FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

8:07 a.m

Monday, June 16, 2003

Marriott Washingtonian Center - Rio
9751 Washingtonian Boulevard
Gaithersburg, Maryland

ATTENDEES

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LAWRENCE HAUPTMAN, PH.D.
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VINOD KUMAR, M.D.
JAMES RAWLS, PHARM.D.
RIMA VAKIL

ALSO PRESENT:

LYNN GOLDMAN, M.D.
MAUREEN SCHWEERS

C O N T E N T S

DISCUSSIONS ON THE WHITE BLOOD CELL (WBC)
MONITORING SCHEDULE FOR PATIENTS
BEING TREATED LONG-TERM WITH CLOZAPINE

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P R O C E E D I N G S

(8:07 a.m.)

DR. RUDORFER: Good morning. I'm Dr. Matthew Rudorfer. I'll be acting chair this morning of the Psychopharmacologic Drugs Advisory Committee. I'd like to welcome you all here this morning.

As you know, we're here to discuss the possibility of changes in white blood cell monitoring frequency for patients taking long-term clozapine. We'll have an interesting discussion during the day, and I believe that everyone with a perspective on the issue will have a chance to address the committee.

Seated here at the table are members of the committee and consultants and FDA staff, and perhaps we'll begin by going around the table and introducing ourselves. Dr. Mehta, could we start with you?

DR. MEHTA: I'm Dilip Mehta. I'm the pharmaceutical industry representative on the committee.

DR. LEIBENLUFT: I'm Ellen Leibenluft, member of the committee.

DR. WEISS: Sheila Weiss. I'm a consultant to the committee, epidemiologist.

DR. WANG: Phil Wang, Harvard Medical School, psychiatrist and epidemiologist.

DR. RYAN: Neal Ryan, University of Pittsburgh,

psychiatrist.

DR. LEON: I'm Andrew Leon, a biostatistician at Cornell Medical College.

DR. MALONE: Richard Malone, a psychiatrist from Drexel University.

DR. GRADY-WELIKY: Tana Grady-Weliky, psychiatrist from the University of Rochester and member of the committee.

DR. RUDORFER: Again, I'm Matt Rudorfer. I'm a psychiatrist at the National Institute of Mental Health.

MS. PATEL: I'm Anuja Patel, Executive Secretary for the committee.

DR. ORTIZ: Irene Ortiz, psychiatrist, University of New Mexico.

DR. KECK: Paul Keck, from the University of Cincinnati, psychiatrist.

MS. BRONSTEIN: Jean Bronstein, registered nurse, retired. Consumer representative.

DR. HAMMAD: Tarek Hammad. I'm a safety reviewer in the Neuropharm Division.

DR. RACOOSIN: Judy Racoosin. I'm the safety team leader in the Division of Neuropharmacologic Drug Products.

DR. KATZ: Russ Katz, Division Director of Neuropharm Drugs, FDA.

DR. RUDORFER: Thank you.

Why don't we begin with some opening comments from the FDA. And before we do, Anuja Patel, our Executive Secretary, will inform us about the conflict of interest statement.

MS. PATEL: Good morning. The following announcement addresses conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting.

We would like to note for the record that Dr. Dilip Mehta is participating in this meeting as a non-voting acting industry representative.

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

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

DR. RUDORFER: Thank you.

And now it's my pleasure to introduce Dr. Russell Katz, Director of the Division of Neuropharmacologic Drugs Products of the FDA. Russ?

DR. KATZ: Thanks, Matt. I just really want to say welcome. I see a number of faces who've been on the committee for a while, so thanks very much for making the trip here again today. And a number of new faces. So I want to welcome and thank very much our consultants and members-to-be of the committee.

I won't make any substantive comments about the issue under discussion. Dr. Racoosin will give you a detailed background and overview of the issues that we'd like to discuss.

I just want to say thanks for the work that you've done in preparing for it, and thanks for the work you're about to do today. I think it's fair to say we've brought you another interesting problem and a somewhat complex one as well. So I thank you for your help.

I just want to make one clarifying comment. In our briefing document, the first document for the

committee, at the end lays out some of the questions we want to deal with, which are actually different from the questions that we actually will ask you because our document mentions that the company's proposal is to switch the monitoring to every month after a year. That was based on an earlier draft document that the company had submitted to us. So I believe it's fair to say that in the current company document there is no recommendation, and so the questions will be asked accordingly. We just wanted to clear up any potential confusion at the outset.

Anyway, with that I'll turn it over to Dr. Racoosin, who's head of our safety group, who will give you a detailed overview of the issues.

DR. RACOOSIN: Good morning. I'm going to be giving an overview of the issues for today's discussion, and I'll wind up with the specific questions we're going to address today.

Briefly, I'm going to be giving a little bit of an introduction to this topic, and then I'm going to cover the background rates of agranulocytosis in the general population. I'm going to discuss the incidence of agranulocytosis with other drugs that are marketed in the U.S. I'm going to give a brief summary of the July 9, 1997 PDAC meeting in which this topic was addressed for the first time. I'm going to briefly go over the current U.S.

labeling and then lay out the questions to the committee for today.

The clinical development program of Clozaril identified agranulocytosis, which I'm going to refer to as "agran" from here on out, as a serious adverse event associated with the use of the drug. The FDA-approved labeling at the time it came onto the market required that the drug only be available through a restricted distribution system that ensured weekly white blood cell monitoring, the so-called "no blood, no drug" rule.

The data on white blood cell counts and agran occurrence have been collected by the Clozaril National Registry, and since the generic version of clozapine became available in late 1997, the generic companies have also been responsible to maintain a similar registry. The purpose of that registry is to not allow patients who've developed agran related to clozapine to be rechallenged.

Previous analyses of this database have suggested that the incidence of agran decreases substantially after the first 6 months from drug exposure.

There have been three studies that have addressed the background rates of agran in the general population. The oldest one is from Bottiger and Westerholm in 1973, and it was a medical record review of all patients discharged from the hospital with a diagnosis of a blood

dyscrasia in the Uppsala health care region of Sweden between 1964 and 1968. Their definition of agran was less than 180 neutrophils per cubic millimeter, and they came up with an all-cause agran rate of 12.8 cases per million per year.

Subsequently there was the international agranulocytosis and aplastic anemia study that was a population-based case control study conducted in eight sites in Europe and Israel. The definition of agran used was less than 500 neutrophils per cubic millimeter, plus symptoms such as fever, chills, or sore throat. They came up with an overall rate of agran of 4.7 cases per million per year, and the range across the eight sites was 1.7 to 7 cases per million per year. There was an extension conducted at one site in Sweden and two sites in the U.S., and that showed a rate of 3.4 cases per million per year.

Subsequent to that, conducted by Strom, et al. and published in 1992, was a study of Medicaid billing databases in Minnesota, Michigan, and Florida, and that was done to estimate the agran incidence excluding recurrent or chronic neutropenia. The study was based on hospital discharge diagnosis with medical record verification, and they used an agran definition of less than 500 neutrophils per cubic millimeter. The incidence rate was 7.2 cases per million per year. That was overall, and the range by state

was 2.3 to 15.4 cases per million per year.

This slide just summarizes the three studies that I just described, and you can see that across the three studies the ranges are in a close ballpark between about 5 to 13 cases per million persons per year, and I think the thing to identify here is this is a rare condition and it's occurring rarely in the general population.

Of course, the question that we'd like to ask is, well, what is the background rate in patients with schizophrenia, and we've not been able to identify any data in the medical literature that speaks directly to that point. One could speculate that due to chronic exposure to medications, the background rate of agran may be higher in patients with schizophrenia than in the general population, but we don't have any data that speaks to this directly.

Moving on to the other marketed drugs in the U.S., there are five drugs that have a box warning for agran: clozapine, ticlopidine, carbamazepine, procainamide, and tocainide. The drugs on this slide, I'm not going to read them all out but they have a discussion of agran in the warning section of their labeling.

As I get into specific drugs, I just want to be clear about a couple of definitions. When I speak about the risk of agran, I'm talking about the number of cases in

the numerator and the number of people exposed in the denominator. When I speak of a rate, that's again the number of cases in the numerator, and in the denominator is the sum of the person-time exposure, so that implies a time component.

With regard to phenothiazine-associated agran, the data on this particular issue is derived primarily from case series in the 1950s and '60s, and in this series the agran risk ranges from .004 to 6.8 cases per 1,000 person-years. In the International Agran and Aplastic Anemia Study, phenothiazine use did not differ significantly between cases and controls.

With regard to ticlopidine, the data on the risk of agran comes from their clinical trials. They use a definition of agran of less than 450 neutrophils per cubic millimeter, and a definition of neutropenia of 450 to 1200 neutrophils per cubic millimeter. They identified a risk of agran as 8 cases per 1,000 persons, and the risk of neutropenia as 16 cases per 1,000 persons, and those cases all occurred early in treatment within the first 3 months. In the labeling there's a recommended white blood cell monitoring of every 2 weeks for the first 3 months of therapy.

There have been two studies in the literature that have addressed sulfasalazine-associated agran, and in

both studies the agran was defined as less than 500 neutrophils per cubic millimeter. The first study comes from the Swedish Adverse Drug Reactions Advisory Committee case series, and they calculated the risk of agran using the number of cases reported over a denominator estimate of persons at risk, which they calculated based on an average daily dose which came from pharmacy records. And the risk that they published was 0.57 cases per 1,000 persons. I estimated person-years from exposure from the distribution of the estimated length of drug use in the 35,000 patients and came up with a rate of 3 cases per 1,000 person-years.

There is also a study from the United Kingdom's General Practice Research Database Study. That data was submitted by primary care physicians, and they came up with a risk of .68 cases per 1,000 persons. Again, I estimated person-years of exposure from number of reported prescription fills and came up with a rate of 3 cases per 1,000 person-years.

The sulfasalazine labeling has a recommendation regarding white blood cell monitoring that says CBC's should be done "frequently." I think I added the quote. It just says frequently.

Moving on to the first PDAC meeting that addressed this issue in July of 1997. These are the questions that we posed that day, at that meeting, and

they'll look similar to what we pose today. The main question was, should the frequency of white blood cell monitoring be reduced at some time point after initiation of therapy, and if so when, and what reduced frequency of white blood cell monitoring would be acceptable, with subquestions being, should white blood cell monitoring stop altogether at some point, and if so, when? And a more broad question, should the program be changed overall? For example, should it become voluntary, as is most advice in labeling regarding monitoring for adverse events?

At the 1997 PDAC, we discussed the agran rates in the first 5.25 years of the Clozaril National Registry, and as you can see, in those first 5 years we identified that the peak risk of agran was in the first 6 months, with a rate of 8.6 cases per 1,000 person-years. It fell substantially by the second 6 months of treatment, and then continued to fall slightly subsequent to that. But the confidence intervals overlap in this range.

Here is just the same thing shown graphically, the substantial fall in rate after the first 6 months, and then the subsequent low rate after that, although it never goes to 0.

An additional issue that was discussed at that meeting was, there was a modeling done to project the rates of agran, given a change in monitoring frequency, and

that's described in the sponsor's briefing book somewhat. What the projections looked at was if the monitoring were to change from weekly to biweekly to monthly, or to no monitoring at all after 6 months, a year, 2 years, to see what might happen to the agran rate.

Based on the discussion at that meeting, the recommendation of the PDAC was to allow a decrease in monitoring to biweekly after 6 months, as long as the patient's white blood cell counts were stable.

This algorithm comes from the current Clozaril labeling, and I'm going to use this as sort of a way to summarize what the recommendations are currently. I should just mention one thing that's not on this slide, is that in order to initiate clozapine, a patient should have a baseline white blood cell count that's greater than 3500.

This algorithm speaks to what happens if a patient has their therapy interrupted for some period. If you look at less than 6 months, if there's no abnormal blood event, meaning the white blood cell count stays over 3000, the ANC stays over 1500, and there's no break in therapy that's greater than a month, a patient can just continue on their weekly monitoring from wherever they are in their 6-month clock.

Here in the second, there is no abnormal blood event, and the break is greater than 1 month. The

recommendation is to reset the 6-month clock, so a patient who has never been on clozapine for more than 6 months and they have an interruption greater than 1 month, they have to start their 6-month clock over.

In this third box, an abnormal blood event, meaning a white blood cell count below 3000, or an ANC less than 1500, and the patient is rechallengeable. You'll hear more about this, but rechallengeable refers to the fact that their white blood cell count hasn't gone below 2000. So if the patient's white blood cell count goes below 2000, they are non-rechallengeable and their name goes into the registry as being that. But if they go below 3000 and stay above 2000, they are rechallengeable, and in that case the 6-month clock is reset.

If a patient is on the drug for greater than 6 months, and they have an interruption but there's no abnormal blood event and the break is less than a year, then they continue biweekly.

If there is no abnormal blood event and the break is more than a year then they go back to weekly for 6 months.

And if there is an abnormal blood event, meaning their white blood cell count goes below 3000 but they remain rechallengeable, they go back to weekly for 6 months after they've recovered from the event.

So this is a general summary of what are the current recommendations.

So today, again, this is the question that we're going to be asking your input on: should the frequency of white blood cell monitoring be now further reduced after some duration of biweekly monitoring, and if so, when and what reduced frequency of white blood cell monitoring would be acceptable? Again, a subquestion, should white blood cell monitoring stop altogether at some point, and if so, when, and should the program be changed overall? For example, should it become voluntary?

Then a second issue that we're going to raise is, should the ANC be required as part of the white blood cell monitoring? Currently, and as you saw in that algorithm in the last slide, the ANC is mentioned as criterion for taking certain actions in the U.S., but it's not actually required, and it's not required that particular action be taken based on the ANC alone. It's really based on what the white blood cell count is.

In contrast, in the UK the ANC is a factor that is routinely monitored and used to direct therapy. So that's another issue that we'll be raising for discussion today. And we look forward to the discussion.

DR. RUDORFER: Thank you, Dr. Racoosin. We're going to move on now to presentations from Novartis

Pharmaceuticals Corporation. I'll mention for the benefit of the committee that we'll have a question period for the sponsor after their talks. If it would be helpful, we could certainly have a clarifying question or two after each speaker, if it would help with understanding as we go along. We will begin with Dr. James Rawls.

DR. RAWLS: Thank you, Dr. Rudorfer. Members of the FDA, members of the advisory committee, colleagues and guests, welcome. My name is James Rawls and I'm Associate Director in the Department of Regulatory Affairs at Novartis Pharmaceuticals Corporations.

Novartis is delighted to be here once again, and I say "once again" because as Dr. Racoosin mentioned, we were here in 1997 to discuss this very topic with you. We were here again in late 2002 to discuss the recently approved indication for Clozaril, that is, for patients with recurrent suicidal behavior, who have schizophrenia or schizoaffective disorder, and now today.

So the purpose of my presentation is really just to provide you with an overview of the interactions that have taken place between the FDA and Novartis over the past several years, specifically regarding this topic and the frequency of monitoring for Clozaril-treated patients. I will also provide you with an overview of our presentation that we have prepared for you today.

But first let me begin with just some brief background regarding Clozaril's pharmacological characteristics. It's considered a dibenzodiazepine that binds to specific dopamine receptors, and the dopamine binding characteristics of Clozaril differ from the products in the marketplace that were used for the treatment of schizophrenia that preceded it. It also is associated with a low occurrence of extrapyramidal side effects, EPS, and because of the dopamine binding characteristics and its paucity of EPS, Clozaril was considered the first atypical antipsychotic that was available in the United States.

At Novartis we have had a long history of use with this product. It has been available actually since 1969 in Austria for the treatment of patients with schizophrenia. However, when it was approved in the United States in 1989, its use was restricted to the more severely ill patients with schizophrenia, and that was due in part, as Dr. Racoosin has mentioned, to the clinical trial data and the data that we had from post-marketing experience regarding the rate and frequency of agranulocytosis. As I mentioned earlier, it was recently approved for the treatment of recurrent suicidal behavior for patients with schizophrenia and schizoaffective disorder.

So now let me move into a discussion or provide

you some background in terms of the interactions we've had with the agency regarding this topic. In 1989, as I mentioned, the product was approved in the United States, and at that time because of the frequency of agranulocytosis identified with the product, the weekly monitoring schedule was implemented for Clozaril treated patients. That weekly monitoring schedule was in place until 1998, when the committee in 1997, based on the question that is before you today, the main question before you today, recommended that the frequency of monitoring be reduced from weekly for life to weekly for the first 6 months, and then biweekly thereafter.

One of the other recommendations of the committee at the time was that an evaluation of the reduced frequency and the impact it might have had on agranulocytosis be conducted at some point in time.

One other important note to keep in mind during your discussions today is that the first generic was approved in 1998. So then that changed the amount of information that was recorded in the Clozaril National Registry. Novartis was no longer the sole keeper of information regarding agranulocytosis monitoring frequency overall for clozapine-treated patients.

As I alluded to earlier, at the 1997 advisory committee there was a recommendation that we reevaluate the

impact the reduced frequency had on the rate of agranulocytosis, and in 2001 the agency contacted us at that time and requested that we provide them with that information. There was a series of discussions that took place with the agency and Novartis, and we finally agreed upon some methods that we could use to actually answer that particular question. Once those discussions concluded, we submitted the analyses and the data to the agency in late 2002 and early 2003. At the time the agency, after their review of the information, felt that it was once again appropriate to discuss the frequency of monitoring for Clozaril-treated patients before you. So that's what brings us here today.

Just to describe our presentations to address the questions before you, the objective of our presentation is to present data that will facilitate the discussion that you will have regarding the various questions that were posed by Dr. Racoosin. So to accomplish that objective, let me introduce our program to you.

Over the next several presentations, you'll be seeing a lot of data regarding the rate of agranulocytosis and some might consider those rates to be relatively low. But to put those data into their proper perspective and to give you background as to what one adverse event or what one event of agranulocytosis means to the health care

community, to patients, to caregivers, and to define what agranulocytosis actually is, we've invited Dr. Stan Gerson, who is a professor of hematology at Case Western Reserve University, to provide you with that perspective.

Following Dr. Gerson's presentation, Dr. Vinod Kumar, who is the Executive Director at Clozaril and Global Medical Director for Clozaril at Novartis Pharmaceuticals Corporation, will provide you with an overview of the registry data from countries where we have a less frequent amount of monitoring for Clozaril-treated patients, specifically in the United Kingdom and Australia.

He will also provide you with the data comparing the original monitoring frequency schedule with the one that we currently have, and you will notice that there were certainly some unexpected findings with regard to those data. To offer up some quantitative analysis or quantitative explanations for those unexpected findings, we have invited Dr. Lawrence Hauptman, who is a statistician at Novartis Pharmaceuticals Corporation, to analyze those data and then to present to you some possible explanation as to why those findings were unexpected.

And then to offer some final thoughts and to wrap things up, we have invited Dr. John Kane, who is a professor of psychiatry at Albert Einstein College of Medicine, to wrap up our presentations for you.

So that is our agenda and our program, and I will now turn it over to Dr. Gerson, who will provide you with an overview of agranulocytosis. Thank you for your time.

DR. GERSON: Thank you, Dr. Rawls. So I am Stan Gerson and I'm a hematologist, so that's good and bad. I'm probably the only hematologist in the room and I'm also not a psychiatrist. I don't know too much about the efficacy issues, but I've been dealing with Clozaril as a compound since I was introduced to it in 1987, when the first cases of agranulocytosis were beginning to appear in the U.S. I offered my advice on the management and the monitoring system back then before the drug was approved, and since that time I've been actively involved with difficult case management situations.

So first let's just define agranulocytosis as we'll be talking about it today. It is in fact a drop in the neutrophil count or the granulocyte count -- those words are used interchangeably -- to less than 500 per millimeter cubed in the peripheral blood. Now as the cases proceed, it really is associated with a very high incidence of morbidity from neutropenic fever, which occurs in about 80 percent of affected individuals.

The duration of agranulocytosis directly impacts on its severity and its morbidity and a low

frequency of mortality, so that fever is seen in about 100 percent of patients who have a duration of agranulocytosis in excess of 5 days. Mortality is really related not to the agranulocytosis itself but to the infections and the sequelae of those infections. And it, as we've heard, is rare in the absence of a comorbidity, serious illness, or drug administration.

Now, here's just a case that I'd like to review with you. There are two lines on this graph. The top line is the WBC count. The bottom line is a neutrophil or granulocyte count. You'll see that they really run in parallel. This individual was on medication for a total of 68 days, about 10 weeks, had some characteristic features that are common. First is a mild rise in the WBC count during the early phase of treatment, then a 3-week prodromal period in which their white count fell, still in the normal range, and ultimately the medication was stopped on day 68, just at the time of the 10th blood count.

You'll also notice that at the time that the drug was stopped, the neutrophil count was still above the lower limit of normal, and that it continued to fall precipitously, lowering to a value of almost 0, where it stayed for about 12 to 14 days, and then gradually recovered up into the normal range. This individual developed a pneumonia, was hospitalized, treated with

antibiotics, and recovered normally, and as you can see, at the end of the day, had a white count that was right back to the normal range.

So what do we know about Clozaril-associated agranulocytosis? Well, it really is a serious disease in the affected individual, and for this reason it represents a significant burden to the health care system, let alone the individual. Early detection decreases the risks, perhaps by both reducing the incidence, but also certainly by allowing, through early recognition and management, decreasing the morbidity and the mortality. We all know historically that there was an exceptionally high rate of mortality associated with agranulocytosis in the early '70s and '80s, and that has come down, and we'll look at those rates as we go forward.

Now, there are some key issues with clozapine-associated agranulocytosis that I think are worth, at least again from my perspective as a hematologist, to bring up. One is its really protracted course. There are many drugs that can cause a severe neutropenia. You stop the drug and the blood count comes back up to normal in 3 to 5 days. But Clozaril is special because this is the typical bone marrow of an individual, and this shows the lymphocytes, these darker, very round cells, and then myeloid precursors are just absent, and all you have left are the red cell

precursors. So it takes a long time for this marrow to recover because the precursor cells just aren't there.

Now, if we did a bone marrow on somebody with mild or even moderate neutropenia, all their white cell precursors would be there, and that's why those individuals, if the drug is stopped, will recover very quickly. But in a true case of agranulocytosis, there just aren't any myeloid precursors around, so the stem cells have to regenerate them and that takes about 2 weeks in the absence of the growth factors, and even with growth factors, it takes 8 to 10 days.

So what are the key features, just to summarize? First, as we saw in that first case, an onset may take 1 to 3 weeks and in that period can be detected by monitoring. In the early course of Clozaril, in the first 10, 12, 18 weeks, it's more common to see a rapid onset of agranulocytosis that may or may not be preceded by a mild drop in the counts. And there is clearly benefit from early detection because the drug can be stopped.

Now, when the drug is stopped, the WBC count is typically in the 2000 to 3000 range, and often the ANC is between 300 and 1000. It's not 0. So the unique features are there's a severe drop in the granulocyte and neutrophil count that continues beyond the time that the drug is stopped, that there's a prolonged duration, as we've seen,

8 days with the use of growth factors, 15 to 16 days in the absence, and the significant risk because of the duration of neutropenic fever and severe internal infection.

So here's just a second case and I would just like to point out a couple of key issues and then move on to some management discussion. First, again, you can see another case where the white count actually goes up, a prodromal period where it falls, and then it seems to recover, and then it fell again. And here in this individual this happens at about 160 days. When the clozapine is stopped, there's actually a little bump in the white count, which is again not uncommon, in the neutrophil count as well, and then it goes down and stays quite low for about 16 days. This is actually a patient that I observed when I was called to see the patient at this point, and this patient developed a severe cellulitis of the leg which had to be treated in the hospital with antibiotics, and then the patient of course recovered.

We can also look at this to address the issue which we'll come back to of the monitoring frequency. So if you're monitoring every week, then you get these nice blood levels, but if you try to imagine a 4-weekly count or 2-weekly count, you'd sort of miss half or three of these values. If you just happen to catch this value on your monthly count, the next monthly count is out here

someplace, and it may be 2 or 3 weeks into the severe neutropenia or agranulocytosis case.

