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Hilton Gaithersburg
Perry Parkway
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PARTICIPANTS

Wayne K. Goodman, M.D., Chair
Karen M. Templeton-Somers, Ph.D., Acting Executive Secretary

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Andrew C. Leon, Ph.D.
James J. McGough, M.D.
Philip S. Wang, M.D., M.P.H., Dr.P.H.
Dilip J. Mehta, M.D., Ph.D. (Industry Representative)
Delbert G. Robinson, M.D.
Daniel S. Pine, M.D.
SGE CONSULTANTS (VOTING)

Matthew V. Rudorfer, M.D.
Carol A. Tamminga, M.D.
Andrew Winokur, M.D.

SGE PATIENT REPRESENTATIVE (VOTING)

Gail W. Griffith - Washington, D.C.

FDA

Thomas Laughren, M.D.
Paul Andreason, M.D.
Gregory Dubitsky, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. GOODMAN: I thought it would be worthwhile, since this is a different group of participants, different audience members, just to go around the table quickly and introduce ourselves.

I am Wayne Goodman, Chair of Psychiatry at the University of Florida, and my research specialty is in obsessive compulsive disorder.

DR. TAMMINGA: I am Carol Tamminga. I am at the University of UT Southwestern, and my specialty is schizophrenia research.

MS. GRIFFITH: I am Gail Griffith. I am the Patient Representative to the committee. I am the author of a book about teen depression called Will's Choice.

DR. LEON: I am Andy Leon. I am Professor of Biostatistics in Psychiatry at Cornell Medical College.

DR. MEHTA: I am Dilip Mehta, retired pharmaceutical executive from Pfizer about seven or

eight years ago, and I am the Industry Representative on the committee.

DR. LAUGHREN: I am Tom Laughren. I am the Director of the Division of Psychiatry Products at FDA.

DR. ANDREASON: Paul Andreason. I am the Deputy Director.

DR. DUBITSKY: Greg Dubitsky, Medical Officer, FDA.

DR. ROBINSON: I am Delbert Robinson. I am at the Albert Einstein College of Medicine and the Zucker Hillside Hospital, and my specialty is early psychosis.

DR. PINE: Danny Pine. I am a child psychiatrist at the NIMH Intermural Research Program.

MS. BRONSTEIN: I am Jean Bronstein, a registered nurse. I am retired and my area of expertise was psychiatry, and I am the Consumer Representative.

DR. WINOKUR: Andy Winokur. I am Director of Psychopharmacology at the University of

Connecticut Health Center in Farmington, Connecticut.

DR. WANG: Phil Wang. I am a psychiatrist and epidemiologist at Harvard Medical School.

DR. McGOUGH: Jim McGough, Child and Adolescent Psychiatry, UCLA.

DR. GOODMAN: Dr. Rudorfer, do you want to introduce yourself?

DR. RUDORFER: I am Matthew Rudorfer. I am a psychiatrist. I am Acting Chief of the Adult Interventions Branch at the National Institute of Mental Health.

DR. GOODMAN: Before we formally begin today's proceedings, I wanted to add a footnote to yesterday's meeting. For those of you who were there, know that we went to some efforts to--we had some concerns about how the press and the public were going to greet our decision, and we went to some effort to craft a statement, although it wasn't a very smooth and beautiful process, and the final product wasn't exactly poignant, I think we made the point that we intended. After all, who

knows how Tom Jefferson would have done sitting in front of the audience with a laptop computer.

But anyway let me just read a couple of excerpts from a Reuter's newswire release on yesterday's meeting.

Panelists agreed long-term data could help doctors treat patients, but voted unanimously against new requirements, siding with patient and industry representatives concerned about slowing the delivery of new medicines.

Concerned about how the public would react to their decision amid such safety concerns, the panel took a second unanimous vote to support joint efforts between the industry and government agencies to study how the drugs worked overtime in order to help doctors.

Why couldn't we have said it that way? But anyway I think the point came across that our decision was acting in the behalf of public interest.

For the record, there is a number of statements that need to be read by our Executive

Secretary, Karen Templeton-Somers.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda 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 present no potential for an appearance of conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. Section 208(b)(3), full waivers have been granted to the following participants:

Dr. James McGough is a member of a competitor's speakers bureau. He receives less than $10,001 per year. He also is a consultant to a competitor and receives less than $10,001 a year. Lastly, his employer has contracts with two competitors. Each contract is funded for less than

$100,000 per year.

Dr. Andrew Winokur's employer has various contracts with three competitors. Each contract is funded for less than $100,000 per year. Dr. Winokur's employer has a contract pending with a competitor, but no funding has been received to date.

Dr. Andrew Leon is a member of two competitors Data Safety Monitoring Boards and receives less than $10,001 per year from one and hasn't received any compensation to date from the other. He is also an advisory board member for a competitor, however, he hasn't received any compensation to date.

Dr. Carol Tamminga's employer has a contract with a competitor funded at less than $100,000 per year.

Dr. Wayne Goodman's employer has various contracts with two competitors. Each contract is funded for less than $100,000 per year. In addition, his employer has a contract with a competitor. The funding received is between

$101,000 per year and $300,000 per year.

Dr. Bruce Pollock is a member of a competitor's speakers bureau. He receives less than $10,000 a year. He is also a member of two advisory boards for a competitor. He receives less than $10,000 per year per board. He is a member of two advisory boards for a competitor. However, he hasn't received any compensation to date. Further, Dr. Pollock is a facility member of a management board for a firm that is affiliated with one of the competitors. He receives less than $10,001 a year. Lastly, Dr. Pollock's employer has a contract with a competitor, however, his employer hasn't received any compensation to date.

Lastly, Ms. Jean Bronstein has been granted waivers under 18 U.S.C. 208(b)(3) and 21 U.S.C. 344(n)(4) of the Food and Drug Modernization Act for owning stock in an affected firm and a competitor. The stock in the affected firm is valued between 10,001 to $25,000, and the stock in the competitor is valued at less than $5,001.

Ms. Bronstein also owns a bond in an

affected firm and a competitor valued between $50,001 to 100,000.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

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

Lastly, we would also like to disclose that Dr. Dilip Mehta is participating in this meeting as an industry representative acting on behalf of regulated industry. Dr. Mehta's role on this committee is to represent industry interests in general, and not any one particular company. Dr. Mehta is retired from Pfizer.

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.

Thank you.

DR. GOODMAN: Thank you, Karen.

Bruce Pollock is not with us today. He had a family emergency. So, we have 11 voting members around the table.

I would like to ask Dr. Tom Laughren to give an overview of today's meeting.

Overview

DR. LAUGHREN: Thank you, Wayne, and good morning, and welcome back to today's meeting.

The topic today is the drug EMSAM. EMSAM is a patch formulation of the drug selegiline. It is being developed for major depressive disorder. It is an irreversible monoamine oxidase inhibitor.

This application has been under review for several years. It received a non-approval letter in March of 2002 based on our concerns about the adequacy of efficacy data. That concern was subsequently addressed, and we issued an approvable letter in January of 2004.

The company has responded to that letter, and there are several issues that are still under review, but the one issue that we would like the

committee's advice on today is the question of dietary restrictions for the 20 mg strength of this patch.

There are three strengths being proposed: 20, 30, and 40, and it is the 20 mg strength that is the topic for today in terms of dietary restrictions.

I am sure you are familiar with what is known as the "cheese reaction," which is a great concern for orally administered monoamine oxidase inhibitors. There is a dietary amine tyramine, which is a pressor substance if it enters the systemic circulation.

Ordinarily, this substance is metabolized by monoamine oxidase A that is present in the gut wall and in the liver, which prevents tyramine from entering the systemic circulation.

Now, the nonselective oral monoamine oxidase inhibitors, for example, phenelzine, block

MAO-A in the gut wall and in the liver, and therefore, they allow tyramine to enter the systemic circulation, which causes an increase in blood pressure.

Now, certain foods, for example, aged cheeses have a high content of tyramine and, hence, the name cheese reaction.

Now, the selegiline patch would be expected to have an advantage with regard to the cheese reaction, because it bypasses the gut wall, so there would be a decreased opportunity to inhibit monoamine oxidase A.

Now, the company involved, Somerset, has accumulated a substantial amount of data which they feel support the view that the 20 mg patch is relatively free of the risk of the cheese reaction.

They have indicated a willingness to accept dietary restrictions on the 30 and the 40 mg patch, because there is not as much data supporting the safety of those strengths without dietary restriction.

Now, why is this important? One issue to

keep in mind is that having to worry about dietary restrictions is a major disincentive for using monoamine oxidase inhibitors, and there seems to be a strong belief that there is some fraction of patients with major depression who may benefit uniquely from monoamine oxidase inhibitors, so there is a place in the armamentarium for a drug which would not need to have--a monoamine oxidase inhibitor which would not need to have dietary restrictions.

Now, the medical officer for this NDA, Dr. Greg Dubitsky, has concerns about risks even with the 20 mg patch if it's used without dietary restrictions, so he has argued strongly against permitting it to be marketed without dietary restrictions.

The Division has not reached a conclusion on this matter, and that is why we are seeking your advice. You have received Dr. Dubitsky's review in your package and a copy of his slides, and you will hear his arguments here today following my comments.

You have also received materials from the company and you will hear their arguments here, as well.

I think there is agreement on several issues. First of all, it seems clear, if you look at all the data, that the risk of a tyramine reaction with the 20 mg patch without dietary restrictions is probably far less than what is seen with the orally available typical monoamine oxidase inhibitors, but it is also true, and I think everyone would probably agree with this, the risk is not zero.

On the other hand, as I pointed out, not having dietary restrictions would likely increase the use of this monoamine oxidase inhibitors in those patients who may benefit from it.

So, after hearing the data and the arguments here this morning, there are two questions that we would like you to vote on, and I can bring those up.

The first question is: Do the available data for the EMSAM 20 mg patch support the

reasonable safety of this formulation without the need for dietary restrictions?

The second question is: If the EMSAM 20 mg patch formulation could be considered reasonably safe for marketing without the need for dietary restrictions, would it be acceptable to market the 20 mg patch without dietary restrictions and at the same time require dietary restrictions for the 30 and 40 mg patch strengths?

So, here the question is would this be confusing for clinicians and patients to have dietary restrictions on the higher strength, but not have dietary restrictions on the 20 mg strength.

So, those are the questions, and I will stop there and turn it over to Dr. Dubitsky.

FDA Presentation

DR. DUBITSKY: Good morning. My task this morning is essentially 4-fold.

First, I would like to provide you with a brief overview of this novel drug formulation.

Second, I would like to give you a short

review of tyramine and tyramine physiology, and how the effects of tyramine are measured, particularly with respect to blood pressure.

Third, I would like to review some of the high points of the data from tyramine challenge studies that were performed by the sponsor.

Last, I would like to review some of the pros and cons of the question that Tom mentioned, that is, whether the 20 mg patch could safely be used without dietary restrictions, and then I will present my recommendation and conclusions.

[Slide.]

What is EMSAM? EMSAM is a transdermal delivery system for selegiline. As many of you may know, selegiline is an irreversible inhibitor of monoamine oxidase. There are two forms of monoamine oxidase: Type A and Type B.

Selegiline shows relative selectivity for MAO-B at low clinical doses, but loses that selectivity as you go up to higher doses. I will say more about that later.

There is an oral formulation of selegiline

that has been available for many years. It has been marketed for Parkinson's disease, goes by the trade name of Eldepryl.

[Slide.]

The proposed indication for EMSAM is major depression and the presumed mechanism of action is inhibition of both MAO-A and MAO-B in the brain.

[Slide.]

There are three patch strengths which would be marketed. I have listed them here. I will refer to these simply as 20, 30, and 40 milligram patch strengths, and I have also provided the approximate amount of selegiline that is delivered by each patch over a 24-hour period.

[Slide.]

This gives you some idea of what the comparative pharmacokinetics are. For our purposes you can ignore the top curve. That reflects intravenous selegiline infusion, but if you look at the bottom two curves--I don't know if you can make out the first curve there--it has a very sharp peak early. That reflects the oral selegiline

preparation that has been marketed.

The middle curve, which reflects more of a continuous release of selegiline over a 24-hour period, it tends to build up sort of slowly, then, levels off, then drops shortly after 24 hours.

This just gives you some idea of how the pharmacokinetics or the selegiline patch compare to the oral selegiline capsules.

[Slide.]

A key issue before us this morning is can low dose, the 20 mg transdermal patch be safely used without tyramine restrictions.

[Slide.]

But before we delve into that, perhaps many of you, like myself, don't think about tyramine on a day-to-day basis. So, I do want to provide just a brief review of tyramine and the effects of tyramine and, in particular, some important terminology that you will hear repeatedly this morning.

[Slide.]

Tyramine is formed by the degradation of

protein in foods. Protein with aging or decay breaks down into free amino acids, one of which is tyrosine, which is then converted to tyramine. Therefore, foods that have undergone an aging or a decaying process do tend to have high amounts of tyramine, such as many aged cheeses.

[Slide.]

What does tyramine do? Structurally, it is similar to epinephrine and norepinephrine, but it does have a slightly weaker action. Once it is systemically absorbed, it is taken up by adrenergic neurons and displaces norepinephrine from synaptic vesicles. This causes large amounts of norepinephrine to be released into the synaptic cleft.

[Slide.]

Clinically, this produces what has been known as a "cheese reaction." One of the classic symptoms is a huge increase in systolic blood pressure. Early studies with tyramine and high tyramine foods did show a mean increase of about 55 millimeters of mercury.

Usually, the systolic increase is higher than the diastolic increase in blood pressure. You can also see an increase in pulse, palpitations,

headache, nausea, vomiting, diaphoresis, photophobia, and there are some rare reports of strokes, cardiac failure, and death from severe cheese reactions.

[Slide.]

The body does have a natural protective mechanism to protect against excessive tyramine. That is, tyramine is metabolized by monoamine oxidase Type A. Most of this occurs pre-systemically by MAO-A in the intestinal wall and also some MAO-A in the liver, which occurs as a first-pass effect.

Very small amounts of tyramine normally are absorbed systemically after getting through the gut and first-pass liver effect, and that small amount is further metabolized by peripheral adrenergic neurons.

[Slide.]

Traditional MAOIs, such as

tranylcypromine, do inhibit MAO-A at clinical doses and do allow large amounts of tyramine to enter the systemic circulation, producing a cheese reaction. Therefore, when these agents are used, foods and beverages with high tyramine content are prohibited.

Also, the inhibition that you see with these traditional agents is irreversible, that is, these agents are enzyme killers. After treatment, MAO-A must be regenerated, and that takes about a 2- or 3-week period of time.

[Slide.]

What are some foods that are rich in tyramine? As I mentioned, aged cheeses are probably the most common, also, air dried, aged, and fermented meats, sausages, and salami, soybean products, tap beer, broad bean pods, sauerkraut, pickled herring. This list isn't all-inclusive, but I have included some of the things that are most commonly ingested here in the United States.

[Slide.]

The effects of oral selegiline on MAO-A

are irreversible and, as I mentioned, it does inhibit MAO-A in a dose-dependent manner. At clinical doses of about 10 mg, you don't see much inhibition. At 20 mg, it becomes a little bit more measurable, you can see some effects. By the time you get up to 60 mg of oral selegiline, the degree of inhibition of MAO-A that you see does approach tranylcypromine or some of the traditional MAO-A's.

[Slide.]

As Tom alluded to, the rationale for transdermal delivery of selegiline is that in theory, selegiline would bypass the gut and the liver, and therefore produce only minimal inhibition of MAO-A in the intestine and the liver, and therefore, it might not be necessary to have a tyramine-restricted diet when selegiline is delivered transdermally.

The question we have is: Does this theory translate into safe clinical use?

[Slide.]

The sponsor conducted a number of number of studies, which I will describe in detail

shortly, to look at this issue to see what the actual clinical effects are of selegiline on MOA-A.

The objective of these studies is to provide a clinically relevant measure of the degree of MAO-A inhibition as reflected by the estimated minimum dose of tyramine that produces a clinically significant rise in blood pressure.

The lower the tyramine dose is taken to imply a greater degree of inhibition of MAO-A, and I will describe these studies in a little bit more detail.

[Slide.]

There are some common study characteristics that I just wanted to point out. These studies were generally small. They only had maybe 10 to 20 subjects. Generally, they studied young to middle-age healthy volunteers. These were usually conducted under fasted conditions, although there are one or two exceptions that I will point out later.

Tyramine in these studies was administered in capsules, and very few of these studies did

include a comparator group, and that latter point is important because it does raise a caveat about some of the data I will present in that some of the comparisons you will be looking at are not based on head-to-head comparisons within a study, but rather cross-study comparisons, so some of the variability you may see may be due to differences, small differences in study design or study population or study execution.

[Slide.]

Tyramine in these studies was dosed according to the algorithm. I have given you one example here. The challenges were done on 3 consecutive days. On the first day, a dose of tyramine that was thought to be reasonably safe, an estimated dose was administered, and depending on the response to that dose, the dose for the second day was determined.

So, in this case, if 50 mg of tyramine was administered on the first day, and you did see a positive response, a significant increase in blood pressure, on the second day, a lower dose was given

to see if the same response could be obtained with a lower dose, and similarly, if no response was seen on the first day, a higher dose was given, and the same process was repeated on the third day.

Again, the objective of this is to try to find the minimum dose of tyramine that did produce a clinically significant increase in systolic blood pressure.

