases per 100,000 person-years, or .05
14 cases per 1,000 person-years since that's the unit
15 that I've been using. So, that's the best estimate
16 that we have and it's based on that relative risk from
17 that International Agran and Aplastic Anemia Study.

18 DR. CASEY: So, if we carry that further,
19 your Clozapine number was 5.5? 5.2, worst case
20 scenario?

21 DR. RACOOSIN: Yes. If we're looking at--

22 DR. CASEY: So, we're comparing .05 --

23 DR. RACOOSIN: Right. We're looking at
24 five cases per 1,000 person-years compared to .05
25 cases for carbamazepine.

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1 DR. CASEY: Thank you.

2 DR. RACOOSIN: Yes.

3 CHAIRPERSON KANE: Carol?

4 DR. TAMMINGA: Yes, I have one more
5 question. When you did your analyses, do you use
6 various sampling intervals and then there was a no
7 monitoring case. Presumably, nobody would suggest no
8 monitoring at all, but a switch to a voluntary or non-
9 mandatory monitoring. How did you figure that into
10 your calculations?

11 DR. RACOOSIN: Well, the data that I
12 showed for that is Dr. Weiss' data, okay? And he did
13 have a category called no monitoring. What we did was
14 just to calculate 95 percent confidence limits on the
15 rates that he had calculated from his projections. So
16 that no monitoring is based on the projections that he
17 presented earlier this morning.

18 DR. TAMMINGA: Because I guess some of the
19 things that we have to consider is what the compliance
20 with recommended monitoring is. I mean, how one
21 estimates that and whether one estimates that
22 differently for different pools of physicians. Like
23 whether hematologists might monitor more rigorously
24 than psychiatrists or something.

25 DR. LAUGHREN: Clearly, that was an issue

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1 that was factored into the original decision to have
2 the system. You know, our view that probably routine
3 labeling for Clozaril would not accomplish the goal of
4 weekly monitoring, you know, and be given all the
5 factors that are pertinent.

6 CHAIRPERSON KANE: Dan and then Steve.

7 DR. CASEY: Dr. Weiss' Table G is
8 something that I think is instructive in helping us
9 get to the question of that Dr. Leber summarized just
10 before break which was the number of cases projected
11 to occur beginning six months after initiation by
12 timing of reduction in frequency of WBC monitoring.

13 I'm wondering if you've looked at Table G?
14 I guess the carousel is down. You can have mine if
15 you want to look at.

16 What it does is shows the risk per 1,000
17 patient years. I see as the time extends, I've
18 circled the .02 risk. We get biweekly at six months
19 of .02. Then at one year, we get .02 at biweekly or
20 monthly. Then two years, .02 at monthly or no
21 monitoring.

22 DR. RACOOSIN: Could I just clarify one
23 second? This table refers to the mortality from
24 agran. That's not an issue that I specifically
25 addressed.

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1 DR. CASEY: Okay.

2 Could I take the general concept and see?

3 DR. RACOOSIN: Sure.

4 DR. CASEY: Have you applied your worst
5 case analysis to Dr. Weiss' analyses and come up with
6 any different qualitative conclusions? I understand
7 there's some quantitative differences that you
8 presented, but have you got qualitative differences?

9 DR. RACOOSIN: Basically, what I did was
10 to just to start with Dr. Weiss' projections and just
11 put on 95 percent confidence limits to see, okay,
12 well, with some variation, what might occur.

13 DR. CASEY: Okay.

14 DR. RACOOSIN: Then what we did was
15 because of the modeling process that they use to
16 develop the projections required several assumptions
17 to be made, we decided to try and just simplify
18 matters and say -- because in his worst case scenario,
19 there are 401 cases of agran. About 80 percent of
20 patients who develop moderate or severe agran would
21 progress on to -- of the 581 patients developing
22 either severe or moderate leukopenia, his worst case
23 scenario suggests that 400 of those would develop
24 agran. That's about 80 percent.

25 So, we just took this a little bit further

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1 and said, "well, what if all 581 develop agran, then
2 what might we see?" We didn't use any sort of new,
3 specific modeling. We just took the simplest approach
4 and said, you know, "the worst case scenario was 80
5 percent of patients developing agran. What if 100
6 percent of them?" So, that's the only difference.

7 DR. CASEY: Okay, thank you.

8 CHAIRPERSON KANE: Dr. Simpson? Dr.
9 Marder. Sorry, Dr. Marder.

10 DR. MARDER: In one of your tables in a
11 figure, you broke down the rates of agran into these
12 larger epochs of, I guess, a year-and-a-half or a
13 little bit longer and it continued to drop. You said
14 that you weren't confident about whether that was a
15 real difference.

16 DR. RACOOSIN: Right. Well, the
17 confidence limits overlap for the .7, .4, and .2. You
18 can see that in -- there's a table that lists those
19 four time periods and then the confidence limits.
20 Because they overlap, it's not clear whether that's a
21 real decline over that period.

22 DR. MARDER: Can you extrapolate back to
23 cases of, say, moderate neutropenia or other things to
24 see whether or not those numbers are -- to give you
25 more confidence in that?

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1 DR. RACOOSIN: We didn't apply that
2 specific approach to just looking at the numbers of
3 moderate or severe leukopenia. We did apply some
4 modeling to try and understand whether there was a
5 real decline there. And in certain modeling, it did
6 look like there was some suggestion that during those
7 last three time periods, that there was a decline in
8 rate.

9 CHAIRPERSON KANE: Dr. Simpson?

10 DR. SIMPSON: I guess this shows a lack of
11 clinical knowledge but you've presented this
12 information on agran. What are the implications of
13 that? If you're not monitoring or you're monitoring
14 at a wider interval, how are you going to pick up the
15 cases of agran? I mean, if they have fever,
16 presumably they'll come in. But that, from what I
17 heard, is the worst scenario. They don't do well when
18 they have fever. So, what is the way they would be
19 picked up at all before they actually had these severe
20 symptoms?

21 DR. RACOOSIN: Other than doing a
22 screening type of --

23 DR. SIMPSON: Yes, yes.

24 DR. RACOOSIN: Well, I don't think that
25 there is any sort of middle ground. Are you asking

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1 why other drugs --

2 DR. SIMPSON: I mean, I guess I must be --

3 DR. RACOOSIN: Are you asking about the
4 other drugs, why they specifically picked out their
5 monitoring or --

6 DR. SIMPSON: I guess what I'm asking,
7 really, is the question how do we relate the rate of
8 agran with mortality?

9 DR. RACOOSIN: Well, I think that was
10 addressed somewhat this morning. My sense was that
11 people who have thought about this quite a bit are
12 having trouble coming up with an estimate of what the
13 mortality from agran is.

14 PARTICIPANT: It's three percent.

15 DR. SIMPSON: But it's three percent with
16 monitoring.

17 DR. LEBER: It's an estimate.

18 DR. RACOOSIN: Right.

19 DR. LEBER: I mean, clearly, the questions
20 that were raised, could, in fact, the case fatality
21 rate for agran be a function of the drug? A function
22 of the epoch? Are there secular trends in the
23 treatment of agran that would affect the case fatality
24 rate? We think there are.

25 We think there could be variation among

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1 drugs. But since you have no really good handle on
2 what the drug-specific contribution to the case
3 fatality rate actually is, it's a guesstimate. All we
4 know is that in Finland in 1974, the case fatality
5 rate when no one understood it I think was about 50
6 percent. There were maybe eight cases, maybe more.
7 I don't remember. Obviously, it has come down and it
8 stands to reason -- I emphasize the rational rather
9 the empirical side of this -- that if you were at risk
10 of having an infection and the infection could prove
11 fatal because you don't have the defenses in place to
12 prevent the march of the infection, at the earlier you
13 detect that period of vulnerability, the better off
14 you'll be.

15 That's why Tom said earlier that if we
16 could continuously monitor, you'd be better off. So,
17 the case fatality rate -- again, logically, not
18 empirically -- is probably a function of the time of
19 detection. And all of this is pretty loose because a
20 lot of this is in the mind's eye rather than evidence.
21 The one place we have evidence, and it is a sole
22 function of this Clozapine Registry that we have it.
23 This detail in this magnitude is because it was
24 distributed this way. There's nothing that comes
25 close.

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1 I think that all the other estimates,
2 except perhaps in areas where we're dealing with
3 cancer where people actually treat you so that you
4 will produce it, and then you have in-hospital
5 observations. But the question becomes, is that a
6 relevant model for this type of -- and we don't know.
7 But anyway, I don't think that's a question anybody
8 can answer, really.

9 CHAIRPERSON KANE: Tom?

10 DR. LAUGHREN: But again, just to
11 emphasize a point, there was no real modeling of the
12 influence of changing the frequency of monitoring on
13 mortality. All the modeling was focused on the agran
14 because that's where you have all the data. It's just
15 pure, you know, bracketing with the mortality,
16 assuming that the agran projections are correct and
17 then multiplying by the mortality rate.

18 CHAIRPERSON KANE: Carol?

19 DR. TAMMINGA: Yes, I would like to make
20 a comment about Dr. Simpson's comment. If doctors use
21 a drug that there's some knowledge about and some
22 warning about that there's some adverse effect, the
23 presumption is that they'll monitor in some regular
24 way for that effect. A good example would be a drug
25 like carbamazepine where I think most doctors probably

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1 do a routine monthly blood level monitoring.