So my sense is that there's not that big a difference, especially as the incidence falls, in picking up cases by biweekly monitoring. If you move to monthly monitoring, you're likely to miss at least a quarter of the cases before the onset of symptoms.

Now, when the cases are presented, what's our orientation toward managing our patients with agranulocytosis? Well, hospitalization of the patient is recommended, especially in the schizophrenia population, with daily observation for fever, infection, culture, and imaging, if possible, sites of infection as appropriate in a medical setting. Some patients receive prophylactic antibiotics, of course, when a fever develops, and everyone should receive intravenous antibiotics to start and then perhaps outpatient antibiotics.

Growth factors are now recommended because it really can reduce, and has been shown to reduce, the duration of the neutropenic period. Still, the duration of illness is 8 to 25 days, and this represents a substantial cost of treatment both in terms of hospitalization, use of antibiotics and of growth factors.

So the advantages of the monitoring system that we've seen is that it allows early detection prior to the

onset of symptoms, it allows the drug to be stopped early, which may either prevent some cases but certainly decrease morbidity in others. It enables early initiation of treatment and management of agranulocytosis, and it provides a considerable degree of reassurance to both patient, family and health care providers.

So in conclusion, we've seen that Clozaril is associated with agranulocytosis episodes, which represent a serious illness to the affected individual. Monitoring allows detection prior to the onset of the illness rather than just the onset of the agranulocytosis, and early detection can limit morbidity by prompt institution of management, and we've also seen that management is costly in and of itself.

I'd now like, if there aren't questions, to introduce Dr. Vinod Kumar will go over the registry data.

DR. KATZ: Can I just as one question? With regard to the question of the duration of the agran when the drug is discontinued, are there any published series of these patients in whom the drug has been discontinued because of agran to sort of prospectively look at some cohort to see in general how long the agran persists? Are these slides based on your personal experience with the cases?

DR. GERSON: They certainly are based on my

personal experience. We have published one case series, a relatively small case series, in the Lancet where we actually compared a small group of patients with and without the use of growth factors. But there hasn't been a large case series of the course of agranulocytosis, and maybe that's a good idea.

DR. KATZ: You had mentioned that if the monitoring is moved out to every month, you would miss a quarter of the cases. Where does that number come from?

DR. GERSON: That data just comes from looking at, frankly, hundreds and hundreds of agranulocytosis prodromes and observing the time that it takes to drop. Now, the sudden onset cases really happen within a week, and the agranulocytosis, in its classic form with absence of neutrophil precursors, probably takes about a week to 10 days to occur, and then because there's a sudden stop in the production of neutrophils, that takes again about 3 to 5 days for the case to become apparent, with a drop in the granulocyte count. So that process physiologically probably takes about 2 weeks.

So if you add in now another 1 to 2 weeks of prodromal period, then the likelihood is with biweekly monitoring you'll pick up most of those cases before symptoms occur, but monthly it just physiologically is too long for how the medical condition arises. So if randomly

it's happening somewhere during that 4-week period, you'll miss about a quarter. That's how I come up with that estimate.

DR. LEON: Can I ask a question about the ANC and the WBC. How are they related, and how would adding the ANC increase in case detection, or what would we lose by not adding it?

DR. GERSON: Right. We have to discuss this at some point, so I'll go ahead and give you my sense about it.

Early on we used the WBC because it was a very highly automated, reproducible number, so for screening purposes it's great. It takes 10 minutes. A machine does it. You do it five times, you get the same number.

The ANC is a manual evaluation. As long as it's high, you can do it automated, but if it starts to fall, you've got to do it by performing a blood smear and having a laboratory technician look under the microscope and do a differential cell count. So that's a more variable number. It takes longer to do, has more lack of reproducibility. So when you move to the ANC, you're going to have a higher false positive detection problem. You're just going to because it's a manual evaluation.

Normally they track quite well, and you saw in the two samples that I gave -- and those are pretty common

-- that the numbers just track. It's normally 40, 50, 60 percent of the total of WBC count.

DR. LEON: Would the lack of reproducibility ever result in a low false negative?

DR. GERSON: Usually the issue is that if you're going to have an error, you're going to under-report. So instead of 70 percent neutrophils, you report 20 or 30 percent neutrophils. If they're not there, it's hard to count them. So the ANC is sort of a gold standard and will remain so for the definition of agranulocytosis. You're just more likely to have more false positives requiring a person to come back and be tested again. I certainly have seen many studies and evaluations in clinical settings in which you just get this nagging incidence of a low ANC that's not real. But be that as it may, the critical questions are, what's the definition? The definition is an ANC of less than 500. It's not a WBC. The proper definition is an ANC.

The second question is, what's the chance that the current system misses a case? So I just reviewed with the Novartis folks in the last day or so, and about 3 percent of the 573 cases of agranulocytosis are in the registry with a WBC above 3500 and an ANC of 500 or below. So 3 percent. That's 19 cases. So through this huge monitoring program and case detection, it's an unusual

event -- not rare but unusual -- to actually miss based on the simple determination of the WBC of 3500.

DR. MALONE: Is there any good estimate of what percent of patients who develop agran go on to die? Especially I guess if it's not caught that early.

DR. GERSON: I just can't answer the "not caught that early." Well, we have the Clozaril database, which is a caught-early database, if you will, because everybody's either managed weekly or biweekly. Would you like me to comment on that or do you want to?

DR. RAWLS: That's something that we can address after Dr. Kumar's presentation. We do have some data on that that we can share with you, if you don't mind waiting.

DR. GERSON: I could comment only on the general medical literature of death rate from agranulocytosis, and that literature is not perfect, let's face it, because it's all sorts of different diseases in different patient populations, et cetera. So there are certainly case report clusters of a high death rate from other drug-induced agranulocytosis.

If you look at a publication in 2000 of ticlopidine, which is a review of all the published literature about ticlopidine, in that setting where there's a recommendation but not a requirement for monitoring, the

death rate is 7 percent. So that's the most recent data that I can give you.

DR. KECK: Could I ask just two quick questions? Sorry. Just when you thought it was safe.

The time course of onset of agranulocytosis, does it matter depending on when it occurs following clozapine exposure? In other words, can you have rapid onset in the rare cases that happen a year-and-a-half later compared to, say, within the first 6 months?

DR. GERSON: Typically not. Typically the rapid onset falls or in the first 6 months.

DR. KECK: So it's more insidious later on.

And secondly, how responsive is clozapine-induced agran to colony-stimulating factor treatment? I'm not aware of the Lancet publication.

DR. GERSON: What we've been observing is that with the prompt administration within the first 2 or 3 days of growth factors, you can shorten the course about 8 to 9 days. So 6 to 8 days after the institution of growth factors, you'll see a count recovery. So in the absence of that, it's typically 14, 16, 17 days. A good solid 2 weeks.

DR. KECK: Thanks.

DR. WANG: Can I ask one quick question before you leave? What has the temporal trend been in use of

these growth factors? Does it mirror sort of the secular decrease in agran?

DR. GERSON: You know, that's a very good question. I really don't have any denominator data. I know that it's commonly administered but I really don't have any denominator questions. I get phone calls about it and I advise it. That's not a very good answer. So I don't really know.

DR. RYAN: A quick question. After 6 months or whatever, you said the onset of the agranulocytosis is more insidious. What's the sort of curve like for the onset? What does a slow onset look like?

DR. GERSON: Well, you saw the second case. It was about 6 months, and that's the typical. 2 weeks or so of falling counts.

DR. LEIBENLUFT: Just one question to follow up on Dr. Wang's. Around when, for what period of time have people been using the growth factor? When was that introduced in the course of all this?

DR. GERSON: It's almost a decade. It's not a very recent phenomenon.

DR. KUMAR: Good morning. I'm Vinod Kumar, Executive Director, Clinical Development and Medical Affairs at Novartis Pharmaceuticals Corporation.

My presentation will provide a historical

perspective on factors leading to the establishment of hematological monitoring systems for Clozaril-treated patients; an explanation of Clozaril registry policy and objectives worldwide and an overview of data collection; data on rates of leukopenia and agranulocytosis under various monitoring frequencies from national patient registries in the United Kingdom, the United States, and Australia; and finally the results, summaries, and conclusions based on analysis of these data.

Before the establishment of hematological monitoring systems for Clozaril-treated patients, the rates of agranulocytosis associated with Clozaril treatment and mortality were significant. The rate of agranulocytosis reported in Europe prior to monitoring was 1 to 2 percent per year, and in the U.S. during pre-marketing clinical trials, the rate was 1.3 percent at 1 year. Mortality among agranulocytosis cases was 32 percent. These incidence rates led to the requirement of the mandatory monitoring by health authorities and to the Novartis policy of "no blood, no drug." In other words, patients who do not undergo mandatory blood tests should not be prescribed Clozaril.

The first initial monitoring systems were established in 1990. The objective today for all monitoring systems is the same as it was 13 years ago; that

is, the early detection of moderate leukopenia in order to reduce or prevent the occurrence of severe leukopenia, agranulocytosis, and death.

To achieve this objective, the most intensive monitoring schedule must take place during the time when the patients are at highest risk. As is clearly evident from the results of hazard rate analysis shown in this slide, the period of highest risk for moderate leukopenia and agranulocytosis is during the first 6 months of treatment. The hazard rate for moderate leukopenia begins to stabilize after about 18 months, at approximately 9 per 1,000 patient-years and at approximately 0.3 per 1,000 patient-years for agranulocytosis.

The continuing risks of agranulocytosis can be seen more clearly on the next graph using the same agranulocytosis hazard data. The risk of developing agranulocytosis at year 8 is approximately .3 per 1,000 patient-years. And although it appears to reach 0 at year 8.5, this may be misleading due to the small number of patients remaining in the cohort.

Since 1990, in the United States, UK, and Australia, registries have collected more than 22 million lab records. Although these data were collected to ensure individual patient safety and not for research, the resulting database is a rich source for epidemiological

study. In addition to WBC counts, the industries collect patient's initials, identification numbers, date of birth, gender, and race.

A key safety effect of the Novartis Clozaril patient registries is this non-rechallengeable database. This database is shared with all generic manufacturers and ensures that no patients who are discontinued from clozapine because of blood dyscrasia are ever exposed again to the drug. One key point to bear in mind is that separate registries are also maintained by generic clozapine manufacturers.

Now, let us move on to the data. The analyses which we will discuss today were performed on data from over 215,000 patients in three countries. I will explain the differences between monitoring systems in the U.S., UK, and Australia, and present the results of separate analyses performed on data from each country's registry. It should be noted that because of the different policies, procedures, and information compiled in each registry, comparing the results from one country with another is not recommended.

I will begin with the United States Clozaril National Registry, also known as CNR. The focus of this part of my presentation will be to present the unexpected finding that the reduced monitoring schedule initiated in

1998 did not result in an increase in the rate of leukopenia or agranulocytosis.

Here we see that the first patients were entered into the Clozaril National Registry in 1990. WBC monitoring was performed weekly for the duration of the treatment until 1998 when the following advisory committee recommendations, monitoring after the first 6 months of treatment was reduced to at least every 2 weeks also referred to as biweekly.

Noteworthy is the fact that generic clozapine was introduced at about the same time as the reduction in monitoring frequency and may have contributed to the unexpected results that I will describe in a moment.

First, however, let us look at the criteria for action used in the course of Clozaril treatment to ensure patient safety. Clozaril should only be prescribed if the WBC count is 3500 or above and is accompanied by weekly monitoring for at least 6 months. If a patient's WBC count is recorded between 3000 and 3500 and his or her ANC is above 1500 monitoring is increased to twice a week until it returns to normal. A drop in the WBC count to between 2000 and 3000 and/or their ANC falls below 1000, those patients are prevented from further exposure to clozapine by entry into Novartis' non-rechallengeable database.

Now, that you have an understanding of the

registry actions in the U.S., I will begin my discussion of the U.S. data by describing the cohorts included in the analyses.

More than 178,000 patients were included in these analyses. They were divided into two cohorts referred to as the initial system and the current system. The initial system includes over 138,000 patients who entered the system prior to October 1997 under weekly monitoring. Data on these patients are included in the analysis up to April 1998 only. The current system includes over 39,000 patients who began entering the system in October 1997 and underwent 6 months of weekly monitoring, followed by biweekly monitoring for the duration of the treatment. It is important to note that patients exposed to generic clozapine were not included in the analysis.

My next slide shows definitions used in the analysis for moderate leukopenia, severe leukopenia, and agranulocytosis. Moderate leukopenia was defined as a WBC of 3000 or below; severe leukopenia, a WBC of less than 2000; and the definition of agranulocytosis was a WBC of 1000 or below or an ANC of 500 or less.

Now, to the following results that show comparisons of rates of moderate leukopenia, severe leukopenia, and agranulocytosis across cohorts, as well as

overall trends for agranulocytosis over time.

During the first 6 months of treatment, patients in both the initial and current systems were under a weekly monitoring schedule. Although one would not expect to see any difference between these two groups of patients under identical monitoring, as you can see the rates of severe leukopenia and agranulocytosis were significantly lower in the current system than in the initial system.

After the first 6 months of treatment, when patients in the initial system remained on weekly monitoring and the patients in the current system changed to biweekly monitoring, one might expect an increase in the rates of blood dyscrasia under the less frequent monitoring frequency in the current system. However, the rates of moderate leukopenia, severe leukopenia, and agranulocytosis were similar in both groups.

When we compared rates of leukopenia and agranulocytosis after 1 year of the treatment under weekly monitoring in the initial system with the same length of treatment under biweekly monitoring in the current system, the rates of moderate leukopenia and severe leukopenia were similar cohorts. However, the rate of agranulocytosis was significantly lower at .11 per 1,000 patient-years in the current system than in the initial system.

One can speculate that the introduction of other atypical antipsychotics and generic clozapine at about the time monitoring frequency was changed might have decreased the number of high risk patients in the Clozaril registry consequently reducing the rates of leukopenia and agranulocytosis. This is supported by the following results.

This graph shows a continuous decline in the rate of agranulocytosis over time. Interestingly, there's a parallel decline in the number of new patients entering the system. If the decline in new patients is due to high risk patients starting treatment with other atypicals, this development would have contributed to the decline in the rate of agranulocytosis. As is apparent from the next two slides, there were no clinically meaningful differences between the demographic characteristics of the patients in the initial system versus the current system that would explain the unexpected decline in the rate of agranulocytosis.

As you can see, there are no meaningful differences between age, gender, or race in the initial system when compared to the current system for all patients. Furthermore, this holds true for patients who developed agranulocytosis.

Now, the results of the U.S. analysis can be

summarized as follows.

Comparing initial system data with current system data, the rates of moderate leukopenia were similar under both systems during and after the 6 months of treatment.

The rates of severe leukopenia and agranulocytosis were unexpectedly less during the first 6 months under the current system and similar under both systems after the first 6 months.

Interesting to note is that after more than 1 year of treatment, rates of moderate and severe leukopenia were similar where the rate of agranulocytosis is .11 per 1,000 patient-years and is significantly lower in the current system than in the initial system.

The results were not related to demographic differences between the monitoring systems.

The rate of agranulocytosis declined over time, which may be related to the introduction of newer antipsychotic agents or generic clozapine.

Now to the other side of the Atlantic. The first patients were entered in the UK and Ireland Clozaril Patient Monitoring Service, also know as CPMS, in 1990. Unlike the U.S., where the initial monitoring frequency was weekly for the duration of the treatment, in the UK and Ireland, monitoring was performed weekly for only the first

18 weeks and then reduced to at least every 2 weeks for the duration of the treatment. In 1995 in the UK and in 1999 in Ireland, the monitoring frequency after the first year of the treatment was decreased to at least once a month.

Let us look at the criteria for action used in the course of Clozaril treatment to ensure patient safety in the UK. You will notice some significant differences between the U.S. and the UK in this regard.

Like in the U.S., Clozaril should only be prescribed if the WBC count is 3500 or above. However, in the UK, the ANC must also be above 2000. The initiation of the Clozaril treatment is accompanied by weekly monitoring for at least 18 weeks. Similar to the U.S., patients with WBC counts recorded between 3000 and 3500 or an ANC between 1500 and 2000 are monitored twice a week until they return to normal.

The biggest difference between the U.S. and UK actions are that no temporary discontinuation is permitted in the UK, and permanent discontinuation occurs at the higher WBC count which is 3000. As we discussed in the U.S., the permanent discontinuation occurs at a WBC count of 2000.

As in the U.S., such patients are prevented from further exposure to clozapine by their entry into Novartis' non-rechallengeable database.

I'll begin my discussion of the UK data by describing the cohorts included in the analysis. More than 27,000 patients are included in these analyses. As in the U.S. analysis, they were divided into two cohorts referred to as the initial system and the current system.

The initial system includes approximately 6,000 patients who began entering the system in 1990 under weekly and biweekly monitoring. Data on these patients are included in the analysis up to 1995 only when the monitoring frequency after 52 weeks changed from biweekly to monthly.

The current system includes over 21,000 patients who began entering the system in 1994 and underwent 12 months of weekly and biweekly monitoring, followed by monthly monitoring for the duration of the treatment.

It is important to note that generic clozapine is not available in the UK, and therefore, unlike in the U.S., there are no generic patients to be excluded from the analysis.

My next slide shows definitions used in the analysis for moderate leukopenia, severe leukopenia, and agranulocytosis. The only difference between definitions for analysis in the U.S. and the UK is that in the UK ANC values are collected and may be used to identify patients

with moderate or severe leukopenia.

The following results show comparisons of rates of moderate leukopenia, severe leukopenia, and agranulocytosis across cohorts, as well as the overall trend for agranulocytosis over time.

During the first 18 weeks of treatment, patients in both the initial and current systems were under a weekly monitoring schedule. Although one would not expect to see any difference between these two groups of patients under identical monitoring, as you can see, the rates of moderate leukopenia were significantly lower in the current system than in the initial system. As expected, the rates of severe leukopenia and agranulocytosis were similar.

From 19 to 52 weeks of treatment, patients in both the initial and current systems were under a biweekly monitoring schedule. Here too the rates of moderate leukopenia were significantly lower in the current system than the initial system. As expected, the rates of severe leukopenia and agranulocytosis are similar.

After 52 weeks of treatment, patients in the initial system remained on biweekly monitoring and patients in the current system changed to monthly monitoring. The rate of moderate leukopenia was significantly lower in the current system. The rate of severe leukopenia was similar

in both the initial and current systems, but the rate of agranulocytosis under monthly monitoring was approximately double the rate under biweekly monitoring. However, this difference was not statistically significant.

As in the U.S., analysis of the data from all UK patients shows a continuous decline in the rate of agranulocytosis over time, and a parallel decline in the number of new patients entering the system.

Analysis of patient demographics produced similar results in the UK and the U.S. There were no clinically meaningful differences between the demographic characteristics of patients in the initial system versus the current system that would explain the results of the analysis. As you can see, there are no meaningful differences between age, gender, and race in the initial system when compared to the current system for all patients. The same holds true for the patients who developed agranulocytosis.

Now, the results of the UK analysis can be summarized as follows.

Comparing initial system data with current system data, the rate of moderate leukopenia was significantly lower in the current system than in the initial system.

The rates of severe leukopenia were similar

under both initial and current systems.

The rates of agranulocytosis were similar under both initial and current systems under weekly and biweekly monitoring. However, monthly monitoring was associated with an approximate 2-fold increase in the rate of agranulocytosis, as I mentioned earlier.

These results were not related to demographic differences between the monitoring systems.

Lastly, the rates of agranulocytosis declined over time which may be related to the introduction of newer antipsychotic agents.

Now let us turn our attention to Australia. Since the establishment of the Australian registry in 1992, monitoring frequency has been weekly for the first 18 weeks, followed by monthly for the duration of the treatment. Incidence rates of leukopenia and agranulocytosis were analyzed in this single cohort of approximately 10,000 patients.

Registry actions for Australia are identical to those in the UK.

The definitions used for the Australian analysis, however, are the same as those used for the U.S.

I will now present the results of the Australian analysis.

The rates of moderate leukopenia, severe

leukopenia, and agranulocytosis observed between week 0 and 18 decreased significantly between weeks 19 to 52 and again after 52 weeks. As shown in the previous slide, the rates of moderate leukopenia, severe leukopenia, and agranulocytosis decreased over time. The agranulocytosis rate after 52 weeks under monthly monitoring was 0.5 per 1,000 patient-years.

I will now draw some overall conclusions from the individual country results I have just presented.

Clearly, all three Clozaril registries effectively accomplish the global objective of detecting moderate leukopenia, reducing severe leukopenia, agranulocytosis, and death.

After 52 weeks, the rate of agranulocytosis under monthly monitoring in Australia is similar to the rate observed in the United Kingdom.

In the UK, results show that a change from biweekly to monthly monitoring was associated with a decrease in moderate leukopenia and an increase in the incidence of agranulocytosis.

In the U.S., the reasons for the observed decline in the rates of severe leukopenia and agranulocytosis during the first 6 months of the treatment are not clear.

The change in monitoring frequency in the U.S.

from weekly to biweekly was not associated with an expected increase in the rate of severe leukopenia and agranulocytosis. In fact, if you look at the data after 52 weeks of treatment, the rate of agranulocytosis was significantly lower in the current system under biweekly monitoring than in the initial system under weekly monitoring.

In the next presentation, Dr. Larry Hauptman will look at the U.S. data more closely and give some possible explanations for unexpected results of the U.S. analysis. Thank you very much for your attention, and Dr. Larry Hauptman.

DR. RUDORFER: A question from Dr. Weiss.

DR. WEISS: Thank you. On your tables 17 and 18, could you explain to me how you adjusted for the length of treatment? The U.S. rates for greater than 6 months and greater than 52 weeks.

DR. RAWLS: So you want CNR:17 of this presentation.

DR. WEISS: 17 and 18.

DR. RAWLS: 17 and 18. How we adjusted for the?

DR. WEISS: Length of treatment.

DR. RAWLS: For the length of treatment.

Zahur, do you want to answer this? It seems to

be a statistical question about the methods for the length of treatment, how we adjusted for this.

DR. ISLAM: My name is Zahur Islam. I'm a statistician at Novartis Pharmaceuticals.

On slide number 17, these rates are reflecting the incidence rate after 6 months. So essentially we compute the duration of treatment of the patient after 6 months, total it up. That gives you the total person-years, converted into years and the number of events.

DR. WEISS: So that was from 6 months --

DR. ISLAM: Onward.

DR. WEISS: And so there was no control for whether patients were on it for 1 year or 8 years or 5 years. Is that correct?

DR. ISLAM: No. It is correct. That's correct. Essentially you're assuming the incidence rate after 6 months for any duration.

DR. WEISS: Thank you.

DR. ISLAM: If you want that kind of adjustment, probably the hazard graph will give you that appropriate answer, what you're looking for.

DR. RAWLS: You want us to handle questions now or wait until the next few presentations, which last about 15 minutes, and then we can come back and answer all your questions.

DR. RUDORFER: Dr. Wang.

DR. WANG: Yes, a similar question about the same slides. I just question your conclusion because there was not an adjustment for the duration of clozapine use. There actually was a difference in the analyses where you did adjust for that in the life tables and in the analyses where your incidence rates were broken down for smaller periods. If you look within the 6- to 12-month periods, there actually was an increase in the rates of agranulocytosis and leukopenia. So I'm just questioning --

DR. RAWLS: Do you have a question or is there a particular slide or set of data that you're referring to?

DR. WANG: In the material. Maybe we'll go over it later.

DR. RAWLS: All right, if you can find it, and we'll try to address that for you later on.

DR. LEON: I'm confused. Why would you say there's no adjustment for duration of treatment when those two slides are presented in 1,000 person-years?

DR. RAWLS: Zahur?

DR. ISLAM: If we assume the rate after 6 months is pretty much fixed, what you have seen in the hazard curve is pretty much flat, then you don't need any adjustment there because you are assuming the incidence rate is pretty much the same over the period.

DR. LEON: Where does the rate per 1,000 patient-years come in if you're not adjusting for duration of treatment?