[Slide.]

The overall design of these studies is depicted here. There were usually two baseline tyramine challenges. Again, each of those consisted of these 3 days of successive approximations to determine a minimum dose of tyramine that produced an effect.

Following the two baseline challenges, patients were administered the study drug, usually to steady state and sometimes longer, and following treatment with study drug, a third on-drug tyramine challenge was performed. Again, the idea was to see whether or not there was a difference between the minimum amount of tyramine that produced a response

at baseline compared to on-drug.

[Slide.]

Blood pressure was assessed at baseline, usually taken as a mean of 3 consecutive readings, and then after tyramine, blood pressure was measured about every 5 minutes for about 2 hours, then, about every 15 minute for 4 hours.

Just as an aside, the Tmax for encapsulated tyramine is approximately an hour or so, so we would expect that these measurements would pick up any increase in blood pressure that you might see when tyramine was administered.

The blood pressure endpoint was defined in these studies as an increase in systolic blood pressure of 30 millimeters of mercury or more compared to pre-tyramine systolic blood pressure readings, and that increase had to be seen usually for 3 consecutive readings.

[Slide.]

There is some terminology that you will hear later this morning, and I think it is important that we all be clear on just what these

terms mean.

First, the pressor dose for TYR30 is the estimated minimum tyramine dose required to produce a blood pressure endpoint at each challenge.

Baseline pressure dose was taken as the mean of pressor doses for the 2 baseline challenges.

Last, is a tyramine sensitivity factor, or TSF, which is the ratio of the baseline pressor dose to the endpoint pressor dose.

So, you can see if the pressor doses were comparable at baseline and after treatment, the TSF would be approximately 1, but as the endpoint pressor dose decreased, you would see a corresponding increase in TSF.

[Slide.]

So, how do we interpret these studies? A lower tyramine pressor dose or a higher TSF does imply a greater degree of MAO-A inhibition.

Based on previous studies that were done using a wide variety of foods and where people actually homogenized various foods and measured the

amount of tyramine, it has been estimated that tyramine-rich meals are thought to contain no more than approximately 40 mg of tyramine. Thus, pressor doses of about 40 mg or below do indicate a possible risk of a cheese reaction. You start to get a little bit worried when you do see minimum pressor doses in that neighborhood.

[Slide.]

Now, I would like to just present some of the tyramine safety data with EMSAM. Again, this isn't intended to be an exhaustive review of all of the safety data or I would be here probably all weekend.

DR. LEON: You mentioned the worry point for the pressor dose. What is it for TSF?

DR. DUBITSKY: Well, for TSF, well, that actually touches on an issue I am going to bring up a little bit later. It could be very variable, and I think one point I intend to make, and I am jumping ahead of myself here, but to answer your question I will do that, I don't think looking at the TSF itself is particularly informative.

If you want to determine the absolute risk in a particular clinical situation, for instance, somebody could have a baseline pressor dose of 800

mg, and an endpoint of 200 mg, which would give you a TSF of 4.

At the same time, if you had a baseline pressor dose of 200, and you dropped to 50, that would also give you a TSF of 4. But I think the latter situation would be a little bit more worrisome since the endpoint dose that you see 50 is much closer to that 40 mg sort of cutoff, so I don't think looking at TSF alone is particularly informative.

[Slide.]

I won't go through an exhaustive review of all the data from these studies, and these aren't even all the studies that were conducted, but these are the most relevant ones for our purposes here this morning.

This just gives you some idea of what studies were done, the number of patients, the doses and durations, baseline and on drug, pressor

doses that were seen and the mean TSFs that were seen.

I am going to take the data from these studies and look at it in a little bit more detail right now.

[Slide.]

At this point, the FDA and Somerset do agree that tyramine restrictions will be recommended for the two higher patch strengths, the 30 and 40 mg patches based on current data.

[Slide.]

Let me go through and just say a little bit more about why we think that those two higher patch strengths may be problematic.

One of the studies done, Study 48, did look at the effect of EMSAM 30 mg for 10 days in 10 healthy subjects under fasted conditions. In this study, the mean pressor doses were 470 mg tyramine at baseline and 210 on EMSAM, which gives you a mean TSF of 2.4.

So, what you do see here, as Tom mentioned, is there is an effect, there is no doubt

about that, EMSAM even at, well, the 30 mg dose does affect MAO-A activity.

[Slide.]

From that same study, if you look at the distribution of the minimum tyramine doses that produced an increase in blood pressure, you do see that two patients did have a pressor dose of 100 mg, and about six patients had 200, and the other couple of patients had tyramine pressor doses of 3- and 400 mg.

So, it is not terribly concerning because the lowest pressor dose you see is 100, so it does provide some margin of safety, but clearly, it is having an effect.

You move up to the 40 mg strength--

DR. PINE: A couple of questions. Can you go back to that last slide?

Am I right that everybody agrees, you agree, and the sponsor agrees that, you know, even though the ratio is 2, and the lowest dose in these 10 people was 100 mg, that that still is of sufficient concern that everybody would agree that

dietary restrictions should appear?

DR. DUBITSKY: Well, I wouldn't say that everybody would agree. This, I think is more suggestive than it is clear evidence of a significant safety problem, and there is one other factor, too, that I will mention in just a minute, and that is, that the experience with the 30 and 40 mg patches in Phase III studies isn't nearly as much as it is for the 20 mg. So, we don't have as much experience plus this, you know, it could be a problem, but I wouldn't say that everybody would agree on that.

DR. GOODMAN: One other question. Oh, you had one, go ahead, Dr. Winokur.

DR. WINOKUR: The way these data are shown, a question I was going to ask you about later, so to the extent you can comment on it in other data presentations, the distribution with different doses, so that you might talk about mean or model data, but I think it is also important to find out the percentage of people who are particularly sensitive to inhibition outside of the

mean range. In this case, a couple of the 10 showed a higher--even though these is a sufficient safety margin, there was a subset that showed clearly more sensitivity, and if you can comment on that in other data, that would be helpful.

DR. DUBITSKY: Yes, in fact, I am going to get into that once I discuss some of the pros and cons of the arguments.

DR. GOODMAN: According to the theory that you espoused earlier, with the patch, you shouldn't have significant inhibition either in the gut or the liver, so where is it occurring?

DR. DUBITSKY: Well, that is an interesting question. One possibility, there are a number of--and these are speculations--but one possibility is that some of the drug may be secreted into the gut after it is absorbed systemically.

Another is that as the drug does pass through the liver, not as a first pass effect, but just as part of the general circulation of the drug, it may cause some inhibition in the liver, so

those are just two possibilities. I don't think we clearly know, but perhaps the sponsor might have some further ideas about that.

DR. GOODMAN: Dr. Leon.

DR. LEON: I don't know if you just said it this morning, but were these pressor doses there rounded, is that correct, are these rounded? So, these could be they are rounded to the nearest hundred, is that right?

DR. DUBITSKY: Well, if you look at the endpoint doses, not baseline, endpoint tended to start with lower doses. If you go back--let me see if I can go back here and find that algorithm--for instance, here, yes, there is rounding, and it does tend to slight overestimate the actual pressor dose, probably in most circumstances.

So, for instance, here, you know, if someone's actual pressor dose was, say, 25 mg, you wouldn't see a response at the 12.5, but you would see it at 37.5, but it would overestimate the actual pressor dose by about 7.5 mg.

But with the endpoint doses, the

granulation is a bit more fine. So, here, you know, there are differences of about 12.5 mg. Yes, somebody could have an endpoint pressor dose of 12.5, 25, 50--I am sorry--12.5, 25, 37.5, 50, 75, 100, or 200.

At baseline, however, they did start out with higher doses of tyramine, and the granulation isn't quite as fine, and there, there could be an error up to about 100 mg.

DR. LEON: But at this lower level?

DR. DUBITSKY: At the lower level, the increments in the tyramine dosing are much smaller.

DR. LEON: Okay. Thank you.

DR. GOODMAN: One more question and then we will let Dr. Dubitsky proceed.

DR. RUDORFER: Thank you. Could you clarify the relationship of the dosage in the patch to the oral? I mean you had said earlier that the 30 mg patch delivers about 9 mg of selegiline over 24 hours, but yet the 10 mg oral dose provides minimal MAO-A inhibition. Is that comparable?

DR. DUBITSKY: I don't think you can make

a direct correlation between the amount of orally administered selegiline and the transdermal selegiline, simply because the metabolism of the drug once it gets in the body is entirely different.

With the patch, you know, you are bypassing the gut, you are bypassing the liver, whereas, with the orally administered, it is getting metabolized in the liver as a first-pass effect. In fact, the first-pass effect with the orally administered selegiline is huge, it is very large.

So, you do see, if you look back at those graphs of the Cmax for the two were approximately the same, but the AUC, the exposure for the patch was much greater because you do get that continuous release of selegiline over a 24-hour period, whereas, with the oral, it tends to peak and then drop off very quickly. I don't know if that answers your question.

DR. GOODMAN: I will permit one more question. Dr. Robinson.

DR. ROBINSON: It's just for my information. Do we know in terms of the tyramine effect, is there any age effect, for example, since

antidepressants are frequently used in the elderly, should we be concerned about, you know, are these results generalizable to that sort of population?

DR. DUBITSKY: Well, we don't have a lot of experience. As I mentioned, most of these studies were done in young to middle-aged adults.

There is not a lot of experience, there is some, and I think maybe the sponsor will present some of that data later, experience with the patch in elderly patients, but in terms of tyramine challenge studies, we really don't know a lot, but it certainly is a point worth considering.

DR. ROBINSON: None of these mandated studies have any geriatric volunteers.

DR. DUBITSKY: I don't believe any of the studies that I am going to discuss do. I don't know, and the sponsor can jump in if you want, I don't think, though, that any tyramine challenges studies were done specifically in elderly patients.

DR. GOODMAN: Any comment on that from the sponsors?

DR. SHAROKY: We will present data. In the tyramine studies, we did study older patients. The studies went from ages 18 to 63. Although predominantly it was a younger population, but

there were a number of patients approximately 30 over the age of 50.

[Slide.]

DR. DUBITSKY: Moving on the 40 mg match strength, Study 201 was a tyramine challenge study in which the 40 mg patch was administered up to 90 days in healthy males.

This study was done under fasted conditions. The data after the first 30 days did show that with a mean pressor dose of 575 at baseline, the endpoint on drug mean pressor dose was 84, so here you are seeing a much greater effect at 40 mg with a mean TSF of about 11.5.

[Slide.]

If you look at the distribution of pressor doses from this study in 18 subjects, you do see

that 4 subjects did have a pressor dose of 25 mg, one at 37.5 and seven at 50. So, I think this clearly does show that there may be some risk of a tyramine reaction at the 40 mg patch strength, much stronger data than at the 30 mg.

[Slide.]

As I alluded to a few minutes ago, there is less clinical trial experience with the two higher strength patches. Only about one-third of the patients in the EMSAM depression program used the 30 or a 40 mg patches, and that is out of approximately 2,600 patients.

[Slide.]

So, the outstanding question is: Should tyramine restrictions be recommended with the 20 mg patch?

[Slide.]

What I would like to do is just point out a few of the important findings, just summarize some of the important findings from these tyramine challenge studies.

First, there was evidence of a dose-response over the therapeutic range. There was evidence of some time dependency over the first 30 days of EMSAM administration, and there did appear

to be a food effect, and I will say a little bit more about each of those points.

[Slide.]

This displays the evidence that we have suggesting a dose-response for mean TSF. If you hold duration of treatment constant, and look at patients who were exposed to EMSAM for 9 to 10 days, you can see sort of a stepwise progression from 20 to 30, 40 mg.

If you look at the 30-day data, patients who received EMSAM for 30 days, here again you do see--and we only have data for two strengths, the 20 and 40--but you can see a marked increase in tyramine sensitivity between the 20 and the 40 mg patches.

[Slide.]

Just rearranging those bars and looking at the time-dependency factors, now we are going to hold those constant, and look at the effect of

duration of treatment, at the 20 mg patch strength, you can see an increase in tyramine sensitivity from 9 to 10 days of treatment up to 30 days, not a huge increase, but some increase.

At the 40 mg patch strength, you do see a large increase from 9 to 10 days up to 30 days, but in Study 201, which did go out and look at tyramine sensitivity at 60 and 90 days, you see it actually sort of even drops off, so we don't think that there is an increase if you go out beyond 30 days, but there does appear within that first 30-day period to be an increase in tyramine sensitivity.

DR. GOODMAN: What was the N there?

DR. DUBITSKY: Well, in 201, as I recall, the N was 18. I do have to caution you. The three bars, at the 40 mg patch strength, 30, 60, and 90 days are within a study, so those are head-to-head comparisons within the subjects. The 9 to 10-day data is from a separate study, so bear in mind that caveat that there may be some variation because those weren't strictly head-to-head comparisons, but in Study 201, the N was about 18 subjects.

[Slide.]

The evidence for a food effect--and this derives also from Study 201--is depicted here at 40

mg. What they did was to administer tyramine under fasted conditions at 30, 60, and 90 days, and then subsequent to that, at approximately day 96, the challenge was repeated under fed conditions. Here, you can see that under fed conditions, food does tend to decrease tyramine sensitivity considerably. It went from approximately 11 down to about 4. So, it does seem to decrease tyramine sensitivity approximately two-fold. So, that is something to bear in mind, too, knowing that most of these studies were done under fasted conditions.

[Slide.]

Now, I would like to get into some of the pros and cons of supporting the sponsor's proposal to market the 20 mg patch strength with tyramine restrictions, and I will also throw in a couple of my own caveats about interpreting this data.

[Slide.]

Argument No. 1, the mean pressor doses

with the 20 mg patch do suggest about a 10-fold safety margin. In the fasted state, mean pressor doses on drug were approximately 200 mg or greater.

Also, as I just mentioned, in the fed state, pressor doses do tend to increase about 2-fold, and since a tyramine-rich meal is expected to contain not more than 40 mg of tyramine, there does appear to be about a 10-fold safety margin. I don't know if everybody follows that, but I tried to make it as clear as I could.

So, that is one argument.

[Slide.]

The caveat that I alluded to earlier is that I think looking at mean pressor doses only gives you part of the picture. I think it does have some limited usefulness when you start considering the absolute safety of tyramine.

I think a more relevant question here is: What is the lower end of the pressor dose range, that is, do any subjects have a pressor dose of about 40 mg or below?

[Slide.]

As an example, from Study 45, this is the study where 20 mg was administered for 30 days. The mean pressor dose after treatment was 204 mg,

which does suggest a pretty wide safety margin considering that 40 mg cutoff that we have talked about.

But if you look at the distribution or pressor doses, it's a little bit more worrisome. There was one subject who had a pressor dose of 50 mg, and that patient, in fact, required a labetolol rescue, as I recall, because they had some pretty significant increase in the systolic blood pressure. There was also one person at 100 mg.

So, although the mean does suggest safety, when you look at the actual doses, and particularly if you think that you can extrapolate this to what might happen in a clinical setting, it looks a little bit more worrisome.

DR. GOODMAN: Just a clarification on the choice of 40 mg as the tyramine dose that seems to be standardized. In real terms, would that correspond to a dietary indiscretion of somebody

who took, ingested aged cheese in what would be the usual scenario of somebody who committed a dietary indiscretion, how much would you expect that they are going to ingest of tyramine?

DR. DUBITSKY: Well, from what I have read in the few literature articles where they have actually analyzed, done these analyses of tyramine and food, it would be at the high end. That would probably be more than just a mild indiscretion. That would be a fair amount of cheese.

There is a lot of variability in how you look at this, because even people who have analyzed cheese say that the tyramine content, if you consider the part of the cheese around the holes in the Swiss cheese is different from around the end of the cheese, so it is very variable, but I would say from what I have seen in the literature, and the sponsor may have more to say about this later, too, but I think the 40 mg would be a large amount of tyramine, probably more than just a minor indiscretion.

[Slide.]

Moving on to the second argument, this derives from Study 9802. This was not a typical tyramine challenge study. This has a slightly

different design. In this study, they took 12 subjects and actually fed them food that was felt to have large amounts of tyramine. They did this before and after EMSAM 20 mg for 13 days.

The mean estimated tyramine content of the meals was about 323 mg. This was actually done in two different meals. There was a low dose meal and a high dose meal. I am just going to focus on the high-dose meal here.

The range in that meal was about 244 to 378, but again these are estimates, so you have to take it with a small grain of salt.

Blood pressure measurements in this study were done about every 10 minutes for 5 hours post-meal. I would point out that the pharmacokinetics of tyramine when it is administered as food as opposed to in capsules is probably different, but even there, from what I have heard from people who do have some experience with this, it does appear

that probably the Tmax for tyramine ingested as food is probably longer, maybe 3 to 4 hours, but even there, I think in the study, an increase in blood pressure would have been detected since they are going out about 5 hours after the meal.

[Slide.]

So, how did this study turn out? Well, 3 of the subjects did have one-time systolic blood pressure increases after EMSAM treatment, anywhere from about 34 to 84 millimeters of mercury, and I do have to say that again these are one-time increases, and I think given the frequency of blood pressure monitoring in this study, and the fact that they only occurred on one occasion, does speak to the fact that probably these aren't true tyramine reactions, so I am not terribly concerned about that finding.

Also, no subject in the study did reach a pressor endpoint, which is defined here as greater than 30 millimeters of mercury, a 30-millimeter increase in systolic blood pressure based on moving averages from 3 consecutive readings.