2 So that, just to emphasize again that the
3 no monitoring list would presumably mean no monitoring
4 for some physicians. But more characteristically, I
5 would hope, it would mean some sort of a regular
6 voluntary monitoring.

7 CHAIRPERSON KANE: Any other questions for
8 Dr. Racoosin?

9 Dr. Tsuang?

10 DR. TSUANG: Your conclusion talking about
11 the base on six months weekly monitoring and the
12 projection was even the worst -- similar to other
13 kinds of drugs in terms of the agranulocytosis. If we
14 change the duration of the weekly monitoring to rather
15 than three months -- rather than six months, three
16 months, six months, one year, any significant trend of
17 differences, the question which I'm addressing is that
18 apparently the data shows six months seems to be the
19 secret, secret criteria there.

20 My question is that have you analyzed the
21 three months, six months, one year in terms of the
22 differences?

23 DR. RACOOSIN: No, we haven't done that
24 analysis.

25 DR. TSUANG: So, you recommended the six

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1 months --

2 DR. RACOOSIN: We're actually not making
3 a specific recommendation. I'm just trying to show
4 what's been observed with Clozapine, divided up in the
5 way that we showed in the analysis how that compares
6 to other drugs.

7 DR. LAUGHREN: But you're right. The
8 modeling made the assumption that there was six months
9 of weekly monitoring and looked from that point
10 forward in time. That assumption was made.

11 DR. TSUANG: Yes. So, what I'm saying is,
12 it has become more of a research question. That if we
13 start off with the weekly for the first month, then
14 biweekly, say, for instance, the second month, then
15 the third and fourth and come to six. Then we can
16 estimate that based on the different criteria, are
17 there any differences? That is what I'm asking.

18 DR. LAUGHREN: Well, I mean, we know very
19 precisely the shape of the risk curve --

20 DR. TSUANG: Yes, yes.

21 DR. LAUGHREN: -- during the first six
22 months, and we know that it peaks at three months.
23 So, I mean, that's the reason why the assumption is
24 made that you're going to have frequent monitoring
25 during that high risk period.

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1 DR. TSUANG: Yes. So, in three months
2 rather than six months, are there any significant
3 differences?

4 DR. LEBER: Maybe somebody could put up
5 the incidence density with this --

6 DR. TSUANG: Yes, I saw that. I saw that.
7 But even with the three months, after three months,
8 the rate may be higher than the other medication which
9 you are talking about. I don't know the data.

10 DR. LEBER: The first six months was about
11 eight, right?

12 DR. RACOOSIN: Right. Averaging over the
13 first six months, the agran incidence was 8.6 cases
14 per 1,000 person-years. But if you look at the hazard
15 curve which is one of the earlier slides in Dr. Weiss'
16 presentation, you can see that it's almost 30 cases
17 per 1,000 person-years during that two to three month
18 period.

19 I understand you're curious about how
20 things might change if you, you know, changed after
21 three months as opposed to six or a year and it's hard
22 -- we don't know of another drug that has a rate as
23 high as 30 cases per 1,000 person-years in that first
24 three months, although it's certainly possible that
25 ticlopidine may have had something very close to that

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1 because they did see all of the agran cases in those
2 first three months.

3 CHAIRPERSON KANE: It's my sense that
4 there's not going to be a major push to reduce weekly
5 monitoring short of six months from my conversations
6 with people. If that were the case -- perhaps we can
7 come back to that issue again --

8 DR. LEBER: Well, I was going to say, we'd
9 certainly like to hear your view. I mean, remember,
10 if we go back now some seven years, this was
11 considered a very controversial decision. It was not
12 unanimously endorsed by the entire Advisory Committee.
13 There's always been those who would say physicians
14 have a right to practice medicine unfettered by any
15 kind of regulatory constraint and that you could have
16 made the case with a boxed warning that this drug
17 posed risks and leave it to the practitioners to
18 monitor as they saw fit.

19 We chose not to do that as a society.
20 That doesn't mean that we're right. I think one of
21 the things we'd like the committee to look at, all
22 possible scenarios. The third questions says, "well,
23 perhaps these are risks" -- and they're risks to other
24 people, not to us, but to society as a whole -- that
25 we're willing to take because we think the gains are

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1 such. I don't know how you'd measure them, but you
2 may even know how to do that. That we would get
3 something out of having no restrictions either because
4 of costs or increased prevalence of use, whatever.

5 But that's why we want your advice. It's
6 really what you believe. We know you can't calculate.

7 DR. TSUANG: Yes, and may I respond to
8 that again?

9 Apparently from the data, six months seems
10 to be very important. But probably, the research
11 question is are there any -- to get to this six
12 months? If this is a six month, what are the
13 mechanisms under which the six months stood out? For
14 me to make a good judgement about the decision, I
15 would like to know. That is my curiosity. So, any
16 answer to that? Why six months?

17 CHAIRPERSON KANE: Well, I think when we
18 posed the question to Dr. Gerson regarding possible
19 differences in pathophysiology or outcome between
20 early and late occurring cases, so far none have been
21 identified.

22 Any other questions for Dr. Racoosin?

23 Paul, did you have another comment?

24 DR. LEBER: Maybe I can draw this out.
25 What would you have the result be? I mean, where do

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1 you want to go? This is not necessarily a research
2 question. Perhaps it is a practical question about
3 how labeling change. What advice would you, as an
4 advisor, have to us about how to modify labeling?
5 Should we delay all testing until Week 4 and only do
6 testing at a weekly interval throughout the period of
7 maximum risk? How do you define that? Or increased
8 risk?

9 How would you see it modified and for what
10 gain? I mean, that's the kind of discussion we want.
11 It's not that we don't need more information.
12 Everybody wants more information. We have what you
13 have. Given the facts as we understand them, is this
14 enough to change what we're doing? What do we change
15 and what would you see in its place? Maybe put it
16 that way.

17 CHAIRPERSON KANE: Okay, I think that's an
18 excellent segway into the actual discussion.

19 If it's all right with the committee, I
20 was going to suggest that we delay lunch for at least
21 a half-hour so that we can begin to get into the
22 discussion? Then we'll come back and resume.

23 There is one other piece of information
24 that I was made aware of. There was some reference
25 made to a risk benefit analysis that was done. It was

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1 published in the archives last year regarding a change
2 in the monitoring. I think Dr. Honigfeld would be
3 prepared to share some of those data with us if you'd
4 like to see that.

5 DR. LEBER: There's only one -- we're not
6 prepared actually, at the moment, to critique it. So,
7 to a certain extent, analyses of these kind are model
8 dependent, as they like to say. So that, that's the
9 rub, I think. Your pleasure, nonetheless, with that
10 caveat given.

11 CHAIRPERSON KANE: I mean there are,
12 obviously, many data sets that could be presented and
13 discussed. I just wanted to make you aware of that
14 opportunity.

15 How many people would like to see those
16 data? I think it's a minority.

17 All right. Let's go on to the discussion.
18 The first question that's been posed is: "Should the
19 frequency of WBC monitoring be reduced at some time
20 point after initiation of therapy? If so, when? What
21 reduced frequency of WBC monitoring would be
22 acceptable?"

23 I'd just like to maybe add one comment
24 that I think was really evident in a number of letters
25 that we received, just to make sure that that point of

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1 view is appreciated. The comments from patients'
2 families and physicians really centered around the
3 monitoring, the extended once-weekly monitoring as
4 being an obstacle for patients either starting on
5 Clozapine or continuing on Clozapine. It was their
6 feeling that that was a disservice to an important
7 segment of those with chronic and severe mental
8 illness. We didn't focus very much earlier on the use
9 of this medication in non-schizophrenic patients, but
10 it is becoming increasingly widespread.

11 We've also heard that Clozapine does
12 provide enormous benefit to a subgroup of patients
13 with treatment or factory schizophrenia. There's
14 extensive literature now listing various possible
15 advantages: reduction in substance abuse, suicide
16 rates, and so forth. Many of these data are from
17 uncontrolled trials. But one of the things that
18 challenges us now is to how we might view some
19 reduction in these obstacles and therefore, wider
20 utilization of Clozapine. And again, that's an
21 assumption. But how we would weigh that against the
22 potential risks associated with a reduction in
23 monitoring.

24 Unfortunately, we don't have data on the
25 number of people who refuse Clozapine because of the

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1 monitoring. We don't have good data on the number of
2 people who discontinue Clozapine because of the
3 monitoring. And the communications that we've gotten
4 are largely anecdotal. Although we did hear from Dr.
5 Anand that about two-thirds of patients seem to derive
6 important benefits from Clozapine, yet over 50 percent
7 of patients discontinue Clozapine. We don't know why
8 those discontinuations occur.

9 We also know that certainly within the
10 last several months, or perhaps the last three years,
11 many clinicians have attempted to switch patients on
12 Clozapine to other second generation drugs with the
13 hope that they would be able to replicate Clozapine's
14 novel clinical effects. And again, we don't have an
15 extensive database to inform us as to whether those
16 switches have been successful or not. But I just
17 wanted to sort of frame some of the discussion in that
18 regard.

19 So, let's hear some comments on should the
20 frequency of WBC monitoring be reduced?

21 DR. SALZMAN: Can I make a comment first
22 since we're in partly the non-data portion of this?

23 There's another side to the monitoring and
24 that is that it does bring patients in to the
25 awareness of the medical establishment. And so, one

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1 could even consider that the monitoring enhances
2 compliance, at least to some extent. I think, at
3 least in our own experience, and what I've heard
4 informally without any data is that there's probably
5 a point early-on, where the monitoring really helps
6 compliance. It may be that later on, it begins to
7 interfere with compliance. Virtually all the letters
8 talked about difficulty that the family member was
9 having a year or years after starting. Nobody really
10 talked about it the first six months or so and that
11 would be consistent with our own experience. That, in
12 fact, the early monitoring is a positive compliance
13 factor rather than a negative compliance factor.