DR. ISLAM: Let me just say as for example. If I would have done the same thing for computing the overall rate from 0 to whatever it is, and if I would have used the same method, then the rate should have been adjusted. The standardized rate should have been computed, and that's what I did.

DR. WANG: The issue isn't duration of clozapine use. It's the time since initiation. We know that the rate decreases over time that you've been on clozapine.

DR. ISLAM: Right.

DR. WANG: So if you look just within a period of, say, greater than 12 months or greater than 6 months, you have some people who have been on it for a long time and a short time. You need to know who's who in order to sort it out. I'll look or these tables that you show that there's --

DR. RAWLS: So you want us to continue with the presentation?

DR. HAUPTMAN: I'd like to make a clarification to that, though. The rates are adjusted for time. That's person-years. After 6 months, we're saying, based on the

hazard rate, which looked to be fairly stable, that no further adjustment was needed because whether you're on for 6 months to a year or 6 months to 10 years, the hazard rate is relatively stable over that period. So the person-years adjustment would suffice. I think that's what was underlying our presenting person-years that way. We wouldn't have presented rates in the first 6 months compared to rates after 6 months because you see by the hazard rate that there is a difference.

DR. LEIBENLUFT: That actually gets to a question I had which is the previous speaker said in the presentation that the hazard rate decreases after 18 months. And I wasn't sure exactly what that was based on. In fact, it says that also in the briefing book.

DR. HAUPTMAN: Maybe it's easiest if we just leave these questions for the question and answer period.

DR. RUDORFER: Why don't we continue with the presentations, and then we'll come back to these issues in the overall discussion.

DR. HAUPTMAN: Good morning. My name is Lawrence Hauptman. I'm a statistician with Novartis' Drug Regulatory Affairs Department.

My presentation is going to have a fairly narrow focus. I'm just going to look at the U.S. data. I'm going to concentrate on agran rates after 6 months of

treatment, where the initial system differs from the current system.

I'm going to look at certain factors that may have contributed to the lower-than-expected agranulocytosis rate after the monitoring frequency changed from weekly to biweekly after 6 months of treatment. Now, what exactly do I mean by lower than expected?

When the advisory committee addressed this issue back in 1997, there was an implicit assumption that the rate of agran would increase with less frequent monitoring. The issue was whether the magnitude of that increase would be acceptable. Ultimately the FDA decided that the estimated increase would be acceptable and the monitoring frequency was changed to biweekly after 6 months of treatment.

However, when we compare the agran rate after 6 months of treatment for the current biweekly system, .37 per 1,000 patient-years, to that for the initial weekly system, .4, we see that the rate did not increase at all. This is what I mean by the rate being lower than expected. You've already seen this result in, I think it was, CNR:17 actually, in Dr. Kumar's presentation.

I'm going to examine data from the two monitoring systems with respect to the rate of moderate leukopenia and various factors that may have affected the

agran rate. Certain factors have already been discussed by Dr. Kumar, so I'll skip those for now. The factors that I will address are the overall rates of moderate leukopenia, the percentage of moderate leukopenia cases found with a WBC less than 2000, the rate of moderate leukopenia by calendar year, the WBC count at treatment discontinuation, and the overall discontinuation rate.

A lower rate of moderate leukopenia would have been consistent with a lower-than-expected agran rate because most patients travel through moderate leukopenia before developing agran. However, this was not the case. The rates were essentially the same: 8.92 per 1,000 patient-years versus 8.0 per 1,000 patient-years for the current system.

So if the rates of moderate leukopenia were the same, maybe the actual WBC counts, when moderate leukopenia was first detected, were different. This would be important because patients detected with a lower WBC count were more likely to progress to agran. This shows that the patients whose moderate leukopenia was detected when the WBC count was less than 2000 was 17 times as likely to progress to agran than were the patients who were detected when their WBC count was between 2000 and 3000; that is, if the first time we saw somebody below 3000, he was already below 2000. There were 64 such patients. 24 progressed to

agran, for a rate of 37.5 percent.

If we first saw them when their rates were between 2000 and 3000, of the 2,642 such patients, 57 progressed to agran, for a rate of 2.16. And the ratio of 37.5 to 2.16 is roughly 17. So in essence it's riskier to be found here than it is to be found here in terms of progressing to agran.

If, in the current monitoring system, fewer patients with moderate leukopenia had been found in this high-risk group with a WBC count less than 2000, that would have been consistent with a lower-than-expected agran rate. However, the percentages of moderate leukopenia cases found in this high-risk group were essentially the same in both monitoring systems: 2.4 percent versus 2.8 percent.

The last factor relating to moderate leukopenia is its rate by calendar year. If the rate had decreased over time, particularly since 1998 when the new system was put into effect, one would expect to see fewer agran cases. However, this did not appear to be what happened except for a few blips. The rate of moderate leukopenia after 6 months of treatment was fairly stable in this, at about 8 per 1,000 patient-years.

The last two factors relate to treatment discontinuation. The first involves the WBC count at treatment discontinuation and the second addresses the

overall treatment discontinuation rate. In both cases, the issue is whether the patients who might have been at a higher risk of agran were more likely to have been discontinued under the current system than under the initial system. If this were true, the agran rate observed under the current system would have been artificially lower compared to that observed under the initial.

Now, what we wanted to do was look at the WBC count of patients who discontinued because of a low count. However, the Clozaril National Registry does not consistently capture the reason for treatment discontinuation. So what we did is we looked at the WBC count for all patients who discontinued and for those patients who discontinued with a count between 3000 and 4000, under the assumption that these patients discontinued because of a WBC count that was sufficiently low to concern their physician.

In both cases, the median WBC counts, as well as the 95th and 5th percentiles, were quite similar regardless of the monitoring system. These are not confidence intervals. These are the 5th and 95th percentile. So it does not appear that on the basis of their WBC counts higher-risk patients were more likely to be discontinued under the current monitoring system.

However, when the overall treatment

discontinuation rates were compared, we do see that patients under the current system are more likely to be discontinued during the first 6 months than patients under the initial system. Under the current system, 57.6 percent were discontinued by 6 months of treatment, and under the initial system, it had only been 36.4 percent.

So if the patients who were discontinued were more likely to develop agran than those who did not, then this could account for the lower-than-expected agran rate in the current system. However, we do not really know whether these patients who discontinued early did so because of a higher risk of agran.

So in summary, the similar results in both monitoring systems for these factors -- this one was already addressed by Dr. Kumar, and I've just addressed these last four -- did not provide any evidence that explains the lower-than-expected agran rate after 6 months of treatment in the current biweekly system.

On the other hand, these factors might explain that lower-than-expected rate, but only the patients who switched to alternative therapies or patients who discontinued early were, indeed, at a higher risk of developing agran, and we just do not know whether this is true.

So, in conclusion, we were not able to find any

convincing explanations for why the agran rate did not increase when the monitoring frequency decreased every 2 weeks. This unexpected result, which we have not been able to explain to our satisfaction, may just reflect the limitation of the Clozaril National Registry, which after all, was set up to protect individual patients and not to be used as a research tool to try to answer questions about the underlying rates of agran or moderate leukopenia, severe leukopenia, for that matter.

I'd like to introduce Dr. John Kane, who will -- well, I'd like to, but I'm not going to.

(Laughter.)

DR. RUDORFER: A question from Dr. Leon.

DR. LEON: Thank you.

What I haven't heard is a little more about the people who switched to generic. Specifically, what percentage of Clozaril patients did switch? It could have a great deal of impact on the question you were just searching for an answer, but I haven't heard it. Was it 3 percent or was it 50 percent of those on Clozaril?

DR. HAUPTMAN: Let me give you a short answer, and then if anybody from Novartis can provide a little more information. I don't know that we can tell which patients switched or which patients actually started on a generic and then went over to clozapine. What we can tell from the

registry is when there are gaps in the WBC counts. So if there's a gap and then they pick up again, maybe that means patients during that gap were being given a generic. Patients who start on a generic and then go to Clozaril, it's my understanding we have no way of knowing how many such patients there are.

DR. LEON: How are sales affected by the introduction of the generic?

DR. RAWLS: We can gather some of that information from some of our representatives of the marketing department, who could provide you with some more figures. Zahur may have some data as well in terms of how we analyze this.

DR. LEON: Have there been any studies? We saw some demographic characteristics, but not even of those who switched to Clozaril. Have there been any studies that compared clinical characteristics of those who stayed on brand Clozaril and those who switched to generic? Was the more vulnerable patient more likely to switch to generic?

MR. DODSWORTH: I'm Roy Dodsworth from Regulatory Affairs at Novartis. The state substitution laws don't allow us to determine what type of patient switches from brand to generic. That's really driven by prescribing practices and by state substitution laws, so I don't think there are many of those types of studies that

I'm aware of.

To answer your earlier question, I don't think we can give you a categorical number, but the sales of Clozaril as a brand have been slowly eroding since the introduction of the generics, and currently about 60 percent of clozapine sales in the U.S. are captured by the generic companies, with about 40 percent of the brand. There's no guarantee that those who have switched have necessarily switched to a generic clozapine. They could easily have switched to some other atypical antipsychotic as well, so it's pretty hard to put a number on exactly how many patients have or have not switched from the brand to the generic.

DR. KECK: On your stat:7 slide.

DR. RAWLS: You have to give us some time to go back to these slides to pull them up. So stat:7?

DR. KECK: Sorry. It's not a question about the data on the slide, but one thing I've been wondering about is if there were a way of raising the threshold for warning of incipient agranulocytosis. Could you have, when someone passed that threshold, a more frequent targeted monitoring? And toward that end, do you have any data on the probability that someone will go on to develop agranulocytosis for a white count between, say, 3000 and 4000 or 3000 and 4500, in other words, a slightly higher

threshold that might give you an earlier warning, and how many of those people go on? I know it's not there, but is that something you could look at?

DR. RAWLS: Your first question, have they passed through this threshold of less than 3000, if there's some sort of increased frequency monitoring that is in --

DR. KECK: No. I know that doesn't exist.

DR. RAWLS: Actually it does. The action criteria that Dr. Kumar went through addressed some of the intense monitoring that takes place if they pass that threshold, and I think Dr. Racoosin also went through the algorithm as well.

Then the second question was 3000, 4000. Larry, did we do anything with --

DR. KECK: Or 3000 to 3500, something just a little bit higher.

DR. HAUPTMAN: The short answer is, no, we didn't. We do have that data and we could come up with percentages like this for patients who were first caught at any level, for that matter. I guess we could try to see if we can do that during the break and lunch period and maybe come back. Were you specifically interested in a --

DR. KECK: Well, just what the probability of agran was.

DR. HAUPTMAN: For what range? I don't know

if, given the time, we'll be able to do it for a number ranges. We could try between 3000 and 3500.

DR. KECK: Sure.

DR. RAWLS: So a table similar to this, 3000 to 3500, the probabilities for those patients going to agran. Is that correct?

DR. KECK: Yes.

DR. RAWLS: Okay. We'll see if we can get that for you.

DR. RYAN: And perhaps the time interval. Once you're doing that, it's the time interval that you care about almost as much as the probability.

DR. KECK: Exactly.

DR. RAWLS: Can you clarify what you mean by the time interval?

DR. RYAN: Sure. Somebody goes through 4000 or 3500, how long before they hit the agran. Do you have a month, do you have 2 weeks?

DR. RAWLS: So how long, the mean duration of time that those patients progress?

DR. RYAN: For the people who go below 3500 and 4000 and who go on to agran. But equally importantly, what's the range of time intervals of the ones who go on to agran. Not everybody. Of the ones who go on to agran, what's the time interval and what's the median and the

range of the time intervals.

DR. RAWLS: I think we're clear on that.

DR. WEISS: While you're on the slide, do you have a breakdown of this on the different cohorts? In other words, does the probability of progression differ?

DR. HAUPTMAN: This is for the initial system, what may have been called cohort 1 and 2 in your briefing document. We could do it for the current system but there are only 10 cases in the current system, and so you'd be basing these results on very small numbers and we felt that basing it on these larger numbers gave you more credibility in the probabilities you get here, than you would see when you try to over-analyze 10 cases.

DR. WEISS: What did you see with the 10 cases?

DR. HAUPTMAN: Actually I don't recall. We can do it. I'm not sure we did it, for the very reason I just told you, is that we didn't think we could put much faith in whatever those numbers were anyway. But we can get that too.

DR. WEISS: Thank you.

DR. RAWLS: So just to clarify, you just want for the current system, the same slide. Okay.

DR. WEISS: Please. Thank you.

DR. RAWLS: Two requests during lunch. Okay.

DR. WANG: Can you bring up your analyses

showing the white blood cell counts at the time of discontinuation? Did you do any sensitivity analyses with a longer gap than just 2 weeks? It seems like you might have folks that -- if someone's worried about a lowering, a decrease in a white blood cell count, it seems like a prescriber might wait longer than 2 weeks before restarting. And also if they're worried, they would probably be checking the WBC during that time period. I just wondered if you tried a longer sort of definition of what discontinuation was and what those results might show.

DR. HAUPTMAN: I don't think we did, no.

DR. RAWLS: So do you want to invite Dr. Kane up for his final thoughts? All right. We'll do that.

DR. HAUPTMAN: Actually I want to do that. And now I'd like to invite Dr. John Kane up to wrap up our presentation by giving his clinical perspective on the issues that we've discussed so far today.

DR. KANE: Thanks very much. My own personal background in this is that I've been working continuously with Clozaril for the last 25 years, since 1977. I was fortunate to be involved in the design and to lead the study that led to the marketing of Clozaril, with enormous input from the agency and particularly Paul Lieber. So at that time we were very, very concerned on this whole issue of how to manage the potential risks associated with the

marketing of clozapine.

It's turned out that I think it's been able to be managed in a much safer manner than anything we had anticipated 10 to 15 years ago. So that was the beginning of the "no blood, no drug" policy.

The last time this issue came up I was actually sitting in Matt's chair, so I'm pleased to be back again to discuss this issue, although I think the nature of the questions have evolved from what they were in 1997.

I think it's been very clear that despite the introduction of five other so-called atypical or second generation antipsychotic drugs over the last decade, that Clozaril continues to really have a unique role in medicine and psychiatry. I think, therefore, any discussion as to how to take safe and effective advantage of Clozaril's full potential does have important public health considerations.

So to just frame some of the discussions for today, we're aware of the approvals, most recently for the treatment of recurrent suicidal behavior.

Agranulocytosis is clearly a serious disease in an affected individual, and outside of drug-treated populations it's a very rare event. It does represent a significant burden to the health care system. I should also point out that as a center that's been very actively involved in clozapine research, we've had eight cases of

agranulocytosis in my own hospital. This is a very serious possibility.

Early detection decreases risk clearly. The mortality associated with agranulocytosis is much less than we feared that it would be 10 or 15 years ago, but there certainly remains to be that risk.

"No blood, no drug," obviously.

Early detection of moderate leukopenia in order to reduce or prevent the occurrence of severe leukopenia, agranulocytosis, and death. So the question that's facing you all this morning, should the frequency of monitoring be reduced? If so, when? That is at what time point in the course of treatment. How? Should it be mandatory, should it be voluntary, et cetera, and to what frequency? Are we talking about monthly? Are we talking about something less frequent? Are we talking about discontinuing it altogether?

So clearly there are benefits of the monitoring system and I think this has been borne out over a long period of time. The monitoring system was introduced amidst a lot of controversy, as many of you will recall. Through early detection of leukopenia and/or agranulocytosis, which reduces morbidity and mortality.

Also by maintaining a non-rechallengeable database so that any individual who's actually had an

untoward effect on Clozaril can be identified and one can avoid rechallenging that patient. I should point out that the large number of people in that database, 4,500, that does not necessarily mean they have developed blood dyscrasia or agranulocytosis. They're in that category for other reasons as well. It provides a very important safety net, clearly, to those very vulnerable patients who may be receiving this medication for the treatment of psychosis or suicidal behavior.

So the disadvantages of frequent monitoring. It is inconvenient to patients and caregivers. It certainly is possible that patients who may benefit from Clozaril never start receiving the medication because of the monitoring requirement. It's also highly likely that a number of patients discontinue prematurely from a trial of Clozaril or from continued treatment with Clozaril because they are unwilling to continue with the burden of the blood monitoring.

You've already seen much of these data. It just points out that looking at agranulocytosis rates after 52 weeks in several different countries we did not see significant differences after changes in the systems. There are trends, as was pointed out in an earlier talk, in the UK. The rate essentially doubled but it was not statistically significant.

I think one of the concerns about some of the trends that we've seen -- and obviously, there's going to be more discussion about some of the data -- is that when we're talking about reductions in the apparent incidence or risk of agranulocytosis over time, or in different monitoring situations in different countries, we're hard-pressed to explain those differences. My sense is that when I find it hard to explain something that's happened in the past, it also makes me concerned that I might not be able to predict something that's going to happen in the future. That's something we have to keep in mind as we make these decisions today.

Data that support a reduction in the monitoring frequency. Certainly changes in monitoring frequency did not appear to be associated with a statistically significant increase in the rates of moderate leukopenia, severe leukopenia, or agranulocytosis. The rate of agranulocytosis has decreased by calendar year, again something that I think may be difficult for us to fully explain. And the risk of developing agranulocytosis is greatest during the first 6 months of treatment and stabilizes thereafter, and that's a very important point, obviously, which we need to continue emphasizing.

The considerations that do not or may not support a change in the monitoring frequency. We saw the

trend in the UK, essentially a doubling of the rate of agranulocytosis after 52 weeks. Again, not statistically significant, so it's a question of what can we conclude from that signal. It may diminish the ability of the system to detect moderate leukopenia in order to reduce or prevent the occurrence of severe leukopenia, agranulocytosis, and death. And again, as Dr. Gerson pointed out, sort of the cutoff point at which you're willing to take that chance is an important consideration.

It may put patients at increased safety risk in addition to what we can project, but that cannot be estimated from the existing data, and that's obviously something that you need to keep in mind as well.

So the monitoring systems work, and that's been very, very encouraging. The data don't preclude a less frequent monitoring schedule. On the other hand, the data don't rule out entirely an increase in the rate of agranulocytosis with less frequent monitoring, and obviously that will depend on to what degree one reduces the frequency.

One other thing I'd like to add is that I know many people in the advocacy community and patients and families have expressed considerable concern about the burden of monitoring, and that this can be a limiting factor in the use of Clozaril. I would just suggest from a

sort of clinical perspective that when we initiate a trial of Clozaril, the key decision point for us is often in the first 6 months in terms of evaluating whether or not the patient has benefitted sufficiently from this unusual drug to warrant continuing on the drug. That decision is usually made in the first 6 months. I don't think anyone is proposing to reduce the frequency of monitoring during the first 6 months. The question as to what happens thereafter may also be influenced by the patient and family's recognition of the very important gains that have resulted from that first 6-month trial of Clozaril, so that needs to be entered into consideration.

I would also point out in my experience -- and we've done a lot of so-called knowledge transfer as part of our NIMH intervention center related to the use of clozapine, for example -- the obstacle is not necessarily the monitoring. There are many, many other obstacles that have to do with physician attitudes, system support, et cetera. So the notion that by reducing the monitoring, we are somehow going to make Clozaril much more widely available to the community that needs it is something that we need to think very carefully about.

I think it remains an enormous challenge to the medical community to encourage more widespread utilization of clozapine or Clozaril from my perspective, and again I'm

speaking as a clinician and investigator at this point. That is a challenge to the medical community which has not been met and we need to think about ways to meet that. I'm not sure that reducing the frequency of the monitoring is the answer to that question.

Thanks very much.

DR. RAWLS: We can address the one question I think that Dr. Malone brought up about the deaths, to provide him with the data that he requested there. And Dr. Kumar and I will moderate the questions and request the appropriate individuals come to answer your question.

The first one, if we can have that slide and Dr. Kumar can address this for you.

DR. KUMAR: In the U.S. registry, we have 22 deaths so far, and when you look at the rate, it's 3.55 percent. I did indicate in the beginning of my talk that before the monitoring system was introduced, the death rate was 32 percent. So, in fact, if you look at it, 3.55 percent, and this happens to be in what year that occurred, so that reduction following monitoring, about a seven to eight times reduction in the death rate.

DR. RACOOSIN: We have a slide in our presentation that will break out the mortality by the first 6 months and the subsequent 6 months, which might address your question more directly than the calendar year.

DR. KUMAR: In fact, all of these 22 deaths, 20 deaths were during the first 6 months, and two after 6 months. And that is a part of your slide.

DR. RUDORFER: Another question?

DR. LEIBENLUFT: I'm not sure if this is something that you're going to address again later, but again just the issue about the hazard rate and what happens to the hazard rate for agran after 6 months. I mean, we know it drops after 6 months, but what happens to it then at a year, year-and-a-half, 2 years, et cetera?

DR. RAWLS: Just the hazard rate. If we can go to Vinod's slide that describes the hazard rate, the first slide, and then after 6 months, we'll use that to answer that question.

DR. KUMAR: This one I think you'll see the 39th week, this is for moderate leukopenia and here is for agranulocytosis. This is the hazard rate per 1,000 patient-years. And what I indicated during my talk also when you look at them at 15 months, it stabilizes. These are over time hazard rates. Both of these are moderate leukopenia and agranulocytosis.

Next slide. This is interesting. When you blow up the previous slide and look more closely here at what happens here. This is about 7 years, and if you draw a line here, it appears to be .3 per 1,000 patient-years,

between 7 and 8 years. This is decreasing. In fact, this point is 1 percent of the total population, about 1,600, 1,700 patients.

DR. LEIBENLUFT: Do we have any more fine-grained analysis of what happens like between 6 months and 2 years? I guess we've got a time point there. You've got one time point at 15 months. Is that right? But we don't have any real data to address, for example, is it different between 6 to 12 months than between 12 to 18, 18 to 24? Do we have any more fine-grained data?

DR. RAWLS: Do we have anything more specific just to those treatment periods for just that particular time? Like between 0.5 and 1 year, 1 year and 2 year, those sort of cuts?

DR. LEIBENLUFT: Well, really, I think 6 to 12, 12 to 18, 18 to 24 seem to be particularly germane.

DR. RAWLS: We don't have it in that sort of a cutoff. This is it.

DR. ISLAM: This is 6 months to 12 months, this is 12 months to 24 months. We do not have 18 months. And then 24 to 36 months.

DR. WANG: That's the slide that I was looking for where your most stable estimates are going to be for the .5 to 1 year. You won't have stability in other estimates. But in that, you see an actual increase in

cohort 3 relative to the others. And this is probably still an underestimate because it's not taking into account the secular decrease. I mean, this only takes into account the time since initiation of clozapine. I was curious about your original conclusions, that there isn't an apparent effect of the change in monitoring policy.

DR. ISLAM: Estimate looks higher and it can also be seen in the hazard curve, but the difference is not statistically significant.

DR. RUDORFER: Dr. Katz?

DR. KATZ: Yes, a couple of things. The only place where it looks like things get worse if you decrease the frequency of monitoring is in the UK system where the rate goes from .3 to .6 once they went to monthly from biweekly. It's not statistically significant. The p value is .27 or whatever was presented. But how many cases was that estimate based on?

DR. RAWLS: Do we have the number of cases in the UK, that .3 to .6? I do think we have that information. We can just give you those numbers.

DR. KUMAR: For 6 months, we had 2 patients, and for 0.6 we have 18 patients.

DR. KATZ: Could you just give those numbers again?

DR. KUMAR: For the 2 months monitoring, we

have 2 patients. That rate is .3 per 1,000 patient-years --

DR. RYAN: (Inaudible.)

DR. KUMAR: No. Every 2 weeks.

DR. RYAN: I'm sorry. I asked if you meant every two weeks versus 2 months? You meant a twice-a-month interval?

DR. KUMAR: Biweekly. So there we have 2 patients for .3, and we have .6, 18 patients, for monthly monitoring.

DR. RUDORFER: Dr. Leon?

DR. LEON: Yes, in the book the sponsor provided us with, the briefing materials, there is a great deal of effort put into projecting the number of new cases, if the monitoring system was changed. I haven't heard anything about that. Do you want to describe that briefly?