So, this study does provide some reassurance that maybe the 20 mg patch would be safe.

[Slide.]

Argument No. 3 is that the TSF with the 20 mg patch is similar to that of Eldepryl, the marketed oral selegiline product. If you compare the two, the 20 mg patch with oral selegiline 5 mg bid for 9 to 10 days, you do see comparable tyramine sensitivity factors. Just to point out that the oral selegiline product has been marketed for several years without tyramine restrictions.

[Slide.]

This just displays the data for the mean TSFs for the patch comparing it to the oral selegiline, and you can see that the TSFs are very close.

[Slide.]

If you compare the 20 mg patch and the 5 mg bid oral preparation, in terms of the distribution of tyramine doses, pressor doses, you can see that with the oral preparation, there is

almost a normal curve there. You do have one patient with a pressor dose of 100. With the EMSAM patch, the distribution does appear to be slightly skewed towards the lower end, however, nobody did have a pressor dose less than 200.

Again, just as a hint here, since these two studies did involve different numbers of patients, I wouldn't pay too much attention to the magnitude of these, the height of these bars, but rather the general shapes of the two curves.

[Slide.]

One caveat I do want to mention is that there have been some rare hypertensive reactions with recommended doses of oral selegiline in patients who have ingested tyramine-containing foods, and this is from the Warning Section of Eldepryl labeling, so it may not be entirely clean, but there is a fair amount of experience, and there are just these few rare reports.

[Slide.]

Argument No. 4 is that the TSF with EMSAM is much lower than with the traditional MAOI

tranylcypromine.

[Slide.]

Here I have the TSF's for the three EMSAM patches, 20, 30, and 40 mg, and as you can see tranylcypromine is worse EMSAM in terms of tyramine sensitivity. Again, these are from separate studies, but I think the difference here is pretty remarkable. So, you are not seeing nearly the degree of inhibition of MAO-A with EMSAM that you are with tranylcypromine.

[Slide.]

Just to elaborate on that, in Study 9941, looking at the pressor doses for the 20 mg patch versus tranylcypromine 30 mg, you can see that everybody, 9 out of 9 subjects treated with tranylcypromine had a pressor dose of 10 mg, whereas, everybody on EMSAM had a pressor dose of 200 or higher. So, this just provides another way of looking at the data.

[Slide.]

Argument No. 5 is based on a clinical trial, safety data primarily from Phase II and III

studies. Over 2,500 patients in these studies who had depression were treated with EMSAM in doses ranging from 20 to 40 mg without dietary restrictions, that amounted to about 820 patient years of exposure.

The sponsor has done a number of searches that they will elaborate on to see whether, in fact, there were any hypertensive reactions in these studies among these patients, and to date, they have not identified any reactions.

DR. LEON: What percentage of those patients and patient years were 20 mg?

DR. DUBITSKY: The vast majority, I think it is about two-thirds, but I don't know if the sponsor wants to clarify that, but I believe it was approximately two-thirds of the experience was with the 20 mg patch.

DR. McGOUGH: Do you know if in the trials, did they exclude people with blood pressures above a certain limit?

DR. DUBITSKY: I believe that was an exclusion criteria.

SPONSOR: Would you ask the question again?, please.

DR. McGOUGH: Yes. Was there an exclusion

for people who had a blood pressure at baseline above a certain level for the clinical trial? And I guess, if so, what was the exclusion?

DR. SHAROKY: I am Mel Sharoky. I am the President and CEO of Somerset Pharmaceuticals. The answer to that question is the study protocols were excluding patients who were not normotensive or who were not treated with hypertensive medications and were normotensive, so the majority of the patient had normal blood pressure, and we can give you those numbers of how many patients were on medication and what they did over the course of the study.

DR. TAMMINGA: But they could be included if they were treated?

DR. SHAROKY: Yes.

[Slide.]

DR. DUBITSKY: There is one important caveat I do want to mention, and that is that in

the Phase II/III studies, blood pressure was not frequently monitored. Vital signs were usually checked, you know, every one to two weeks and frequently less often than that, so there is the possibility that some hypertensive reactions may have been missed.

[Slide.]

As I have presented, there are several strong arguments in favor of approving the 20 mg patch without tyramine restrictions, but now I want to present some of my concerns about approving the 10 mg patch without the restrictions.

[Slide.]

Concern No. 1, and this goes back to some of the data I presented earlier, there is no large difference in the minimum fasted tyramine pressor doses between the lowest and the highest patch strengths.

If you look at the distributions and look at the minimum pressor doses for patients treated with 20 mg versus 40 mg, you do see that the minimum pressor dose at 20 is 50 mg, and at the 40

mg patch, 25 mg. It is not a huge difference, particularly when you consider the fact that there may be some error in the way pressor doses were estimated using the tyramine dosing algorithm that I presented.

[Slide.]

Concern No. 2 is somewhat tied in with the first concern, but it is basically the variability that you see in tyramine sensitivity.

[Slide.]

Looking at Study 45, the range of pressor doses was 50 to 400 mg, which is an 8-fold difference. So, there is considerable between-subject variability in tyramine sensitivity, so one concern here is that individuals at the lower end of the range may be at risk for a hypertensive reaction.

So, I think it is again, I think I made the point already, but just to say it again, I think it is misleading just to look at mean pressor doses. I do think you have to look at the range and consider the lower end of that range.

[Slide.]

There is also considerable variability within subjects over time. One thing I did was to

go back, since we did have repeat tyramine challenges at baseline, we had 2 baseline tyramine challenges, to go back and see just how much variability there was within subjects at baseline.

In Study 45, 3 of the 12 subjects did have a difference--and these again were baseline assessments that were done about one week apart--3 of the 12 had a difference of about 200 mg in tyramine, and 2 of the 12 had a difference of 300 mg, which is rather significant, so it raises the possibility of, over time, an individual's tyramine sensitivity is not fixed, but can vary quite a bit.

[Slide.]

So, the high degree of variability in tyramine sensitivity, I think requires a large safety margin, that is, pressor doses well above 40 mg.

It does make it unlikely that the tyramine safety profile for the 20 mg patch is distinctly

different from the 30 mg and 40 mg patches, which at least at the current time would be marketed with tyramine restrictions.

It seems to me like if you looked at tyramine sensitivity, you are going to see a large overlap in patients treated with 20 mg versus patients treated with the two higher patch strengths.

DR. GOODMAN: Could you go back to a point, Dr. Dubitsky, so you are arguing that there is even intrasubject variability, and I may have missed this, but were most of the obvious variables controlled for, such as fasting, and if so, what do you think can explain that intrasubject variability?

DR. DUBITSKY: Most of these challenges were done under fasted conditions, and in terms of what explains it, if you go back and look at the literature on the tyramine and MAO-A for the past several years, authors do seem to report that there is considerable variation both between subjects and within subjects.

Why that is, again, I could speculate, people have speculated on everything from gastric emptying time and intestinal transit time to how

soon the dose is taken after a meal, and to other factors that we frankly don't know. There is a lot more research that could be done in this field, but unfortunately, we don't have real good answers to your question.

[Slide.]

The third and last concern we have is the potential for misuse and confusion in the marketplace. I think Tom alluded to this earlier.

[Slide.]

One possibility is that approving the 20 mg patch without restrictions may cause some patients to say, well, if it's okay at 20 mg, it is okay to use the 20 mg patch without restrictions, maybe it is okay at 30 and 40, as well.

Another possibility is that prescribers may get confused and forget, well, is it the 20 mg patch that is safe without restrictions, or is it the 20 and 30, you know, I don't remember, I kind

of get these mixed up in my mind.

So, although this isn't an extremely strong argument, in my opinion, it is something that I think has to be considered and we would like to hear some discussion of what you, as experts, think about the potential for confusion in the clinical use of EMSAM if it is marketed with a difference in the tyramine restrictions.

[Slide.]

In conclusion, I would say, on average, the EMSAM 20 mg patches do appear to provide a reasonable safety margin for use without tyramine restrictions.

However, it does seem likely that a small proportion of patients at all doses may experience some increased sensitivity to a potentially hazardous degree. So, again, if you focus on averages, I think it looks fine, but if you dig down at the patient level and patient level data, and look at the minimum pressor doses, it's a little bit more worrisome, and I think there is a subset of patients which could not be easily

identified that may have some problems if we do approve this without tyramine restrictions.

[Slide.]

So, my recommendation is that this drug, if approved, would be marketed with tyramine precautions at all three patch strengths in all three doses.

DR. GOODMAN: To clarify, by "precautions," you are not meaning a black box? How would those precautions appear on the labeling?

DR. DUBITSKY: As I recall, I think for the traditional MAOI', it does appear in the Warning Section. I don't know if you want to comment on that, Tom.

DR. LAUGHREN: Yes, it's a warning statement, it's not a black box.

DR. GOODMAN: Is it bolded? People care about this, as you know.

DR. LAUGHREN: I don't have the label in front of me. Maybe the sponsor has, because I am quite sure that the label that you are proposing is similar.

DR. DUBITSKY: I don't believe it is bolded, but I can't say for certain.

DR. GOODMAN: Well, we can come back to

this later, but I wanted to make it clear that we are not talking about a block box warning, correct? Okay.

Questions.

DR. PINE: It seems like Study 45 obviously, based on your review, is very important, where subjects have 30 days with the 30 mg and we look at the distribution of the doses, and in your discussion, you provided it as an example of where there are 12 patients.

Given how important that specific question is in that specific study, it would be nice to know in a larger group, you know, than just 12, were those one or two subjects just flukes or is that representative of what we would expect to see in treated patient.

Are there any other data that you could find or that you reviewed as far as 20 mg exposure for 30 days looking at that response?

DR. DUBITSKY: Well, just as background, as Tom mentioned, this review has gone over about a three- of four-year period now, and the studies that were submitted originally were reviewed by another reviewer.

However, I do think that the data I

presented is the most relevant. Although there are other data, some of those data were done with other formulations, that is, formulations that won't be marketed, or I know of at least one case where the criteria for a pressor dose, that is, how much of an increase you would see, et cetera, was different.

So, I don't think you can make good comparisons between some of those earlier studies and the studies I presented here, but perhaps the sponsor will say more about that later.

DR. ROBINSON: Also, on Study 45, it seems that there is one subject who had a pressor dose at 50 mg, and that seems to be our sort of cutoff of a potential danger signal.

Did the sponsor provide you with any

additional information about this subject as to potentially why they might have been an outlier or what their baseline pressor response was, et cetera?

DR. DUBITSKY: Well, I believe the tyramine sensitivity factor in that patient was in the range of about 5 to 6, so the baseline dose was approximately 300. They did provide some information on specific blood pressure readings. I don't have that data right here in front of me, maybe they can comment on it later, but in terms of exactly why we think that patient had it, I really don't know. It's due to unknown factors.

DR. GOODMAN: Dr. Winokur.

DR. WINOKUR: I had a few questions, if I might.

The first is you talked about the variability in tyramine sensitivity, which I think is an important parameter.

Is there any broader way to get a handle on variability in response to MAO inhibition with this agent? I know at least in the old days,

looking at platelet MAO inhibition was one measure, and I am just wondering whether there is--because you are looking at a very specific physiological marker--but I am wondering if there is any other way to get a sense of that, and comparing with the 10 mg oral where there is a lot of experience, how this preparation is affecting the system.

DR. DUBITSKY: There are some data looking at monoamine metabolites that was done with EMSAM. I didn't present those data, because I thought probably the clinically relevant endpoint, that blood pressure measurements are more important, but if you wanted to pursue that, perhaps the sponsor has more information on that, but I just don't have it right here in front of me.

DR. WINOKUR: The second question, you mentioned in passing with the experience with Eldepryl, there were a few cases of rare, but hypertensive crisis, what was the outcome of those cases?

DR. DUBITSKY: Honestly, I don't know. Those cases were reported actually to a different

division, because Eldepryl is approved for Parkinsonism. I never did actually see the actual reports, so I don't know the details of those cases. Also, I think it has been several years since they have been reported, so I don't know the details of the cases, I am sorry.

DR. WINOKUR: My final question is you presented the core clinical trial experience with, as I recall, about 2,600 patients where in that context, to the extent that we have data, it actually looked quite favorable.

I am wondering what sort of pragmatic experience do you think would be sufficient to allow us to feel reasonably comfortable, and a subset of those patients were at 30 and 40 mg.

DR. DUBITSKY: Also, I do want to point out that approximately 100 of the 2,600, though, were in a study where tyramine restrictions were enforced, so it is actually only about 2,500 that used EMSAM without restrictions.

Your question is a good one. In fact, it is a question I was going to ask the committee. I

am not entirely sure just off the top of my head what would be adequate evidence, are these data irrefutable, or is there something they could do to further demonstrate the safety of tyramine with the 20 mg patch or even the 30 or 40 mg patch. That was something I hoped that maybe you all would discuss later this morning

DR. GOODMAN: Dr. Tamminga, then Griffith, then Wang.

DR. TAMMINGA: Dr. Dubitsky, I had two questions. One, around the issue of the variability in tyramine sensitivity, have you seen any plasma levels that would make you think that the 20 mg dose is different than the 30 and 40 mg, such that systemic levels increased at the 30 to 40?

DR. DUBITSKY: Well, there is considerable variability in selegiline pharmacokinetics. I did go back for some of the patient with low tyramine doses, for instance, the patient who had the 50 mg dose, to see whether or not there were differences in the plasma levels of selegiline that might

explain it, and I can't say I found anything. The levels for those patients with low tyramine doses looked comparable to other patients, so I don't think there is a real close connection between levels of selegiline and tyramine sensitivity.

DR. TAMMINGA: I just had one more question, and that was in their total safety database, 2,500 patients that were treated, there was no known hypertensive reactions, but your caveat was that blood pressure was not frequently measured.

Were there other symptoms, like syncope, or other things that gave you some pause?

DR. DUBITSKY: Well, there were a few patients, and I think I did describe a couple of these patients in my latest review who did have some symptoms suggestive of a possible hypertensive reaction.

Unfortunately--well, fortunately, we had some data on the dietary intake of these patients--unfortunately, it wasn't detailed enough for me to really interpret it. For instance, we didn't know

the amount of cheeses that were eaten, we didn't know when they were eaten relative to an increase in blood pressure or, say, other symptoms that would have suggested a hypertensive reaction.

So, there were a few cases that were suggestive, but there just wasn't enough data to say, yeah, these were clearly hypertensive reactions related to the use of EMSAM while ingesting tyramine-rich foods.

DR. TAMMINGA: And there weren't any untoward responses that could be tied to this elevated blood pressure?

DR. DUBITSKY: You are talking about strokes and things like that? Not in these patients, no, no. These patients, the ones who had elevations in blood pressure were treated and didn't have any serious sequelae.

MS. GRIFFITH: My question has to do with the variability in tyramine sensitivity in two different populations, and you went into some detail in your lengthier report.

You talk about the sensitivity in elderly

patients, particularly elderly female patients wherein if a patient were treated with a 20 mg patch, it might resemble how as younger patient would react with a 30 mg patch.

My second part of that is you also talk about females using oral contraceptives, and since this may be a targeted medication for that particular group, there was some concern about how they may be ultra-sensitive.

Can you talk about those two?

DR. DUBITSKY: I am glad you mentioned that. Since my review was written back in August, since then those issues have been looked at by our biopharmaceutics staff in more detail, and with respect to age, there is an analysis that does show a very small increase in selegiline levels with age, and that particular analysis did show that if you compared fairly old females, let's say 70 years old, to 20-year-old females, there did seem to be an increase in selegiline levels.

However, I have just recently talked to the staff who looked at that, and they are not

entirely convinced that it's a significant effect, but they do say that in doing this analysis, they did identify a couple of patients who had very high levels of selegiline, two, in fact, and they don't know why, it is hard to predict, and more importantly, when these two particular subjects were exposed to a different dose at a different time of selegiline, they again saw the high level, so it was a replicated finding.

But in terms of why we don't know, but there does appear to be, for unknown reasons, some variability in a small subset of subjects.

In terms of the oral contraceptive issue, after looking at some data that was presented by the sponsor and some papers published in the literature, our biopharmaceutics staff really felt that they couldn't interpret the data, so at this point we don't really know whether oral contraceptives could be a problem or not.

DR. GOODMAN: Dr. Wang.

DR. WANG: Given the analogy between Eldepryl, you know, 5 mg po and the 20 mg patch in

terms of pressor doses, I am just curious. Did you review what was submitted for the approval of the 5 mg po just because why was that not considered an issue?

DR. DUBITSKY: Well, that was done back about 16 years ago, even before I came to the FDA, so, no, I didn't look at that, and I am not familiar with that.

DR. GOODMAN: Tom, you had a response?

DR. LAUGHREN: Yes, I just wanted to comment that the neurology group that has primary responsibility for Eldepryl have been involved in our recent discussions of the concern about tyramine sensitivity with the patch, and they are quite comfortable with not having restrictions on the Eldepryl 10 mg a day, despite the occasional case of hypertensive reaction. I think the sponsor is going to comment on that, but the neurology group is comfortable with no having restrictions on Eldepryl at that dose.

DR. WANG: The second question is you mentioned these case reports that have emerged, you

know, postmarketing. Any formal pharmacopeia studies of, you know, the frequency of hypertensive crises on this 5 mg po Eldepryl?

DR. DUBITSKY: Not that I am aware of. I don't know of any.