14 The other clinical comment is that just
15 because people discontinue Clozapine, it may not have
16 a whole lot to do with the blood draw. Our experience
17 is, they discontinue Clozapine early-on, not for the
18 blood drawing reasons at all. If they don't want
19 their blood drawn, they won't take the drug right off
20 the bat. They never actually get on the drug or don't
21 stay more than a week or two. But if they're on
22 Clozapine for, say, four months and they discontinue,
23 rarely are they discontinuing because of the blood
24 drawing. It's usually some other side effect, or
25 series of side effects which can be quite troublesome

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1 with this drug.

2 CHAIRPERSON KANE: Dan?

3 DR. CASEY: I would take the position of
4 offering the guidance to the Agency that a graded
5 attempt at monitoring might serve best everybody's
6 needs in getting to that unmeasurable risk benefit
7 ratio. And that early-on, monitoring is an asset.
8 Later on, the monitoring may not be the asset that it
9 was before and could be a detriment.

10 I go back to Table G that Dr. Weiss
11 presented about deaths. Given all the imprecisions we
12 have about the systems, that Table G may offer some
13 guidance to the Agency about what the risks are for
14 death. It gives me some sense of what the risks are
15 and that a graded response over a period of years may
16 work best. So that, if we look at those death rates
17 at one year with biweekly or monthly, it's .03 for the
18 three percent rate, and it's higher for the 15 percent
19 rate. Then after two years, you get .02 again for
20 monthly monitoring.

21 So, it seems like you could manage what we
22 know about the risk of death issue, which is the
23 serious outcome issue, by a graded response to the
24 monitoring. And I think in addition, that I would
25 make the caveat that I would maintain or recommend

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1 maintaining the Clozapine National Registry because it
2 does seem to carry considerable value, although it
3 does have expense.

4 So, rather than an absolute yes, no, I
5 think a graded response to the issue would provide the
6 most benefit and manage the risks.

7 CHAIRPERSON KANE: Dr. Simpson?

8 DR. SIMPSON: I do agree with your
9 viewpoint. I disagree with your reasoning, I guess.

10 The table that you're referring to, I
11 think looking at the -- I mean, we do have imperfect
12 data. But looking at the case fatality of three
13 percent and 15 percent as fixed depending on how often
14 you monitor is misleading. Because I think from what
15 is being said that that case fatality rate will
16 increase the bigger the gap between monitoring. So,
17 whether you start off with the three percent or you
18 start off with the 15 percent, the longer you leave
19 between monitoring, I think the case fatality would
20 increase. It's not a constant rate. So, I think it's
21 a bit misleading to use these figures as a guide.

22 CHAIRPERSON KANE: Dr. Marder, Steve?

23 DR. MARDER: Yes, I would agree with the
24 idea of a graded response. I think the frequency of
25 the monitoring becomes a -- can really have a negative

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1 effect on outcome, on social outcome in patients later
2 on in the illness who are doing better. The
3 burdensome monitoring becomes a problem.

4 I was wondering if there was any way to
5 give clinicians guidance about which patients should
6 be monitored more often at later stages? That is, do
7 patients who have frequent bouts of leukopenia, or
8 have had several episodes of moderate leukopenia --
9 are those individuals who should be -- at least
10 clinicians should be advised to monitor these patients
11 more often, whether it's every two weeks instead of
12 every four weeks after three-and-a-half years or
13 whatever decision is made. And maybe whether the
14 database can be used to look at those questions.

15 CHAIRPERSON KANE: I think that gets back
16 to some of the questions that -- was raising before.
17 Certainly, there may be other targets of analysis in
18 that data set that could help to form that.

19 Carol?

20 DR. TAMMINGA: Well, in line with what
21 Steve was saying, I would go along with the idea of a
22 graded over time sampling monitoring system, voluntary
23 after a certain point. Even modified by age since it
24 seems like that would be one of the kind of factors
25 that you'd be talking about, Steve, because it seems

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1 like age is such an important factor.

2 Although one can always say that there is
3 not enough data here, it seems to me that the
4 Clozapine National Registry certainly provides a
5 substantial amount of risk data of the kind of quality
6 that we don't usually get. So, it really seems to be
7 an unusual situation where we actually have numbers
8 over time, divided by age, divided by sex to really
9 look at in order to understand risk, even if we don't
10 have such quantifiable data to understand gender.

11 In addition to what Carl was talking
12 about, about early monitoring enhancing patient
13 contact, I also think that it makes clinicians more
14 comfortable with using the drug and probably increases
15 the number of patients who are actually exposed to
16 Clozapine because physicians feel more confident that
17 the safety, during a dangerous period, is being
18 monitored in a regular way.

19 CHAIRPERSON KANE: Dr. Risby?

20 DR. RISBY: I thoroughly support sort of
21 a graded monitoring system, possibly biweekly after
22 the first six months and then increasing it to monthly
23 after a year. I think that seems like a reasonable
24 option that should ensure some safety and it should
25 ensure that the mechanism for tracking patients who

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1 may be vulnerable to developing agranulocytosis will
2 still be picked up, the majority of the cases. It's
3 not foolproof, but it should be adequate. Clearly, it
4 would be much more of a safety net than what we
5 currently have with some of the other drugs that have
6 this potential.

7 CHAIRPERSON KANE: Dr. Simpson?

8 DR. SIMPSON: One of the things I'm not
9 clear on, I guess, is if it's mandatory that they're
10 monitored or if it's voluntary, would the HMO be
11 equally likely to pay, or whoever is paying?

12 CHAIRPERSON KANE: Well, the question is
13 pay for what also? But that's hard for us to answer,
14 I think.

15 DR. SIMPSON: Because I think that enters
16 into, to a certain extent, the decision of whether
17 it's mandatory and voluntary, doesn't it?

18 CHAIRPERSON KANE: I'm not sure that we
19 can base a decision on issues of reimbursement. My
20 sense is that we should make a judgement as to what we
21 think is medically necessary.

22 DR. MARDER: And if I could clarify what
23 I was suggesting? It was a graded mandatory system,
24 but to maybe, outside of this, recommend to Novartis
25 or others that clinical guidelines be developed for

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1 monitoring certain groups, whether it's individuals --
2 you know, women over 65 or something like that, that
3 may need somewhat more frequent monitoring, or people
4 that have other risk factors.

5 MS. CURLL: Sir, if I may interject, in
6 private practice, I notice that if the patient can't
7 afford it, they just don't get it. I notice in some
8 of the letters from the families that some of the
9 carriers were denying the lab, is that correct?

10 CHAIRPERSON KANE: Because it was raised
11 in one of the letters, we perhaps should mention it.
12 But it does get back to the issue as to what role
13 reimbursement should play in this discussion. But the
14 issue that they raised was not that the cost of the
15 laboratory test was not being reimbursed, but that the
16 cost of a physician visit, which was deemed to be one
17 aspect necessary to review the laboratory results. I
18 think there are a number of different ways of handling
19 that.

20 But again, it's really beyond the scope of
21 our discussion to think about reimbursement issues and
22 the availability of Clozapine from a reimbursement
23 standpoint.

24 Dan?

25 DR. CASEY: To comment on Dr. Simpson's

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1 comment on my comment, I think we agree more than we
2 disagree and it's a quantitative difference about the
3 confidence limits and the error that's in the estimate
4 about the change in risk related to the change in
5 monitoring rate. So, I sense the committee has a
6 consensus on a graded response to the monitoring
7 issue. It's a matter of debate as to how that should
8 be numerically quantified.

9 CHAIRPERSON KANE: Right.

10 DR. CASEY: I would like to be clear in my
11 response that I am not yet ready to say a voluntary
12 system sometime is the way we should do. It's
13 somewhat different than Carol's view, I think. She
14 mentioned that a voluntary system somewhere would be
15 an amenable approach and I think that is still too
16 early to come to a point where we say it's voluntary.
17 This drug is too good, and yet the risks are too
18 considerable to put the patients at risk for either
19 not getting it or for getting it without careful
20 consideration.

21 CHAIRPERSON KANE: Okay. Can we hold off
22 on the voluntary/non-voluntary discussion? That's
23 point number three. Let's try to reach closure on the
24 first point.

25 I think Dan's summary is appropriate. All

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1 of the comments that we've heard so far have indicated
2 acceptance of the idea that the frequency of WBC
3 monitoring should be reduced at some time point. Is
4 there anyone who disagrees with that?

5 Okay, so let the record show that no one
6 voiced any disagreement with that conclusion so far.

7 Then the second part of that question
8 becomes when. At what time point should the reduction
9 in frequency occur? And then after we discuss that,
10 the next part of that is what reduced frequency would
11 be acceptable? And just to start the discussion, I
12 think we've certainly heard the six month time point
13 alluded to in a number of the discussions and a number
14 of the data analyses. Just to get the discussion
15 going, what would people think about a six month
16 point? I just would comment that in the analyses that
17 we saw, I was not struck by the difference between
18 implementing a biweekly monitoring system at six
19 months or at one year. It looked like there was
20 relatively little to be gained by delaying that to one
21 year, if I read those tables correctly.