DR. RAWLS: What would you like to know specifically in terms of those projections?

DR. LEON: Do you have a slide that could review those for us, please? That's my first question. And after that, as we heard from Dr. Kane at the very end just now, with decreased monitoring we might expect more patients to use Clozaril, and where there were increases -- as Dr. Kane said, we might expect more patients to use Clozaril if the monitoring were decreased. Were those

possible increases in patients factored into these projections?

DR. HAUPTMAN: I'm not sure if this answers part of your question. This goes back to what was done when we first presented to this committee back in 1997, where after 6 months of treatment, there were 63 patients who had agran, and if we put it now on a per patient-year basis, that was a rate of .52 per 1,000 patient-years. At that time, we predicted that if we switched to biweekly monitoring at 6 months -- it's the middle row -- that 63 would have been 111. That would have corresponded to a rate of .92 per 1,000 patient-years, not quite a doubling of the agran rate.

Then when we look at what actually happened when we switched to biweekly monitoring -- that's the third row; that's the current system -- it turns out that what we observe, 10 out of 27,000 patient-years, gave a rate of .37, which was substantially lower than what we predicted it would be.

Although we do have -- and I think they may be in the briefing book -- predictions starting at this point of what might happen if we go to monthly, we just feel uncomfortable in putting much credibility in them because we're using essentially the same methodology that appears to have failed us so miserably back in 1997.

So it could be that there are other factors that aren't picked up by the Clozaril National Registry, or maybe the methodology we used was too simplistic, but we just don't put a great deal of faith in using the same kind of methodology in predicting the future, given what happened to us based on the past.

DR. LEON: Well, it was your future projections that I was referring to in my question. In your briefing book, it's on page 28, table 11, and these projections show an estimated number of additional cases of agran and severe leukopenia. One of my questions was, did this factor in the possibility that more patients would be taking Clozaril with decreased frequency of blood monitoring?

DR. RAWLS: Did we factor that into any of the models at all, more numbers of patients into the system.

DR. HAUPTMAN: I don't see how that would make things different -- of course, we did it on a per-patient year basis -- unless you would assume that the extra patients that --

DR. LEON: If there are more patients, there would be more patient-years. Table 11 on page 28 -- maybe I'm reading it wrong. I don't believe it's presented in patient-years. It's absolute number of patients.

DR. HAUPTMAN: Yes, that is, but I'm not sure if it's in the book. We do have this translated into a

rate per patient-years.

DR. LEON: But would it be fair to say if the number of patients who took Clozaril doubled with a decrease in blood monitoring, if that number doubled, would these numbers, projections also double?

DR. ISLAM: Table number 11 is actually saying that if the cohort 3 patients, the patients who are under current system, if they would have started, say, monthly monitoring instead of biweekly monitoring after 6 months, what would have happened to those patients by the data cutoff date. That's what it is saying.

So this part, if you just go with the number of patients, additional cases, it does not project for the future. If you want to get an interpretation for the future, if you believe the model is right, then we have to go to -- it's not included here. Then we have to convert it into the rate by person-year. So if we had an additional number of patients, if the patients doubles, then we can convert it into rate per person-year, but this table doesn't show that.

DR. RAWLS: Do you want Dr. Kane to clarify his comment for you at all?

DR. LEON: No, thanks.

DR. RUDORFER: Dr. Katz?

DR. KATZ: I have one more question. It's a

question of interpretation of the data. As has been pointed out, in the first 6 months the rate of agran actually went down significantly in cohort 3 under the new system, although the new system for the first 6 months is exactly the same as the old system. So that was unexpected. When you look at the rate of agran after 6 months, under the new compared to the old, it's the same, .4, .3, something like that.

Does the unexpected decrease, the fact that basically patients in cohort 3 are sort of starting out with a different rate of agran after 6 months compared to cohorts 1 and 2, have any effect on the interpretation of the apparent equality of the rate of agran under the new and old systems after 6 months? Is that clear?

DR. RAWLS: Not entirely.

DR. KATZ: Again, and we're going to talk about this in our presentation, but I'm just wondering, the rates after 6 months in the new and old system are the same compared to each other.

DR. RAWLS: Right.

DR. KATZ: But they're different in the first 6 months, new to old system. Does that difference in the first 6 months affect the interpretation of the observation that they actually look the same after 6 months?

DR. RAWLS: Larry, I think you mentioned

something about this before, looking at how the rates were different during the first 6 months, but did they end up being different after 6 months? The same after 6 months. So was there anything in that first 6 months that might influence why they were the same after 6 months?

DR. HAUPTMAN: One way of looking at it, since they were roughly half under the current system in the first 6 months, versus the old system, is to say that whatever led to that happening, maybe those factors were still in play after 6 months. So instead of looking at the .4 and .37 as being equal, maybe we should re-inflate the current system by that factor of 2 and actually it would be .4 versus .7 something.

We did think of it that way, but there were so many assumptions in that, again because we just couldn't figure out what was happening, what led to it being the way it is, that we think that's a little over-interpreting the data. So we're not quite sure how much credibility one would put in saying, well, if you do that, the rates almost doubled to the current system. I know we would feel uncomfortable with that kind of manipulation. We just assumed the committee would be too so we didn't try to make much of that at all.

DR. RAWLS: Another question?

DR. WEISS: I understand after 6 months it's

very hard to look because there are so few cases, and you were quoting 10 cases. And I understand from the briefing material there were actually 13 cases of agran that occurred post 6 months, although 3 of them had stopped treatment in the first 6-month period and then later developed agran. Could you show us the course of history for those 3 cases that were excluded?

DR. RAWLS: Some sort of history or narrative of those 3 cases? Do we have that, Zahur?

DR. WEISS: In other words, how long were they on treatment, how long did they stop, and when did they develop the disease?

DR. RAWLS: Do we have that, or is it something we have to get during the break?

DR. ISLAM: Just one correction is that the total agran happened after 6 months of the start of Clozaril. Of those 10, 3 had stopped drug before 6 months.

DR. WEISS: (Inaudible.)

DR. ISLAM: Not 13. 10 total. So 7 had agran with duration of treatment longer than 6 months.

DR. RAWLS: So specifically what information would be useful for you on those patients?

DR. WEISS: I'd like to see how long they were on therapy, and when they stopped, and then when they developed agran, and also if you had when they were

detected.

DR. RAWLS: When they developed agran and when they were detected and what the rate was.

DR. WEISS: With leukopenia or agran, exactly. The natural history.

DR. RUDORFER: Dr. Keck, then Dr. Leibenluft.

DR. KECK: I had a question for Dr. Kane. John, in your disadvantages of frequent monitoring slide, are you aware -- I assume you would have presented it if you were, but I'm not aware of any data that's actually looked at the impact of scheduling and monitoring on quality of life or compliance. Do we have anything empiric on that?

DR. KANE: No, I'm not, and I had the same reaction that you did, you know, why hasn't anybody collected these data, because it would be interesting. And it's something that everyone talks about but it has not been looked at systematically.

DR. KECK: Thanks.

DR. LEIBENLUFT: If I remember right, you've presented us a lot of data that compares rates under the old system and the new system where it's 0 to 6 months and then greater than 6 months. But there's only one slide where you presented it, where you broke out the 6 months to 12 months, and that was the last one that you just showed.

Right? And indeed, in that slide there was an increase under the new system. So when you lump all the data together, post 6 months, you get a decrease under the new system. But when you segregate out the 6- to 12-month period, you in fact get an increase under the new system. Is that correct?

DR. RAWLS: Yes, can you bring that slide back up, Maurice?

DR. ISLAM: Yes, as I said before, the rate apparently looks increased, but if you do the confidence interval over the rate, it doesn't show a statistical difference.

DR. LEIBENLUFT: Right, but it's still an increase. Right? Where you get into the decrease is when you lump everything together and presumably wash out whatever you had going on from 6 to 12 months. Granted, there's a wide confidence interval. The n I small I assume.

DR. HAUPTMAN: It's a little hazardous when you take sparse data and start to do fine cuts of time because, for all we know, if we did that not from 6 to 12 months but 6 to 11 months, that might show a decrease. So there's not a lot of data, and what you'll see when you do that is how those numbers fall out may be very dependent in this case on when that extra increase came from in that 6-month

interval. So you've got to view that with a grain of salt because it could be an artifact of exactly how you choose the intervals.

DR. LEIBENLUFT: Right, although given the data you showed us on hazard rates, it's not arbitrary to focus on, say, the first 18 months of treatment. You know what I'm saying? There's a reason to be concerned potentially about, as I was saying before, 6 to 12 months, 12 to 24 months. There's certainly a reason to be more concerned under 24 months. That's why I was asking the question.

It would be interesting to break it out further. I hear what you're saying, but it's not like those are 6 months that are just pulled out of the air. They are of particular interest based on the hazard rates you showed.

DR. RUDORFER: Dr. Ryan?

DR. RYAN: Do you have deaths after 6 months, U.S., UK, and Australia, from agranulocytosis, and then do you have all-cause deaths? Just the absolute number and the rates per person-year or something?

DR. RAWLS: So specifically the deaths after 6 months in the U.S., UK and --

DR. RYAN: Yes, after 6 months, after a year, U.S., UK and Australia, just the total number, and then the rates per person-year or something like that.

DR. RAWLS: Do we have it after 6 months? No, we don't have it after 6 months.

DR. RYAN: Or after a year. Do you have anything that excludes the 6 months, or could you calculate that? I mean, you told us in the U.S. there were only 2 deaths, absolute number, after 6 months.

DR. RAWLS: No, we don't have it after 6 months. Right?

DR. KUMAR: No. In Australia there were no deaths, and in the UK 0.

DR. RYAN: So it's a total of 2 deaths after 6 months across the entire data set?

DR. KUMAR: Yes.

DR. RAWLS: But we don't have per 1,000 patient-years. It's just 2.

DR. RYAN: I can divide 0 by any number you choose.

(Laughter.)

DR. RUDORFER: Dr. Malone?

DR. MALONE: This isn't entirely related to the discussion, but since Clozaril was approved for suicide, do you have any idea how many patients went on Clozaril for that indication?

DR. RAWLS: So specifically since the indication was approved in December, do we have any

information on the number of patients that are treated specifically for that indication? Within the Clozaril National Registry, I don't believe we collect that information. Right? So we would have to have a database that actually collected that information. Do we do that in any of our databases?

DR. KATZ: We're going to present a slide which shows use since it was approved for that indication -- but not for that indication. Just total use. We'll present that data.

DR. RUDORFER: I have a question. Is there any information on concomitant medications used in the national registry?

DR. RAWLS: Do you want to go back to that slide in Vinod's presentation as to what exactly we collect in the Clozaril National Registry, and Rima, if you have any other additional comments on this as well, please feel welcome to add.

MR. DODSWORTH: In fact, the CNR does not capture con meds, nor does it capture the prescription, so it would be very difficult for us to tell you how many patients have been administered Clozaril for the recurrent suicidal behavior indication. Our patient counts continue to drop on a regular basis as the patients are switched to generic clozapine, so it would be awful difficult to try

and answer that question I think with any degree of accuracy.

DR. LEIBENLUFT: Do we have any data on the patients who are temporarily discontinued and then restarted?

DR. RAWLS: Specifically what data are you interested in?

DR. LEIBENLUFT: Rates of leukopenia, agran.

DR. RAWLS: So patients that discontinued, then restarted, any rates of agran on those? Did we calculate that at all? We did not.

DR. LEIBENLUFT: Is that something we could see? Since that's one way in which our monitoring system obviously differs from UK and Australia.

DR. ISLAM: Yes, we talked about it. The problem was if a patient temporarily discontinued from Clozaril, it was highly likely now that the patients could be taking generic clozapine, so that may not be a discontinuation because they just don't report to us that the patient was switched to a generic. So those gaps in our database may not be a real gap in clozapine treatment. That's why we didn't do it.

DR. LEIBENLUFT: I guess I meant the ones who were discontinued and had low blood counts at the time they were discontinued. In other words, who fell into that

particular category in the algorithm.

DR. RAWLS: The patients who discontinued and the rate of agran for those patients that discontinued. Just the WBC at the time discontinued, but not the rate of agran is her specific question.

DR. LEIBENLUFT: The specific question is follow-up.

DR. RAWLS: Any follow-up information. No.

DR. RUDORFER: Dr. Ortiz?

DR. ORTIZ: I have a question, or I guess just an inquiry. It refers to Dr. Kumar's slide 35, which has a comment that the rate of agranulocytosis declined over time and may be related to the introduction of new antipsychotic agents. My question actually may go to Dr. Gerson. I'm just wondering if there's information or data on atypical versus the traditional antipsychotics and their effect on agranulocytosis or any other immune parameters.

DR. RAWLS: So let's pull up Dr. Kumar's slide 35. Dr. Kumar, can you address this a little bit, and then Dr. Gerson, your comments as well.

DR. KUMAR: The number of, I think, factors why we think maybe introduction of atypicals may affect the rate of agranulocytosis, one is the case whom a physician may think, in the range of a WBC count of 3000, 3500, 4000, that this may not the right patient to put on Clozaril

treatment. So before they even come to be on this treatment, they may prescribe another antipsychotic agent. That's one aspect of it. So serious patients who may, in the future, have agranulocytosis or leukopenia are not coming to the registry. That's why this factor may be important. But we do not have data, in fact. So one has to do the studies and get the data from other antipsychotics, but we do not have those data in our possession.

DR. RUDORFER: Dr. Grady-Weliky?

DR. GERSON: I just have a very brief comment.

DR. RUDORFER: Sorry, Dr. Gerson.

DR. GERSON: It was actually Dr. Racoosin who presented the data about the list of other drugs associated with agranulocytosis, and the newer antipsychotics don't show up on that list, as I understand it. So there aren't any other hidden data about other agents. And we also don't have any data on concomitant administration, except that occasional case report that comes in that I happen to review. So there are occasions in which it's possible that another drug might be associated, but for the most part that's not the case.

DR. GRADY-WELIKY: I just have another question for Dr. Gerson around the value of ANC. We know it tracks the white blood cell count, but is there any special reason

to get that as relates to management of a person going into agranulocytosis?

DR. GERSON: In the ideal world, it would be fine just to monitor the ANC, so if the ANC was performed accurately 100 percent of the time, that's the right value to get and don't worry about the WBC. For a large population monitoring program, it's a little tougher because there's more scatter in the number. That's the issue. So you're going to have more chances of it being wrong than the WBC because the WBC is an automated test.

DR. GRADY-WELIKY: Right, but does having the ANC help in terms of treatment or management?

DR. GERSON: Oh, sure, so that as their count falls, it's really the ANC you need to look at because people are at risk when the ANC is below 500. They're not at risk with whatever WBC if the ANC is above 500. So the risk issue is usually the ANC. So 500 has proven the test of time. It's a very good cutoff.

DR. RUDORFER: Dr. Katz.

DR. KATZ: Yes, I have a question I'd be interested in the company's response, but also maybe the thoughts of our epidemiologist and statistician. One could argue that when the monitoring goes from 2 weeks to 4 weeks, in the UK the rate goes up at .6, I guess, per 1,000 patient-years. In Australia, where it's always been

monthly, after a certain period of time, the rate is .5, if I remember the numbers correctly. The estimates are very similar.

Do you make anything of that? Do you think that represents truth, ultimate truth in patients with schizophrenia treated with this drug, or is that just a random similarity?

DR. RAWLS: From our viewpoints we'll have Dr. Kumar address this. This was in Dr. Kane's presentation, I think maybe the next to the last slide, and maybe, Dr. Kane, can also offer some comments on those rates as well.

DR. KUMAR: One thing that is interesting that it's not only after 1 year the rates are higher when we compare in the UK and Australia. If you look at the rates, these are rates at 52 weeks. This is the rate at every 2-week monitoring. This is monthly monitoring, these rates here. This is U.S., UK, and Australia. Here the U.S. initial system was .39 per 1,000 patient-years, and this is UK. These are after 52 weeks. So they are really comparable rates and after 2 weeks -- when we look after 52 weeks, they are initial biweekly monitoring, and it looks similar.

But the problem is that if you come back to the post 6 months or after 6 months, the other slide, the rates are much different even in the first 18 weeks, post 6

months in the UK and Australia than in U.S. So it becomes very difficult to compare.

But here, these rates are higher and one has to keep in mind that there's again the possibility that if we change our system, these rates may be higher in the U.S.

MR. DODSWORTH: But to answer your question, Russ -- and the question is, I think, do we think this is truth -- I think the answer to that is probably this is the best estimate we can come up with. I think it's probably more than just coincidence that in both the UK and Australia, when you go to 4-weekly monitoring, the numbers are relatively similar when you use similar type of criteria to identify the patients for identification in the systems. I think that's the best we can do at this point in time.

DR. WANG: I think that's the most reassuring data that if you went, for example, to a monthly monitoring system you aren't going to see some dramatic increase. The absolute values of the agran rates are within levels that seem tolerated currently under the monitoring practices here. The UK data, in particular, are reassuring because there's not this secular decrease going on over time, so you at least know those aren't potential under-estimates of what you might see in a monthly monitoring system. So they're reassuring, it seems.

DR. RYAN: While we're on that slide, I feel a bit like Woody Allen perseverating on death, but on the UK and the Australian ones, we know that there were 0 deaths. How many total n were there on who got agran under the current system in the UK and Australia combined?

DR. RAWLS: After 52 weeks, what was the n, the .59 and the .52, the total n? We'll get that for you, but while we're getting that, maybe, Dr. Kane, do you want --

DR. RYAN: And then what's the confidence interval on the death rate given agran?

DR. RAWLS: Okay, and while we're getting that maybe, Dr. Kane, do you want to offer some thoughts?

DR. KANE: I was just going to comment on confidence intervals also. Obviously, we're dealing with really small samples here, so it's hard to --

DR. RYAN: But the UK was 20-ish or something, so 0 out of 20 dying, and Australia picks up a few, it still puts a reasonable interval on what your death rate is given agran under those --

DR. KANE: Right. In terms of the proximity to the truth on this, I think it's informative but it's not everything that we'd like to know.

DR. RACOOSIN: I just want to add a point that it's a little bit hard to completely take what's observed in the UK and Australia and think about how it informs what

might occur in the U.S. because the patients in the UK and Australia are not allowed to be rechallenged once they go under 3000, whereas patients in the U.S. are, and it's hard to know.

Now, the whole point of having a non-rechallengeable database is because patients who develop clozapine-associated agran, when they are rechallenged, they get it again and they get it sooner and perhaps more severely. So we don't know if patients who are allowed to be rechallenged would get into trouble again. And with the limitations of the database, the CNR, with switchers and people coming in and out and gaps, it's hard to gather that data out of the current database.

But as far as taking .5 to .6 as being an estimate of what might occur here, we just don't know because of the fact that patients in the UK and Australia are not rechallengeable.

DR. WEISS: Actually can I ask you a question on that, or over here? When you use all the analyses for the U.S. data, once someone stops treatment and has a gap, they're excluded from any further analysis. Is that correct? So in other words, we wouldn't see people who are dropped temporarily because they had lower counts. We wouldn't see them again in the rates because they would be gone from the analysis.

DR. RAWLS: It's popping up. I just want to clarify. So what happened to those patients that were in that discontinued, did we include those in the analysis or not? Zahur.

DR. ISLAM: If we definitely know that the patient started generic, then we have excluded that data, but if we do not know whether the patient started generic or not, but we have the WBC count in our record after the gap, we have included those.

DR. WEISS: How long a gap did you allow before you excluded people, period, from the study?

DR. ISLAM: For this analysis, we didn't exclude any patient data due to the gap. The only way we excluded it, if we definitely knew that the patient started generic after the gap.

DR. RUDORFER: I'd like to thank everyone for a stimulating discussion. We'll have a lot more time for further questions and discussion, but now I'd like to preserve the sanctity of the break.

(Laughter.)

DR. RUDORFER: We'll reconvene at exactly 10:50. Thank you.

DR. RUDORFER: We're going to resume with the second part of our morning session. We'll turn now back to the FDA for a presentation of selected safety data. Dr.

Tarek Hammad will speak.

DR. HAMMAD: Good morning everyone. I will share with you this morning some data from the generic drugs, some of the registry data, and then I will raise a few issues under what are entitled "Are we seeing the full picture" to draw your attention to some pertinent issues in the safety data. Then Dr. Racoosin will present the agran rate stratified by the monitoring frequency after 6 months in the U.S. and after 1 year in the UK, just to get a feel of how it looks like under different monitoring systems.

First, the generic data. Data was collected sometime after 1997 up to 2001, actually September 2001, and we chose this cutoff level to make it compatible with the so-called current system in the U.S. system. The data was provided by two manufacturers.

Because the risk is highest at the first 6 months, we only confined the analysis to the new patients, but because of that, we only included about 10 to 20 percent of patients, of the available records actually. So the result was that we had a very small number of person-years, about 1,000 person-years before 6 months and about 3,000 person-years after 6 months. That's across the two databases pooled together.

The first observation that we had was that the demographics were reasonably similar between the generic

databases and the U.S. system. So the results are not confounded by some differences in the demographics.

This graph displays the rates of the moderate leukopenia, severe leukopenia, agran in three cohorts. This is the U.S. initial and current system, then the generic. Now, recall that generic time line is supposed to be comparable to the current system, but the rates here are not consistent. It looks slightly higher, but only the agran actually -- the confidence interval did not overlap, but in these two, the confidence interval overlapped.

The other issue also is the fact that these are based on a very small number of person-years. So have that in mind when you are evaluating these numbers.

This graph shows the same parameters after 6 months, the initial, the current, and the generic databases. As you can see, the numbers look more or less the same in all three parameters. So there are no surprises here.

Now, moving to the next point that I will talk about, these graphs were already presented by the sponsor and they show the rates of the moderate leukopenia, severe leukopenia, and agran. I apologize. For some reason, the title here did not show up. But this is to remind you that there was a substantial drop especially in the severe leukopenia and the agran in the 6 months when everything

was the same. And the reasons we don't really understand, but the point I'm trying to make is -- I think that Dr. Katz already made this point -- that because there is an apparent substantial drop here, these numbers are not comparable, and the sponsor already commented on that.

Now, the second component in what we think why you might not be seeing the full picture is whether we are capturing all the patients with moderate leukopenia in a timely fashion. This actually came up when we were reviewing the UK data. We realized that the UK system uses both the white blood count and the ANC systematically, but not the U.S. I mean, if you think of it in theory, if you are screening for cases and you use two tests in parallel, your sensitivity will be more likely to be higher than if you only use one test. Of course, these are not two independent tests, but still the goal here is to capture the potentially vulnerable patients early on before they deteriorate.

So the premise of the issue with using only a white blood count is that patients with low ANC preceding low white blood count are detected later in a system that follows only white blood count, like the U.S. So the question is, is the U.S. sensitive enough as it is or not? This actually might explain the apparent higher rate in the UK. I think most of the issues I'm raising now were

already raised, but of course, in the preparation, I was not sure what would be raised and what would not be raised.

For comparison reasons, the sponsor stratified the rates of agran by the first period, 0 to 18, 19 to 52, and more than 52. They stratified the U.S. data also to conform with the way the UK data is analyzed. As you can see, this is just to show you the much higher rates in the UK versus the U.S. system, and this is true for the moderate leukopenia and for agran and for the severe leukopenia also. This is just an example to show that the rates are higher. This really makes the comparison across systems very hard to do.

But one piece of information that I thought might be complementary here is to see how the mortality rates stack up in different systems, again stratified by the way the UK system was collected. As you can see here, although there are apparently higher rates of agran or moderate leukopenia and everything in the first period, the mortality in the UK is not that much higher than the initial cohort in the U.S. There is apparently lower mortality here in the current U.S., but just remember that you might not be seeing the full picture.

The other observation here is that although the UK system after a year has moved to the monthly schedule, the mortality is not much higher than the U.S. system. So

this is actually the ultimate outcome, how much are we protecting patients. This outcome might not be affected as much by the definition of where you cut off or if you use ANC and WBC or not.

Now, the third section Dr. Racoosin will talk about.