DR. GOODMAN: I would like to pursue that question just a little bit more, Dr. Dubitsky. Given the rather large database on Eldepryl and at least equivalent peak doses, is there anything in those data that give you concern about the choice of not having dietary restrictions?

I mean it would seem to me that there would be some comfort level provided by those data.

DR. DUBITSKY: I would tend to agree. Again, the only caveat I have is that since blood pressures weren't measured real frequently, and if you go back in the literature, there have been some reports of patients having significant increases in blood pressure without any symptoms, it is conceivable that there may have been hypertensive reactions, but again, you know, it is speculation, and I don't know of any particular cases where I

could say yes, this definitely looks like a hypertensive reaction.

DR. GOODMAN: Dr. Rudorfer.

DR. RUDORFER: If I could make a 16-year-old comment just about the introduction of Eldepryl, back at that time, many of us in the field of psychiatry were excited by the prospect of a new MAO inhibitor coming on the scene, although the problem seemed to be, as we have been discussing, at the higher doses, selegiline orally was just another MAO inhibitor, so it didn't seem to offer any advantages.

When it was released as an adjunct for Parkinson's, it got a lot of very favorable publicity naturally enough since it was a real advance, and Newsweek magazine had a particularly favorable story quoting many family members who reported how their afflicted relatives with Parkinson's were doing much better on Eldepryl.

This concerned me because the way I read the article, I thought many family members might look at this and say, well, if Uncle Mike is doing

so much better on one pill a day, maybe he should take two or three or four, and there was no discussion of MAO inhibition or dietary restrictions.

Since I was not yet a member of a prestigious advisory committee, and the FDA had no websites, and so there was no web, I went to my superior at NIMH and I said can I write a Letter to the Editor, which seemed appropriately low tech for the time, and no one had a problem.

So, my letter was published saying in so many words that this seems to be a real advance in Parkinson's disease, but watch out because more is not necessarily better. I didn't say MAO inhibitor, I didn't say cheese effect, but I just made some reference to complications and interactions at higher doses, hopefully, thereby saving the world for EMSAM.

My other semi-rhetorical question, though, is fast-forwarding to the clinical trial safety data you referred to, I am curious, though, why so many people were studied at the higher patch doses

without either the dietary restrictions or just closer blood pressure monitoring, so that we don't have those data now.

DR. DUBITSKY: Well, unfortunately, I came on the scene a little bit late, I didn't have the opportunity to review those studies when they came in as protocols to the FDA.

I do know that the one study, in fact, I believe it was Study 9802, was considered to be the study that showed that at least at 20 mg, EMSAM looked safe and therefore we wouldn't require restrictions in studies, and future studies looked at that dose.

I am not entirely clear why restrictions weren't in place for the higher doses. It's a good question, though.

DR. GOODMAN: I have been advised that we don't have any public participants who have signed up, so that gives us a little bit more time this morning to do our work.

What I would like to do is call a brief 10-minute break at this time and then come back for

the sponsor's presentation. I want to remind you we are operating in the sunshine. The committee members should confine their discussions to this forum and also ask that members of the audience or the sponsors help them refrain from discussing anything outside this room. Thank you.

Let's be back in 10 minutes.

[Break.]

DR. GOODMAN: We are going to be hearing a series of presentations from the sponsors. I am assuming that this is going to be a highly integrated presentation, so I would ask the committee members to limit their questions to those for clarification during the course of the presentations, because I think there will be plenty of time, we will make sure there is plenty of time afterwards for more in-depth questioning and discussion.

Our first speaker is Melissa Goodhead, and if you can come forward and introduce yourself.

Sponsor Presentation

Introduction

MS. GOODHEAD: Good morning. I am Melissa Goodhead. I am the Group Director of Regulatory Affairs and Quality Assurance for Somerset

Pharmaceuticals.

On behalf of Somerset Pharmaceuticals, we would like to thank Dr. Goodman and the panel for being here today. We would also like to thank the FDA for bringing this discussion before the committee.

[Slide.]

As FDA stated, there is concurrence about the safety and efficacy of EMSAM, our selegiline transdermal system. This product was developed to treat major depressive disorder.

Today's meeting will focus on an outstanding issue: the risk of tyramine-induced hypertensive crisis while on EMSAM without dietary modification. What you will hear today from Somerset and our consultants is a summary of the extensive data generated for our clinical development program.

These data will demonstrate that it is

safe to administer 20 mg EMSAM without dietary modification. This represents the removal of a major impediment for using MAOIs as a therapeutic option in the treatment of major depression.

[Slide.]

As outlined in Dr. Dubitsky's presentation, FDA is seeking guidance on two questions.

[Slide.]

To answer these questions, we prepared the following presentation.

First, Dr. Sheldon Preskorn will provide a brief overview of the MAOI class of antidepressants and the tyramine issue that has limited their use since their inception.

Next, Dr. Larry Blob will review the data that Somerset generated to fully characterize the tyramine sensitivity as it relates to the safety of EMSAM and supports our proposed labeling of 20 mg transdermal selegiline without dietary restrictions.

Then, Dr. Chad VanDenBerg will describe

for you Somerset's education plan for providers, pharmacists, and patients that would ensure the safe use of EMSAM.

Finally, Dr. Mel Sharoky will conclude our presentation and be available to answer any questions you might have.

Now, let's begin with Dr. Preskorn.

Overview

DR. PRESKORN: Thank you.

I am Sheldon Preskorn and I am here as a consultant to Somerset.

[Slide.]

In my presentation, I am going to cover five points:

1. Some discussion about clinical depression.

2. History of monoamine oxidase inhibitors.

3. Oral monoamine oxidase inhibitors tyramine and the hypertensive crisis.

4. The medical need for monoamine oxidase inhibitor without dietary restriction.

5. The concept of transdermal delivery of monoamine oxidase inhibitor and how this addresses the medical need.

[Slide.]

Briefly, major depressive disorder is a highly prevalent condition which causes significant morbidity and mortality. It is a heterogeneous disorder in the sense of age of onset differences, course differences, family differences, symptom clusters, and most importantly, for today, response to antidepressants.

No single antidepressant treats all patients with major depression. Moreover, 30 percent of patients with major depressive disorder do not respond when treated with a series of currently available antidepressants alone or in combination. Thus, there is the need for additional effective therapies.

[Slide.]

Monoamine oxidase inhibitors were the first effectively proven antidepressants back in the 1950s. They affect three neurotransmitters

believed to be important to the pathophysiology of major depression, that is, serotonin, norepinephrine, and dopamine.

Despite their proven efficacy over 50 years, they are infrequently used in part because of the need for dietary restrictions.

[Slide.]

IMS data from 2005 demonstrate that one-tenth of 1 percent of all antidepressant prescriptions in the United States are for monoamine oxidase inhibitors.

The practice guidelines for the treatment of major depression by the American Psychiatric Association specifically cites dietary restrictions as a reason to limit the use of monoamine oxidase inhibitors.

Surveys done over the past 15 years of American psychiatrists have consistent found dietary restrictions as a major deterrent to the use of monoamine oxidase inhibitors.

[Slide.]

As has already been mentioned, monoamine

oxidase in the gut is a barrier preventing the systemic absorption of tyramine. It is virtually impossible to normally eat enough tyramine in food to overcome this barrier.

[Slide.]

However, oral monoamine oxidase inhibitors can substantially inhibit intestinal monoamine oxidase. Thus, tyramine can enter the systemic circulation, and when in the systemic circulation can release norepinephrine in sufficient amounts to cause a sudden dramatic rise in blood pressure.

[Slide.]

This is what we refer to as a hypertensive crisis. It is important to distinguish this from chronic or essential hypertension. It is instead a medical emergency requiring immediate treatment because of the substantial elevation of blood pressure above 180/120 mm of mercury, and will lead to end organ damage particularly in the brain, but also in the heart and kidneys.

A tyramine-induced hypertensive crisis occurs within 10 minutes to 2 hours after the

ingestion of a high tyramine meal. This is a florid reaction which typically presents in the emergency room and is difficult to miss.

[Slide.]

Therefore, on oral monoamine oxidase inhibitors, it is important to watch a tyramine-restricted diet. That includes aged cheese, fermented and spoiled meats, and some yeast products. As has already been discussed, the maximum content of tyramine that can be consumed in a meal if 40 mg.

Again, the need for the diet and the potential risk of hypertensive crisis has significantly discouraged the use of monoamine oxidase inhibitors.

[Slide.]

Therefore, there is a clinical need for the efficacy of an oral monoamine oxidase inhibitor without the need for tyramine-restrictive diet.

[Slide.]

Now, this cartoon illustration illustrates the difference between oral and transdermal

delivery of a monoamine oxidase inhibitor.

On the left is oral delivery, on the right, transdermal delivery. With an oral delivery, the drug is delivered to the gastrointestinal tract. As it is absorbed across the gastrointestinal tract, recall that it is an irreversible enzyme inhibitor, so it is partially cleared in the absorption across the gut wall by irreversibly inhibiting monoamine oxidase.

[Slide.]

Therefore, a smaller fraction enters the portal circulation where it is delivered to the liver. Here again it undergoes first-pass clearance in part by covalently binding to the enzyme monoamine oxidase in the liver and also by cytochrome p450 metabolites to inactive metabolites.

[Slide.]

As a result of these two clearance, one across the bowel wall, one through the liver, a small fraction of the oral dose is delivered to the brain, which is the target organ of interest in

terms of the treatment of major depression.

Now, we will contrast that with the transdermal delivery.

[Slide.]

With transdermal delivery, the drug is delivered to the skin. From there, it directly enters the systemic circulation without going past the gut first.

[Slide.]

Therefore, a significantly larger fraction can be delivered to the brain where it again will irreversibly inhibit the enzyme.

[Slide.]

And a smaller fraction will be delivered to the gut. This is a critical difference that goes to explain why the difference in the PK profile that was shown by Dr. Dubitsky, that is, a sharp, short peak Cmax in terms of the oral delivery, and a sustained Cmax with regards to the transdermal delivery.

This allows substantial inhibition of monoamine oxidase in the brain, while preserving

the tyramine barrier in the gut.

[Slide.]

This has actually been tested in both animal studies and in human studies. This is one of the animal studies. This is in living guinea pigs, administered either on the left, oral selegiline, or on the right, transdermal selegiline.

The x axis is the dose administered. The y axis is the percent inhibition of monoamine oxidase achieved in 3 different target organs. The pink represents the duodenum; the green, the cortex; the blue, the liver.

As you can see, with every dose of orally delivered selegiline, you have great inhibition of monoamine oxidase in the duodenum than you do in the cortex, up to 70 percent inhibition.

Now, the reason why 70 percent inhibition is critical is earlier studies done showed that inhibition of 70 percent monoamine oxidase in the brain is necessary to get measurable increases in norepinephrine, serotonin, and dopamine, the

putative mechanism for antidepressant response.

Now, we will contrast that with the transdermal delivery in which you can achieve 70 percent inhibition of monoamine oxidase in the brain with only 20 percent inhibition in the duodenum and virtually none in the liver, meaning that one achieves a meaningful concentration in the brain and yet leaves the tyramine barrier intact in the gut.

[Slide.]

So, then the question is: Can 20 mg of transdermal selegiline be delivered in such a way as to provide antidepressant efficacy without the need for dietary restrictions?

[Slide.]

The focus of today's meeting is not on the antidepressant efficacy of transdermal selegiline, because that has already been established, but I thought it's useful to at least 3 positive placebo-controlled studies that demonstrated the statistical superiority of transdermal selegiline over placebo.

Two of these studies were acute efficacy trials, one was a relapse prevention study. One acute efficacy trial used a fixed dose of 20 mg of

selegiline, the other used a flexible upward titration to 40 mg.

[Slide.]

Now, Dr. Larry Blob from Somerset will present the safety data on tyramine.

Thank you very much.

Safety- Tyramine

DR. BLOB: Good morning. I am Larry Blob.

Transdermal selegiline at a dose of 20 mg does not require dietary tyramine modifications. Dr. Preskorn has just presented some important concept regarding tyramine content in food, hypertensive crisis, and monoamine oxidase inhibition.

This section of the presentation will concentrate on the body of evidence that supports the use of 20 mg transdermal selegiline for the treatment of major depressive disorder without dietary modifications.

[Slide.]

There are four categories of evidence.

First, the safety of the 20 mg dose of transdermal selegiline is supported by the 16-year safety profile of oral selegiline, which is safely administered with a normal diet.

Second, the tyramine challenge program demonstrated that 20 mg transdermal selegiline and 10 mg oral selegiline, the recommended daily dose, caused the same low level of inhibition in the intestinal MAO.

This level of inhibition for these two formulations of selegiline is small enough to preserve the natural tyramine barrier in the intestine. Further, the program demonstrated the safety of transdermal selegiline by clearly distinguishing it from oral MAOIs, such as Parnate, that inhibit MAO in the intestinal tract to a degree that destroys the natural tyramine barrier.

Third, the food challenge studies showed that in clinical practice, transdermal selegiline is safe because patients will not be able to eat

enough tyramine in food to cause a hypertensive crisis.

Fourth, the entire transdermal Phase III program demonstrated the safety of transdermal selegiline, not only to dose of 20 mg, but also at the higher doses of 30 and 40 mg. The program studied 2,500 patients up to the age of 95, all on normal diets. There were no events of hypertensive crisis. Transdermal selegiline contains the same active ingredient as oral selegiline or Eldepryl.

[Slide.]

While both formulations contain selegiline, the transdermal formulation achieves antidepressant levels in the central nervous system at the 20 mg dose, and the oral formulation does not at the 10 mg dose.

Both formulations preserve the intestinal barrier to tyramine as demonstrated in our tyramine challenge program, which will be discussed shortly.

Because of the similar low inhibition of intestinal MAO, the safety profile of oral selegiline supports the safety of the transdermal

formulation without dietary modification.

[Slide.]

Oral selegiline has been approved in the United States since 1989 for the treatment of Parkinson's disease. This population is older than the major depressive disorder population, therefore, is potentially more vulnerable to adverse cardiovascular events.

Over the past 16 years, more than 1.5 million patients have safely used oral selegiline without dietary modifications. Epidemiologic data support this safety record.

[Slide.]

There are over 250,000 patient years of exposure to oral selegiline administered without dietary modifications in the AERS and IMS health records from 1997 to 2005, the period that represents the most updated computerization of this database.

Despite the potential limitations of pharmacovigilance data due to underreporting, it is possible to make cross-drug comparisons assuming

the rates of underreporting are similar.

In this database, there are 4 cases reported as hypertensive crisis on oral selegiline, yielding a rate of 1.56 per 100,000 exposure years. There are 19 cases reported for the positive control parnate, which is a rate of 43.36 per 100,000 exposure years.

[Slide.]

The reports of the hypertensive crisis in oral selegiline may not be related to tyramine sensitivity at all. To date, we have been able to obtain the clinical histories of 3 of the 4 cases.

All 3 histories showed that the cases were not related to tyramine exposure. Instead, they were related to pharmacodynamic interactions with and among multiple drugs that resulted in sympathomimetic effects. We have the details of those cases available today for your review.

We have not yet been able to obtain the details of the last report, so for now this case must be considered a tyramine-related hypertensive crisis. That means that the tyramine-related

hypertensive crisis rate in this elderly population is less than 0.4 per 100,000 exposure years.

[Slide.]

This safety profile is robust particularly in a population of this age and potential vulnerability. More evidence of the safety of the 10 mg dose of oral selegiline comes from a large placebo-controlled trial called DATATOP.

DATATOP investigated the effect of oral selegiline and vitamin E in the treatment of Parkinson's disease in 800 patients for up to 10 years. There was no increase in mortality between oral selegiline-treated patients with Parkinson's disease in this study and a separate population without Parkinson's disease matched for age and gender.

The annual mortality for the oral selegiline treated patient in DATATOP was 2.1 percent while the matched cohort had an annual mortality of 2.7 percent.

Not only was there no increased rate of mortality on oral selegiline, but there is also no

increase in the rate of cardiovascular or cerebral vascular events with oral selegiline, a drug that has been safely prescribed without dietary modifications for 16 years.

DR. LEON: Could you go back to the previous slide, please. Can you describe the size of the sample, the matched cohort, and the ways in which that sample was matched, please?

DR. BLOB: It was matched for the number of patients and for age and gender.

DR. LEON: 800 in each, so it was pairwise matched?

DR. BLOB: That is correct.

DR. GOODMAN: Was it 800 per cell or 400?

DR. BLOB: Well, the DATATOP study is a complicated study from the perspective of when people were on and off selegiline, so it was matched for--the number was about 800. It may have been slightly less, 700 and some patients.

DR. TAMMINGA: [Inaudible question.]

DR. BLOB: No, the initial randomization of DATATOP was 400 patients, actually, 200 patients

in 4 different groups, but all patients eventually go selegiline, all patients were eventually exposed to selegiline, and then re-randomized.

[Slide.]

There was no increased risk of myocardial infarctions, stroke, or TI on oral selegiline. The rate of myocardial infarction per 1,000 patient years was 6.4 while on oral selegiline, and 8.1 while on placebo.

Stroke and TIA, grouped together in this database, had an incidence of 6.7 on oral selegiline and 13.0 on placebo.

[Slide.]

The tyramine challenge program demonstrated that the levels of intestinal MAO inhibition of the 10 mg dose of oral selegiline and the 20 mg dose of transdermal selegiline are similar.