22 Carol?

23 DR. TAMMINGA: Yes, I think that the
24 tables that are in the brown booklet that we got were
25 very detailed and complete. If you draw the line at

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1 six months on any of the graphs and presentations,
2 almost all of the increased risk -- in the first six
3 months. So, this is a point on which we have real
4 data to base a suggestion and recommendation.

5 CHAIRPERSON KANE: Dr. Salzman?

6 DR. SALZMAN: Well, I concur. We also
7 have the Canadian experience. They've been doing it
8 this way, according to the brown book. It seems to me
9 that Novartis might actually be able to enlighten us
10 about Canadian experience. But it would seem that
11 it's the six month cutoff.

12 Then after that, John, you're right.
13 Whether it's six months or a year, it doesn't make an
14 enormous amount of difference.

15 CHAIRPERSON KANE: Ming?

16 DR. TSUANG: I asked for more data, but as
17 a clinician, we have to draw the line. Take off my
18 research hat. The clinician has to make the decision.
19 Somewhere you have to do it. The data so far, I can
20 not elicit any particular artifacts or confounding or
21 any other factors to indicate that the six months
22 duration from the data available is a misleading
23 figure. I'm trying to figure that out.

24 So, on the basis of available data,
25 probably six months is pretty good. That is my

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1 feeling. We see some clinical sense into it. But I'm
2 still not quite clear biweekly or month or weekly.
3 That, I still am not quite clear. I fully agree with
4 the data available, six months seems to be pretty
5 good. But whether it should be biweekly or weekly or
6 monthly, from these hypothetical examples, they miss
7 one. But I am still not very clear where is a cutting
8 point.

9 We have to agree with what Carl said.
10 Each patient is different. I think Carol said the
11 same thing. As a clinician, each patient's response
12 is so different. We need clinical guidance and not
13 just the straight jacket on each patient. Have the
14 mandatory requirement for everyone after six months.
15 And I already agree with the six months.

16 But what, with regards to -- digress a
17 little bit for me to really say what I want to say.
18 You may discuss that later -- is that the registry
19 actually has contributed a great deal to come up with
20 good data. But from this morning's early session, I
21 asked another question. Many questions are
22 unanswerable. So, just to continue with the
23 collection of data as it is has served some purpose
24 already. We know the incidence. We know some risk
25 factors. But actually, in order to do it properly for

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1 us clinicians to be able to use the data, we need to
2 take the sub-sample of them and really analyze them
3 intensively to make some contribution for us to make
4 the judgment in the future.

5 Currently, what we are talking about is
6 based on our intuition, our clinical judgement and
7 some of the incidence data in terms of the duration.
8 So, I'm not all clear whether the current system of
9 the registry should be continued as it is, or need to
10 do some modification. That is probably what I'm
11 talking about.

12 CHAIRPERSON KANE: Okay.

13 Carol?

14 DR. TAMMINGA: To speak to that point,
15 actually, there is some data in our brown book where
16 Novartis has calculated the duration of the prodrome.
17 In all of the duration of treatment periods, less than
18 six months, six months to one year, one to two years,
19 and greater than two years, the duration of the
20 prodrome is pretty stable through that time as to 24
21 -- I think the unit is 24 days. And the 25th
22 percentile, which would be the lowest one, is on the
23 order of 14 days.

24 So, there would be some reason to think
25 that with some degree of safety, one could move to

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1 every other week instead of every week. Extrapolating
2 from these mean data, you have to do an analysis to
3 see what the risks would be of somebody starting
4 agranulocytosis just after you've done the last normal
5 sample and being in some danger range two weeks later.
6 But at least the average data would suggest you'd
7 still have enough time.

8 CHAIRPERSON KANE: Other comments?

9 Dan?

10 DR. CASEY: I would agree with the
11 biweekly at six months going forward. To me, the next
12 question is then when does another change come in the
13 graded response?

14 DR. TAMMINGA: Dan, comment on the
15 biweekly, less than six months.

16 DR. CASEY: Did I say less than six?

17 CHAIRPERSON KANE: No. I think Dr. Casey
18 was just agreeing with Dr. Tamminga that biweekly made
19 sense.

20 Could we just hear comments from some
21 other people? That's been sort of the proposed
22 recommendation that it would be biweekly after the
23 first six months. We have not yet said for how long.

24 Dr. Dominguez?

25 DR. DOMINGUEZ: No doubt, this is a unique

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1 drug, period. I will echo Dr. Salzman's earlier
2 comments that adherence to treatment and continued
3 favorable clinical outcome has tremendous amount -- is
4 highly related to the frequency of visits and the
5 contact with mental health team.

6 In our setting, for example, where we
7 treat a very large percentage of Hispanic patients
8 where we do end up treating not only the patient, but
9 the entire family, issues surface, obviously, very
10 early that can be addressed. Certainly, after six
11 months to go to biweekly monitoring, I think is
12 reasonable based upon the data we have. Whether a
13 further change should take place after that, I am not
14 sure whether it should take place simply because it
15 will tar the outcome that I think is so greatly
16 associated with the increased contact with the
17 patients and their families.

18 CHAIRPERSON KANE: I think you're raising
19 an important issue, but I also think it's a difficult
20 one. Because when we first discussed marketing
21 Clozapine altogether, I think we were challenged with
22 trying to solve problems in the delivery of mental
23 health care in the United States while we were trying
24 to make a treatment available to people. I think
25 here, also, we're hearing some comments that the

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1 weekly monitoring has been very helpful clinically for
2 other reasons. But we should ask ourselves whether we
3 can justify insistence on immunologic monitoring
4 because of the secondary gains that that brings about?
5 I just want to throw that out.

6 So far, I think we've heard a consensus
7 that biweekly monitoring would be a reasonable step
8 after the first six months. Is there anyone who
9 disagrees with that? Other comments?

10 Ming?

11 DR. TSUANG: Yes, biweekly after six
12 months, this seems to be the principle of which we are
13 talking about. How about after one year? Are we
14 talking about the biweekly until when? When should we
15 start monthly? When should we start biweekly? That
16 kind of a concept, we need to start thinking about it
17 before we make the decision.

18 CHAIRPERSON KANE: Well, but do we have a
19 consensus though that biweekly is the next step?

20 DR. TSUANG: Yes.

21 CHAIRPERSON KANE: There may not be a
22 third step. We haven't decided that yet. But we have
23 a consensus that biweekly is our recommendation for
24 the next step.

25 Okay, now, the question is, how long

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1 should biweekly monitoring continue? One possibility
2 would be indefinitely. Another possibility would be
3 for another six months. What thoughts do we have
4 about that?

5 Dan?

6 DR. CASEY: Is the question when should we
7 change it again since we have consensus to biweekly?

8 CHAIRPERSON KANE: We seem to have
9 consensus that biweekly is the next step. That we
10 should recommend substitutes for weekly monitoring
11 after the first six months. Now the question is,
12 should there be a third step and if so, when?

13 DR. CASEY: I would have a third step. I
14 would have it at six months is a reasonable time range
15 to me. It could be six months later. It could be
16 nine months later, 12 months later. We could put a
17 caveat in that providing the patient has been
18 clinically stable for psychiatric and hematological
19 parameters or something like that, that increases the
20 level of awareness for the practitioner to pay
21 attention to a number of important clinical variables,
22 which they should be doing anyway.

23 I think to give them the guidance that a
24 less frequent system of monitoring is possible later
25 on when things are going well would be an addition to

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1 therapy rather than a detriment.

2 CHAIRPERSON KANE: Carl?

3 DR. SALZMAN: Well, once again, we have
4 the Canadian system. It might be useful to know
5 what's happened with the Canadian system. Theirs, I
6 gather according to this book, has been indefinite,
7 although it may be just changing. I wonder whether
8 there are Canadian data that can guide us?

9 The other comment is to revisit the age
10 question which Carol mentioned is getting lost in this
11 discussion. As a geriatric psychopharmacologist who
12 has treated older people, very old people with
13 Clozapine and reviewed the literature, I would be very
14 nervous about reducing the frequency of monitoring in
15 people over 65; certainly over the 70-year-olds with
16 that ten-fold increase. That starts to make this all
17 more complicated because, see, then one size doesn't
18 fit all and it may make it impractical. But since
19 we're just having a discussion of the best of all
20 possible worlds, the best of my possible worlds, I
21 would want older people to continue to have weekly
22 monitoring, indefinitely.

23 CHAIRPERSON KANE: Okay. And it gets back
24 to Steve's point earlier that, obviously, there will
25 be further discussions between the Agency and the

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1 sponsor following the recommendations that we make
2 today. We haven't yet gotten to the
3 voluntary/mandatory issue overall. But within that
4 context, it may be possible for guidelines to be
5 issued. Steve had suggested that specific subgroups
6 have a different recommendation.

7 Dr. Risby?

8 DR. RISBY: Well, actually, you answered
9 my question that basically, the sponsor may have some
10 guidelines for clinicians in using the drug outside
11 the labeling recommendations like you currently have
12 when the white count drops below 3,000. Then you make
13 a recommendation that the CBC be monitored twice-a-
14 week, which is not a mandatory but a guideline. I
15 think that's probably what you will do if we changed
16 the monitoring system to biweekly.

17 I support Dr. Casey in recommending to the
18 FDA that after six months of biweekly, that we
19 recommend that the monitoring be extended to monthly.
20 Again, a particular patient having some problems
21 during that six month biweekly period, the sponsor may
22 have some recommendations that that person not be
23 switched to monthly. But it appears to me that for
24 most patients, if they're clinically stable, then
25 after six months of biweekly, then it seems reasonable

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1 to recommend a monthly monitoring.