DR. RACOOSIN: We wanted to just raise this issue because the way that the recommendation is laid out is that in the U.S. after 6 months, patients have been monitored biweekly in the current system, and in the UK after a year, they're monitored monthly. But in actuality the numbers that we see are an averaging of the different frequencies, so that even after 6 months in the U.S., there's some proportion of patients who are still being monitored weekly, and that's probably, we think, for two reasons.

One is they've had some instability in their white blood cell count. They've gone into the moderate leukopenia. They have to be temporarily discontinued, and then they have to be restarted on their weekly. So even though they may have been in the system for more than 6 months, they're being monitored weekly.

The other thing is we have some suggestion that either by patient preference or by physician preference, that for safety, patients continue to get weekly monitoring

even when there's a recommendation for biweekly.

And then the same thing is going on in the UK where after a year, there's a mix of patients. There's some heterogeneity. Some patients are being monitored weekly, some biweekly, and some monthly. And if you break out the agran rates by those different actual monitoring frequencies, there are some interesting observations.

This is in the U.S. after 6 months. If you look at everybody, there are about 27,000 person-years of exposure and a total number of cases of moderate leukopenia of 214, and that comes out to a rate of about 8 per 1,000 person-years, which we've already seen presented. If you look at the people being monitored biweekly, they're accounting for about 93 percent or so of the total person-years, and if you look at the rate in that population, it's close to what the overall rate is. But if you look in the people being monitored weekly, it's a small proportion. It's only about 7 percent of the total person-years, but within that group, there's a substantially higher rate. This wouldn't be surprising if the people being monitored weekly are less stable hematologically.

And you see a similar pattern for the agran where the overall rate of 0.4 is -- again, this is about 93 percent of the patients. The rate is 0.2, and it's substantially higher, 3.3, in patients who are being

monitored weekly.

And then in the UK, we see a similar pattern. There are about 31,000 person-years of exposure, and for moderate leukopenia, 228 cases, accounts for a rate of about 6.5 per 1,000 person-years and about 85 percent of the exposures in patients being monitored monthly. And they have the lowest rate of moderate leukopenia and of agran. If you look at those being monitored weekly, they have a much, much higher rate. Again, this is a very small proportion, maybe 3 percent or so, of the total exposure, but they have the highest rate. And then the every 2 weeks is intermediate to that, but closer to the monthly. So I just really want to keep in mind the fact that when you see these rates, that they're actually a summary of some heterogeneity that's observed with the different monitoring schedules within that after-1-year period.

Then finally, we thought it was just interesting to note that -- and this is in the UK -- if you identify the group of patients who are now caught at moderate leukopenia, that for those being monitored monthly and those being monitored every 2 weeks, they go on to agran at a similar rate. One possibility is that patients who are being monitored monthly, when they are caught in moderate leukopenia, they are further along. So although the understanding would be that these patients had been

more hematologically stable, those being monitored monthly than those being monitored every other week, or biweekly, that once you get into moderate leukopenia, you're as likely to go on to agran.

That concludes the points. Oh, I'm sorry. There was one additional point that came up earlier in the questions, and that was since the approval of the suicidality indication, there was a question as to what had happened to prescribing or new users. These are from the innovator and then from the generics. The approval came during December of 2002, towards the end, so that's included in the 4 months before the approval. These are the 4 months after. We don't see a lot of difference in those 4 months before and 4 months after. But the main issue is it's still early and there's not much time to really observe a trend in one direction or the other. But since there was a question about it, we thought we would show the data.

DR. RUDORFER: We're open to questions from the committee to the FDA.

I've been asked to remind people, please state your name, just for the sake of the transcription. Thanks.

We'll start with Dr. Leon.

DR. LEON: Could you go back two or three slides please from the end?

DR. RACOOSIN: In this last section?

DR. LEON: Right, when you broke them down by 1 week, 2 weeks, and 4 weeks.

DR. RACOOSIN: The UK?

DR. LEON: Right. Or no, actually the U.S. Either one we could use.

The naive observer of this slide might say more frequent monitoring leads to higher rates of problems. So, of course, we saw a slide earlier this morning that said that a bad test early on you can't -- I forgot exactly how that was defined, but if you had low white blood cell counts early on, you couldn't switch to biweekly. So I assume they make up a great number those in the top row.

But to get at the question that we've been asked to addressed, what if you only looked at every other observation, every other piece of data from the people in the top row? How many cases of moderate leukopenia or agran would be missed?

And likewise, in the next slide where you even go out 4 weeks, what would happen here if we looked at every other or every fourth piece of data from those who really have four observations per month? How many cases would we lose by only looking at what I thought was proposed, but apparently now we're just considering it hasn't been proposed to switch to 4 weeks? Have you looked

at that?

DR. RACOOSIN: No. We have not had access to the actual -- we worked from summary data and requested data. And I don't know if the sponsor has looked into that. No.

DR. RYAN: But they would have changed the treatment at that point. If you do it every week and you got a low value, you stop the Clozaril. So one 3 weeks later wouldn't be representative of what happened if you hadn't looked. So I'm not completely following the value of that analysis.

DR. LEON: Another point. The slide you showed about the generic, compared to the slides we saw earlier today where it was based on hundreds of thousands of person-years, here we had, I believe it was --

DR. RACOOSIN: For the first 6 months?

DR. LEON: The slide before that.

DR. RACOOSIN: There's no question that these are small numbers.

DR. LEON: Let me ask my question. Could you go to the slide before that please?

DR. RACOOSIN: This is the first 6 months.

DR. LEON: There, the second-to-the-last bullet. It says 1,000 patient-years over 6 months. Although they're relatively small numbers, that is 2,000

patients. Is that correct? If this is 6 months per patient, we'd need 2,000 patients to get 1,000 person-years. Or am I reading this --

DR. RACOOSIN: Yes.

DR. LEON: So it is 2,000. It's not a trivial number.

DR. RACOOSIN: Right, but it's much less stable than the data from the innovator.

DR. RUDORFER: Other questions for the FDA? Dr. Malone?

DR. MALONE: I wanted to ask, there is a difference in the definition of becoming non-rechallengeable in the United States and in the UK. From what was said, I guess once you get agranulocytosis, you have a high risk of getting it again. I think that the U.S. definition is if you get moderate, you can be rechallenged, but in the other countries you can't.

What led to that decision in having a different definition of non-rechallengeable? Is it that moderate doesn't really predict so well what's going to happen later? How did that ever come about?

DR. RACOOSIN: It appears to be before the time of everyone from the agency here. So I apologize for not having an answer to a very good question. It certainly has occurred to us as well, but I don't think that we can speak

to that specifically. That doesn't mean that it needs to stay this way, and we certainly could consider taking the approach that other countries have. But I can't speak right now to why that decision was made.

DR. WEISS: I have a question on the case finding for agranulocytosis. I understand that you get the leukopenia cases directly from the registry through the white blood cell counts for the U.S. But the agranulocytosis is not so clear cut how you identify cases. Could you explain how they're identified?

DR. RACOOSIN: I'm going to defer that to the sponsor.

DR. RAWLS: We just need to clarify your question. How do we identify patients that develop agranulocytosis?

DR. WEISS: Right, because it seems like it's a totally different process from the leukopenia which you get directly from your registry, and I'm concerned with what proportion of cases are actually identified and how.

DR. RAWLS: So if you want to show the one slide in Vinod's presentation, the definition for agran where we have the WBC count and the ANC. The WBC would come from the Clozaril National Registry. Some patients who just have ANC count may come in to us through our safety and epidemiology group. So they may make up that

proportion of patients.

So you see there agran is defined as WBC less 1000 or ANC less than 500. Those ANC ones could be from patients that were reported to us through out CS&E Medwatch forms.

DR. WEISS: I guess my question revolved around requirements reporting and other thing. So I can see moderate leukopenia you identify through the registry, but what happens when someone develops leukopenia, stops taking the medication, so they're not necessarily reporting back to you, but they could go on to develop agranulocytosis? Are there any reporting requirements or any estimates of the cases that you do miss?

DR. RAWLS: So just to clarify, a patient that develops moderate leukopenia that gets discontinued, but then they're still being treated, that they would go on to develop agran, are they in our system? How do we find out if they are in there?

DR. WEISS: Yes.

DR. RAWLS: I think maybe Zahur can answer this and also, Rima, maybe you can just talk about that as well.

DR. ISLAM: According to the PI, after the patient reaches moderate leukopenia, the patient is supposed to have daily WBC counts and differential count too. So we do get their WBC records. The ANC record --

the physician gets it but it's not recorded in the registry, but if the patient gets agranulocytosis, then through the Medwatch, they report that this patient has developed agranulocytosis and this was the ANC count. Then from our medical affairs group, we call and confirm it.

DR. WEISS: But I understand that that's not a requirement for the doctors to report that a patient in the registry has developed agranulocytosis. Is that correct?

DR. RAWLS: No. If that's a severe adverse event, that is reported to us through our Medwatch. Then it's picked up that way and then it's entered into our CNR.

DR. WEISS: If the doctor chooses to report it.

DR. RAWLS: He has to.

MR. DODSWORTH: The way the CNR works is if a call comes in where the white count is low, it comes into the CNR which is manned by a staff of professionals. That call is immediately referred to our medical affairs group for follow-up with the physician and for follow-up on the patient. Then under the agency's normal reporting guidelines for reporting serious unlabeled adverse events or serious labeled adverse events in the annual report to the NDA on a regular basis, these reports go into the file. But each and every patient where we get a call from a physician on a low white count, it's immediately transferred to one of our medical staff in the medical

safety and epidemiology group within Novartis.

I don't know if that answers your question or not, but that's how we capture the individual patients.

DR. WEISS: I guess my question is do you have rates on follow-up? Do you follow up 100 percent of the patients with low count to see what their sequela is?

DR. RAWLS: I guess your concern is that we may be missing certain patients in our database.

DR. WEISS: Absolutely.

DR. RAWLS: Do you want to clarify me? Because I guess you're concerned that if someone is developing agran, that they don't get into the Clozaril National Registry or the non-rechallengeable database. I think through our mechanism they do not.

DR. RUDORFER: Please give your name.

MS. VAKIL: Yes. My name is Rima Vakil from the Clozaril National Registry, U.S. of course.

I just want to understand your question. You said if the low WBC was reported to the CNR, do we follow up on a regular basis, and the answer is yes. As soon as the WBC count was reported and if it was less than 2000, we would follow up with the physician, the pharmacy to make sure and confirm the WBC was, in fact, accurate or if it was an error.

DR. RAWLS: And as soon as it becomes agran --

MS. VAKIL: We would notify medical services and we would change the patient's status to non-rechallengeable.

DR. WEISS: I guess my follow-up question is what proportion do you have definitive whether they developed or whether they recovered.

MS. VAKIL: We don't follow up on whether the patients have recovered or not. Post WBCs, if they come in, we would enter those.

DR. RAWLS: I guess we could look at the number of patients that developed moderate leukopenia and whether or not then they developed agran or they just returned to normal. It would be one way maybe to look at that in terms of a recovery or a treatment. Do you think that would answer the question? I think we have that information. Those who develop moderate leukopenia and then go on to agran. Those who don't go on to agran, then obviously must have recovered.

DR. WEISS: Or they could be missing. And that's my question. Do you have any idea of what you're missing?

DR. RAWLS: Well, if they're missing, it's missing because they didn't develop agran. They're not missing because they developed agran and we didn't catch it. So if it's missing, it's because they became normal.

DR. KATZ: How long do you follow them to decide that it hasn't developed into agran?

DR. RAWLS: Do we have a specific rule as to how long we follow them or just until --

MS. VAKIL: Once we change the patient's status, we don't follow up --

DR. ISLAM: If the WBC goes below 3000, moderate leukopenia, then the PI-mandated follow-up is 4 weeks, but if the patient's WBC goes below the agran thing, they are recommended to continue, do differential count, and provide us the data. But that part gets voluntary then. Until the patient gets better, we are supposed to get the WBC count that we get until the normal range.

DR. KATZ: What if they have severe leukopenia but not agran and they're discontinued? I'm still not exactly sure how you find out that they have agran, how that information makes its way into the system. Presumably you have affirmative outreach to find out what those results are, if they have agran.

Suppose they have severe leukopenia when they are discontinued. What's the duration of follow-up before you decide that it hasn't become agran? Is there some mandated minimum amount of time that those patients are followed?

DR. RAWLS: So there's no mandate. It's

patient-specific. We follow them until either they recover. Now they're going to be continued on the therapy, or if they develop agran, now they go into the non-rechallengeable database.

DR. KATZ: So you know for essentially all patients who develop, let's say, severe leukopenia that either they recover or they go on to agran.

DR. RAWLS: Right.

DR. KATZ: And you have essentially complete follow-up on that cohort of patients.

DR. RAWLS: Exactly, in moderate leukopenia as well.

DR. KATZ: I was going to say similarly for moderate leukopenia as well.

DR. RAWLS: Right.

DR. KATZ: So in your view, you have complete capture of patients who get agran essentially.

DR. ISLAM: We believe the agran reports are correct, but if you check the WBC, like suppose a patient develops severe leukopenia on day 70 and they reported agran on day 90, theoretically we are supposed to have WBC between the days 70 and 90. In most of the cases, we have but not always.

DR. RUDORFER: Ms. Bronstein?

MS. BRONSTEIN: I'd like to change the subject

back to the generics.

I'm trying to determine whether the sample -- I know the sample size is small, but do you feel that the sample size is representative enough to tell us that the rest of the data we're looking at from the sponsor is really representative of this issue over time? Do you understand my question?

DR. RACOOSIN: I'm not sure that I do, so I'll answer your question and if it doesn't hit the mark, you'll let me know.

MS. BRONSTEIN: Thank you.

DR. RACOOSIN: Because our analysis of the generics data is limited to 10 to 20 percent of the patients, it's very small. It's 1,000 person-years compared to tens of thousands to hundreds of thousands of person-years. So it's an unstable estimate. We have to judge it for what it is. Maybe that's not what you're asking. You're saying do we believe what the generics data is and do we believe what the innovator data is and that they're somewhat discordant?

MS. BRONSTEIN: Or are they somewhat similar.

DR. KATZ: Tarek, the slide that just went off, I don't know if this will help clarify the question or the answer, but you said that the demographics are similar. Maybe you could talk about what's included in the

demographics. Are there disease measures or is it just age, race --

DR. HAMMAD: Just age and race.

DR. KATZ: Somebody asked this question earlier about what the clinical status is. There's no clinical information.

DR. HAMMAD: No.

DR. KATZ: So we don't know if those patients are the same as the patients who --

DR. HAMMAD: Yes. If you mean to have some kind of representation for the overall new patients, it's really hard to say with just 10 percent of the whole records. I think that's what Julie was saying. It's very hard to say for sure.

That's why we draw this confidence interval, and they're usually much wider. They actually affect our confidence in the data, how confident we are in our estimates. And they overlap with the current estimates and with the initial system. So in a sense to the best of what we see, they do represent the same kind of trend, except where the agran is slightly higher and the confidence interval is not overlapping.

DR. RUDORFER: Dr. Leon.

DR. LEON: With these preliminary data, might you say that the more vulnerable people are switching to

generic?

DR. HAMMAD: We had actually that thought before, and we tried to find information to speak to this particular issue. But we couldn't. Unfortunately, the system is not designed to collect such clinical information. There's no way you can know if perhaps more severe patients are switching over to perhaps --

DR. LEON: Well, just based on what's on this slide, it looks like the rates are higher in those who switched to generic.

DR. HAMMAD: These are new patients.

DR. LEON: Oh, they're new patients.

DR. HAMMAD: Yes.

DR. WANG: But it still raises the possibility, not that the most severe or recalcitrant patients or noncompliant patients are being switched, but just in general are patients being started on clozapine, whether generic or branded -- are they more recalcitrant now than previous. Your data are potentially suggestive of that or also consistent with the possibility that patients who are now put on clozapine are just more non-adherent over time.

DR. HAMMAD: The assumption here is that this the real data. The problem with the very wide confidence interval is you're not sure where your rate estimate fits within this -- actually we don't have the estimates. I'm

sorry. But these actually overlap. These three groups overlapped. But only the agran did not have an overlapping confidence interval. So the assumption on the differences between the populations is based on the fact that we are observing different rates, but we are not or we might not be observing different rates.

DR. WANG: I'm sorry. I wasn't referring to this slide. I was referring to your previous one where you showed differences in rates over the different monitoring strategies which show a secular decrease essentially, as we saw in the sponsor's data. And I was just curious, did you have any additional sort of insights or thoughts for the explanation, and do you have any data -- it sounds like you don't -- to suggest that maybe it's an issue of more recalcitrant patients or more non-adherent patients over time getting put on generic clozapine?

DR. HAMMAD: I don't think we have any data to speak to this.

DR. RUDORFER: Right. It also occurred to me -- and I don't know if we have these data either -- whether patients in the public sector are more likely to be put on clozapine with a generic form available.

Dr. Weiss?

DR. WEISS: I'm just concerned that we're putting too much emphasis on confidence intervals, because

what I'm understanding is we have everybody, that this is a required registry and there's 100 percent case finding is what I'm hearing. So I would say that just statistically speaking, a difference is a true difference because they're actual rates. Especially with the small numbers, I don't think we should put so much emphasis on whether or not the confidence intervals overlap.

DR. HAMMAD: They are everybody, but they are not everybody who will ever start on clozapine. So we are still sampling the new patients that will start on clozapine sometime in the future also. So this is still a sample of the new patients that will be put on clozapine. That's why we need to put in consideration the confidence interval.

DR. WEISS: I'm sorry. You're telling me that this is a sample or is this everybody?

DR. HAMMAD: No. It's everybody. In a sense we can consider it a sample of the new patients that will be put in the future, sort of predicted.

DR. RACOOSIN: It should just still be pointed out, though, that there's a segment of patients that we don't know about and those are for people who are switched during the first 6 months, either in one direction or the other. We don't know. We have not been able to capture those in a database because of the way these things are set

up. But we don't know where they would fall in this range, but that is a group that's not identified or identifiable.

DR. RUDORFER: So for those patients, if someone, say, switched from brand Clozaril to generic, their 6-month clock would just start all over again when they switched?

DR. RACOOSIN: I think as long as it's been observed that they have been on brand, that they wouldn't have to restart their clock, as long as there's evidence that they've been on the drug. There seemed to be some flagging systems that identify patients that have been switched.

DR. RUDORFER: Because I had gotten the impression that other than flagging patients who should be on the non-rechallengeable list, that there didn't seem to be communication across the registries.

DR. RACOOSIN: It seems to be somewhat variable based on the pharmacist that is dispensing.

DR. RUDORFER: Other questions from the committee for the FDA? Dr. Ryan?

DR. RYAN: I think I'm asking a question that has no answer, but does anybody have any data that would contribute toward the question of how many suicides or other deaths we'll prevent if we use this compound more widely in this population? I mean, what's the up side of

doing a change which might make it more widely used, as well as the down side? We're obviously talking about the down side.

DR. RACOOSIN: That's something that we have not addressed. This, as we are presenting this, is not the benefit and risk assessment. This is a risk assessment. So I can't speak to that. I don't know whether the sponsor has a particular opinion on that. I think that was part of what Dr. Kane was getting at.

DR. KANE: I think it's a very tough question. It's obviously extremely important. The number needed to treat to prevent one suicide attempt was 13 and that was obviously against a specific comparator. To sort of put that in the context of this I think is hard. There are other benefits to Clozaril in treatment refractory patients and sort of how you quantitate those and put a value on those is very hard to say. To me, we should be doing everything we can to make this drug more widely available. Whether changing the monitoring is the answer to that, I'm not sure.

DR. RYAN: I guess in for a penny, in for a pound. Do we have any good estimate on the mortality rates with the other atypicals, the all-in mortality rates from diabetes and from whatever? Is that available from the FDA or from industry?

DR. KANE: I don't. I think that's an evolving issue because I think the mortality from diabetes and cardiovascular side effects is going to be a very long-term question. We're just beginning to get some sense of that.

DR. RACOOSIN: In general, outside of a clinical trial, the way that we make some understanding of mortality rates would be through spontaneous reporting data. We don't have long-term control data or even ways of making that comparison. Spontaneous reporting is notoriously hard to make sense out of. There's under-reporting. There's variable reporting across different drugs, across indications. We certainly don't have the data to speak to that, how it compares across the class.

DR. RUDORFER: Other questions from the committee?

DR. WANG: Just to follow up on Dr. Ryan's comment, does the sponsor have any plans to conduct a decision analysis similar to, I think it was, Jong? It was an Asian name. A decision analysis that was done around the time of the last clozapine monitoring change. It's been a while since I saw it, but is there a similar plan to conduct such an analysis?

DR. RAWLS: Could you clarify what you mean by decision analysis?

DR. WANG: It was essentially trying to take

into account both the benefits and the potential risks of different monitoring strategies.

DR. RAWLS: Through a particular study? No, we are not engaged in such an activity, but maybe, Dr. Kane, you know some evidence.

DR. KANE: No. I was just going to say it was very sobering to look at the projections that were presented this morning in terms of what we anticipated would happen when we met in 1997 and how wrong we were and that we don't really understand what accounted for that. So at this point in time, I'd be hard-pressed to pick a particular model that we'd have enormous confidence in.

DR. RUDORFER: Any other questions from the committee?

(No response.)

DR. RUDORFER: If not, then I think we'll pause for now and look towards an early lunch. We're scheduled to reconvene with the open public meeting at 1 o'clock, and we'll reconvene at that time. Thank you.

(Whereupon, at 11:38 a.m., the committee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:01 p.m.)

DR. RUDORFER: Good afternoon. Welcome to the continuation of the Psychopharmacologic Drugs Advisory Committee meeting.

Looking ahead a little bit, we had left a few issues on the table. There were several questions that the committee raised that Novartis has been looking into. We will begin our discussion in a little while with the answers to those questions.

But first, it's now time for the open public hearing portion of the meeting. As was brought out late in our morning session, today we're focusing on a very important risk-related issue in the use of clozapine, but as we've been hearing, the decision to prescribe and to use this medication is based on a more complex consideration that we usually lump under the rubric of the benefit-to-risk ratio. Often the committee is very helpfully informed about the larger perspective by the open public hearing speakers. So I'm pleased that today we have two individuals who will address us.

First is Dr. Lynn Goldman.

DR. GOLDMAN: Good afternoon. I'd like to start by thanking you for this opportunity to address you today. I'm going to talk to you about this issue from a

perspective of my family. These are the members of my family who have been working on this issue over the last couple of years, doing so out of concern for one of my brothers. I'm fortunate to have a number of brothers, a couple of whom are on this slide, I think one of whom was at an earlier one of these meetings, David Goldman; my brother, Daniel Goldman, who is an epidemiologist; my father, Armond Goldman, who is an immunologist and Professor Emeritus at the University of Texas.

I happen to be a professor at the Johns Hopkins Bloomberg School of Public Health. I'm a pediatrician and an epidemiologist and also a former regulator. I worked at EPA for a number of years.

I should say at the outset that we have no financial associations with any drug, device, or biologic related to this issue, and I'm here on my own nickel. I did at one time in my life regulate Novartis, but that's about the only association.

What I'm going to present here is first our view as a family of the risks of agranulocytosis that are associated with various monitoring options, some questions that we have about the way neutropenia has been defined in this context, other risks and benefits that we feel should be considered in this kind of a decision, and what we recommend in terms of a monthly monitoring program.

We've looked very carefully at the registry data, which was made available to us on Thursday when it was posted for the public. I don't need to belabor the point except that, of course, it's very obvious that the majority of the risk is in the first 6 months of treatment, and after 6 months, you see less of what is called moderate leukopenia or agranulocytosis in the monitoring program. We also see that there is still a negligible risk after that first 6 months, that this is not a risk-free drug. Few drugs are risk-free.

We also read with great interest the theoretical model that was presented by Novartis in the materials in terms of looking at the rate of decline of leukocytes over time in order to project what would happen with alternative monitoring schemes.

I think you're all probably familiar with what the U.S. requirements look like and also the requirements in the UK and Australia.