The studies used the well-established validated model used for over 30 years to compare tyramine sensitivity among MAO inhibitors. This test is the benchmark for all drugs that affect

intestinal MAO because it is a safe surrogate measure of the potential for a drug to cause a hypertensive crisis.

[Slide.]

In our tyramine challenge program, 214 subjects across 14 studies received multiple challenges with oral tyramine capsules before and after treatment with transdermal selegiline or a comparator drug.

Tyramine sensitivity was studied relative to the following variables and comparators: Time of exposure, up to 96 days; dose - 20 to 40 mg of transdermal selegiline; fasting versus fed conditions, and comparator drugs - oral selegiline or Eldepryl, which is labeled for a normal diet; fluoxetine or Prozac, also labeled for a normal diet; and tranylcypromine or Parnate, which requires tyramine-modified diets.

Prior to joining Somerset, in my capacity as a board-certified physician in Emergency Medicine and Internal Medicine, I treated over 100 patients with hypertensive crisis, although none of

them were related to tyramine.

Somerset selected me as the principal investigator in 10 or 14 studies. I am prepared to answer questions specifically about the various details of these studies if those questions go beyond my presentation this morning.

[Slide.]

The model used in the challenge program is called the "tyramine pressor test." This test is designed to measure the amount of tyramine needed to cause a sustained increase in blood pressure of at least 30 mm of mercury after exposure to an MAO inhibitor.

There are three phases to the standard tyramine pressor test model, two challenge phases, and one treatment phase. The first phase is a challenge with tyramine before subject receive any medication. During the second phase, subjects are treated with the study drug, and during a third, while continuing the study drug, subjects are re-challenged with tyramine.

[Slide.]

Each challenge titrated doses of oral encapsulated tyramine in order to determine the minimum tyramine dose needed to reach the

experimental endpoint. Endpoint is reached when the subject has sustained an increase in systolic pressure of 30 mm above that day's pre-challenge systolic blood pressure.

Because the 30 mm increase is a moderate change that can occur due to a number of external and internal stimuli, the model requires 3 consecutive elevated blood pressure reading, each 3 minutes apart, to eliminate the possibility of spurious results.

This 30 mm standard is a safe surrogate indicator of tyramine sensitivity, but it is not a hypertensive crisis. It does show that the study drug has begun to breach the tyramine barrier in intestinal tract.

The minimum amount of tyramine that causes this increase is called the "minimum pressor dose." The minimum pressor dose is the smallest dose of tyramine that elicits the endpoint of 30 mm

increase in systolic blood pressure.

In this example, the minimum pressor dose at baseline was 400 mg, and after drug treatment, the minimum pressor dose was 200 mg.

To put these numbers into perspective, it is generally accepted that a high tyramine meal can contain up to 40 mg of tyramine. The minimum pressor dose is the best assessment of how sensitive an individual subject is to oral tyramine under various test conditions.

On the other hand, the best assessment of how drugs compare one to another across subjects is determined by the tyramine sensitivity factor or the TSF.

[Slide.]

The TSF is a ratio of the minimum pressor dose at unmedicated baseline divided by the minimum pressor dose in the medicated active treatment phase. Once again, while the minimum pressor dose is the best way to assess the effect of study drug on an individual patient, the TSF is the best way to compare one study drug to another, because it

adjusts for inter-subject variability and the baseline tyramine sensitivity.

One strength of this model is that each subject is his or her own control.

In this example, the ratio between baseline and active is 2, so this drug would have a TSF of 2. Even though this signifies a 2-fold increase in tyramine sensitivity from baseline to on-drug conditions, a TSF of 2 is low and safe.

[Slide.]

By comparison, if the minimum pressor dose in the pre-medicated phase were still 400 mg, but the on-drug minimum pressor dose was 10 mg, the TSF would be 400 divided by 10, or 40. This 40-fold increase in tyramine sensitivity would be high and would make it unsafe to eat a meal that was high in tyramine content.

The data from our tyramine challenge program, 14 studies and 214 subjects, was derived using this model. The program included 3 comparator studies.

[Slide.]

There were 2 key crossover studies. One compared 10 mg of oral selegiline to 20 mg of transdermal selegiline, and the other compared 20

mg of transdermal selegiline to 30 mg of tranylcypromine, a classic oral MAO inhibitor antidepressant.

A separate study examined the TSF of fluoxetine or Prozac, a widely prescribed SSRI antidepressant as our negative control.

The results showed that oral selegiline, fluoxetine and 20 mg transdermal selegiline all had essentially the same low, safe TSF, whereas, tranylcypromine had a TSF that was 14 to 20 times higher.

[Slide.]

In this crossover study, 13 subjects were challenged with tyramine after 10 days of exposure to oral selegiline, and one month later were re-challenged after 10 days of exposure to 20 mg transdermal selegiline.

The vertical axis shows a tyramine sensitivity factor of the TSF. The horizontal axis

shows the study drug. Each of the dots represents a TSF of an individual test subject.

For the 3 subjects that received 20 mg transdermal selegiline, the TSFs ranged from approximately 1 to 3 with a mean of 1.75. When they were treated with oral selegiline, their TSFs ranged from approximately 1 to 5 with a mean of 1.67. Both TSFs are low and safe. These almost identical TSFs demonstrate the similar intestinal MAO inhibition of these two formulations of selegiline.

Beyond the comparison of the two drugs using TSF, we can determine the clinical significance of these relative sensitivities by looking at the amount of tyramine that was necessary to evoke a blood pressure response.

In yellow, above the graph, are the mean pressor doses. These pressor doses represent the amount of tyramine that had to be administered to reach the endpoint for each drug.

What we see is that the mean pressor dose for both forms of selegiline were well over 300 mg.

These are large numbers especially compared to the 400 mg of tyramine that one person can eat in a high tyramine meal--40 mg, excuse me. Thank you.

[Slide.]

The results of the negative control with fluoxetine were similar. The fluoxetine TSFs ranged from about 1 to 3 with a mean of 1.43. The data from these tyramine pressor tests show the similar impact that these three drugs have on the gastrointestinal barrier of the tyramine; 20 mg transdermal selegiline has the same tyramine sensitivity factor as oral selegiline and fluoxetine, two drugs safely administered for more than 16 years with no dietary modifications.

Tranylcypromine, a long used oral MAO inhibitor that does require dietary modification, showed markedly different results in this model and served as a positive control.

[Slide.]

Ten subjects were challenged in the crossover design comparing 20 mg transdermal selegiline and 30 mg tranylcypromine or Parnate.

On this graph, which has a larger scale on the y axis than the previous slides, the TSFs for transdermal selegiline ranged from 1.3 to 2.5. The TSFs for tranylcypromine, by contrast, ranged from 30 to 55.

When tranylcypromine was first approved in the early 1960s, it caused many hypertensive crises which led to its withdrawal. Because of its well-accepted efficacy, it was subsequently reintroduced, but with dietary modifications.

In spite of this efficacy record, the use of Parnate in other oral MAOIs has been limited because patients and physicians are reluctant to use drugs requiring tyramine dietary modifications.

The results of the tyramine challenge studies confirm the known tyramine sensitivity of tranylcypromine, as well as the large difference between the TSFs of tranylcypromine and that of 20 mg transdermal selegiline.

DR. WINOKUR: Similar to the discussion that we had with Dr. Dubitsky, do you have any comment about the scatter of data for the mean

pressor dose across the series of studies you just commented on? In other words, to what extent was there a subset of patients showing service on the mean pressor dose closer to where there might be concern?

DR. BLOB: I will be discussing that in detail a little later on.

DR. LEON: Were these healthy subjects?

DR. BLOB: Yes, they were healthy volunteers.

DR. LEON: They were all healthy volunteers.

DR. BLOB: Yes. The range of the healthy volunteers were from 18 to 63, not necessarily in this specific design on this specific study, but the range over all was 18 to 63.

DR. LEON: And the mean age here, do you know?

DR. BLOB: I can find that for you, but I don't know off the top of my head.

These three comparator studies showed that the TSF for oral selegiline and fluoxetine, and 20

mg transdermal selegiline were similar and markedly lower than the TSF of Parnate.

These studies reflect a similar inhibition of intestinal MAO for fluoxetine and both formulations of selegiline, and marked difference in the effect of tranylcypromine.

These results form the scientific basis for the safe use of oral selegiline without dietary modification.

[Slide.]

Now, these studies looked at selegiline administered for 10 days to explore the development of tyramine sensitivity for transdermal selegiline over a longer period. We conducted additional TSF challenges for extended periods up to 90 days of treatment.

Steady State tyramine sensitivity is achieved by 30 days of exposure. There is no increase in mean tyramine sensitivity after 30 days, and even though on the highest dose of 40 mg, there continues to be a 4-fold difference in mean tyramine sensitivity between transdermal selegiline

and tranylcypromine.

DR. GOODMAN: Could you go back to that slide just for a moment. I was going to ask as question earlier of what you though constituted or signified a level of TSF that would be unsafe. I was estimating that it would be about 10. Would you say that is correct?

DR. BLOB: I would agree actually with Dr. Dubitsky in this. It is wiser to look at pressor doses, and later on in this discussion, the pressor doses, their whole range of subjects, I think I will answer your question. If not, I will get back to it later.

DR. PINE: I have a question about that slide, as well. So, this was within-subjects design where the same subjects were at day 30, 60, or 90, or between-subjects design?

DR. BLOB: No, that is the same subjects, 30, 60, and 90 days.

DR. PINE: So, I was wondering, you know, in thinking about the variability in response, what was the correlation in terms of getting some sense

of the stability coefficient for the replicability of the response across those repeated tests.

DR. BLOB: Although there was some variation, there was a great deal of stability from one subject, the same subject across the period of time.

DR. PINE: I mean I guess based on the presentation we heard this morning, I got the sense that that wasn't the case, which is why it would be nice to have a number, a correlation.

DR. BLOB: In the question and answer period, we will be able to show you many more data points especially for the 20 mg transdermal selegiline, it will give you an idea of the stability.

DR. GOODMAN: I can understand why the mean or minimal pressor dose may be more informative, but nevertheless, if most of your studies start at 400 mg, and they changed from 400 to 40, that is a ratio of 10, so I just want to get a ballpark of how to translate the TSF into something that is clinically meaningful.

DR. BLOB: Right. Well, the range in the pressor dose in these studies is basically 25 mg to 300 mg on the 40 mg transdermal selegiline, this

study we are looking at right here.

DR. GOODMAN: But you start at baseline with 400?

DR. BLOB: No.

DR. GOODMAN: Not always.

DR. BLOB: Not on this study. On this study, we started at a baseline of 50. So, it was different than our 10-day studies in the 20 mg patch.

DR. SHAROKY: Can I make a comment? I think Dr. Blob will get to it in a few minutes in the slide, but the reason that question is not an easy question to answer in terms of the TSF cutoff, as Dr. Dubitsky pointed out, that has really to do with the non-medicated baseline stage where someone may come in and have--well, firstoff, we have to give an enormous amount of tyramine because they are not on an MAO inhibitor, so anywhere from 300 to 700 mg may be needed for any one individual to

impact the tyramine barrier in the gut.

On the other side, where they have been on a medication, it's the pressor dose, it's the pressor dose. So, essentially, someone, as his example was, somebody might have 600 mg in a non-medicated, and on the medicated, have 200, so they would have a TSF of 3. Someone could still have a 200 as a pressor dose, but have a non-medicated side that was entirely different.

So, the TSF will vary, but in the design when you study the various drugs, you have the ability to compare one TSF to another to show similarity, but the pressor doses are what is critical in how sensitive a subject may be in terms of that 40 mg tyramine meal.

DR. GOODMAN: I follow now. You wouldn't want to give 400 mg to somebody who is medicated as a starting dose.

DR. SHAROKY: In fact, the study design specifically takes that in consideration in the non-medicated side, you have to give an enormous amount of tyramine, on the other side, you start at

a lower dose. Where we started at 400 mg on the non-medicated, on the medicated side we start at 200, for example, and go in small increments. Is that helpful?

DR. GOODMAN: It is.

[Slide.]

DR. BLOB: While studies based on ingesting tyramine capsules in the fasted state are important for establishing a theoretical threshold and confirm data from the literature, for patients in the real world setting, the most informative studies are based on consuming tyramine with or in food. The ultimate question is tyramine sensitivity and tyramine safety in patients on MAOIs who will be exposed to tyramine in foods and beverages.

Two pharmacodynamic studies in the fed state address this issue. In one study designed to challenge subjects with actual food rich in tyramine, subjects ate cheeses documented as foods containing the highest quantities of tyramine before and during Steady State treatment with 20 mg

transdermal selegiline.

Despite eating all the cheese they could possibly eat, at no point did any subject treated with the transdermal selegiline reach the blood pressure endpoint.

The results of this study were the basis for Somerset's agreement with the FDA to remove the requirement of dietary modifications from transdermal selegiline clinical program. From that point forward, all Phase III trials, 2,500 subjects across the dose ranges of 20, 30, and 40 mg were conducted on subjects with normal diets.

Because selegiline-treated subjects in this cheese study were unable to consume enough tyramine-containing food to elicit blood pressure changes, we developed a second study design in order to simulate a high-tyramine meal by providing encapsulated tyramine in the middle of a standard meal.

[Slide.]

In an extension of the Steady State study that exposed subject to transdermal selegiline for

up to 90 days, 8 subjects continued on 40 mg transdermal selegiline for an additional 3-day phase.

In this phase, they were challenged with encapsulated tyramine in the middle of a meal. This meal contained approximately 50 grams of fat, 135 grams of carbohydrate, and 30 grams of protein.

This is a standard meal based on USDA guidelines and published literature. On the left, mean tyramine pressor dose in the fasted state was 64 mg. On the right, the mean pressor dose in the fed state increased to 172 mg. This is an increase of 2.7 times over the fasting state to 172 mg, which is more than 4 times the 40 mg in the high tyramine content meal.

This is important because in a real world setting, it is difficult to consume 40 mg of tyramine in food and nearly impossible to consume 172 mg.

DR. GOODMAN: Can you show us the range in addition to the mean on that pressor dose, or just describe that to us?

DR. BLOB: The range in the fasting?

DR. GOODMAN: 40 mg fasting, yes.

DR. BLOB: From 25 to 300 mg, and in the

fed, from 75 to 200 mg.

DR. LEON: And what were the samples, the sample size?

DR. BLOB: Eight subjects. Two subjects in this study who had a fasting TSF of 25 mg, fasting, had fed pressor doses of 75 for one and 100 for the other.

DR. GOODMAN: I am sorry. So, there was one subject at 25 mg had the pressor response in the fasting state. Were there others below the 40 mg, level 2?

DR. BLOB: In the fasted state, yes, there were others that had 25 mg, four, one that had 50, and then several that had higher pressor doses in the fasting state. It is important to keep in mind, the difference and the importance of converting this to a fed state, because that is real-life conditions.

So, when we did this study, and 8 subjects

participated, the smallest ratio or smallest difference was a factor of 2.7 change from fasted to fed, in other words, 2.7 times their fasted number would reach what their fed number was.

DR. GOODMAN: Why do you say fed is more clinically relevant?

DR. BLOB: In the real life sort of situation, people are going to be eating food containing tyramine.

DR. GOODMAN: How about a cheese snack?

DR. BLOB: Even then, it will be food which is a high lipid food that they will be eating.

DR. SHAROKY: Can I make a comment? When we conducted--excuse me--have you gone over our cheese study?

DR. GOODMAN: Yes.

DR. SHAROKY: When we conducted our cheese study, the concept was to give as much, to actually recruit people to eat as much cheese as possible, and we did that, and we could not see a response in their blood pressure on the medicated.

So, although that removed the restriction in our clinical trials and allowed us to go out and do that, it wasn't adequate. What we were trying

to do is look and see the range and get a response on the other side.

Studies done in the past would frequently make the mistake of administering tyramine in food substance where you really don't have control over how much tyramine you are giving, so what we wanted to do is create the most extreme example where you gave encapsulated tyramine in a fasted state.

So already when you start, it is not a realistic life situation. You don't consume tyramine in a fasted state. The issue about this is diet. Now, there is tyramine in various liquids, which we will address, but, in general, the tyramine, the vasoactive amine comes in food. It comes in cheese, it comes in sauerkraut, and so the whole concept of dietary restrictions is food, and the various food substances will impact how much tyramine is absorbed.

So, after we completed our program in the

fasted state to generate the most extreme example, to find the most sensitive subject, we then did this study that Dr. Blob has described, that at the end of 90 days, gave people food to show that when we gave food in combination with encapsulated tyramine, so we gave a little bit of a meal, standard meal, a little bit of the normal encapsulated tyramine, and more food, all combined. That is as close as we could get to control it rather than just try to give food, we already did that with the cheese study, we were able to show that we could increase the amount, the pressor dose, making the patient much more safe when you gave food, and it was roughly 2.5 to 3 times what one requires.

So, the data from a scientific point of view is being presented in a fasted state, but the whole concept is tyramine is in food, and that's the danger.

DR. GOODMAN: Dr. Leon.

DR. LEON: Could you clarify, you said in the clinical trials of 2,500 subjects, there were

no dietary restrictions based on the earlier data. In the informed consent that each of these volunteers read and signed, was there any reference to dietary restrictions or risk of eating cheese while taking this for these 2,500?

DR. SHAROKY: For the 2,500 patients, in the informed consent, what we informed them about was the signs and symptoms and concern of hypertensive crisis. At the same time, we informed investigators about hypertensive crisis. All patients were on normal diet.