2 CHAIRPERSON KANE: I guess I'd like to
3 hear the committee discuss the value of monthly
4 monitoring at all. I mean, given what we heard about
5 the prodrome, I'm just curious what people's thoughts
6 are. Are we doing that because we're gradually
7 withdrawing monitoring? Or are we doing that because
8 we think it has other advantages? Or are we doing
9 that because we really think it will have a
10 significant impact on the risk of full-blown
11 agranulocytosis and mortality?

12 Carol had a question or a statement?

13 DR. TAMMINGA: All I was going to point
14 out was to agree with Dr. Risby that monitoring be
15 reduced further after 12 months. Because at that
16 point, the risk of agranulocytosis with Clozapine is
17 well within the risk of agranulocytosis from other
18 drugs, for which even no specific monitoring has been
19 recommended. So, it would really bring Clozapine more
20 in line with the other FDA approved compounds that
21 have agranulocytosis as a risk.

22 CHAIRPERSON KANE: Paul?

23 DR. LEBER: I have a question I'd like to
24 raise. One is this business about expanding the time
25 between adjacent monitoring period. To begin with,

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1 monitoring may have no practical value at all, even
2 though you're doing it. For example, we did it every
3 six months. We might then look at the distribution of
4 prodromes and say, "everyone already had it, so the
5 monitoring doesn't work." I think we have to examine
6 whether or not a monthly monitoring is any monitoring
7 at all.

8 Maybe that's the other side of what John
9 was getting at. Is it an effective policy? That may
10 be semi-quantitative, but we can try to get at it. I
11 don't know. What fraction of cases, if we believe in
12 prodrome, are actually likely to be detected with a
13 once monthly? Or is it equipment they're not
14 bothering to monitor?

15 CHAIRPERSON KANE: And I guess part of
16 that is, if someone came to us with a compound which
17 had the risk of agranulocytosis associated with this
18 compound after one year, would we be requesting
19 monitoring at all? I mean, that's part of the
20 question. I think to some extent, what we're dealing
21 with here is not a halo effect, but a horns effect, I
22 guess.

23 We know that the risk is higher in the
24 first six months. We know that it is certainly higher
25 than the population at large beyond that. We're

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1 having a discussion about gradually withdrawing, or
2 gradually reducing the frequency of monitoring. Is
3 there some point where it makes no sense?

4 Dr. Simpson?

5 DR. SIMPSON: I guess I just had a
6 question sort of about some of the practical issues.
7 If somebody in the moment that they're monitored if
8 their white blood cell count drops, then they get
9 taken off and they get put back on again. So, do you
10 start counting the gradation period back at the
11 beginning or just from when they first started the
12 drug?

13 CHAIRPERSON KANE: I think that's a good
14 question. I don't know how that's been handled in the
15 Novartis database.

16 Does the clock restart when someone has a
17 brief interruption in treatment?

18 DR. LEBER: It doesn't matter because it's
19 weekly.

20 DR. SIMPSON: Yes, it doesn't matter.

21 DR. LEBER: When they get to 3,500,
22 they've recovered the episode. At that point, I think
23 they're back where they began.

24 CHAIRPERSON KANE: Dan?

25 DR. CASEY: I agree with the mathematics

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1 that once you get out to a certain infrequent
2 monitoring point, you have a de facto no monitoring or
3 minimal monitoring to detect the event you're looking
4 for. Given that, I would still make the cautious
5 determination that until we get more experience,
6 perhaps we could revisit this issue again in a few
7 years as to whether, once we've gone to this graded
8 monitoring system, that maybe there is a period of
9 time when no monitoring would be not different from
10 routine monitoring.

11 I asked the question earlier to the
12 statistician to do a mathematical modeling of a power
13 analysis of how many patients for how long a period of
14 time would you need to know that answer. They've had
15 7,000 so far, I believe, for two-and-a-half years, or
16 three-and-a-half years or more. So, there is a point
17 where we can at least get some of that data.

18 Until that time, I'm in favor of a
19 monitoring system, given that the value of that
20 monitoring system for detecting a hematological event
21 goes down. It does not go down to zero. If the
22 prodrome is really 14 days, then -- every 28 days --

23 DR. TAMMINGA: Twenty-five days.

24 DR. CASEY: But the lower confidence limit
25 is the one that probably has the higher risk. So

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1 that, even at two weeks, you are likely to intersect
2 that prodromal period to some degree with a one month
3 analysis, but not terrifically so. Still, I have the
4 sense that there's a value to a monitoring system as
5 we know it now. For some time in the extended period
6 though, I get on thinner and thinner ice in defending
7 the value of that monitoring system. That the math
8 isn't there. The clinical intuition is the basis of
9 wanting to keep in contact on a scheduled, regularly
10 performed evaluation.

11 Given that I may be learning less and less
12 about the hematological merits, until we get a little
13 more experience, I think I'll make the cautious
14 determination to have some period of monitoring which
15 is implied then in that last question we'll get to.
16 Because if we come with no monitoring, we may change
17 our enthusiasm for the last question we have.

18 CHAIRPERSON KANE: Paul?

19 DR. LEBER: I mean, there are obviously
20 going to always be some patients who will be missed no
21 matter what the monitoring are. And obviously -- I
22 think obviously, as a function of the start point for
23 the decline and the slope of that decline. Those are
24 two variables we don't know that much about in terms
25 of their distribution in the population. You probably

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1 have it for this particular sample that we have so
2 far. But clearly, with time, there may be individuals
3 who are coming down slowly that you will capture on a
4 very infrequent monitoring. But people who have a
5 very high slope and a low start point are going to be
6 missed. I mean, that's what goes back to the
7 original.

8 You have to decide, as a committee, that
9 we will probably increase the risk at which this
10 adverse event occurs. Can we as a society tolerate
11 that? I think precision of how much you're going to
12 actually capture it is not going to be easy to come
13 by. The guidance that you keep talking about that we
14 ought to have as guidelines, well, it is in labeling.
15 We can write labeling which will provide general
16 guidance. But that's different than saying "this is
17 the policy one must use."

18 I think, at this point, we're trying to
19 find out what is the minimum acceptable set today in
20 mid-1997, that you would tolerate? It doesn't all
21 have to be done today. You might adopt one policy for
22 a period of time and then say, "providing this works
23 well, then we can reconsider." So, I don't think we
24 have to march out to the very end of time right now.

25 CHAIRPERSON KANE: Ming?

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1 DR. TSUANG: I think from the available
2 data, I can see that it's serving a very, very
3 important role for the six months, but I'm still very
4 skeptical about the after one year, in general after
5 one year. What is the value there, after one year
6 from the data available?

7 Therefore, it might be important --
8 several of the members already alluded to -- is to
9 develop the criteria for which subgroups: the older
10 group, for any particular group who has ever had any
11 particular history of some kind, like a DSM-4.
12 Develop the criteria. Two of the four for those
13 people -- sub-population, we need to continue to
14 monitor. Otherwise, the after one year monitoring may
15 not be necessary.

16 So, from the data available, I can see
17 that after one year, there is no great benefit. That
18 that is pretty much what I can see from the data.

19 CHAIRPERSON KANE: Okay. I think we have
20 a range of opinions here. Just to emphasize the point
21 that both Drs. Casey and Leber made is that this can
22 be reevaluated in the not too distant future and
23 recommendations can be made at that point whether
24 further changes are necessary.

25 So, it sounded like most of the people who

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1 spoke were recommending monthly monitoring after the
2 first year. Although again, there's certainly a
3 question as to whether that's appropriate. One way of
4 framing it might be that the recommendation now is to
5 do it monthly after the first year. But we'd like it
6 to be reevaluated in the not too distant future.

7 Steve?

8 DR. MARDER: Yes, and since the curve is
9 a little bit less precise after a year -- it appears
10 flat but we're not really sure if, indeed, it is --
11 something that FDA might consider would be to take the
12 safe margin and make it monthly after two years until
13 there's more data between one and two years. I mean,
14 there's still uncertainty about the effects of going
15 to monthly monitoring in that particular period.

16 CHAIRPERSON KANE: Well, would it be fair
17 to say that there's a consensus that monthly
18 monitoring should be attempted at some point after the
19 first year, but it's not clear exactly when. It could
20 be 12 months; it could be 18 months?

21 Dr. Simpson?

22 DR. SIMPSON: If you look at Table 120 and
23 Table 121, you can see that there is a sort of six
24 months difference in the drop of the rate. I don't
25 know how real it is, mind you, but depending on

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1 whether they're over 40 or under 40. So, there's
2 actually a six month window, as it were, where you
3 might want to drop the monitoring, the more spaced out
4 monitoring, to later for the older aged group.

5 CHAIRPERSON KANE: Yes, I think the issue
6 of subgroups, I think we need to come back to that a
7 little bit later. I think we've certainly --

8 DR. SIMPSON: Well, I think you might want
9 to do the biweekly longer for the older, not aged.
10 The older.

11 CHAIRPERSON KANE: Right. I think the
12 question is going to be how we frame that
13 recommendation though, when we get to point number
14 three, in terms of voluntary versus mandatory.

15 Would we be prepared to propose more
16 frequent mandatory monitoring for a particular
17 subgroup? Or would we propose that guidelines be
18 developed which would make it clear to clinicians
19 which need to be monitored more frequently on a
20 voluntary basis? And then another aspect of that is,
21 is there a point in time where the system shifts from
22 being a mandatory system to a voluntary system?