And by the way, our slides are available at your desk, and we also have a brief paper that kind of summarizes the talk, but in somewhat more detail than what I'm doing today.

It is interesting actually. One of my "less than" symbols was translated into a Spanish exclamation point, upside down, by the computer.

(Laughter.)

DR. GOLDMAN: I don't know that happened.

But there are some slight differences between the requirements in the U.S. and the UK and Australia which are important in terms of the later points that I'm going to make.

So the question, of course, that we're very interested in is what are the hazards of agranulocytosis after 6 months of treatment under these various regimes that might be proposed. What was presented to us by Novartis is that in three different cohorts that have been evaluated, that answer has been slightly different, whether you're looking at the first, second, or the third cohort. Interestingly, the hazard of agranulocytosis has been lowest for the third cohort, which had less frequent monitoring, and I don't really know that we have any explanation for why that might be the case.

The projection for monthly monitoring, based on the model, looking at the rate of decline of leukocytes among patients who have developed agranulocytosis is fairly high and kind of scary, but we see the actual experience in the UK is that you wouldn't see that large of an increase, but you do see an increase in the UK from about .3 per 1,000 person-years to about .6 per 1,000 person-years. From our perspective, this is a rather low risk. However,

it is a greater risk, and I think that's one of the cruxes of the issues to look at.

So we do conclude, from looking at the data, that one, we think the actual data from the UK and Australia are better than the model. In fact, there's probably something wrong with using a linear extrapolation. This would be what I would guess, is that it's not a correct model. Rather, probably we would expect to see an increase from about .3 to .6 cases of agranulocytosis per 1,000 person-years if you had monthly monitoring.

We don't know what to make about the data on moderate leukopenia. We medically don't really recognize that as a diagnosis, frankly. It's a laboratory finding that probably appropriately is being used to trigger risk management guidelines, but it's something that can occur very commonly as a finding. For some reason in the UK and Australia, you see a lower rate of moderate leukopenia with decreased monitoring, but we think this is probably spurious, and after hearing the presentations earlier today, I would say it probably definitely is spurious.

Hematologic considerations. Certainly the definitions that are being used for agranulocytosis and leukopenia don't correspond with those views by hematologists and leads to some confusion and probably an overestimation of the risks. This is probably an area that

could be improved upon.

Leukopenia itself, of course, could be due to lymphopenia, reduced lymphocytes, not just reduced neutrophils, and there are many things that can cause you to have reduced lymphocytes. This is something that's probably worth also considering.

We looked carefully through the medical literature and also the data that were presented late last week by the FDA on the web site for cases of late onset neutropenia that might be of concern. Do we have evidence that there's much going on down the line after years of treatment? Quite honestly, there isn't much that we could find.

We found a case of a 41-year-old male who had received clozapine for 89 months, did develop severe neutropenia, but he had also been placed on risperidone which is, of course, a related agent.

A 28-year-old male with clozapine for 3 years was also being treated with human recombinant interferon-alpha for chronic hepatitis C. There are literature reports that this therapy, the interferon-alpha, can be associated with neutropenia.

And then in the report from the FDA late last week, one of the deaths was a 35-year-old female who had received clozapine off and on for 5 years. I'm not really

sure that this actually is a case, looking at the documentation that was provided, because it didn't seem to be well documented. Her compliance with the drug was not well documented. However, she did develop agranulocytosis. She did die, the cause of death not reported. And she also was on quetiapine -- and I hope I'm pronouncing that drug correctly -- which is another related drug.

I would say in all three of these cases, it's not clear that clozapine even caused the neutropenias. One of the things that is kind of frustrating, from the standpoint of family members concerned about this, is the quality of the data and the ability to really see that there are clear diagnoses in these data.

So why would we want to see a family member continue on clozapine? Well, first, if you have a member of your family who has improved significantly, does not have side effects, it's unclear whether other drugs may be efficacious, which it certainly is, and that the newer drugs may also have side effects, maybe neutropenia, maybe side effects yet to be identified, also of course, that inadequate or inappropriate treatment for schizophrenia is itself highly hazardous. And I think it's important not to forget that this is a disease that has a very high mortality rate. It's extremely risky for people who have it. Treatment is so important for the survival of people

who have this disease.

We did look in the FDA post-marketing data, and we do note that there are numerous reports of neutropenias with various of these atypical antipsychotic drugs, no information about incidence. That 3 percent rate is the initial incidence of neutropenia that occurred in the first cohort with clozapine. We don't see any incidence data. There's no way for us to compute incidence data because we don't know how many of these patient-years these neutropenias relate to. But this is to say that the alternatives are not risk-free.

Monitoring is costly, and I have to say that these figures are conservative. Probably the costs are much higher than this. But I think it's another thing that needs to be considered, that this is not a free good, that you're talking about venipuncture, CBCs, doctor visits, and the indirect costs to patients and their families for having to, every 2 weeks, take the amount of time, the hours that are required in order to continue your medication.

But the non-monetary costs are also costly. Damage to peripheral veins. We're aware of people who have gone off of the drug because of lack of access for being able to get blood. Loss from work and other activities. Limitation upon the freedom to travel. This is one of the

things that has been most frustrating for our family for my brother, the fact that you can't be away for more than 2 weeks at a time. Now, none of us have to live our lives that way. It is very, very difficult. And the stigmatization that is associated with this disease is enormous, and I would submit that the monitoring contributes to that.

I believe that this does discourage compliance, although I have to say in the case of my family member that he does not complain. He does comply. He is appreciative that I'm here doing this today. He would like to have a less frequent blood draw and he's quite cognizant of all of these issues that we've been discussing. But he will continue to comply regardless of the decision that's made.

So what we're proposing is the following schedule -- between 0 and 6 months, weekly; 6 to 12, every 2 weeks; greater than 12, monthly -- of course, with the proviso that the patient is hematologically stable and is not developing neutropenia and, of course, that the physician could exercise medical judgment and monitor more frequently if needed. I think that is an important point to make. It's certainly true in the UK and Australia, and we would hate to see a situation where doctors would not be compensated for more frequent monitoring if they felt it were medically indicated or that, for some reason, the

patient required it.

In conclusion, revised monitoring would certainly decrease damage to veins, the trauma from procedures, the stigmatization, loss of time from work or education, and overall costs to patients, their families, and the health care system, increase the freedom to travel, job and school opportunities, and a sense of independence.

Some questions that we wanted to pose, one being whether there could be some benefit from some expert hematologists and immunologists regarding definitions and mechanisms of drug-induced neutropenia. And by mechanisms, what we mean is that most likely the risks are not equal for everybody, that there are probably subsets of patients who are more at risk for this side effect than others. This is probably an area that would be very fruitful for further research and exploration. It could possibly be in the future that you could identify those individuals who are susceptible.

Also, are there data on the risks of significant neutropenias in patients who take other antipsychotic agents for many years? I don't think that the data are clear on that.

In summary, we believe our proposal is in keeping with the 1998 decision by this advisory committee, that it would not hamper the identification of neutropenias

during the period of greatest risk, that there is a large increase in risk that the theoretical calculations would point to, but that we think that the experience supports that it's a smaller change and that overall the benefit to patients, families, and the health care system outweighs that risk.

The concludes my presentation.

DR. RUDORFER: Thank you very much, Dr. Goldman.

Our next public hearing speaker is Maureen Schweers who will be addressing us on behalf of the National Alliance for the Mentally Ill.

MS. SCHWEERS: You pronounced the name just perfectly, which is a rarity.

Good afternoon. My name is Maureen Schweers, and I'm a member of NAMI, the National Alliance for the Mentally Ill. I'm representing NAMI today. I'm providing our views on clozapine and the frequency of blood test requirements.

My little brother is a true clozapine success story. He completed his bachelor's and master's degrees at a prestigious engineering school with honors and is now working on his Ph.D., all while taking Clozaril. This medication has worked wonders for my brother, giving him his life back.

However, after 5 years of regular blood testing, I must say it's a constant source of frustration for him. The frequent blood tests are a constant obstacle as he tries to maintain a normal school and work schedule, along with a social life. The weekly blood testing has not proven to be simple for him. It often involves a complicated coordination between the doctor, the lab, and the pharmacy, which my mom, fortunately, helps him a lot. His doctors have tried placing him on other medications because of this testing requirement, but none has been as successful as Clozaril has. After more than 5 years on this medication, incident-free, he would have been an ideal candidate for reduced or voluntary testing.

Many NAMI members have a very similar story to tell. In the last week, NAMI circulated some questions on clozapine to consumers and family members across the country on its web site. In just two days, 112 individuals provided feedback.

The overwhelming message from NAMI members was the success story that clozapine has provided for so many of them, like my brother. Dozens of consumers and family members told how clozapine saved their lives, prevented hospitalizations, permitted greater independence and productivity, where other medications have failed.

One family wrote that their son "has been

stable on Clozaril for a few years. This medication has changed his life and given him the ability to go back to school, succeed academically, and reclaim a part of his life that we all thought would be lost forever. He has fully embraced the reality of his illness and maintains his scheduled medical care by himself. He will be 26 this month and was diagnosed with paranoid schizophrenia almost 7 years ago. He has returned to school, an Ivy League college, last year. He has one term left."

Another parent wrote to us that "after several hospitalizations and attempts to treat his illness with various medications, my son was placed on Clozaril about 10 years ago. Since that time he has not been hospitalized and has maintained a part-time job. Today he is stable and happy with his life."

So the first point that I want to make is how important clozapine is to so many consumers with schizophrenia. Most of the NAMI members who wrote us last week also favor less frequent blood testing, some describing the frustration that they encounter with this requirement. One mother wrote, "Every two weeks as a mother, I deal with the doctor, the pharmacy, and labs to ensure that my son gets his prescription. I have encountered so much trouble, heartache, and anguish getting this medicine that if I was a patient and had to go through

all of this hassle, I would have quit long ago."

Another family member stated that, "I think there needs to be flexibility here. Our family member stopped using this medication because it was too hard to get the prescriptions filled because the lab was always late in sending the blood test results. Plus as a working parent, taking our family members to get blood work always had to be done on Saturday, and there were not many labs open, making us have to drive long ways."

As an example, my brother's 2-week testing program once fell during a holiday and only a pharmacy's error, which earlier had given us an extra pill, gave him enough medication to prevent a potential hospitalization and an extremely detrimental setback in what has been an amazing recovery. If just two doses of Clozaril are missed, patients like my brother face the risk of relapse.

Frequently, due to human error, a failed fax transmission, or the office closing during the holidays, there are communication breakdowns that could lead to missed dosages. I personally think that the risk of relapse by patients going off meds, either due to frustration with the system or due to an error in this chain of events, should be considered as a serious side effect of the current testing program.

The comments raise questions about which we do

not have data, to my knowledge. How big of a problem is biweekly testing to consumers, families, and providers? What issues are frequently faced by patients? We think that problems presented by frequent blood testing should be studied so that decisions are more fully informed by the clinical reality faced by consumers and family members and that specific problems be addressed.

We believe clozapine is gross under-utilized. Some doctors and pharmacies will not even handle the drug due to all the paperwork required, and it could benefit many more consumers, and that the risks of blood testing requirements contribute to this under-utilization.

We also believe that consumers and family members should be more involved in the risk/benefit analysis and determination with their provider of the best blood testing schedule after the first year.

Many NAMI members did give voice to the view that weekly and biweekly blood testing is not a problem. It may even have some benefits. This opinion reflected an acceptance of medical requirements to stay on a medication that has proven to be so helpful. It also reflected the view that the safety of the consumers is paramount to our members.

One consumer wrote: "Clozapine is a miracle medication for me. No other medicine was able to give me

the same level of sanity. Where I once had needle-phobia, I am no longer afraid to have my blood taken."

Another family member stated: "Clozapine has saved our son's life. The blood tests are a hassle, but if it takes blood tests to keep the medicine, we will definitely continue."

Still another parent stated: "Despite the fact that the need for frequent blood testing of my son made using Clozaril prohibitively inconvenient for me, I would not advocate less frequent testing unless sufficient data indicated minimal risk."

Still another family member wrote: "I would want the significant evidence of safety to be paramount, that extending a time between blood draws poses no greater risk, or that risk factor rates after extended use of Clozaril are no greater than that of other medications. My daughter takes the Clozaril blood draws in stride as a cost factor attributed to the medicine which has restored her sanity and rescued her life."

Another NAMI member told us that "my daughter was one of the first 10 clients in Alaska to receive Clozaril. It was the first medication that allowed her to handle her symptoms and to be released from the state hospital. She is now 50 years old and has been on every medication available since the onset of her illness at age

19. She has never seemed to mind the blood draws. They are just routine for her. If we could be assured that less frequent testing would be safe, that would be fine, but continuing as it is no problem either."

Several consumers and family members reminded us with their comments that while medication does pose risks, including decreased blood cell counts, but also weight gain and others.

We also should note that many people with schizophrenia not only have a chronic illness, but have complex comorbidities and take more than one medication. How do these factors affect the impact of clozapine on white blood cell counts?

A couple of NAMI members even suggested that ongoing blood testing at weekly and biweekly intervals may have benefits improving compliance and assuring regular contact with a medical professional, which is so important in dealing with schizophrenia. Still, we heard that blood testing does not always go hand in hand with seeing a physician regularly, and a few individuals noted that appointments with a psychiatrist were far less frequent than the biweekly blood tests.

We are in no position to scientifically assess serious blood count risks and how different schedules of blood testing protect patients. The data offered for

today's meeting suggest that monthly testing after an initial period of more frequent tests can protect patients, although we noted that the experiences in the UK and Australia did lead to higher rates of agranulocytosis with monthly blood testing. We can state for the many consumers taking clozapine, weekly and biweekly testing have proven to be frustrating, costly, and even an obstacle to living a normal life. We also want to make it clear that protecting the safety of these individuals is paramount to our members and that for many, frequent blood testing is a price that they are willing to pay.

Given the unanswered questions, such as those about the barriers posed by biweekly blood testing in the real world, and the results of monthly testing in terms of the risks posed to consumers with these chronic and complex conditions, we would like to suggest that less frequent testing on a monthly basis be implemented in the United States. We also believe that monthly testing will be sufficient for those who have been on the medication for several years and think that this population should be given the first option of monthly testing with the results studied and to be reported on. We further urge exploration of the barriers and benefits posed by weekly, biweekly, and monthly blood testing in this population so that data can inform future FDA decision making.

Thank you so much for your consideration and the opportunity present our viewpoints.

DR. RUDORFER: Thank you very much.

I'd now like to turn back to Dr. Rawls who has been working hard while the rest of us were relaxing to revisit some of the issues we had left on the table at the end of our morning discussion.

DR. RAWLS: Thank you, Dr. Rudorfer. Actually I haven't been the one working so hard. I'm just showing you the data. So I did enjoy a little lunch.

Let's get back to some of the questions that were raised. The first one that we have was the confidence interval for the mortality rates after 6 months in the United States, the United Kingdom, and Australia. If we can put that slide up please.

So here we have the United Kingdom, Australia, and the United States. You can see there were no fatalities after 6 months in the UK or Australia and 2 in the U.S. Here are the incidence rates per 1,000 patient-years. Obviously, they're all pretty close to 0, and then the confidence intervals. The confidence interval is in 1,000 patient-years well.

Yes.

DR. LEON: The confidence interval in the bottom row, does that include the estimate there? It looks

like it does not include the actual estimates.

DR. RAWLS: Is it .09? All right. We'll correct that. The incidence is actually .01 rather than .001? We can go to the next one, Maurice. We'll look into that.

The next slide was the rate of agranulocytosis in the U.S., the United Kingdom, and Australia after 52 weeks. This was the slide that Dr. Kane presented, and there was a request for the actual n's that made up the rates. Here in the initial system in the U.S. and the UK, you can see that there were 101 patients and then 2 here in the United Kingdom.

Turning to the current system with the less frequent monitoring schedules in the U.S. and the United Kingdom, 2 patients in the U.S., 18 in the United Kingdom, and then 14 in Australia.

The next was a summary of the information presented by Dr. Hauptman, and this is the probability of progression after 6 months of therapy for those patients with moderate leukopenia, those within the 2000 to 3000 category. There were 208 cases, 1 resulting in agranulocytosis, for your probability. And then the WBC less than 2000, that high risk group of patients, there were 6 cases of moderate leukopenia but none developed agranulocytosis. This is, once again, just for cohort 3

patients. Dr. Hauptman presented information on the cohort 1 and 2 combined.

Then finally, there was a request for more detailed information on the 3 patients in cohort 3 that developed agran. Here we have the 3 patients, patients 1, 2, and 3. Sorry. The slide is a little busy, but we wanted to cram a lot of information that was requested on this one slide. So their first white blood cell count, their last white blood cell count; if they developed moderate leukopenia, when that occurred; and then the date that the agran was reported.

This is the day, meaning day on treatment, so day 1, and their first WBC for this patient, 3600. Their last WBC in the CNR, so the Clozaril National Registry, occurred day 55 for patient 1, and that was 3300. This patient actually did develop moderate leukopenia on day 42, so prior to leaving the Clozaril National Registry. This is the WBC on that day. Then they did subsequently develop agranulocytosis on day 293 of therapy, reported to us. So now they are in our non-rechallengeable database. That occurred on day 293 of therapy. We don't have the actual WBC count at the time agranulocytosis was reported.

Patient 2 started with a WBC count of 8200. By day 50 it was 10,000, the last reported date in our CNR. The patient did not develop moderate leukopenia while in

our database, but we did receive a notification of agranulocytosis on day 349. I understand that this patient also was deceased. This patient was deceased. Correct? Patient 2.

DR. ISLAM: Yes.

DR. RAWLS: And then patient 3, day 1, 5700; last day in the Clozaril National Registry, 3300 on day 246. Did not develop moderate leukopenia while in our system. Well, they developed agran on day 233. So that occurred on November of '99.

So these counts you can see came in after the development of agran. So it answers a bit of your question, Dr. Weiss, do we also track those patients once they have a report. This is an example of one of those patients where it was developed and we obviously began to track them as their last WBC was 3300.

DR. WEISS: The only thing that I'm missing is when did they go off the drug.

DR. RAWLS: We would have to get that one. We know the last time they were in our system for these 2 patients. Now, we will assume that at that point they went to generic, but we don't have any documentation of that. We just know that later on in therapy they developed agranulocytosis. There's a point in time here where we don't account for. This particular patient never went off

drug since they developed the agran while still having reports in the Clozaril National Registry.

DR. WEISS: So why would the third person be excluded then from the counts?

DR. RAWLS: Excluded from?

DR. WEISS: From the tables. These were the three people that you excluded?

DR. RAWLS: Oh, yes. Do you want to explain why these three were excluded?

DR. ISLAM: There are some tables where we have included them like the hazard curve. When we have done the hazard analysis in this, we have included them. But when we tried to explain that what percent of patients had moderate leukopenia first and then become agran and the moderate leukopenia happened after 6 months, in those analyses, these 3 patients were not included. Agran happened after 6 months, but the patients didn't have moderate leukopenia after 6 months according to our WBC records.

DR. RAWLS: That's all we have. Those were the four questions posed to us.

DR. ISLAM: I can give you the correction for the confidence intervals. This one should be .007, and this one should be .0009. The point should be replaced this side. That one is actually 0.026.

DR. RUDORFER: Thank you.

At this point to help keep us focused, I'd like to read the specific questions again that we're asked to address by the FDA. There are two questions, though the first has several parts.

Question 1, should the frequency of white blood cell monitoring be further reduced after some duration of biweekly monitoring and if so, when and what reduced frequency of WBC monitoring would be acceptable?

Should WBC monitoring stop altogether at some point, and if so, when?

Should the program be changed overall, for example, should it become voluntary, as is most advice in labeling regarding monitoring for adverse events?

And question 2, should the absolute neutrophil count be required as a part of WBC monitoring?

If anyone would like to start tackling these or ask further questions of the sponsor or of the FDA, please be my guest. Dr. Ryan.

DR. RYAN: I have to think it's folly to start, so that called out to me.

(Laughter.)

DR. RYAN: I realize I've perseverated on death, but let me see if I can get in my memory this correct, that the suicide rate for randomly selected white

males and 18- to 20-year-olds is about 20 per 100,000 per year, and it's about half of that on females are sort of the recent numbers that I remember. Does somebody remember better numbers? Those are approximately correct.

But from what I understand on the last slide here -- the international data is compatible with the U.S. data. The U.S. data is just so much larger. It provides us the best confidence intervals on the hazard from death from clozapine after 6 months or after a year from agranulocytosis. Obviously, there's a question of all-cause death that would be interesting to look at, but that comes out to be something like -- the upper values of the 95 percent confidence interval comes out to be like 3-something per 100,000 per year.

So if you assume that schizophrenia, which it clearly does, has some greater hazard than the population base rate at the same age, certainly the hazard to these individuals we're talking about from suicide is enormously higher than the hazard from the agranulocytosis. So then you're left with the question of how many -- now, you'd say, okay, then that's your answer, but of course, it's not because you could have a system where you monitor some people and don't monitor other people, a blended system where the people who wouldn't take it if you monitored or you wouldn't monitor. The people who would take it if you

did monitor would presumably give you the best blended rate. And we asked earlier -- and it's possible that industry or Dr. Kane or some of the advisors could give us even some gestalt on this issue.

But certainly it looks like the hazard from the agranulocytosis is relatively small compared to the other known hazards we're going thorough here, and to the anti-suicide effect of this compound that we discussed earlier. So certainly I'm leaning in favor to thinking about how you could do less monitoring. It seems to come down that way for me.

DR. RUDORFER: Dr. Wang?

DR. WANG: We have data only for relaxing the monitoring to perhaps a monthly schedule. Beyond that even further, voluntary or not at all, we have no data. So it seems like that's a very difficult question to start to tackle. But if it just is looking at this narrower question of going to monthly from biweekly, the data -- again, I think I said earlier, the most reassuring apsects seems like, granted there are non-comparabilities between the U.S. and some of the Australian and UK data, but they do give some absolute values that suggest there won't be an epidemic of agranulocytosis if you went to a monthly monitoring scheme. Again, the actual absolute values of the rates look within the range that we currently tolerate

under biweekly and even previously under weekly monitoring schedules. They're within the range that have been acceptable. Anyway, that's sort of a thought.

DR. RUDORFER: Dr. Katz.

DR. KATZ: Yes. I'm just wondering whether or not it wouldn't be worth to hear sort of a preliminary discussion before we actually talk about the question because the question involves a lot of things like what sort of risk/benefit, and that's sort of getting well down the road. Maybe it would be worth talking about whether or not people feel there is any evidence from what we've seen or what you think or might project that if you decrease the monitoring after a certain period of time, the rate will go up. Then we can talk about whether or not we think it goes up too much or what it goes up to. But I'm just wondering if we can -- this is just my view about maybe dealing with this in a step-wise way, as I say, as a first step to discuss whether or not we think that the rate will actually increase if we go to some other monitoring scheme, let's say, monthly, and what the evidence is that suggests that it either does or it doesn't. Then maybe we can go from there to whether or not, if we think it does, how high does it go. Does it go too high? And then sort of deal with this step-wise. That's just one potential approach.

DR. RUDORFER: Dr. Weiss.

DR. WEISS: I think from the tables it was very clear that the rate does increase, and one of the tables that looked at, I think it was, the first 6 months and then the first year, it looked like there was a doubling. It definitely is pretty clear that the rates are higher in the UK and Australia with monthly monitoring. So I think there is a cost to changing the schedule.

I think that's where it gets harder. Though there is a benefit to patients for reducing it, then the question in my mind that I'm having trouble pulling out of the information is when should you reduce the monitoring. Is at 6 months? Is it at 1 year? Is it at 18 months? Is it 2 years? Because to me it isn't clear it's 6 months and more than 6 months. It definitely looks like there's a downward slope that goes on for at least the first 2 to 3 years, and that data wasn't really clearly presented today and leaves me questions on when you would want to reduce the monitoring, if you do indeed do that.

DR. RUDORFER: Dr. Ryan.