DR. LEON: There was no reference to eating cheese in the informed consent that each subject signed, is that correct?

DR. SHAROKY: Actually, I think we have the informed consent that maybe you could go to.

DR. LEON: Thank you.

DR. SHAROKY: Do you want to see that?

DR. GOODMAN: We would like to see it. I think it's a very good point.

DR. LEON: Sure. My question really is were they even implicitly advised do not eat

cheese.

DR. SHAROKY: No.

DR. LEON: Or maybe their clinician who helped them interpret the informed consent, and understand and make sure they understood the informed consent, did he or she emphasize that cheese--

DR. SHAROKY: No, actually, I can tell you that we went out of our way to make sure that--what our position was is that we were concerned about hypertensive crisis, so we wanted to make sure that the patients understood the symptomatology with the hypertensive crisis, so we made them aware of severe headaches, if they had nausea, if they had vomiting, anything that we thought might be perceived as a hypertensive crisis, and the same with the principal investigator, but we did not discuss any kind of dietary restrictions.

What we did do in the study was ask subjects, when they came back for their visits, we asked them about various foods that they may have eaten, and we attempted, in that diary, to also put

some foods that we thought were not high in tyramine content.

DR. GOODMAN: Thank you. When you find the informed consent, if you could show it to Dr. Leon.

DR. SHAROKY: Can we put it up, please.

[Slide.]

This is the first one. This is the first one where they were under dietary restriction.

DR. LEON: So, this is none of the 2,500.

DR. SHAROKY: No, I thought you wanted to see both.

DR. GOODMAN: We want to see both.

DR. SHAROKY: Yes, you did want to see both, so this is the one where we were concerned and wanted to make sure the patients did not eat the food.

DR. BLOB: The first clinical study before we did the fed study was done with dietary restrictions.

DR. SHAROKY: Our first study was done before we conducted that cheese study. So, we

wanted to make sure that patients did not put themselves at risk.

DR. GOODMAN: So, you are going to show us the other consent when you find it.

DR. SHAROKY: Yes, we have to get it.

DR. GOODMAN: That's fine. Why don't we go ahead with the presentation.

DR. BLOB: Next slide, please.

[Slide.]

Actually, in the United States, most meals contain little or no tyramine. This sample meal that one might imagine eating in a restaurant, composed of generous portions of food that are considered to be high in tyramine contains 39.8 mg of tyramine.

This would constitute a full meal that one might be able to consume within a one-hour period, which approximates the half-life of tyramine. It is hard to imagine eating multiple meals of this sort within the same one-hour period. That would be necessary in order to achieve the levels of tyramine that cause a blood pressure change in this

model.

For example, to consume the 172 mg of tyramine needed to achieve the pressor response on the highest dose of transdermal selegiline, that is 40 mg, in the fed state, one would have to eat four such meals within an hour.

It would be nearly impossible to consume enough tyramine in food to provoke a 30 mm blood pressure increase, let alone the high quantity that could provoke a hypertensive crisis.

These results provide reassurance for the majority of patients based on mean values of tyramine needed to provoke a blood pressure response. This gives a 4-fold safety margin based on mean values.

All the results presented so far have focused on mean values. In terms of safety, we must consider individuals who are at the extreme ends of sensitivity to tyramine, and therefore define the safety margin.

Two extended term studies looked at tyramine sensitivity on the 20 mg transdermal dose

at Steady State, and revealed the range of sensitivity among subjects.

[Slide.]

The two most sensitive subjects out of our total 67 exposed to 20 mg transdermal selegiline were in two different studies conducted at steady State. These studies were conducted in the fasted state, and it is important to keep in mind the difference between fasted and fed conditions.

The result showed a mean pressor dose of over 200 mg of tyramine. Indicated by the arrows are the two most sensitive subjects. These subjects had the lowest pressor dose of 50 mg fasted. Even for these extreme individuals, there is a 5-fold difference between the amount of tyramine required to cause an increase in blood pressure on the 20 mg transdermal selegiline versus the amount required on 30 mg of tranylcypromine.

The safety margin for transdermal selegiline can be defined in two ways. One is the comparison of the minimum pressor dose with the amount of tyramine a person can eat in a high

tyramine meal. The other is a comparison of tranylcypromine, a drug that is known to cause hypertensive crisis and serves as our positive control.

Focusing on the two most sensitive subjects in the trials provides a conservative estimate of the safety margin.

[Slide.]

Looking at this from the perspective of how much tyramine a person could consume in food requires a translation of fasting results into fed results using a factor of 2.5. This means the 50 mg result in the fasted state translates into a fed result of 125 mg of tyramine, which is still three times the 40 mg of tyramine that a patient can possibly consume in a high tyramine meal.

This is a 3-fold margin of safety for the two most sensitive subjects on 20 mg transdermal selegiline. For tranylcypromine, the conversion is from 10 mg of tyramine in the fasting state to 25 mg in the fed state.

The comparison between the minimum pressor

dose of 125 mg of tyramine on the 20 mg transdermal selegiline and the 25 mg on tranylcypromine provides a 5-fold safety margin for the two most sensitive subjects.

These results provide reassurance of the safety of the 20 mg transdermal dose since even the most tyramine sensitive patients can't eat enough tyramine to evoke a 30 mm rise in blood pressure, let alone the greater quantity needed to cause a hypertensive crisis.

Looking at safety even in terms of the amount of tyramine in a high tyramine meal, or in terms of a comparison to tranylcypromine, 20 mg transdermal selegiline is a dose with a substantial margin of safety.

DR. GOODMAN: I am sorry, it was probably obvious, what was that N? The two that you identified as being the highest. And what was the denominator, how many subjects were tested?

DR. BLOB: The denominator in the Steady State studies, the two together is about 20.

DR. GOODMAN: There were 20 all together

that you tested. Okay.

DR. BLOB: That's correct.

DR. GOODMAN: I thought it was just a matter of counting up the dots, I just wanted to make sure those were individual patients.

DR. BLOB: Yes, they are individual patients.

[Slide.]

Data following both short- and long-term administration of transdermal selegiline in healthy volunteers demonstrates that with regard to tyramine safety, 20 mg transdermal selegiline has the same intestinal MAO inhibition as oral selegiline and fluoxetine. Even the highest transdermal dose of 40 mg produces a change in tyramine sensitivity that is 4 times lower than tranylcypromine.

Patients taking 20 mg transdermal selegiline were unable to eat enough tyramine-rich food to reach the blood pressure endpoint. This means that they were even further from being able to eat enough tyramine-rich food to cause a

hypertensive crisis.

[Slide.]

In the Phase III program, there were no events of hypertensive crisis.

DR. LEON: You said patients. Are these healthy controls or are these--the previous slide.

DR. GOODMAN: I said patients.

DR. LEON: No, no, on the slide, it says patients, the last bullet. Are these patients or are these healthy controls?

DR. BLOB: I am about to get to the patients in a moment, but essentially, what we are saying is up to now I have been talking about subjects in controlled studies, but we are saying that patients will not be able to eat enough tyramine.

DR. GOODMAN: That's an inference or prediction.

DR. BLOB: Once again in the Phase III program, there were no events of hypertensive crisis.

[Slide.]

Our Phase III clinical program included 2,500 patients with over 820 patient years of exposure to transdermal selegiline at doses of 20,

30, and 40 mg without dietary modifications.

The program was designed to look for hypertensive crisis. Event of hypertensive crisis are medical emergencies requiring immediate medical intervention. They have specific and acute symptomatology and cause end organ damage. In the entire program, there were no deaths and no SAEs of hypertensive crisis.

Investigators were trained to actively look for any sign or symptom that could indicate a hypertensive crisis. They asked questions at each visit to assess any symptomatology that would suggest a hypertensive crisis, and they were to report any such symptoms.

Even though there were no reports of hypertensive crisis, to make certain that there could not have been any events masked by other AEs, we conducted an analysis of the entire Phase III database, and this was a comprehensive two-step

analysis.

[Slide.]

Step I was a computer-generated analysis of COSTART terms that would possibly reveal a hypertensive crisis masked by or misdiagnosis if other events.

During this step, there was also a collection of any occurrence of an increase in blood pressure above a threshold of 160/100. The analysis generated a list of patients with the occurrence of any event of interest. For each patient, there was a record of the dates of the event and all blood pressures recorded during the study.

In Step II, two physician monitors blinded to treatment applied an algorithm to select patients for further review. They found 178 patients and conducted a comprehensive review of each case report form. No patient was judged to have experienced a hypertensive crisis.

There were several patients who experienced blood pressure elevations in the course

of the study. The review found that none of these patients had the signs and symptoms that could indicate a hypertensive crisis.

Nonetheless, we also conducted a separate analysis of patients in controlled trials to determine if there was any increase in events of increased blood pressure on transdermal selegiline.

[Slide.]

This separate analysis looked at any patient who had a 20 mm rise in blood pressure above baseline and who reached a systolic blood pressure of at least 160.

In the controlled trials, the occurrence of these events was 1.4 percent on transdermal selegiline and 1.9 on placebo, demonstrating that there was no excess of events of increased blood pressure on selegiline.

DR. GOODMAN: A priori determination of those thresholds? In other words, how you picked those numbers of 20, why did you exclude it to systolic blood pressures greater than 160, and not, say, 140?

DR. BLOB: At least 160.

DR. GOODMAN: I understand. I just want to make sure that this was an a priori hypothesis.

DR. BLOB: Our decision point there was that there had to be some level which we would consider a dangerous blood pressure or something that might indicate that there was some problem with the tyramine-related reaction. We chose 160 as a number that was essentially fairly conservative in that regard.

DR. TAMMINGA: Could you say, were there equal number of selegiline-placebo, or what was the N for each one of those? I know that the combination is 1430.

DR. BLOB: Right. It was pretty close, but not exactly equal.

There was also no difference in the occurrence of AE hypertension with an incidence of 0.6 percent on transdermal selegiline and 0.7 on placebo.

[Slide.]

The 20 mg dose of transdermal selegiline

is an effective and safe MAOI antidepressant that does not require dietary modifications. This was demonstrated in our Phase III clinical trials and our tyramine challenge program.

The tyramine challenge program included 214 subjects and 14 studies. The program used an established model in which patients served as their own controls. The challenge program demonstrated that 20 mg transdermal selegiline has a lot inhibition of intestinal MAO similar to 10 mg of oral selegiline and 60 mg of fluoxetine, the negative control.

The program also demonstrated a several-fold margin of safety relative to the positive control tranylcypromine and to the amount of tyramine in the high tyramine meal.

Even for the most sensitive subjects, from those studies it is impossible to eat enough tyramine in food to cause a 30 mm rise in blood pressure on 20 mg transdermal selegiline.

After this safety margin was established, the Phase III program across all three doses was

conducted on a normal diet. Throughout the program, there were no episodes of hypertensive crisis, nor were there any increases in events of elevated blood pressure or in report of hypertension compared to placebo in controlled studies.

The totality of the evidence supports the recommendation for the administration of the 20 mg transdermal selegiline without dietary modification.

Unlike 20 mg transdermal selegiline, there are not equivalent oral models for the 30 and 40 mg transdermal selegiline doses.

Although these is evidence to support the safe use of 30 and 40 mg with a normal diet, there is not as much evidence as there is to support the 20 mg dose. Therefore, we are recommending dietary modifications for the two higher doses of transdermal selegiline until more data become available.

We will educate prescribers, pharmacists, and patients regarding the proper use of the

transdermal selegiline specifically with regard to the use of appropriate diet.

Dr. Chad VanDenBerg will now describe the specifics of this educational program.

Education and Communication of

Dosing Instructions

DR. VANDENBERG: Dr. Blob has addressed the first question for this committee.

[Slide.]

The second question asks whether it is acceptable to market the 20 mg patch without dietary restrictions while requiring dietary modifications at the 30 and 40 mg doses.

[Slide.]

We have developed a comprehensive education and communication program specific to the appropriate use of EMSAM and the dose-dependent dietary modifications.

The goal of the program is to ensure high awareness of the dose-dependent dietary modifications of EMSAM versus other monoamine oxidase inhibitors indicated for depression. The

program design is built upon standard educational efforts used for most marketed drugs by adding specific enhancements aimed at healthcare providers, as well as the patients.

Furthermore, our packaging design was created to reinforce these educational messages. Each of these measures is proposed to ensure the safe and effective use of EMSAM.

[Slide.]

The primary purpose of the program is to ensure patients understand and follow dietary modifications at the 30 and 40 mg doses. Beyond this, we have identified two practical issues to be addressed when EMSAM is prescribed.

First, is to safeguard against patients using multiple patches simultaneously by recommending to physicians to have them educate patients to use only one patch at a time and to discard any unused patches whenever their dose has changed.

The second is the need for patients to continue a modified diet for two weeks following

discontinuation of the 30 or 40 mg dose or down titrating to the 20 mg dose.

[Slide.]

We have already conducted market research to test the effectiveness of our message to physicians and patients, and through this research have determined that after a single presentation of the message, 96 percent of physicians and 94 percent of patients clearly understood the need for dietary modifications at the higher doses of EMSAM.

It is important to note that after launch, this message will be received multiple times by prescribers and patients allowing us to reach our goal of 100 percent awareness.

[Slide.]

At the prescriber level, product usage information consistent with the label will be provided through educational programs and sales representatives. Further, sales representatives will provide educational materials that prescribers can distribute to the patients.

Planned materials include patient

information sheets on the diet modifications and wallet size reminders of the foods to avoid while on EMSAM doses of 30 or 40 mg.

Enhancements in the educational program include direction to prescribers to educate patients to use the product exactly as prescribed, apply only one patch at a time, and stay on a modified diet for two weeks after discontinuing treatment on the 30 or 40 mg dose.

A change in prescriber behavior will also be requested. Prescribers will be instructed to write dietary modifications required on each 30 and 40 mg prescription.

To measure the effectiveness of this program on a biweekly basis we will conduct surveys to monitor physician understanding of the dietary modifications and their practices surrounding how they are counseling their patients on these modifications.

As appropriate, corrective actions will be taken consistent with the results of these surveys.

[Slide.]

At the pharmacy level, the message will be reinforced through teleconferences and mailings to educate pharmacists on the dose-dependent dietary

modifications. In addition, many pharmacies utilize third-party prescription services to obtain product-specific information. On an ongoing basis, we will provide the most current approved product information to these services including First Data Bank and Mediplan.

[Slide.]

We will also provide the patient with enhanced education materials in addition to the standard patient information leaflet. A patient starter pack will provide a sample of the product supported by specific educational materials that reinforce the education instructions in the patient information leaflet.

These materials will address key patient education issues including following appropriate dietary modifications, using only one patch at a time, and staying on a modified diet for two weeks following discontinuation of 30 or 40 mg dose.

Patients will also be informed of an EMSAM-specific website where they can obtain information regarding dietary modifications in addition to other product information.

[Slide.]

Finally, unique and distinctive packaging

has been designed to reinforce and solidify these messages for the same use of EMSAM. In addition to the standard package insert and patient information leaflet, there are a number of unique features of the EMSAM packaging.

For the higher dose, there is clear indication for dietary modifications, and this message is also prominent on the patient information leaflet within each carton.

Each dose strength if prepackaged by the manufacturer in a sealed carton of 30 individual patches. In this way, and in contrast to many other medications, no repackaging is necessary at the pharmacy level, ensuring that 100 percent of our patients will receive the key messages.

The packaging is further distinguished by

distinctive colors for each dose strength to differentiate doses and further alert patients to the appropriate product usage.

[Slide.]

Beyond these education and outreach programs, there are additional aspects of the pharmacovigilance program. The pharmacovigilance program also consists of procedures and reporting mechanisms including medical evaluations and database processing of adverse effects, regulatory submission of expedited and periodic reports, standard surveillance for previously unrecognized adverse events, and updates of product information.

Beyond this planned features, there are additional activities proposed to detect any cardiovascular-related signals. Sentinel events of hypertensive crisis and end organ damage will trigger specific case identification and retrieval.

A targeted questionnaire will systematically classify each of these events. The questionnaire results will generate data for individual and aggregated reviews.

Lastly, to provide for longer term safety evaluation, we will work with the FDA to determine the appropriateness of a pharmacoepidemiology study

to implement after approval.

[Slide.]

In conclusion, we have outlined a comprehensive multifaceted plan designed to effectively communicate the message for the same use of EMSAM. This program acknowledges unique prescribing instructions relative to other monoamine oxidase inhibitor antidepressants and utilizes enhanced education and communication tailored for prescribers, pharmacists, and patients.

We have developed distinctive packaging to reinforce these messages to prescribers and consumers. The overall program contributes to the most appropriate use of the product and, ultimately and most importantly, to patient safety.

Dr. Melvin Sharoky will now conclude our presentation.

DR. GOODMAN: While you are still up

there, I have a question about, not the packaging, but the list of foods that have a high content of tyramine. I remember in the days when I used to prescribe MAOIs frequently, I was always searching for a comprehensive, but clear list, authoritative list.

I wonder if you have any example of such a list that you propose to include either in the package insert or other educational materials.

DR. VANDENBERG: We have worked hard to develop a current list.

[Slide.]

Here is the proposed label for the 30 and 40 mg diet. This has been gained through various literature searches, current up-to-date literature on the tyramine content of various food.