23 Carl?

24 DR. SALZMAN: I'm not prepared to go along
25 with that one year consensus because in my own mind,

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1 I have two opposite opinions. I'm very clear about
2 the six months and then the biweekly thereafter. But
3 the hematologic data don't suggest to me that after
4 one year, monthly monitoring is going to save any
5 lives. I think it's just reassuring us. It's sort of
6 we're treating the treater. So, from that
7 perspective, I say if you've gone a year and you've
8 been okay on Clozapine, then good luck.

9 The other side is a clinical issue, not a
10 hematologic issue and may be irrelevant to the FDA.
11 But I'll say it anyway. I do think that having people
12 come in and having their blood drawn can be a
13 therapeutic event if it's not overdone. There are
14 several sub-types of schizophrenic populations. Maybe
15 the patients reflected in the letters who have caring
16 families and will make sure they're taken care, et
17 cetera, that's not the ones they're worrying about.

18 I think it's the ones that Dr. Dominguez
19 and we're taking care of who don't have families,
20 don't have relatives, don't have friends, don't have
21 addresses, don't have anything. And to let those
22 people just go out on Clozapine after a year worries
23 me to some extent. Not so much because of the
24 hematologic problem, but all the other problems.

25 Now, as I say, this may not be an FDA

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1 issue because we can't engineer mental health care
2 systems which is really what I'm talking about. But
3 as a voter, it makes me unprepared to say
4 definitively, one way or another, what I would vote
5 for after one year where I'm really quite clear of
6 what I think for the six month and the six to 12 month
7 period.

8 CHAIRPERSON KANE: Dan?

9 DR. CASEY: To address Carl's issues about
10 the geriatric population and we have to recognize in
11 this Clozapine-treated group, there's a much more
12 heterogeneous at-risk group because there are a
13 substantial number of patients with levodopa or other
14 dopamine agonist-induced psychosis who get Clozapine
15 to treat their psychosis as part of their management
16 for their Parkinsonism. Those people are much older.
17 They are much more likely to be taking concomitant
18 medications across a range of drugs and you then have
19 a much more complicated formula.

20 I would venture that if we put up the
21 agranulocytosis incidence curve for people in the five
22 year epics, 50, 55, 56, 60, et cetera, we'll still see
23 a very similar clear peak of when the risk is between
24 the first few weeks and first few months. Though we
25 didn't see that data, if you just look at the overall

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1 curve, you don't see that the curve has a hump
2 somewhere later on at nine months, or 11 months that
3 would suggest a clear difference in risk.

4 So, we do have data we could look at in
5 terms of the course of the incidence rate by age
6 group. If it's not any different for people who are
7 older, then I'm not sure we have the evidence to
8 clearly say, other than clinical intuition, this is a
9 higher risk group for everything when you get to be
10 much older and the vigilance should increase for a
11 reasonable medical monitoring of many different
12 issues.

13 DR. SALZMAN: Stan commented to me during
14 the break that the general background rate of
15 agranulocytosis and the drug-induced agranulocytosis
16 rate goes up in the elderly. So, it would stand to
17 reason it would go up with this drug too.

18 DR. CASEY: Then I would have no trouble
19 with a comment in the label clearly making that point
20 about the age-related risk of agranulocytosis in
21 general, and that concept should be applied to this
22 drug as to other drugs it might apply to.

23 DR. SALZMAN: This is another sub-
24 population that perhaps Dr. Dominguez and I share, and
25 that is the schizophrenic patient who is a substance

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1 abuser. We are unable to tell from the registry data
2 whether substance abuse is an important factor in the
3 development of agranulocytosis. One of the things we
4 might look ahead to is trying to collect some of those
5 data. But again, that complicates issues farther out
6 because you don't really know. Somebody could turn
7 out to be a substance abuser after one year of being
8 schizophrenic when they haven't been drinking for the
9 first year, and whether that's a relevant issue or
10 not.

11 So, again, for that reason also, I feel
12 unprepared to vote in the long-term. I just don't
13 know how it would play out.

14 CHAIRPERSON KANE: So, in answer to
15 question number two, "should WBC monitoring stop
16 altogether at some time point?", what we seem to be
17 hearing, right now, the answer is no. But that this
18 question should be revisited at some point in the
19 future?

20 Paul?

21 DR. LEBER: I mean, this is not
22 necessarily something the FDA can mandate. But
23 clearly, sitting in our grasp, or within somebody's
24 grasp, is a tremendous collection of data. That
25 doesn't mean that even though it was collected

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1 prospectively that it can't be mined retrospectively.
2 Now, the question is who should pay for it and how it
3 should be done. But there's nothing -- Greg Burkhardt
4 and I have been sitting here sort of talking among
5 ourselves -- from preventing anyone from identifying
6 cases within the cohort, identifying non-cases within
7 the cohort, identifying factors within those cases and
8 trying to find out if there are any predictors.

9 Now, the question is whether we, as a
10 regulatory agency -- I don't think we can force anyone
11 to do anything, but that doesn't mean there aren't
12 proactive things that other groups could do with the
13 corporation to try to find out if some of the
14 questions raised today couldn't be answered with the
15 existing data in hand. It's costly, I think is the
16 problem because this is the equipment -- doing case
17 controls, trying to go back and see what you have.

18 But, see, I don't think we would actually
19 have the right to demand that at the moment because
20 they haven't placed the system we have already set
21 under which the drug can be safe for use and effective
22 in use. If this were a new approval, we might have
23 more of a handle. But I think now, you have to really
24 talk about cooperation. We're not the only federal
25 institution that might be interested in this problem.

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1 CHAIRPERSON KANE: Carol?

2 DR. TAMMINGA: I don't exactly know why
3 one would have to skirt the sub-group issue. If one
4 were sort of putting together some guidelines like
5 Steve was suggesting, it would seem reasonably easy to
6 make one kind of set of guidelines for young people
7 under 55 and older people over 55, because the
8 incidence data are really quite different in each of
9 those groups. So, if one were pulling together some
10 recommendations that physicians could follow -- even
11 in the growing older group of people, not only the far
12 elderly but the growing, like over 55, it would seem
13 like a recommendation for biweekly monitoring would
14 certainly be something that I would support.

15 CHAIRPERSON KANE: I think the question
16 will then become what is mandatory and what is
17 voluntary? How do those sub-groups at-risk fit into
18 that?

19 So, we're approaching that question. We
20 still haven't fully resolved though whether to
21 implement monthly monitoring at 12 months or at 18
22 months or at 24 months.

23 Does the Agency a very specific time frame
24 on that, or can you work that out?

25 DR. LEBER: No, I think -- remember, we're

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1 really trying to get on the table all the concerns and
2 considerations people have and try to get a picture of
3 what your state of mind is about this. There are many
4 things that we can't even anticipate before we enter
5 into more substantive negotiations and I'm sure that
6 this is just the opening game. Let's put it that way.

7 CHAIRPERSON KANE: Carol?

8 DR. TAMMINGA: Would it be safe to say
9 that Clozapine is really sort of out of line for the
10 other drugs that are approved by the FDA with specific
11 monitoring suggestions made? Say, not under 12 months
12 but after 12 months of use, the rates that we were
13 shown for Clozapine seemed, really, quite in line with
14 the agranulocytosis rates for other drugs for which
15 only recommendations are made.

16 DR. LEBER: I don't know whether any of
17 the other drugs are estimated with the precision with
18 which you have Clozapine. The patient populations
19 differ considerably. There's a difference between a
20 patient under medical surveillance being treated for
21 a relatively short term who will, as course and part
22 of medical management, get a lot of epidemiological
23 work. And somebody who might intermittently and only
24 infrequently in a state hospital setting or some other
25 not get medical work. I think all those things went

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1 into it.

2 It's hazardous to compare across
3 therapeutic groups. I think it would be hard for me
4 to know, even though I've been with this throughout
5 the entire period of its development, what all the
6 factors that went into the thinking that allowed us to
7 make the decision we did in 1989, '90. You know,
8 that's lost in history and history is sort of a myth
9 you make up to explain what you did.

10 So, I don't know what went into it, but
11 it's very clear that we thought Clozapine stood out at
12 the time we made the decision. A cumulative risk of
13 1.5 percent of agran within the first year of use,
14 maybe even higher than that, and we were scared. I
15 think Sandoz at the time, before it became Novartis,
16 made this proposal. We didn't make it. They made it
17 and we thought it was a way to solve a problem. I
18 think we've learned a lot. That doesn't mean there
19 isn't more to learn, but as I said before, it might be
20 very useful if people in other parts of the federal
21 government interested in outcomes research and what's
22 governing risk and benefit to spend some money, trying
23 to investigate what I wonder looks like a gold mine of
24 information. Maybe that will inform us about what
25 other subsequent decisions could be made.

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1 CHAIRPERSON KANE: Dan?

2 DR. CASEY: I go on record as being in
3 favor of cooperation, since Paul asked earlier about
4 cooperation. I'm in favor of cooperation.

5 CHAIRPERSON KANE: Is there anyone who is
6 not in favor?

7 DR. CASEY: So, I hope the Agency and the
8 sponsor do come together to mine this very rich
9 database that they have.

10 A part that we've not talked much about
11 are the unmeasured benefits of Clozapine. We've
12 talked about some of the risks, but there's just as
13 much or even more unmeasured benefit. We don't know
14 how many people stop being substance abusers, as Dr.
15 Salzman was alluding to, because of the benefits they
16 get from Clozapine. My experience is, there are
17 substantial numbers of people who do better in many
18 domains than they have in a very long period of time.