DR. RYAN: We may want some more discussion of this because my interpretation of the data was the opposite. I wasn't at all clear that it's -- I mean, I thought it was unanswerable. But I thought the confidence intervals and everything was so big that goodness knows whether the 1 month was a significantly greater hazard than

the biweekly. Certainly the data that Dr. Racoosin presented on the frequency that they were actually monitored as opposed to where they were along the way suggested that the people who were stable -- because on that one I remember the rate was .2 per 1,000 per year on the European and Australian people who actually had monthly monitoring. Yes, that rate was as low as anything we saw on any of the data on the ones who actually had the monthly monitoring as opposed to the ones who were more than that far out. Again, those are smaller samples than the U.S. and so bigger confidence intervals.

DR. RUDORFER: It occurred to me that certainly there are a number of issues that we would have liked to have seen data on, but they simply don't exist. The registry does not capture a lot of the information we talked about, including just the recent expansion of the indication. The fact that diagnosis, for instance, is not captured by the registry means we may not have that information, even in the future, in terms of whether patients who are prescribed clozapine for recurrent suicidal behavior, for instance, or patients who are schizoaffective as opposed to schizophrenic.

But the other thing that I heard in passing a couple of times was that clinicians do exercise a certain latitude in that we heard reference to the fact that if a

patient does have a white blood count that's of concern, even if it hasn't reached the defined moderate leukopenia, say, well, a physician might choose to temporarily discontinue the drug or might choose to introduce more frequent white blood cell monitoring.

I wondered if even as the decade went along, if that couldn't relate to some of that cohort 3 effect that the fact is that clinicians are much more cognizant of these concerns, and if some cases of agran are prevented because physicians may have taken it upon themselves to go the other extreme actually to be more vigilant or to change drugs now that there are more options.

What I'm not clear on is whether the other country systems such as the National Health Service in the UK -- if in fact some of those options are less open, if in fact the physician is more restricted, one can't as easily order extra monitoring or change drugs.

On the one hand, I'm not sure if that happens. On the other hand, the positive spin on that could be that might really be, if you will, the worst case scenario, that in fact something like the UK data might be an example of what happens with the extended monthly monitoring where the system might be more rigid, that in fact there are fewer options for change along the way. I would find that encouraging if in fact that is the case, that nothing

extreme would happen with going to a monthly monitoring.

Dr. Leon?

DR. LEON: Drug development regulation is really driven by data and typically randomized controlled trial data. The data we've been looking at are from the Clozaril registry. It's a monitoring system. It was not designed as a research tool, as we heard earlier. The only clinical information that's gathered are the blood counts.

Also, what's been left out of the discussion today is there's tremendous problems with missing data. A lot of people have not been included in the analyses, as we saw. There were really nine different cohorts in the document prepared. We saw data from three of those cohorts. Everyone else was excluded. Also, people are excluded, and they weren't excluded at random as we might in assigning people to a treatment cell in a clinical trial. They were a non-random sample, typically more ill.

There are a lot of other problems with missing data with the generic. We don't know about the patients who were switched to generic. But the slides we saw from the FDA earlier today suggest they might be a sicker group or a more vulnerable group. That might even account for the drop in rates of low white blood cell counts.

I would suggest, instead of rushing into this, that we consider getting data from a randomized controlled

trial where people are randomized to different levels of frequency of monitoring after 6 months, whether it's biweekly or monthly, and follow them for --

DR. RYAN: You'd need 2 million people to do that.

DR. LEON: Well, there are a lot of people. It could be considered. Right now we don't know what the rates are. Even the sponsor's book concludes by saying these data do not rule out the possibility that less frequent monitoring may result in an increased rate in agranulocytosis. Therefore, there's reason to consider maintaining the current monitoring system.

We don't have data right now that really, truly supports a change.

DR. LEIBENLUFT: I think, first of all, it seems like one of the major problems, as you said, in the database is the going back and forth from generic and losing all the people there. I don't know enough about the regulation to know if there's anything that can be done to make the registry really follow all of the people and not have this problem so that when X number of years from now, PDAC gets together to once again revisit this issue, you really have a database which doesn't have all these questions in it. I guess that's one comment that I have.

The other comment is because of those problems

with the U.S. data, I think we do look to the other countries' data because they do seem to capture everybody. And that's where you do get some consistent numbers I think. If you look at the monthly data for both Australia and the UK, you're at around .5 and .6, and in the UK when they went from biweekly to monthly, it went from .3 to .6. That's what you were talking about. So I do think that there is some way to say that, yes, to begin to quantify. Again, it's not perfect, but to begin to quantify what we would be looking at if we went from biweekly to monthly in terms of increased risk.

DR. RUDORFER: Dr. Malone?

DR. MALONE: I agree there are problems with the data, but if you look at the data that we have, I think after something like 12 to 18 months, the risks really start dropping to the point, say, of sulfasalazine. So they're kind of equivalent rates, at least from the data we get. For that drug, I think there is much less monitoring. So I think it does suggest that you should decrease the monitoring at some point in time, probably between -- the best data we have is 12 and 18 months.

I think you should continue monitoring, though, because I think schizophrenics get bad health care. At least if they were monitored on a regular basis, that would help to prevent them going for a year without being

monitored or many months.

DR. RUDORFER: Dr. Racoosin?

DR. RACOOSIN: I just wanted to mention that those rates for sulfasalazine were 3 cases per 1,000 person-years. So that's actually about 10 times higher than what's being observed after 6 months. But the .3 or .4 that's being observed in the U.S. after 6 months is in a monitored population, and the sulfasalazine is unmonitored. So just keep that in mind when making that comparison.

DR. RUDORFER: I do want to pick up on one point that Dr. Malone mentioned, and people have referred to the adherence issue which I realize is not quite on target in terms of that's not the primary purpose of the monitoring. But it did occur to me -- I just thought I would mention it just to have it on the table -- the expansion of the indication to the recurrent suicidal behavior was based, in large part, on a study which did use the biweekly monitoring paradigm for the duration. It occurred to me that we really have no way of quantifying how much the biweekly monitoring influences treatment adherence, and to the extent that that might have been, if you will, one of the active ingredients of that study, I just thought we should bear that in mind.

DR. LEIBENLUFT: I'm sorry. Do I understand you right? You're saying that it might have been the

monitoring itself which decreases suicidality basically, the frequent contact, the regular contact?

DR. RUDORFER: Well, I'm saying we've heard from a couple of speakers how the regular monitoring does enforce regular contact with the health care system, and to the extent that that keeps people in treatment, I wonder whether that contributes to the overall efficacy.

Dr. Kane.

DR. KANE: May I comment? I think that's an important point, but the intercept trial was designed as a controlled trial. So those patient who received the comparator drug, which in this case was olanzapine, were seen as frequently as the patients who received clozapine. Although the clozapine patients had a blood draw, the olanzapine patients were weighed and had other interventions. But the frequency of contact was the same, so the superiority in terms of preventing suicidal behavior was despite that.

DR. RUDORFER: Yes. Thank you.

But nonetheless, my point still is that for both groups, they had the biweekly contact.

Dr. Malone.

DR. MALONE: I think there is evidence from the data that frequent monitoring does help efficacy and compliance. In the MTA study, the group assigned to drug

was seen at least monthly, and there was a comparison group that was a community treatment where they were not seen as often but received the same drug, and the monitored group did better. Just having visits probably does help adherence and efficacy.

DR. RUDORFER: Dr. Katz.

DR. KATZ: I would just reiterate what I said before. I think it would be very useful for the agency, for the division to just have a little bit more discussion about whether or not the committee members think that the evidence that they've seen actually establishes that the rates go up when you go from, let's say, 2 weeks to a month, which is really, as you say, the only data we have. I think that is sort of a fundamental point. It will help develop discussion, and it will help us think about the problem as well.

DR. WANG: The cleanest data that we've seen are the data where the period after 6 months is broken down and stratified into something smaller than just greater than 6 months. We've seen a few. We saw some life tables and we saw some incidence rates of that period broken down. Probably the only period where you can reliably generate incidence rates is for that 6- to 12-month period, and if you look within that, it looks like numerically there's a doubling. I agree it's not statistically significant, but

it looks like there's a doubling. That seems to be consistent with the British data. Because what I've just talked about doesn't take into account the secular decrease that's been occurring over the three cohorts, it's probably an underestimate of the increase due to that change in monitoring policy.

But, nonetheless, it still then begs the question. In absolute terms, what are you dealing with? Even if this is true, what's the absolute increase in agran rates that you're looking at? That is where I think it leads you.

So the answer to your question from my perspective is, yes, there is some suggestive data that if you relax the policy, it will lead to an increase, but what's the size of that in the sort of overall cost-benefit balance?

DR. RUDORFER: Dr. Leon.

DR. LEON: I brought it up this morning. The sponsor's projections, which really we looked at briefly when I brought it up earlier, do suggest that the rates will go up with decreased monitoring. I don't have it right in front of me, maybe an extra 100 cases. Was that it? 91 cases. So those data suggest that it's going to go up with decreased monitoring.

DR. RYAN: Is there any chance we could look at

your data again on those two slides which broke out the actual monitoring rate rather than how far out they were? Because I again was quite impressed with the fact that presumably people will act in a rational fashion, even after we make whatever changes we do. It looked like if you look at how people actually acted rather than how far out you were, that the ones where people are comfortable going to the biweekly monitoring or the monthly monitoring had remarkably low rates and comparable rates. It's easy to find yourself thinking differently than everybody else, but I'm still in that position, even after listening to my colleagues, where I'm still seeing it's necessarily going up.

So it's .2 per 1,000 on the agran, once you go to every 2 weeks. And what was the prior slide for the British and whatever? So the people that went to every -- this is UK only. And the ones that went to every month was .3. So in both places, where the physicians went to the lowest rate as opposed to where they could have gone to it but didn't, those give really very low rates.

DR. RACOOSIN: Well, presumably these people have to be hematologically stable to get that far.

DR. RYAN: Right. But presumably clinicians will continue to act in a rational fashion because we see here that they don't always go to the lowest monitoring

rate that they can. And in both countries -- in the UK where they went to the lowest monitoring rate they could, which was the 1 month, or the U.S. where they went to the every 2 weeks -- the agran rate was in the UK .3 and the U.S. was .2, but very low rates.

DR. LEIBENLUFT: Could I ask a question, though, about that, Neal? The ones in the U.S. were not the generic database. Right? It was the sponsor database. And so to the extent that people in the generic database are getting their health care within a different system, which may be true, I'm not sure that we can extrapolate from either the sponsor database or the UK database what practitioners' behavior in the generic database would be.

DR. RYAN: That's true, but this is still at least 25,000 person-years. So it could be different, but it would have to be massively different. You'll have people on both panels. You'll have people on a panel that has generic, other people on a panel that has the other one. But it's so many people, you have to hypothesize dramatically different behavior for people on the generic to change that rate.

DR. LEIBENLUFT: Well, and since it may be, say, public care versus private care, we just really don't know. There could be very different health care systems going on here.

MR. DODSWORTH: I think it's important to understand that it's not necessarily driven by the prescriber here. There are state mandatory substitution laws where the prescriber may actually write for the brand and when the patient takes it to the pharmacy, it's substituted. So we can't generalize about what type of patients are or are not getting the brand versus the generic. So I don't think we should hone in on that particular aspect of it.

DR. RUDORFER: Dr. Kane.

DR. KANE: Just to add to that, as a sort of major center for clozapine treatment, we switched to generic a while ago, as have many academic hospitals for a variety of reasons. So I wouldn't assume that there's a difference in the quality of health care. And to the extent that generic data are available, the agency has presented us with what they have, and I think that is somewhat reassuring even though it's a very small sample.

DR. RUDORFER: Dr. Malone.

DR. MALONE: From another angle, we were looking at how quickly agranulocytosis can develop. I think it's inevitable if you go to a longer monitoring system, you're going to have more windows for it to develop. So I think it's always been the theory that if you decrease the monitoring system, you will have a higher

rate of these things occurring, apart from any numbers that we have because the numbers, everyone thinks, have problems. So I think it's inevitable there will be some increase.

DR. RUDORFER: Dr. Katz.

DR. KATZ: Well, perhaps. It certainly seems obvious almost, but of course, part of it depends on how wide the interval has to be before you actually see an increase. For example, in the U.S. database, when you went from a week to biweekly, twice a month, you didn't really see any difference. As everybody has pointed out, there are lots of problems with the data. Lots of people dropped out. We don't know who these people are and lots of other questions, but nonetheless, when you look in the U.S., really nothing changed in terms of incidence of agran over time. There was a change in the first 6 months.

DR. RACOOSIN: (Inaudible.)

DR. KATZ: Right, in certain categories, I suppose right, but overall nothing really changes. We saw a strange, inexplicable change in the first 6 months, but we don't know what that means.

So, yes, I suppose if you could monitor every day, that would be ideal. Probably everybody believes that that would be perfect. You'd probably pick up more cases. But I guess the question is do we think we're going to get

more cases when the interval is increased to what. From every 2 weeks to every month? Is there sort of a general belief either based on evidence, such as it is, or just presumably the pathophysiology of it and biology of it? Is there a general view that if you go from 2 weeks to 4 weeks, it's just clear it's going to increase? Is that sort of the general view of the committee?

DR. MALONE: The other important issue I guess would be where you're going to change the monitoring. It could increase further out, but that increase -- it's hard to know what significance it would have from our data. But if you go from a very low number to another very low number, it might not really have that much significance for patient care if you look at points further out in time.

DR. KATZ: Low number. You mean incidence of agran? When you say low number, you're referring to the incidence of agran?

DR. MALONE: Right, anything that you're looking at.

DR. KATZ: Right. Again, I think the question is will it increase if we go, let's say, to every month, and then if the committee believes it will increase, again either because of the evidence suggests it or because it just seems obvious, then the question is, can we say anything about how much we think it might increase and

whether or not it's worth it? That's ultimately the question.

DR. GRADY-WELIKY: I guess to respond to your question, I would agree with Drs. Leibenluft and Weiss that I think looking at the UK data and the Australian data, I think it's limited, but it looks like it will increase if we were to move from the biweekly to the monthly. So, with all due respect to Dr. Ryan, that would be my opinion based on what we've seen today.

The other question I had for you was, is there a plan to have the CNR database and the generic database interface at all so that we can capture some of this?

DR. KATZ: There is no current plan. I suppose that's something we could explore, but we haven't to date.

DR. GRADY-WELIKY: That's the unknown question in terms of the switchers and other things that we need to know what's happening to those folks who are transitioning to generic or vice versa.

DR. RUDORFER: Yes, Dr. Ortiz.

DR. ORTIZ: I have another question for Dr. Katz. Is there any language in the labeling at this point suggesting that absolute neutrophil counts be done if there should be any decline in white blood cell count?

DR. RACOOSIN: Again, the algorithm offers thresholds for ANC. If you meet a certain threshold, such

and such an action should be done, but there's no requirement for the recording or for the ANC, independent of the WBC, to drive a certain action, whereas in the UK it is. So someone who has, for example, a white blood cell count of 4000 and by itself, they would just continue along. If their ANC, at the time that their white blood cell count was normal, was below 1500 in the UK, that would start a certain cascade of events. That person would become non-rechallengeable on the basis of their ANC alone without their total white blood cell count being abnormal. There's also a certain confirmatory blood test that's needed to ascertain that, but it's not just a spurious lab value. But that is not currently part of the U.S. system, having the ANC independent of the WBC drive the action.

DR. ORTIZ: Can you clarify what the UK system is? At some point is the ANC recommended or required?

DR. RACOOSIN: Can you put up the slide that has the requirements of the UK system?

DR. KUMAR: In the UK system, ANC is required in the beginning. To initiate Clozaril, the ANC must be done, and it should more than 2000. Also definitive steps in the monitoring of the ANC is required. It's done in all the cases.

DR. RUDORFER: In the U.S., does the ANC have to be drawn if one of these leukopenic situations is seen?

If a WBC of 3000 is measured --

DR. RACOOSIN: Our understanding is that the ANC is optional in the U.S.

DR. KUMAR: Yes. In the U.S., ANC is optional. But what happens most of the time, if they have agranulocytosis, it's done and we get reports in our system somehow for most of the cases.

DR. RUDORFER: Dr. Mehta.

DR. MEHTA: In the U.S., at least with twice monitoring, it doesn't seem optional. You had to do both. Only later on it becomes and/or. So either there's a typo there or it is almost compulsory.

DR. LEIBENLUFT: I think what we're hearing is that that is correct. The slide is correct. Therefore, ANC for the twice weekly monitoring is compulsory. To make the switch, it has to be the WBC and the ANC to go to twice weekly monitoring.

DR. RAWLS: We just want to clarify one point. We get ANCs in the system. We just don't record them in the CNR because they come in off the lab records. We just don't record them in the CNR, where they do record them in the UK. So that's one of the biggest differences. So when you're talking about this mandatory use of ANC, then that would force is to include it in the CNR. It's already documented when it comes in in the lab records. But then

generic manufacturers record it in their registries as well.

DR. RYAN: Is anybody else other than me lost at this point? Because I am actually.

DR. LEIBENLUFT: I'm wondering, so is what you're saying that it's obligatory for you at this point to monitor ANC when it enters into a decision to go to twice weekly monitoring, but you don't record ANC when it enters into a temporary or permanent discontinuation because then it's not required? It's the and/or. Is that right?

DR. RAWLS: You have it.

DR. LEIBENLUFT: Is that clear as mud to you?

DR. RUDORFER: Dr. Mehta.

DR. MEHTA: Would you need ANC measurements or do you do measurements during the first 6 months?

DR. KUMAR: In the first 6 months, no.

DR. MEHTA: It's not done at all, not that it's not recorded.

DR. KUMAR: It depends on whatever stage in our system the person is. If the person happens to be -- like initiation of the Clozaril, in the beginning we do not require it. And if they do not have any problem and the WBC doesn't come down less than 3500, then ANC is not done.

DR. RAWLS: You see, they record it in the UK and Australian databases, the ANC and WBC. In the U.S.

database, in the CNR, we are only, off the lab records, entering WBCs.

DR. KATZ: But does that mean in all cases in which you are just entering WBCs, that the ANC is actually done and it's known locally and it drives decisions about what to do perhaps, but it's just not recorded in the CNR?

DR. RAWLS: That's correct.

DR. KATZ: First of all, you presumably would have to get ANCs if you're ever going to diagnose agran.

DR. RAWLS: Exactly.

DR. KATZ: So with every blood draw --

DR. RAWLS: I wouldn't say every.

DR. KATZ: Okay. I mean, essentially for all blood draws, there are ANCs generated. You just don't write them down in the CNR unless there's some reason to do that. But once, let's say, somebody goes on a temporary discontinuation and you're still drawing blood, the ANC is known to people presumably, otherwise how could you diagnose agran if you weren't drawing those?

DR. RACOOSIN: A white blood cell count of less than 1000 is equivalent to agran for the purposes of the registry. So you wouldn't necessarily have to know exactly what the ANC was.

DR. KUMAR: Yes, but also I think when we look in our registry in the U.S., I think more than 81 percent

or more than maybe 90 percent of the patients have ANC data in our system. The CS&E database virtually has all the ANCs, people who have a diagnosis of agranulocytosis.

DR. RACOOSIN: Right. There's something in the labeling statement in particular that says if after the initiation of treatment, the total white blood cell count has dropped below 3500, a repeat white blood cell count and a differential count should be done. So it has a certain implication that the differential count only needs to be done below 3500. That's one of the issues that we're getting at. If their first movement towards agran is to have a normal total white blood cell count, but at the same time, an ANC below 1500, we're not necessarily capturing those patients with this current labeling.

DR. KUMAR: We're not capturing those ANC counts in our registry. However, you are right that if the WBC count is less than 3500, in clinical practice the physicians do ANC as well as WBC.

DR. LEIBENLUFT: But I guess that is a question perhaps for Dr. Gerson which is would this happen. Would you have situations where the ANC is dropping below 1500 or whatever, but the WBC is staying above 3500?

DR. GERSON: Right. So I mentioned this morning in passing that there were 19 out of 573 patients with agranulocytosis recorded in the registry that had, at

the time of their ANC less than 500, a WBC in excess of 3500. So that's 3 percent were missed. It's not 3 percent of possible, potential, at-risk, whatever. It's 3 percent of diseased patients. That's really, after all, the denominator that you're most interested in. Nonetheless, as we stated this morning, the ANC is the number that you're most interested in.

Could I just have the slide of that action plan back up? Since I was old enough to be responsible for at least the discussions about this and there were committee members suggesting it was either muddy or quicksand, maybe we can just show that again.

So the rationale for the twice weekly monitoring using the WBC as the cutoff was to allow patients with a modest leukopenia to remain on the drug as long as their neutrophil count was fine. And that's the reason for this switch, if you will. As long as the ANC was maintained, the WBC became less important. And then the discontinuation again allowed the flip-flop of either a WBC above 2000 or an ANC above 1000. That was the rationale. It was really to help maintain patients on treatment. But it is confusing otherwise.

DR. RACOOSIN: There was an earlier analysis of the UK system done by Novartis a few years ago that used different definitions to look at the white blood cell and

the ANC data. It only required one abnormal value. There wasn't a confirmation required. But in that analysis, about one-third of patients, when they first were detected as having moderate leukopenia, it was detected on the ANC value as opposed to the total white blood cell value. And that was what got us thinking about this issue.

Now, because the definitions used in that analysis are different than those today, we didn't want to put a lot of emphasis on that data. But as Dr. Gerson mentioned, there are cases of agran that had this finding, but presumably there are more cases that -- the idea is if you were to use either criterion as your first entry into moderate leukopenia, at least some proportion of patients you would pick sooner based on their ANC than just by going with their total white blood cell count.

DR. ORTIZ: I have a question also for Dr. Gerson. Is the language currently used in the warning of the differential adequate for the ANC?

DR. GERSON: Oh, geez, I think maybe you could be more clear. Or the package insert could be more clear about requiring or encouraging an ANC. So I really do agree with that.

I would also like to reiterate something that John Kane had said earlier, and that is there really is an impression that the community of prescribing psychiatrists

is pretty mindful of these blood counts. If you look at the cases that aren't switching, if you will, at 6 months to every 2 week monitoring and staying on every 1 week monitoring, if you try to look at some of those individual patient series, you find that they're exactly what you'd expect. The folks who had a drop in their white count from 8000 to 5000 or 4000, that their neutrophil count is hovering between 1500 and 2000. Those are the folks who are appropriately being more frequently monitored. So I don't think it's a black and white, that there are whole lot of physicians out there only looking at the WBC and scratching their head when the WBC count is 4000. I would hunch that many of those instances -- and the rates sort of suggest it -- are physicians who are actually looking at the WBC, as well as the ANC, currently. So having the PI reflect that would certainly make sense.

DR. KATZ: At this point, the sense that I get is that people think that there is likely to be an increase in the incidence of agran if the monitoring frequency is decreased to monthly from biweekly. Is that sort of the sense?

Do people want to say anything about whether or not they think there's any way you can quantitate what that increase would be? Or is there a sense that that's not really easily doable? Because, again, I think that ideally

you would like to have a sense of the quantitative increase before you think about whether or not we ought to change, whether it's worth changing it to that frequency. But, again, I'm not sure the data support much in that regard, but I'm interested in what --

DR. RUDORFER: Dr. Weiss.

DR. WEISS: I think we saw from the differing calculations that it really depended on when you switch because on our briefing booklet from the FDA, page 41, table 2, it talks about the rates of agranulocytosis with clozapine over 5.5 years. This was for the 1997 meeting. It drops precipitously. 0 to 6 months, the rate was 8.6 per 1,000 person-years. 6 to 2 years, it was 0.7, and then it dropped. Between 2 and 3.5 years, it was 0.4. So again, it dropped in half, and then it dropped in half again 3.5 to 5.5 years. So I think what you're going to see whether it's from 10 cases to 20 cases or from 1 case to 2 cases, it's going to depend on how far out you make that switch. I'm assuming you're not going to change the monitoring from 0 to 6 months.

You may not want to switch the monitoring. You might want to keep it biweekly through the first year or even through a year and a half or 2 years. The further out you keep it as it is, the smaller the absolute number and the rate you're going to see. And the question is where's

the balance.