DR. GOODMAN: Can we go back to that a minute? I didn't see any organ meats listed, or I don't know, maybe I am not up to date anymore.

DR. VANDENBERG: I am not going to comment specifically on specific foods. This list was gained by extensive literature review and has been

reviewed also by the FDA.

DR. GOODMAN: I may be getting too compulsive over this, but even in clinical practice--is that the more comprehensive? Okay. That looks better. We are not being asked to do that, but I would just urge, make sure that that is the most comprehensive. What happens in clinical practice is you get bombarded by questions and it is very useful to actually know something about the approximate content of the tyramine, or even a lot of times they will say what is a fava bean, and you will stay away from falafels. I think the information needs to be clear to both the prescriber and the patient. Otherwise, there is a good chance for confusion.

DR. VANDENBERG: I think we would agree with that.

Dr. Sharoky.

Conclusions

DR. SHAROKY: Good morning. Why are we spending all this time and effort over a diet, why is this so important? Because diet is a major

impediment for using monoamine oxidase inhibitors as a therapeutic option in the treatment of depression.

Despite all the existing therapies, depression remains a serious illness with significant morbidity and mortality. MAOIs have been available since the 1960s with proven efficacy, but are underutilized because they required a tyramine diet.

EMSAM (transdermal selegiline) achieves antidepressant activity while maintaining an adequate barrier to tyramine in the gastrointestinal tract. This provides for a safe MAOI without the burden of dietary restrictions

Our clinical program has demonstrated the safety of EMSAM. We conducted an extensive tyramine challenge program using a model accepted for over 30 years as the gold standard for comparing MAOIs.

Our study showed that tyramine sensitivity factor for EMSAM 20 mg is comparable to oral selegiline and fluoxetine, and distinctly different

than tranylcypromine, a drug requiring dietary restrictions.

Oral selegiline with a comparable TSF to EMSAM 20 can serve as a safety model. Oral selegiline has been administered to over a million and a half patients for 16 years without dietary restriction and has a robust safety record.

We have demonstrated in our food challenge study that subjects could not eat enough cheese to meet the endpoint of raising the blood pressure by 30 mm of mercury. Even our most sensitive subjects in the 20 mg program would have to eat three times the amount of food contained in a high tyramine meal to reach endpoint.

In our Phase III program, 2,500 patients with major depressive disorder were administered transdermal selegiline doses ranging from 20 to 40 mg, and no hypertensive crisis occurred. The data that we have presented demonstrates that EMSAM 20 mg can be administered without dietary restrictions.

There is also a margin of safety for the

30 and 40 mg doses. No hypertensive crisis occurred in our entire program. However, since limited data exist for the 30 and 40 mg doses, our current recommendation is for dietary modification at these higher doses.

Most importantly, we are committed to the safe use of EMSAM in patients with major depressive disorder. The product label, the education program, designer packaging, and pharmacovigilance plan work together to make sure that patients understand and follow dose-dependent dietary modifications.

EMSAM 20 mg without dietary restrictions is an opportunity to offer physicians a safe and efficacious monoamine oxidase inhibitor that will make a substantial difference in the lives of patients with major depressive disorder.

Thank you and I am prepared to answer any of your questions.

Questions and Answers

DR. GOODMAN: Yes. Please stay up there if you would.

I want to start with one question or comment. Although our task today is to focus on safety issues, and we have been reassured that

there is sufficient evidence for efficacy at all the doses. It is hard for me at least to make decisions about safety in the absence of weighing benefit and risk.

In particular in this case, maybe this pertains more to Question 2 than Question 1, is there any evidence for a dose-response relationship with regard to efficacy as you step up from 20, 30, to 40 mg? That would allow me, in part, to predict what are the chances that somebody is going to start at 20 mg, find that that is ineffective, and then the clinician is going to move up to higher doses to manage their depression.

DR. SHAROKY: I am going to call on Dr. Dan Oren, my colleague from BMS, to address that question.

DR. OREN: I am Dan Oren. I am Medical Director of Bristol-Myers Squibb, which is working in partnership with Somerset on EMSAM.

To your question about dose-responses, the three pivotal studies that support the efficacy of the transdermal selegiline were not designed to allow us to answer that question directly. There were two, short-term efficacy studies, one which showed efficacy at 20 mg, and the other which was

an encouraged titration study where doses of 20 through 40 were used.

Because of the design of the study, clinicians were encouraged as soon as two weeks into the trial if response was not satisfactory to raise the dose to 30, and then at the five-week point of the eight-week trial, to raise the dose to 40, so by nature of the design it does not allow us to assess specifically from that study what dose will be used.

But the third study that is considered pivotal for supporting the efficacy was the long-term efficacy study where patients, on an open label basis, were assigned to the 20 mg patch for 10 weeks. Fifty-one percent of those responded on an open label basis and then were randomized for

periods of up to a year to EMSAM 20 mg versus placebo, and there was a significant effectiveness at that 20 mg dose up to a year.

DR. GOODMAN: As you said, though, that only verifies efficacy at the 20. I understand you didn't do any comparative studies from what you describe, but do you have any sense in terms of comparative response rates, severity from baseline, any sense that there is, as there usually is, a group of patients who might respond better at higher doses although based upon mechanisms here, perhaps maybe you would predict that it is the MAO-A that is going to be the main mediator of effectiveness in depression.

I want to see if you have any feel that there would be some patients that might start on the 20 in whom you are going to march them up to the higher doses.

DR. OREN: I think it would be fair to say there would be some patients, we can't give you percentages.

DR. TAMMINGA: But even in those cases

where you would be required to use the higher dose, as soon as you would give a 30 or 40 mg dose, you would have already educated both patient and the doctor to use dietary restrictions along with that?

DR. OREN: In the clinical practice, yes, when patients would be moved to a higher dose, the doctors would be instructed to instruct the patients to begin dietary restrictions, and if they moved to a lower dose, below 30 or 40, they would be instructed to maintain those restrictions for two weeks after being on those higher doses.

DR. GOODMAN: Dr. Wang.

DR. WANG: All the analyses we have seen so far have dealt with your outcome as a dichotomous categorical 1. Do you have any analyses that are continuous where we could see, for example, the change in blood pressure in millimeters or something, because, you know, there could be a consequence if there is an increase across a population, if you increase a blood pressure across a population especially if it's experienced chronically?

DR. GOODMAN: Can I just intercede on that? I thought of the same question, but I was wondering, it might not be that informative unless

you knew when they took their meal in relationship to the blood pressure readings.

DR. WANG: You have to assume that this person was eating consistently, you know, this kind of meal, but do you have any analyses where you treat the outcome continuously?

DR. SHAROKY: What we did is if--and if I am not addressing your question, just bear with me--what we did look at was blood pressure across the entire population and what it looked like, and in a dose-dependent fashion, blood pressure either remained normal or decreased across the study, across all patients. Is that your question?

DR. WANG: It is probably not getting it. I would have to sort of think through what the design is, but basically, it is to understand is there a sub-threshold increase in blood pressure on the basis of experiencing some, you know, an unrestricted diet.

DR. SHAROKY: Maybe I can address that and tell you how we did study this and how we looked at blood pressure in this concept.

We clearly designed the studies to be able to look at hypertensive crisis. I mean that is life-threatening issue with MAO inhibitors in the

past.

So, what we did was educate the investigators, educate the patients through informed consent, monitored the blood pressure on visits, but most importantly, hypertensive crisis is clearly a medical emergency. I mean it is not something that would be missed.

It is combinations of signs and symptoms associated with marked elevation of blood pressure, average 55 mm greater or greater systolic. Usually, systolics are greater than 200 associated with end organ damage, that if not treated, results in significant morbidity and mortality.

Given that, we went back through the entire program in a retrospective fashion--can I have Slide 46, please--and from Dr. Blob's

presentation, we went back and looked at any term whatsoever that could be associated with concern about blood pressure.

In combination with an elevated blood pressure, and based on that, saw 278 patients that we thought met that criteria.

In Step II, those case reports, we eliminated 110 patients. An example might be someone who had a history of headaches, mild headaches, had no other associated symptoms, but we looked at that.

Then, we went to Step II and looked at the individual case report forms of any of those subjects that met any of this criteria. So, if they had an elevated blood pressure, if they had a severe headache, so that that was done by two physicians in a blinded fashion to make sure that we did not miss any hypertensive crisis.

So, that is how we looked at hypertensive crisis.

DR. GOODMAN: Dr. Pine.

DR. PINE: Tell me if this is better for

the discussion, but I was a little confused by the summary of the tyramine challenge data here versus Dr. Dubitsky's summary of it, and should I hold that?

DR. GOODMAN: No, go right ahead.

DR. PINE: So, it seems like a pretty crucial point about the most sensitive subjects, and it seemed pretty clear, both from your conclusions and also from Dr. Blob, that the idea is that even in the most sensitive subjects, it would be, quote, "impossible" to eat enough tyramine to get close to the danger point, and there was a 3-fold difference.

When we heard your presentation, I had a very different impression of that, and it seemed to me, just from listening to both of them, that it really swings on the difference between the fed versus the fasting state, that your presentation was talking about the fed state and really emphasizing that that is really the condition that matters, whereas, it seems like you were painting a picture for the worst case scenario, which would

the fasting state, and I am still not clear the degree to which, you know, the fed state is really the only state that is relevant or, you know, we should be concerned because we had that 1 out of 8 subjects who was perilously close to the 40 mg.

DR. GOODMAN: We will let Dr. Dubitsky respond first and then maybe you could.

DR. DUBITSKY: I do want to comment, too, that I agree that there is a difference between fed and fasted, but variables other than that I think may play an even bigger role.

Keep in mind the general variability in this data and whether or not we can say that, you know, somebody had 50 or 100 mg is really safe.

DR. SHAROKY: Can I see a slide that shows me the data from tranylcypromine versus selegiline, and while we are doing that, I would like to take a minute maybe, because we go back and forth between TSF and pressor dose, there were a lot of questions. Let me put this slide up, 36, and there is an additional slide I will go to in a minute.

[Slide.]

I think what is important is that the concept again in these study designs, you know, using a model that has been used since MAO

inhibitors first came about, was to look at tyramine sensitivity factor and try to establish whether or not there was a dose of transdermal selegiline that was comparable in a TSF to what we see with oral selegiline.

When you do that, that is the numbers that we are sharing with TSF. At the same time, for the individual, it is important to get to the pressor dose, but these studies are conducted in a fasted state to get the most extreme example, but tyramine is consumed in food. I mean it is a part of food, so we did food studies to establish, and we did it at the very highest dose to establish what that might look like.

So, right here we have the TSF in this crossover data where the subjects acted as their own control. We have a TSF essentially to compared to 40, so there is a factor of a 20-fold difference, but look at the mean pressor dose,

because I want to start with mean and then I will go to the extreme cases are most sensitive.

The mean pressor dose for these patients in transdermal selegiline, which by the way is repeated. I can show you that data on multiple studies that the TSF comes up for transdermal 20 essentially superimposable. 270 mg by a factor of 2.5 would be close to 500, 600 more milligrams of tyramine on average, that someone that was on transdermal 20 would have to consume.

Now, average is helpful, but again I have already stated that pressor dose, we need to look at the more extreme example. So, can you show me the studies that showed the two subjects that went out at 50, please. Put up Slide 41, please.

[Slide.]

We presented this as part of our program, to try to look at these cases. When you look at this situation here, remember the mean data again is 256, 204, so it is pretty consistent, and this is 30-day data. So, again, the mean data for EMSAM 20 is going to be 500 mg of tyramine that one needs

to consume, which it is not even conceivable that someone could do that.

The two extreme cases, the most sensitive are at 50 mg. At 50 mg--can I have the slide that shows the 125 versus 40.

[Slide.]

Fifty milligrams. This is a calculated number based on a number of different things, based on literature, the tyramine when consumed with food, which again is almost the entire way that one would ever get tyramine, they are not going to get it encapsulated, is a factor of 2.5--our own study showed that it was a factor between 2 and 3--is 125 mg compared to the most extreme tyramine meal that one would have to work at to get 40 mg, so it is a factor of 3.

So, what we tried to do was look at the most sensitive subject in our 20 mg data.

DR. GOODMAN: How much draft beer on an empty stomach would you have to drink to reach 40 mg of tyramine?

DR. SHAROKY: How much draft beer? Fred,

would you like to come up?

DR. GROSSMAN: Hi, my name is Fred Grossman. I am from Bristol-Myers Squibb, Global Medical Affairs.

I just wanted to make sure that we were answering a couple of the questions that were asked. The first distinction is that by virtue of eating anything, that is in a fed state. So, I think there was a question before what if you ate a cube of cheese, that's a fed state, that is not a fasted state even though there might not be contents in your stomach.

As far as beer, I think that is a relevant question, but I think that if you looked at an article by Shulman [ph], who is the expert in this area, who studied actually beer both in tap and bottled, found essentially bottled beer contains little to no tyramine, so one would not be put in that kind of situation.

Tap beers also generally contain low tyramine, and, of course, I would just remind you that the label certainly does caution against using

beer.

The other thing that I would want to alert you to is that the TSF measures and the pressor dose measures are relative ways, as you have heard, to compare drugs, and relatively speaking, there is a similarity between 20 mg selegiline patch and oral selegiline.

I think it is important to recognize the oral database and the fact that there were four listed cases, three have been removed, and there is one case that because Somerset couldn't find the information, was not a tyramine reaction in, you know, in this frail population, who one would assume might eat a variety of different foods.

DR. GOODMAN: Dr. McGough.

DR. McGOUGH: First of all, if there is a separate consent form for the 2,500 people, we would really like to see that, the one that was done after the restriction was lifted. Otherwise, we will just have to assume the one you showed us was the one that you used.

Secondly, in Dr. Dubitsky's study, again

to the TSF issue, his Slide 24, he compared the derived TSFs in the various studies, and the MCM 20, nine to 10 days, it was a TSF of 1.8. The 20 mg for 30 days was 2.9, which is higher than the 30 mg at 10 days.

If this is a measure of relative comparison, I am wondering, it seems odd to me that the 20 mg at 30 days is higher than the 30 mg on which you will have a dietary restriction. So, if you could help explain my confusion away, that would be appreciated.

DR. SHAROKY: I will have to try to find that slide because I don't have any way of--

DR. McGOUGH: It's Slide 24.

DR. SHAROKY: You will have to put the laptop up, okay.

DR. McGOUGH: I will just give it to you.

So, again, the point is if at the 30 mg dose, you have a TSF that is lower than 20 mg at 30 days, why can I feel good about not having a restriction on 20 mg?

DR. SHAROKY: Let me call Dr. Blob up to

address this.

DR. GOODMAN: Your question is about the potential overlap?

DR. McGOUGH: Again, if this is a term to compare relatively, and they are saying there is a need for restrictions with a TSF of 2.4, and the 30 mg, why are we not concerned about the 2.9 that is derived after 30 days on 20 mg.

DR. GOODMAN: Dr. Dubitsky?

DR. DUBITSKY: I would just point out, though, that the 30 mg dose there is based on 10 days of treatment, so part of the explanation I think is the time dependency issue. If you had, in fact, given 30 mg for 30 days, the TSF for the 30 mg dose may have been even higher.

DR. BLOB: That is the explanation, that the number you are talking about for 20 mg transdermal selegiline is at Steady State, 30 days.

DR. McGOUGH: What is the threshold of TSF where there is a concern? Do you have 30-day data on the 30 mg?

DR. BLOB: The 30 mg dose was the dose we

studied least. We did study 40 mg, which is higher, which might give you some sense of comfort looking at that data. Maybe we could put up a slide that shows again the 40 mg data at 30, 60, and 90 days.

DR. McGOUGH: My last question--oh, there it is.

DR. BLOB: Thirty-seven, yes.

[Slide.]

This is a study in which the same subjects were studied on 40 mg transdermal selegiline at 30 days, 60 days, and 90 days, again, the same subjects, and the N for the 30 days is 18. You can see that the TSFs are approximately, you know, the mean TSFs are around 11. It pretty much stays the same at 60 and 90 days, or might be a slight dropoff. The significance of that are not important.

DR. McGOUGH: We all seem to agree that at 10 or 11 we are concerned, but I still don't know what the lower threshold for concern is.

DR. BLOB: I think if you want to look at

threshold of concern, it is still probably more important to look at pressor doses.

DR. McGOUGH: My last question is just by chance, is tyramine available from health food stores?

DR. SHAROKY: Yes.

DR. McGOUGH: Because I would not underestimate the ability of some of the patients who will clearly get this drug to know that and learn that.

DR. SHAROKY: And it will be contraindicated in our label. Let me call Dr. Grossman up.

DR. GROSSMAN: I just wanted to point out that Somerset believes that all three doses are safe, particularly when you take into consideration the fasted versus fed state, and the only reason that the recommendation is for 20 mg is due to the pharmacovigilance database in the comparator oral drug of oral selegiline, that doesn't exist for 30 and 40.

Furthermore, there were more patients

exposed to 20 mg, so Somerset is taking a position that is more conservative than asking for no dietary modifications at all three doses.

I also want to point out Somerset was able to obtain the consent form for that other study where there were no dietary restrictions, and we will provide it for you.

DR. GOODMAN: Dr. Tamminga.

DR. TAMMINGA: I had a question about whether or not, when you did that two-stage safety analysis that you did, did you look at the difference between normotensive subjects and treated hypertensive subjects?

DR. SHAROKY: In terms of blood pressure response over the course of the study?