19 We also know from imprecise data that
20 monitoring probably increases compliance and
21 compliance probably -- though not very well measured
22 -- increases how well one does in this illness, though
23 the risk of relapse on medicine does not go away even
24 in the second and third years of treatment. So, with
25 the intangible benefits of monitoring as intangible as

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1 it is, I would still give some value to that
2 monitoring approach to keep people in treatment.
3 Going to your provider seems, in some general way, to
4 increase the likelihood of getting benefit from the
5 care for that provider. It's certainly probably
6 better than nothing. And you're likely to not
7 participate if you're not getting some kind of
8 encouragement to be compliant and participate. That's
9 the part that leads me to still want to monitor that
10 intangible, as yet unmeasured benefit from this very
11 effective, very good drug. It is really a wonderful
12 medicine to have compared to treating psychosis
13 without Clozapine in our pharmacopeia, and we should
14 keep that perspective also.

15 CHAIRPERSON KANE: Ming?

16 DR. TSUANG: Since Dan mentioned about
17 the gold mine, I think when this was designed, I think
18 from today's data, it's achieved its purpose. But
19 whether that is a gold mine or not, I don't know.
20 Maybe coal mine. They have something there and they
21 already achieved the purpose of estimating the
22 incidence, the mortality.

23 However, this morning I asked a lot of
24 questions. If they'd really like to make it a gold
25 mine, they need to invest in finding other risk

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1 factors for us to be able to make a decision based on
2 data. Currently, what I got is that the six months
3 seems to be all clear and after one year, I don't have
4 any data to vote either way. So, I see the consensus
5 is that from six months to one year, biweekly. But
6 after that, we need to revisit and to see if any
7 guideline needs to be developed for the sub-
8 population. Probably that is the way to go if I
9 listened to the presentation.

10 I'm still not quite clear, after six
11 months need to be biweekly, but the consensus seems to
12 be -- the data do not give me that kind of a
13 confidence. After six months, it's very important.
14 The data seem to show that after one year, we should
15 altogether stop it, but currently, it is too emphatic
16 to say that. We may get analyzing those coal mines,
17 invest more money to correct more systematically, some
18 of the data. Then it will become a coal mine or a
19 silver mine or whatever.

20 Am I correct in saying that the consensus
21 is now, after six months, it's biweekly up to one
22 year. Then later, we'll revisit the issue and in --

23 CHAIRPERSON KANE: Up to --

24 DR. TSUANG: Yes?

25 CHAIRPERSON KANE: Up to at least one

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1 year.

2 DR. TSUANG: Yes, okay.

3 CHAIRPERSON KANE: I don't think we
4 reached closure on --

5 DR. TSUANG: And then the things that come
6 back again is the sub-population. We need to identify
7 the criteria for sub-population in which probably --
8 even after one year, biweekly or even some of them may
9 be weekly monitoring may be necessary for a particular
10 sub-group.

11 DR. CASEY: Ming, I don't know about the
12 geological approach to assessing the care that we
13 provide, but I accept that we have to go to the art of
14 medicine when we don't have the science of medicine to
15 guide us. For me, the art says that at some point in
16 time, we can reduce the monitoring to less than
17 biweekly. The art also tells me that there's value to
18 continuing it at some rate, even less frequent than
19 that. But I'm not sure what that is and when.

20 DR. TSUANG: I think human psychology is
21 changing -- changing is difficult to bear. Once the
22 system is there, we always like to continue. Then
23 using probably -- off the record -- using various kind
24 of reason to sustain. Even the data seems to indicate
25 that a continuation of those are simply based on our

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1 own subjective adjustment. I agree with you, it's an
2 art. Oh, but -- need a science to back up your art --
3 artistic judgment.

4 So, I said already what I want to say.

5 CHAIRPERSON KANE: Okay, thank you.

6 Let's try to address question number
7 three. "Should the program be changed overall? For
8 example, should it become voluntary as is most advice
9 in labeling regarding monitoring for adverse effects?"
10 If at some point it should become voluntary, the
11 question would then be at what point should we
12 maintain, should we recommend that it continue to be
13 mandatory?

14 I'd like to hear some discussion of that.

15 DR. CASEY: I like mandatory and revisited
16 later. We'll have more data. We'll have some better
17 monitoring and power analyses to tell us some more
18 about the hematological risk. We'll still not know
19 the clinical psychiatric benefit as precise as we
20 would like.

21 CHAIRPERSON KANE: So, mandatory
22 indefinitely until reevaluated?

23 DR. CASEY: Correct.

24 CHAIRPERSON KANE: Okay.

25 DR. CASEY: And that would also keep in

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1 place the Clozapine registry. That's not specifically
2 stated, but I see merit to that program.

3 CHAIRPERSON KANE: Okay.

4 Carol?

5 DR. TAMMINGA: Well, I'm going to weigh
6 in, even if just for discussion sake, on the other
7 side of it, suggesting that there be mandatory
8 monitoring for a period of 12 months. Then after that
9 point, along with a rather substantial set of
10 guidelines to really help clinicians, that after that
11 monitoring be voluntary and no longer mandatory. That
12 wouldn't seem to me to have to be something that would
13 destroy the National Registry. I mean, there are
14 other systems where physicians certainly report
15 adverse events to national registries, so I wouldn't
16 suggest disbanding that. It would certainly modify
17 the system somewhat.

18 I think that physicians have become
19 physicians and health care systems have become
20 sensitized to Clozapine. And the weekly mandatory
21 monitoring that we've all done for the last eight
22 years has sensitized the physicians. This kind of
23 partial mandatory/partial recommended monitoring
24 system would allow physicians to do more intensive
25 monitoring in cases where they saw the need and less

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1 intensive monitoring in other cases.

2 CHAIRPERSON KANE: On a voluntary basis?

3 DR. TAMMINGA: Yes.

4 CHAIRPERSON KANE: Carl?

5 DR. SALZMAN: I would agree with that. I
6 would preface my remarks and say, I didn't hear
7 anywhere in this morning's talks or in any of the
8 material presented that any of us thought that the
9 registry had been a bad idea or that it should be
10 disbanded. In fact, I would like to thank Novartis
11 and Sandoz. I think that they did something that was
12 unique. We had a lot of fights about it in the
13 beginning but the data really have been very, very
14 helpful.

15 I think, speaking for myself and agreeing
16 with Carol, that it should be mandatory to continue up
17 until the point at which it seems that the benefits
18 begin to become less clear. Because there is a
19 potential negative side to keeping it mandatory
20 indefinitely, I would hedge my own bet and say, at
21 this point, I would agree with having it mandatory for
22 a year and then after that, I'm not so sure.

23 What I'd like to know in helping me vote
24 is how NAMI would see it after one year? And whether
25 they, the family members, really would feel that it's

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1 necessary to keep it mandatory in order for the active
2 compliance, or whether they would agree with your
3 comment, Carol, that we've all become sensitized
4 enough so that physicians would know to maintain some
5 level of close observation of their patients without
6 there being the no blood/no drug rule. So, I'd like
7 more input from the consumer side as well.

8 CHAIRPERSON KANE: Dan?

9 DR. CASEY: I'd like to remind my
10 colleagues, Carol and Carl, about the data, about
11 physician compliance, and point out that physicians
12 are not very compliant when we have given them
13 treatment guidelines in the past, we find about a
14 quarter of them follow the treatment guidelines.
15 When we remind them and give them incentives to follow
16 guidelines, about half of them do it. Then when we
17 stop reminding them, it goes down again.

18 So, I think the risk of going voluntary is
19 that you dilute the signal of the people who are at
20 greatest risk and the people who should be concerned
21 about rechallenge. I think you want to have a very
22 high sensitivity in that signal because those are
23 clearly the highest risk people if the lower is
24 correct that people who have had it before are going
25 to get it again if they get exposed to the drug.

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1 The optimism you have for physicians being
2 very good about reporting, I think will decrease over
3 time as you get away from the requirement for
4 monitoring.

5 DR. SALZMAN: I think if you say that if
6 a patient has had an episode then it's mandatory, that
7 would solve that problem. But it seems to me that the
8 rate is going to go down rather precipitously, that's
9 going to be a relatively small number in which case
10 you're not tarring the entire population with a
11 mandatory rule for only a small number of people.

12 DR. CASEY: You will not know if
13 physicians have been compliant with "you must report
14 if it has been agran" because if they don't report,
15 they'll be no way to know whether they didn't report.

16 DR. SALZMAN: Well, I guess I feel that
17 the law courts are helpful in this area. If there's
18 a big box warning and it says "thou shalt do this or
19 else the lawyers are going to come after you", my
20 sense is that people tend to do it.

21 CHAIRPERSON KANE: Most of the cases which
22 occur will have occurred during the one year mandatory
23 monitoring, in which case they would be in the
24 national registry. So that, the concern that's being
25 expressed would be about those cases which occur after

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1 one year which are not in the registry. The
2 physicians treating those patients subsequently might
3 not be aware that they developed taginalsitosis. But
4 it seems to me that's a much smaller proportion of the
5 people at risk.