DR. LEIBENLUFT: I think using those same data, it points up how our real problem is not knowing what's going on between 6 months and 2 years because somewhere in there we're getting from 8.6 to 0.7, and we don't know if we're doing it gradually. We don't really know if we're doing it in big steps and, if so, where those steps are. I think, first of all, that points up kind of the issue. The problem that we're struggling with or will struggle with is as to exactly when to change it, but I think also going forward, that's really where we need more data.

DR. WANG: I think to answer your question, there is a natural experiment here that sheds light on what would happen if you went from biweekly to monthly, and that's the UK data. It gives you a sense of the magnitude of increase. Again, there is not a secular decrease, so it's not an underestimate. I think the jump from .3 to .6 per 1,000 person-years gives you a sense. Here, the noncomparability of the UK monitoring system to the U.S. isn't such a problem because as long as it was constant over those two time intervals, whatever is operating, the only change should have been the change in the monitoring frequency.

DR. MALONE: The one problem with the UK data is that they do eliminate a lot of patients and put them on

a rechallenge list who could be rechallenged in the United States. I don't know how many of those patients go on to take the drug for 2 years if they've had moderate leukopenia and then get rechallenged, but I think there would be a slight underestimate of what would happen because they have eliminated the patients who may be at the greatest risk for having problems later on.

DR. LEIBENLUFT: Presumably if we did have some kind of coherent database that included both the generic and the brand, then we'd be able to track those people. One problem is we don't have any follow-up data about the temporary discontinuations.

DR. WEISS: One of the things I hate to do is make algorithms more complicated than they already are, but I think what Dr. Racoosin showed us at the end was very telling that more than half the cases come from the small group of people who stayed on the frequent monitoring. So there's a definitely an understanding of the doctors of who might be at higher risk. Although it's half the cases, the rate is so much higher. I don't know if there's room in the algorithm or the recommendation or if we have enough data to say who should continue or recommend who should continue more frequent monitoring and who could go to a lesser schedule.

DR. RUDORFER: Yes. I was having a similar

thought. In other words, the algorithm here pretty much starts at 3500, but if someone is cruising along and they have 5000, 7000, presumably one is less worried about them than someone who's at 4000.

The other thing, which I don't know if there's any precedent for, is to insert some flexibility in the monitoring where a minimum frequency of WBC monitoring was required but there's a band explicitly stated, for instance, after, say, 1 year, monitoring every 2 to 4 weeks. What I'm thinking of is two things.

One is that many clinicians and health care systems will interpret a requirement very literally and it might be difficult to increase frequency even if a clinician is a bit anxious about a certain patient.

The other, which I don't know the answer to, is whether third party payors might interpret, say, a requirement of monthly monitoring to mean that more frequent monitoring would not be covered, whereas if the requirement was, say, 2 to 4 weeks if a clinician felt that every 2 weeks was indicated, even at particular times, for a given patient, then that wouldn't be an issue.

DR. KECK: I was actually thinking along the same lines but for slightly different reasons. It seems to me, just my overall impression, monitoring works. We know that. It's prevented a lot of people from dying from

agran. We also know from what limited data we have, that we have an apparent doubling of risk from .3 to .6 cases per 1,000 person-years, which seems to me to be small. A doubling of risk sounds drastic, but that's still a small increment overall. On the other hand, if it was your brother, son, father, mother who got the agran and died, that's a risk that suddenly becomes palpable.

I was trying to put myself in not only family shoes but in my clinician role and thinking what about a patient with schizophrenia who I've treated for a year, who's had nice, normal WBCs, for whom it's a burden, as it is for everybody in this protocol, but who seems to be, at least from a medical history and WBCs and ANCs to date, in a low-risk group. This being a free country, what about giving them the option of informed consent. This is what we might recommend. Biweekly would give you this risk, from what we know, of having agran. If we went to monthly, you're going to run a higher risk of this coming about without us detecting it. But it at least gives the person a choice and the person and their family the ability to balance the risks of the burden of monitoring versus the risk of developing some untoward, potentially catastrophic thing, albeit at a low risk. Now, I don't know what the ramifications are from a reimbursement and provider standpoint, but I think that builds in some guidelines with

still giving some flexibility.

I personally would worry about a patient who went to monthly. Like John, I've had people who have agranulocytosis, and nobody died, but it's horrifying. And it would worry me if someone elected to go monthly instead of biweekly, even just that little incremental risk.

On the other hand, if I was sure they understood and their family understood that they were taking that risk, I think we'd all be a little more comfortable.

DR. KATZ: Maybe we're at the point where we can -- I don't know whether you want to go around the table or just get the sense in regard to the first part of the first question -- I would sort of tease it out -- which I think says, do you think we can change this, leaving open the question of what it ought to be changed to or how we ought to change it, whether it's informed consent or whatever the new system would be. Maybe we can get a sense of the committee about whether or not we can take that first step or what the committee feels about the first question which is do we think we're at the point where some change is reasonable, again leaving open the particulars.

DR. RUDORFER: Would people like to go around the table or would someone like to start? The first question reads: should the frequency of WBC monitoring be

further reduced after some duration of biweekly monitoring, and if so, when and what frequency?

DR. LEIBENLUFT: I think the answer just to the first question, as Dr. Katz posed it, is yes. I think we should think about decreasing the frequency. I think there's a big issue as to when it goes down, whether we follow the UK or I think some argument could be made of going down to monthly after 2 years instead of 1 based on the data that we have. But I guess just in the broadest brush, that's kind of where my thinking currently is.

DR. RUDORFER: Dr. Weiss?

DR. WEISS: I'm definitely of the same thought here. I do think it could be reduced somewhere in the 18 months to 2.5 year period -- but I'm not quite sure where the data drives that -- perhaps to monthly. Then, again, I think we can consider if there are some segments of the population that we should highly recommend or require more frequently because they have transient decreases in their rate or, you know, it's not stable.

DR. RUDORFER: Dr. Wang.

DR. WANG: Yes, it seems like it's reasonable to go to monthly based on what we see. Going beyond that, sort of thinking about other scenarios I think is a bit of a stretch at this point given the lack of any data.

DR. KATZ: Just to sort of flesh it out a

little bit. Do you have any sense of when monthly should start?

DR. WANG: The data that we've been shown is probably most generalizable to scenarios that are similar to what we've been seeing. So, for example, if we're using the UK data as sort of suggestive or supportive, then it really is only generalizable to a similar system. So after a year of stability, going to monthly.

DR. RYAN: I think I'd say the same thing as the last speaker. Somewhere after a year to 18 months, going to monthly seems reasonable.

DR. RUDORFER: Dr. Leon.

DR. LEON: I think we should consider reducing the frequency. I don't know I've seen any data that supports a choice of when it should be done.

DR. KATZ: Let me ask you this question then. Do you think the data support any particular interval, like monthly or every 6 months?

DR. LEON: We haven't seen any data that supports any such distinction unfortunately. I'd like to say yes, we have. We saw earlier from Dr. Gerson that the prodrome is about 3 weeks I believe. So if it's longer than 3 weeks, we could miss a new case.

The slopes that were determined by the sponsor suggested that within -- I did the calculations. I think

it was within a couple of weeks, you could drop a couple thousand points, a white blood cell count. We've ignored those calculations all day. Where was it? Yes, based on the slopes that the sponsor estimated, within what was it? It was 126. The drop was 126 white blood cell counts per day, which would translate into in 2 weeks that would be about 1800. In 30 days, that would be a drop of 3500. That's a big drop.

I just feel like we're being asked to make a decision -- to make a good guess without the data. Is absence of evidence evidence of absence?

DR. KATZ: No, it isn't.

DR. LEON: Okay, thank you.

(Laughter.)

DR. KATZ: No. One valid answer, obviously, is that we don't have enough information to make a decision.

DR. LEON: Yes, it's tough.

DR. KATZ: That's obviously a perfectly reasonable answer to the questions we're asking. If that's what people feel, we need to know that. We're not requiring that you give us a particular answer.

DR. LEON: The registry could be tuned up and gather a little bit more information that would help inform this question in the future, some clinical information. That would be very useful. And if there was more follow-up

information on those who go off of Clozaril, that would be very useful in the registry. So if we sat here a year or 2 from now, we'd have more information to work with. Right now it's really intuition, guess, how does it feel, but it's not empirically driven.

DR. RUDORFER: Dr. Malone.

DR. MALONE: I think my impression would be that you should consider decreasing the monitoring. If it's every 2 weeks now and you're going to decrease, I think the next logical thing is every 4 weeks or monthly. At least we have some data, no matter how good it is, about monthly monitoring. Then if you did do that, I would suggest that you keep track of what happened to those people who reduced and revisit the issue.

DR. RUDORFER: Dr. Grady-Weliky?

DR. GRADY-WELIKY: I would agree with what most folks have said around the table, that reducing to monthly monitoring makes sense. It's a harder question about when to do that. Certainly no earlier than 12 months, but given the question of the hazard rates going out to 18 months and 2 years, it begs the question of extending the biweekly from 6 months to 18 months or 2 years, and then at that point beginning the monthly.

DR. RUDORFER: I agree with most of what's been said. I would add, given some of our other discussion and

the open hearing participants reminded us, there are a number of other considerations, and I think it's true also that to the extent that people might avoid using this drug due to the real-life complications of the monitoring, that those are adverse effects in their own way if clozapine, in fact, would be the most advantageous treatment.

Having said that, the thought that occurs to me would be to try decreasing the frequency of monitoring after a year. I still like the 2- to 4-week range and what I'm thinking is that, coupled with the tightening up and, to the extent possible, the integrating of the registries, perhaps would give additional data, say, a year from now in terms of what happens to people who are continued to be monitored biweekly versus those who are reduced to monthly.

The other thing, we commented a lot about the other countries' experience and I would note, for whatever it's worth -- and I guess we're not sure what it's worth -- but I think it's noteworthy that neither in the UK nor in Australia have they gone back and decided that the monthly monitoring was insufficient. So I assume that's a certain real-world validation.

Dr. Ortiz.

DR. ORTIZ: I also agree with the going to monthly, but I think I'd like to see some stronger messages in the package insert. It seems like, at least from the UK

data we've got, that clinicians were pretty conscientious about monitoring people at hematologic risk or whatever the risks were a little more closely, and I think encouraging clinicians to do that, though I suspect, for the most part, they already are.

At what point to do this I'm not clear on. I'm looking at the graph on page 13 of our background booklet, and it looks like at around 18 months, the cohort 2, the agranulocytosis goes up and then goes down closer to 2 years, but neither of the other two, cohort 1 or cohort 3, follow that pattern. So I'm not sure what to make of that, but I think that certainly leaves me the question that I'm not sure where between 12 and 24 months it should be.

DR. RUDORFER: Dr. Keck.

DR. KECK: Well, I think the first difficulty obviously is in predicting anything. I think when you went from 1 week to 2 weeks, that was a leap of faith and one that was a pleasant surprise. The incidence was much lower than anticipated. We can only hope the same thing would happen if we loosened up this time as well.

I guess my answer is just what I said before. It's sort of yes, but. Yes, I think we should consider going to monthly monitoring, especially after a minimum of 12 months exposure.

I'm not that persuaded by the argument that by

doing so we would open the funnel to clozapine treatment of people who would otherwise not take it because trying to convince someone that, oh, yes, just wait a year and X number of blood draws, and you'll be home free is not going to, I think, convince most people to take it. Now, people take clozapine for a lot of other good reasons. I think the problem is at the other end, once they're maintained on the drug and are doing well, to improve quality of life.

Like I said earlier, I think that is an individual and family decision about balancing the risks of the burden of monitoring and their quality of life versus the slight, but apparent increased risk of developing a life-threatening side effect with slightly less frequent monitorings. I think that's a decision that people ought to participate in if possible.

DR. RUDORFER: Ms. Bronstein.

MS. BRONSTEIN: I would like to see us be able to lower the frequency of monitoring, and I don't feel comfortable commenting on the clinical time of that.

But I do think it's an important decision for the consumer and for the family. I like the idea of encouraging some involvement in understanding the risk with that decision. I think that would be very helpful to family members to understand that by changing from 2 weeks to a month, that this has a clinical component that puts

their family member at risk.

DR. KATZ: I think it's very clear how people think.

I just want to make an observation. I think the general conclusion or consensus after the initial part of the discussion was that there probably will be an increased rate of agranulocytosis when the monitoring is made less frequent, but the overwhelming majority of folks believe that it should become less frequent. I just want to make that observation. It's a perfectly reasonable recommendation. I want people to be aware that is as I heard the two parts of the discussion.

DR. RUDORFER: Now, I have not heard throughout the day from the committee any sense that WBC monitoring should be stopped altogether at any point. Is that the case? Would anyone want to comment on that?

MS. BRONSTEIN: I'd like to comment on that. I think it's real clear it can't be stopped, and I think it would be unwise to do anything further than a month.

DR. RUDORFER: Dr. Goldman.

DR. GOLDMAN: Yes, just a comment on that question. We're certainly not asking that it be stopped. But it would appear that there is not a consistent policy about this issue in terms of drug-associated neutropenias. With some medications, there's monitoring; with some,

there's not. And it doesn't seem to relate to the incidence of the side effect. One question that we had about this early on was whether there was any policy, and there doesn't seem to be a policy on this issue.

I do think that from the standpoint of people with the illness, that certainly my brother would like to feel that there's a policy being applied not because he has schizophrenia that it's applied a certain way, but because there's some objective standard out there that says, boy, if you have certain risk of neutropenia, there's a certain amount of monitoring to make sure you're safe. And that would be the case whether it is a drug for schizophrenia or for arthritis or whatever chronic disease.

DR. RUDORFER: Thank you.

Dr. Katz, did you want to comment on that?

DR. KATZ: No. It's a fair question obviously. There is no policy, not one that I'm aware of. The agency is currently, I believe, looking at how this is done with hepatotoxins, drugs toxic to the liver, because there too there's a whole range of labelings with regard to drugs that are known to be toxic to the liver, cause liver failure. Some labeling says monitor every week. Some labeling says here's the problem, you do what you think is best. In that particular condition, as a general matter, we've moved more towards not requiring specific monitoring

requirements in terms of frequency, but just leaving it up to the clinician. But that also has to do with the fact that those drugs cause liver failure presumably much less frequently than some of these drugs cause agranulocytosis. Each drug is different. Each patient population is different. There are different considerations. So I'm not sure there can necessarily be a blanket policy. But the short answer is there certainly isn't.

DR. RUDORFER: Sir.

DR. STASKO: May I make a comment?

DR. RUDORFER: Please.

DR. STASKO: My name is Robert Stasko. I'm a medical officer in the Neuropharm Division of the FDA.

Just a question. Maybe Dr. Gerson can help with this, but I'm wondering a little bit what you're trying to do in your comments about a standard. It's like when a cancer patient or an AIDS patient comes into an emergency room, there's a sense about fever and neutropenia that just gets the whole staff and the nursing staff and phlebotomy, everybody gets such a higher level of concern. I wonder if we do less testing here, if you have any thoughts with how psychiatry or how maybe patient education -- or I don't know if some of this could belong in the label, but just what the education of this community needs around what educational materials that there are with

neutropenia and the risks of neutropenia. Like I said, like an HIV-positive patient comes in the emergency room who's got a fever, everybody is on a neutropenia alert. So it's sort of little bit like sort of your standard question in this population is at risk. I wonder how there the providers and the patients are sort of educated. As I said, I don't know if this can be in the label, but maybe a compromise can be between education and providers to make some similar standard.

DR. GERSON: My sense is that there has been considerable effort. Certainly early on when Clozaril was being marketed, there was a quite large effort to educate the community, families, patients themselves about looking out for the signs and symptoms of neutropenic fever. I think there's labeling in the PI about that. I think there's been a considered effort. It would make quite a good bit of sense to remind folks in the monthly monitoring, should that come to pass, about the need to be alert to the issues of neutropenic fever and the signs and symptoms that are there.

I'd just like to comment on the earlier commentary on why is this drug different from other drugs, if you'll pardon the vernacular. It is because of the late onset and the severity of the agranulocytosis when it occurs. If it isn't unique, it's pretty close to being

unique. There are one or two other drugs that can cause a very sporadic incidence of aplastic anemia and things like that. But the number of cases after a year is really pretty unique in the pharmacopeia.

DR. RUDORFER: Thank you.

A related question that we're asked to address which didn't come up too much during the course of the day is whether there's any feeling on the committee that the WBC monitoring should become voluntary, that it should just be part of labeling or a black box warning and not be mandatory. Any thoughts about that? Dr. Keck.

DR. KECK: Well, that's like saying having no monitoring in a way. It's the flip side of the same question. I think it would lead to extraordinarily high rates of agranulocytosis, akin to not monitoring at all.

DR. RUDORFER: Is it fair to say that's the consensus of the committee? I think so.

The other specific question we were dancing around at various times relates to the absolute neutrophil count. Should we revisit that specifically? I think we were arriving at the conclusion that the requirement for the absolute count was only triggered when the total WBC dropped below a certain level. Is that our accurate conclusion? In other words --

DR. RACOOSIN: That's how it's stated in the

labeling. I think the point was raised that maybe in the community that's an oversimplification, that physicians are watching the ANCs concurrently with the total white blood cell count, but it's not clear that that's an absolute, or that that perhaps could be made rather than just -- at this point it's conscientious watching of the ANC as opposed to a requirement.

DR. RUDORFER: Dr. Katz.

DR. KATZ: I think we heard before that 3 percent of the patients who -- I can't remember 3 percent of which -- but I think there were patients, I guess, maybe 3 percent of the agran patients, had white counts above 3500. Do we know what the numbers are for an absolute neutrophil count of 1000, let's say, or 1500, in other words, not agran but something that you might worry about? How many of those people have total white counts of 3500? Again, the question being if you say you've got to measure the ANC and you pick somebody up at 1000 ANC and the white count is over 3500, you're going to pick those patients up earlier. Do we have those numbers?

DR. RAWLS: No.

DR. KATZ: No, okay. Presumably a higher number than 3 percent.

DR. WEISS: It seems that if they are doing it in regular practice, taking both measurements, and you got

the registries to include that field, that might provide you with valuable information when you review these changes and their implication and perhaps help you identify a higher risk subset. But if you don't collect the data, you'll never know. But I think if it is being done, that would be valuable information to start collecting.

DR. RUDORFER: I wonder if it's as part of the stability requirement for the white count before a next level, say, before decreasing the frequency of monitoring, if a certain requirement for stability of the absolute count were required, if that would be a protective kind of measure. The same way if there's a concern during weekly monitoring, it would not be prudent to go to biweekly, I would think that before biweekly was reduced further, say, there should be either a minimal required absolute neutrophil count or a requirement, maybe over a certain number of measurements for stability of the absolute count.

DR. KECK: I agree.

(Laughter.)

DR. RUDORFER: I think it's fair to say we were impressed that the absolute neutrophil count has real meaning and validity in the hematologic community and, in fact, that clinicians apparently are taking it very seriously. So I think it's the sense of the committee that that should be part of the required monitoring. Am I

correct?

DR. WEISS: Yes.

DR. LEIBENLUFT: Yes, basically since that's the most meaningful number clinically.

DR. RUDORFER: To be fair, I don't know what the cost of that is. I would imagine that's much more expensive than the automated total white count.

DR. RYAN: Could we consider suggesting that the FDA might want to get more hematologic input on that question? There could be a range of algorithms they might consider at what white cell level you do ANC count, and presumably there may be folks even more expert than at least some of us on this committee, myself included.

DR. RUDORFER: Yes, I would agree, as well as the question of what should constitute a satisfactory ANC level where one could feel that the risk was minimized in terms of reducing the frequency of monitoring to the extent that such data exist.

Dr. Gerson.

DR. GERSON: First, obviously, the cost of the differential is more than just doing the automated CBC. We saw an estimate of that cost which is probably reasonable. A CBC may be in different laboratories $25 to $40 with the differential. Without, it's probably $10 to $15. So there is probably a doubling of the cost, time, and effort.

In terms of the safe value, remember that a normal ANC is down to 2000, clinical safety is down to 1000 neutrophils, but certainly it's very reasonable to consider a specified number which you have to achieve stably before which you could cut down to monthly monitoring, and that number might be 2000. 2000 would be a safe buffer below 1500. It should capture about 85 percent of the people in this room. So of normal CBCs, most of us have well above 2000 ANC. So if a person really isn't affected in terms of their blood counts by clozapine, then you'd expect the same neutrophil count.

DR. WEISS: Would there be more value -- this I'm really not sure from the discussion -- to get serial measures, for example, like the last three biweekly measures? In other words, the stability.

DR. GERSON: Sure.

DR. WEISS: To give you more information than just a value.

DR. GERSON: You have to define the word "stable." You have to decide whether you want the FDA to make that in discussion with the sponsor regarding the PI.

DR. WEISS: Well, I guess my question is clinically --

DR. GERSON: Sure. Stable would mean three or four repeat values, would be stable. Sure. That makes

pretty good sense to me.

DR. WEISS: Does that have clinical significance then?

DR. GERSON: Absolutely. First of all, we all bounce, but we all bounce within a range. And the unstable patient bounces like this, and there are different phenotypes. Most of us have our own set and bounce within a pretty tight range.

DR. RUDORFER: Dr. Katz.

DR. KATZ: Just a practical question. We talked about the variability of the various methods used, but let's say we required an ANC to be done and we picked a number like 2000 as sort of a screening value. Could that be done automated? For screening purposes, is that methodology adequate or not adequate?

DR. GERSON: It's pretty good, but you're talking about a national standard here, and so I'm not the expert on whether all laboratories in the country are capable of an automated ANC. There are automated approaches and automated machines that are very good for very normal ANCs, so ANCs in the 3000, 4000, 5000, 6000 range. It's the ones below that that become a problem. So you will have more flags. You'll have more need to repeat values, not to maintain above the 1500, but if you now want to maintain above the 2000 to go to monthly monitoring,

you'll have more instances where people will just have to look and do it manually.

DR. RUDORFER: Dr. Gerson, as long as you're standing, could I ask you a question? In terms of the state of the field, how far are we from a kind of home testing point where with a pin prick, one could get a WBC?

DR. GERSON: I have to be careful only because a home monitoring commercial entity has asked me for advice in development of it. So in a generic way, there are efforts to consider a method for home monitoring using a finger stick. The finger stick technology has historically again been more erratic. Obviously, in some cases it's more preferable. Some folks would prefer a finger stick and some folks would prefer a venipuncture. But there is at least one entity interested in developing a home technique, which would be, obviously, quite helpful.

DR. KATZ: Unless anybody else has something they want to say, I think those are the questions we had, and I think we got clear answers. I appreciate very much folks coming and helping us. It's a very complicated problem.

We do have one comment.

DR. LEIBENLUFT: Just one comment which is that I would like that the committee -- we've said this, but I guess to emphasize that if the FDA is able to do anything

about interfacing the two registries, that that would just be very, very helpful.

MR. DODSWORTH: Actually there are more than two registries because part of the approval process requires that every generic manufacturer that comes along has their own system. So right now there's the CNR that Novartis has. Mylan is now out there with a generic. They had to have the system. Zenith Goldline has to have their own system, and any subsequent generic of clozapine will have to have their own system. So it's going to be very difficult I think to bring them all together, and in the event that you were able to bring them together, someone would have to bear the cost for that.

DR. LEIBENLUFT: But I think it's fair -- and other people on the committee please tell me if I'm wrong, but I think it's fair to say that it's the sense of the committee that that would be an important thing for the FDA to explore because it really did hamper the quality of the data.

DR. RUDORFER: If I can end on a kind of glass half full note, many of us are familiar with promising psychotropic medications that either never made it onto the market or were removed from the market for safety concerns. So I think the good news in our discussion today is that the FDA and industry have come up with a system that works

and that's allowed this very valuable medication to be on the market these last dozen years. So I think that they deserve our thanks for that, and we're pleased to help make the system even better.

Thank you all for your participation.

(Whereupon, at 3:15 p.m., the committee was adjourned.)