6 Yes?

7 MS. CURLL: I certainly feel that
8 mandatory for at least the one year is important,
9 especially for providers to report. However, I'd
10 still like the sponsor to expand the database to
11 include ethnicity, as mentioned before, and secondary
12 diagnosis that may be a contributing factor. And when
13 they do the retrospective studies later see if any of
14 these are significant. Because as I noticed, alcohol,
15 drugs, as well as Parkinson's and some other problems
16 may be of value later in looking at the drug. As you
17 said, it will be looked at again in a year or so.

18 But that, again, is voluntary, is it not?

19 CHAIRPERSON KANE: Yes.

20 Dr. Marder?

21 DR. MARDER: Yes. Since regulation should
22 be based on some consistent logic, it would seem that
23 when you get to a monitoring system, which we agree
24 will not have a major effect on saving lives, then I
25 think it would be reasonable for it to stop being

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1 mandatory and to become voluntary. I mean, it doesn't
2 seem right to me that we should require something just
3 so that the database would be better, in this case.
4 I think when we're doing it to save lives and improve
5 the public safety, but I think when we get to this
6 stage where we're dropping down to a level which we
7 can't be convinced that it's really going to make the
8 drug much safer -- we think it may -- then it just
9 doesn't seem logical to me that we should keep it
10 mandatory at that particular juncture.

11 CHAIRPERSON KANE: Paul?

12 DR. LEBER: I wanted to separate two
13 things. One is, I would say this kind of judgment
14 about societal risk, what proportion of individuals
15 using this drug will, in any interval of time, suffer
16 an event which is considered bad? That's something
17 society will tolerate.

18 The second question is, what fraction of
19 cases that are incipient will be detected and affected
20 by the monitoring system? I don't think that you have
21 enough knowledge to speak about the second one because
22 each one of them is conditioned upon when you develop
23 this, what your prodromes look like in time, what the
24 risk factors are and we don't know them. So, a lot of
25 this discussion has been conditioned on the idea that

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1 we're going to be able to write these guidelines to
2 tell people how to behave.

3 I, frankly, think we'll be able to tell
4 them what you heard today. That there's a lot of
5 information. We have certain things we know. Most of
6 the risk occurs up front. We think that as a society,
7 we want to have rules for this. But after a year, we
8 don't know very much and you're in there with sort of
9 real ignorance along with us. Because you're not
10 going to be advising them something you know. You're
11 going to tell them you don't know anything.

12 CHAIRPERSON KANE: Ming?

13 DR. TSUANG: While we are discussing
14 mandatory and voluntary, we should really think hard
15 about the usefulness of Clozapine. Currently,
16 clinicians tend to use it mostly in treatment
17 resistance of schizophrenics or undiagnosed psychosis.
18 You don't know what is going on and they use it.

19 However, Clozapine has the potential to
20 become a first line medication for psychosis. Having
21 mandatory there is actually an obstacle for the
22 Clozapine to be utilized widely, in comparison with
23 other newer drugs that don't have a mandatory rule.
24 So, clinicians tend to utilize those to stop -- rather
25 than with Clozapine.

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1 So, while we are talking about the
2 mandatory and the voluntary, we have to think very
3 carefully about the utilization of Clozapine in terms
4 of making it mandatory. Essentially, it is creating
5 some obstacles to the -- utilization of Clozapine for
6 the patients who you're treating.

7 Yes?

8 CHAIRPERSON KANE: I think that's true,
9 but I think we're also convinced that the risks are
10 sufficient during the first six months to justify
11 mandatory requirements.

12 DR. TSUANG: Oh, I'm not talking about
13 that. We already decided.

14 CHAIRPERSON KANE: Yes.

15 DR. TSUANG: We already decided in terms
16 of the six months is so clear. I don't know about
17 after that. You see, mandatory may be an obstacle.
18 I think Dan said this is a very good drug. I agree
19 with that. However, given the mandatory forever, it
20 actually an obstacle for clinicians to utilize
21 Clozapine.

22 CHAIRPERSON KANE: Okay.

23 So, we've heard two different
24 recommendations. One is mandatory indefinitely, the
25 other is mandatory for the first year and then

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1 voluntary.

2 DR. DOMINGUEZ: I think that there's
3 another way to go. I believe adherence would be
4 better after a patient has been followed for a
5 prolonged period of time if the recommendation in the
6 labeling is such to point out that some sort of
7 continued monitoring should take place. I think that
8 it could become voluntary, but it could become
9 voluntary after a longer period than one year. It may
10 be 24 months or it may be 30 months, but it may be a
11 longer period than one year. I think that's the other
12 in-between step.

13 CHAIRPERSON KANE: Also, just one other
14 point is that I think, as Carol said, physicians and
15 health care systems in general have learned a lot
16 about the use of Clozapine, have become somewhat more
17 comfortable with it, and have developed systems to
18 assure adequate monitoring compliance with the
19 requirements. One would hope that health care
20 systems, even under a voluntary system, would
21 implement quality assurance measures, et cetera, et
22 cetera, to try to guarantee that the monitoring that's
23 appropriate is taking place.

24 So, we should also keep that in mind.
25 We're in a very different position than we were, I

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1 think, seven years ago when we were very concerned
2 that health care systems would not be able to handle
3 this in the way that we thought necessary.

4 So, we have a range of proposals then, not
5 moving at all from mandatory to voluntary, or moving
6 to voluntary at one year or later.

7 Any other possibilities that we haven't
8 discussed?

9 Dan?

10 DR. CASEY: My position was that we would
11 come back and revisit this rather than it being cast
12 in stone that it's forever mandatory.

13 And I appreciate the comments of my
14 colleagues about having a non-mandatory period. I
15 would not advocate against that. But I do advocate in
16 favor of a mandatory position going forward for some
17 time.

18 DR. SALZMAN: We appreciate your
19 appreciation.

20 CHAIRPERSON KANE: Maybe it would help
21 just to get a feel for where people stand on this.
22 How many people would be in favor of moving from a
23 mandatory to a voluntary system after one year?
24 Seven.

25 And how many people would be opposed to

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1 that? Three.

2 So, that was seven voting for and three
3 voting against.

4 DR. TSUANG: But Dan said we need to --
5 sorry to interrupt this process. He said that we'd
6 like to revisit. So, essentially, we agree on the
7 mandatory up to one year. Then after that, whether it
8 should be mandatory or voluntary -- of course, I'd
9 like it to be voluntary but we don't make the decision
10 at this time.

11 Isn't that what you're suggesting, Dr.?
12 We will revisit that later?

13 CHAIRPERSON KANE: I think Dan was
14 recommending that we continue mandatory monitoring for
15 the foreseeable future, until we reevaluate it. So,
16 he was opposed to doing that at one year.

17 DR. TSUANG: Is that what you're saying?

18 DR. CASEY: Yes, that's a good summary and
19 I welcome you to change your vote.

20 DR. TAMMINGA: This is solicitation.

21 CHAIRPERSON KANE: Okay. I think we've
22 covered most of the questions. Let's try to just
23 reiterate.

24 In answer to question number one: "Should
25 the frequency of WBC monitoring be reduced at some

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1 time point?" The answer was yes. And if so, when?
2 The answer was six months. And what reduced frequency
3 of WBC monitoring would be acceptable? The answer to
4 that was biweekly. Should WBC monitoring stop
5 altogether at some time point? The answer was we're
6 not prepared to say yes to that now, but perhaps that
7 should be reevaluated at some point in the future.
8 Question number three was should the program be
9 changed overall? Should it become voluntary? The
10 recommendation is that after one year of mandatory
11 testing, that it should become voluntary. And to
12 emphasize within all of this that the recommendation
13 was repeated several times that an attempt be made to
14 mine the database that exists and to develop
15 guidelines that could be helpful to clinicians in
16 identifying groups at higher risk than the general
17 population.

18 Is there anything that we have not
19 covered? Have we given you sufficient answers to
20 those questions?

21 DR. LEBER: You've given us a lot to think
22 about.

23 CHAIRPERSON KANE: Any other comments or
24 concerns?

25 DR. CASEY: I would like to compliment the

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1 sponsor and the Agency for coming back to an Advisory
2 Committee with a much less concrete issue, or the data
3 is much less concrete than when we typically look at
4 whether we recommend a drug for approval or not on
5 efficacy and safety. I think it's a very good use of
6 the committee to discuss these issues which have a
7 substantial impact on how we provide the care that we
8 do, recognizing environment is very much different now
9 than from 1988 in the Autumn when this issue was
10 reviewed.

11 CHAIRPERSON KANE: I think we all share
12 that appreciation.

13 DR. LEBER: And we appreciate the
14 committee.

15 DR. TSUANG: May I just say one thing,
16 sir?

17 CHAIRPERSON KANE: Ming?

18 DR. TSUANG: For that data set to become
19 very useful, we, I think, need to have some thought
20 into how to get the more data on the sub-sample so
21 that it could be utilized for our scientific judgment.
22 The person I feel that for this data set in this
23 chaotic situation of the NIMH and NIH in funding.
24 They have done a remarkable job when it was started.
25 But now, what we are asking is not just the prevalence

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1 incidence. We are asking more of the concrete
2 question of what are the risk factors to prevent the
3 agranulocytosis?

4 So that, I hope the company can really
5 invest in that area, to contribute to the science of
6 this because Clozaril actually has a huge market now.
7 They can afford to really look into -- actually, from
8 reviewing all of these data, I'd like to see more
9 specific data set on the sub-sample.

10 CHAIRPERSON KANE: Thank you.

11 I'd like to thank the committee members
12 and our guests for a very useful discussion. Thank
13 you very much.

14 (Whereupon, the meeting was concluded at
15 1:20 p.m.)

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