DR. TAMMINGA: And any of those adverse events that you had identified.

DR. SHAROKY: Well, there were no differences in regard to whether a patient came in and had a history, a past medical history of hypertension and was not just had a history, but was not treated, or had a history of hypertension

and was on medication in terms of the review.

Over the course of the study, if one came in with a past medical history with hypertension, their blood pressure, as normals who came in with no history, either remained the same or decreased over the course of the study, as one might expect with this class of drug.

DR. TAMMINGA: So, hypertension is not a risk factor.

DR. SHAROKY: Based on our data, it is not a risk factor.

DR. TAMMINGA: What about are there any other drugs in addition to health food store compounds that contain tyramine, are there drug-drug interactions between MAO inhibitors? No other drugs contain tyramine, is that right or wrong?

DR. SHAROKY: No, to the best of our knowledge, tyramine is a vasoactive amine that is not naturally occurring in the body, and there are no drugs as we are aware of that have that, although it has been pointed out that they are in supplements that would be contraindicated.

DR. GOODMAN: How about the sympathomimetics and the interaction with SSRIs and serotonin syndrome?

DR. SHAROKY: The combination of transdermal selegiline and SSRIs would be contraindicated, and it is so in our label.

DR. GOODMAN: For the serotonin syndrome?

DR. SHAROKY: Yes. The other part of your question was sympathomimetics? Also, the label for sympathomimetics, although we studied it, is not to be taken with EMSAM. We did study pseudoephedrine. In one of our drug-drug interaction studies, we looked at pseudoephedrine in combination with EMSAM and saw no increase in blood pressure.

DR. GOODMAN: If I remember correctly, in my experience with Parnate and Nardil, actually, hypotension was more common. Is that true for your compound, as well?

DR. SHAROKY: That's correct. In our trials, as I was indicating with blood pressure, because of the mechanism of action with MAO inhibitors, you do tend to see a lowering of blood

pressure although there was no difference between placebo and control in our trials, there was some evidence of hypotension.

DR. GOODMAN: Dr. Robinson.

DR. ROBINSON: Two questions. One is in your patient education literature for people on the 20 mg patch, I just want to clarify. They will know about the cheese reaction and the foods to avoid for 30 and 40?

DR. SHAROKY: Yes. Let me call up my colleague, Mark Altmyer, who maybe can shed a little bit more light on what we will be doing with that.

MR. ALTMYER: Mark Altmyer, Senior Vice President at Bristol-Myers Squibb.

Patients at the 20 mg will receive the patient leaflet information which says that it is fine to have 20 mg without dietary modifications, but then goes through all of the information that was projected earlier that says what foods would need to be avoided if they were titrated up to 30 or 40.

Additionally, the qualitative work we have done with psychiatrists, the majority indicate that prior to even beginning a patient on 20, they want

to inform the patients that if they need to go up, they want them educated on the fact that dietary modifications would be required, because they don't want to hit that point partially through improvements in therapy and then realize that the patient won't accept the dietary modifications.

DR. ROBINSON: For example, if your patient is on 20, they will have the information to say, well, maybe, you know, when I am going to dinner, maybe I don't want the cheese course, you know.

DR. GOODMAN: The Octoberfest reaction was actually what we were thinking would be--you know, draft beer, sauerkraut, and sausage.

DR. ROBINSON: I have one other totally unrelated question, which is MAO inhibitors are frequently used historically for people with atypical depression, and those people do have a substantial sort of comorbidity with people with

eating disorders.

How safe do you think can a bulimic on 20 mg patch eat enough tyramine to get in trouble?

DR. SHAROKY: Let me call my colleague, Fred Grossman.

DR. GROSSMAN: In answer to your question, those that have eating disorders, obviously, those that are anorectic, this wouldn't be an issue. Those that are eating excessively, I think that it's a judgment call, but if you look at the quantity of food that one would have to eat, it's excessive, and granted there might be some patients who can actually eat that amount, if they are bulimic, I am not sure how that would interact. But again I think the quantity of food would have to be high, not only in quantity, but in those foods that contain high tyramine.

I also want to get back to the consent form, because Somerset was able to get some information. As mentioned before, in the initial study, there was a requirement before discussions with the FDA, there was a requirement for dietary

restrictions, and what you saw earlier was that consent form.

Subsequent to that, approximately half of the patients who were in the latter study, particularly including the one that went from 20 to 40 mg, as well as an elderly safety study, the elderly safety study included 765 patients, the second pivotal study included 265 patients, that informed consent was essentially silent to dietary modifications or restrictions with the exception of symptoms that may be associated with hypertensive crisis.

Can I have Slide 1B84.

[Slide.]

This was what was stated in the informed consent in those latter studies.

DR. GOODMAN: Just remind us what that N was.

DR. GROSSMAN: The N in the pivotal study that was flexible, an encourage titration from 20 to 40 mg, was 265, and there was an elderly safety study with an N of 765. So, it's a total of over

1,000 patients.

DR. GOODMAN: Over 1,000 used this consent rather than the cheese reaction? No?

DR. SHAROKY: The question is this informed consent versus the one with diet, the one with diet was only for the first study that was our first pivotal trial that I believe had 153 patients. The total exposure to the major depressive program was roughly 2,650 patients. Only 150 saw an informed consent talking about diet because we were not off of diet control.

The remaining 2,500 patients across all our clinical program had no indication about diet, just concern about symptoms of hypertensive crisis which we were obviously looking for.

Does that answer your question?

DR. GOODMAN: Yes, it does.

Dr. Leon, are you satisfied with that answer?

DR. LEON: Yes.

DR. GOODMAN: Dr. Wang.

DR. WANG: I just want a clarification

about this fed meal model. I think you made a strong case that the fasting encapsulated model is a worst case scenario, but in this fed state, you feed them food without tyramine, and then you give them tyramine, or is it all mixed up? Because if you are coating the gut with non-tyramine food, presumably, that is kind of a best case scenario.

In other words, is the tyramine in the meal, or do you feed the person and then give them the tyramine?

DR. SHAROKY: What we did was take a standard meal based on USDA guidelines, and have a small portion of the meal eaten over a few minutes, give them the encapsulated tyramine, eat some more of the meal, and the effort there was that their load would be the encapsulated tyramine, but associated with food, a still much more conservative model than if the tyramine was actually in the food.

I mean there is plenty of examples that when tyramine is in food substance, for example, food high in fat, food high in protein, even though

it has tyramine, less of tyramine is bioavailable. So, we haven't even talked about that, but that is maybe some of the reason why some people can eat tyramine foods which are reasonably high in content, but actually don't have any kind of reaction with other products or other situations.

So, that is how the study was designed.

DR. WANG: So, tyramine is at some point in the middle of the meal.

DR. SHAROKY: The middle of the meal.

DR. GOODMAN: Any other questions for the sponsor?

Dr. Rudorfer.

DR. RUDORFER: Just one second to return to the interactions question. One of the classic non-tyramine interactions with the standard MAOIs is with meperidine, demerol, and I wonder if that is a contraindication.

DR. SHAROKY: It is contraindicated. Yes, it is contraindicated, it has always been contraindicated with the oral selegiline product.

DR. GOODMAN: Any other questions for the

sponsor? This doesn't stop you from asking other questions of the sponsor. I just want to move on to our discussion phase.

Dr. Leon.

DR. LEON: I want to follow up on the question that Dr. Goodman asked about patients possibly moving from 20 to 30 mg. You say in the second study, the encouraged titration study, they were encouraged, the physicians were encouraged to move them up based on lack of efficacy.

How many subjects started out at 20 mg, and how many moved up above 20 mg?

DR. SHAROKY: The total number of patients, how many patients were in the 20, 30, and 40 mg study? It's a total of 800 patients, right, that started our 20, 30, and 40 mg study?

Dr. Blob, can you come up, please?

DR. BLOB: In the study you are referring to, P0052, the forced titration study, there were 265 patients that started at the dose of 20 mg. The number that Dr. Sharoky was referring was referring to, greater than 700 patients, was in a

safety study that followed that, that also studied all three doses.

DR. LEON: So, of the 265 that started at 20 mg, how many moved beyond 20 mg?

DR. BLOB: Do we have that number? The majority of them did. I am waiting for a slide that hopefully will clear this all up for you.

DR. GOODMAN: Dr. Mehta?

DR. MEHTA: I could not understand the rationale for either package or the patient information sheet, which mentions that 6 mg over 24 hours in parenthesis, and then it says 20 mg. I would have thought that that will be very confusing to the patient, and this is unusual. I haven't seen any labeling like that. This is a model of the drug which is available in the body, but administered drug is 20 mg.

DR. SHAROKY: So, is your question about that there may be confusion, or is your question about why is there a difference between putting 20 and 6 mg?

DR. MEHTA: No, no, no. There will be

confusion, that is what I am saying. The patient gets a package insert and says I can take even 12 mg, which is 40 mg of the drug.

DR. SHAROKY: Well, that's a point that we will have to discuss with the Food and Drug Administration. We put that form down in discussions with them. It is 20 mg. The drug is basically 25 to 30 percent bioavailable. That is how you get what is delivered over a 24-hour period.

DR. MEHTA: Oral drugs are bioavailable sometimes 2 percent, respirone, for example, it doesn't mention that, it just mentions what is in the tablet or what is given to the patient.

DR. SHAROKY: I am saying that I think that the reason that was put there was in discussions with the Food and Drug Administration as to how they would like to see the product represented, what is the dose, and then now much is delivered.

DR. GOODMAN: You are coming with a response?

DR. GROSSMAN: I just want to address the 20 to 40 mg question. As you know, in these kinds of studies, it is very difficult to assess efficacy

in two weeks. It is not something that is ordinarily done. One of the reasons that people are saying "encourage titration" is that there was a concern that the higher doses would not be tested.

So, I think we have to be careful about interpreting whether patients went up based on efficacy, because if it was only two weeks, and therefore, it is very difficult to make any assumptions about dose-response.

I also want to clarify the number of patients who went up in this titration, which obviously would be a high number, because of this encouragement, and Dr. Oren can speak to that.

DR. OREN: Slide 219, please.

[Slide.]

This slide shows you the percentages of people at each of the doses at the key time points of evaluation at the study. The left two bars show

you, in yellow, that 100 percent of patients on EMSAM and on placebo were started at the 20 mg dose.

As was said before, at the two-week interval, if response was not judged adequate in the minds of the investigator, they were encouraged to raise the dose up to 30 mg.

So, at the next evaluation point, at Week 5, you can see that about 90 percent of the patients on EMSAM, or 95 percent of the patients on EMSAM were up to 30 mg already, and a similar percentage on placebo were moved up to 30 mg.

The outcome at Week 5, you can see this was not a primary outcome measure to measure at Week 5, but there was already statistical separation, but it was not a primary outcome and the study continued to Week 8, and the instructions to the investigators at Week 8 were if they were not fully satisfied or if they were not satisfied with the clinical response, to push the dose further.

You see in the righthand two bars of the

slide, that at Week 8, at the end of the study, about 10 percent of the EMSAM patients were on 20 mg, about 30, 40 percent were on 30 mg, and the remainder were on 40.

In the last column, you can see that only about 5 percent of the patients were still on 20 mg of placebo, about 15 percent were on 30 mg of placebo, and about 60, 70 percent were raised to the 40 mg dose.

DR. GOODMAN: That was based on tolerability?

DR. OREN: It was based on response. If the investigators did not consider the response to be sufficient at each of the time points.

DR. GOODMAN: What percentage were responders at Week 8, say, on the 40 mg dose?

DR. OREN: Could we have the slide with responders at the end of the POO52 study, the responder rates in each of the three studies, if you can pull that up. That's not it. There is a table with responders. If you can pull up Slide 2-11, please.

The middle line is this particular study, the POO52 study, and with response being predefined as a CGII improvement score to one or two, the percent improved on EMSAM in this study was 46

percent, placebo 35 percent.

DR. GOODMAN: I am sorry, that was for the 40 mg dose?

DR. OREN: That was at all doses.

DR. GOODMAN: Okay. Again, there is no breakdown.

Thank you very much.

Tom, you had a comment?

DR. LAUGHREN: I am not sure even if you had a breakdown, you could figure out dose-response from that design. It is not our preferred design, but we have not made it a requirement to do fixed dose studies even though we prefer those studies.

DR. GOODMAN: It would have been helpful obviously, in this case. You couldn't know that in advance.

Any other questions for the sponsor?

Okay. Thank you very much.

Now, we are actually scheduled according to the original schedule to go to lunch at 12:00. We have another option here, is to not break for lunch, but see if we could go into our discussion and take a vote, and, say, with a possible target of being completed by 1:00 p.m.

That would be my preference and

recommendation. I see the heads nodding, nobody strenuously objects.

Why don't we take a brief break now and then come back and see what we can do.

[Break.]

DR. GOODMAN: There was a clarification from the sponsor on the sample size of those who had the second consent form.

DR. SHAROKY: When we were talking about informed consent, I corrected Dr. Grossman, and I misspoke about one aspect of it. I would like to have him come back up and clarify.

DR. GROSSMAN: I just want to make sure that we are clear on the number of patients who had, in the informed consent, a lack of dietary

modifications or any restrictions. As I mentioned previously, in the study, that was the encourage titration from 20 to 40 mg. That consent form did not contain dietary restrictions, and that had 265 patients in it.

Additionally, there was an elderly safety study that had 765 patients in it. That did not contain dietary restrictions in the consent form.

DR. PINE: I have a question about that.

DR. GOODMAN: Together, that is about 1,000, is that what you just said?

DR. GROSSMAN: Yes.

DR. GOODMAN: So, it's about half of the entire sample on which you have safety data?

DR. GROSSMAN: Over 1,000 patients did not have dietary restrictions. Approximately, 1,500 patients had, in the consent form, history of a cheese reaction, to clarify what that was, although there were no restrictions, of course, on those patients.

Committee Discussion

Questions to the Committee

DR. GOODMAN: We are going to enter the discussion phase here, and hopefully, voting. Well, not hopefully, definitely, we are going to be

voting.

Question No. 1, just to remind you, is: Do the available data for the EMSAM 20 mg patch support the reasonable safety of this formulation without the need for dietary restrictions?

May I have the second question, as well? Obviously, we are asked to address these separately, but I think it is very hard to. We should be thinking about the implications of our vote on 1 for No. 2.

No. 2. If the EMSAM 20 mg patch formulation could be considered reasonably safe for marketing without the need for dietary restrictions, would it be acceptable to market the 20 mg patch without dietary restrictions and at the same time require dietary restrictions for the 30 and 40 mg patch strengths?

Flip it back one more time to Question 1. We are going to focus on that initially.

I am going to start. I wanted to pose a question actually to Dr. Dubitsky to help me think through this a little bit better. I would also say that I think that we have probably, at least in my opinion, reached about the limits of what we are going to learn today, so I think it really is the

right time to just engage in discussion among ourselves.

Dr. Dubitsky, is there any reason to think that t he 20 mg patch poses any higher risk than Eldepryl as currently marketed for the hypertensive reactions?

DR. DUBITSKY: It's a good question. I think if you look at those, just compare those two, you conclude that it is safe. I am still troubled, though, by the amount of variability we see in tyramine sensitivity at the 20 mg dose. So, I am not sure of my concern in that respect, you know, is satisfied, but--

DR. GOODMAN: When you are talking about the tyramine variability, you are talking about a challenge study and a small number of subjects.

DR. DUBITSKY: That is correct.

DR. GOODMAN: That is obviously very important information. It is really the acid test. On the other hand, we do have the benefit of this experience, the years of experience. How many patient years was it total?

DR. SHAROKY: Sixteen years.

DR. GOODMAN: Patient years?

DR. BLOB: 250,000.

DR. GOODMAN: I knew it was a very high number.

Given that, and unless you are saying that there has been a problem in our surveillance, there have been few identifiable reactions, and as I understand it, there are no dietary restrictions listed in the current package insert.

So, why would we think based upon that experience, that it should be any different with the patch?

DR. DUBITSKY: Well, I think there are weaknesses to postmarketing surveillance that we, at the FDA, are very familiar with. One obvious

thing is underreporting, and the other thing is biased reporting, too.

For instance, if somebody had a hypertensive reaction with a drug that is labeled, or that is a possibility or a hypertensive reaction is possible with a particular drug, some clinicians might be disinclined to report that.

DR. GOODMAN: Other comments or questions from around the table? Dr. McGough.

DR. McGOUGH: I have a couple of concerns if other members of the committee could soothe my anxiety, that would help me.

The first is I am troubled by the one study, I think the 45 study where 1 out of 12 patients had a bad effect, and that is about 9 percent or so. That is either really bad luck in your sampling or to me, it suggests that there could be a wider problem on No. 1.

The second is the fact that all--

DR. GOODMAN: You are talking about one of the tyramine challenges?

DR. McGOUGH: Right, that one person

actually had a crisis develop.

DR. GOODMAN: That was a fasting, wasn't it?

DR. McGOUGH: It was fasting.

DR. PINE: And it wasn't a crisis either.

DR. GOODMAN: He met the threshold of 30 mg for systolic, right? Okay.

DR. McGOUGH: So, you are calming me a little on that. The second is that in the clinical trials, they did exclude anybody who was in the range of being hypertensive. I know in adult ADHD, Tim Willens has shown that there is actually a large problem among adults treated for ADHD, that a lot of them are silently hypertensive, nobody knows it, and psychiatrists are not very good with a sphygmomanometer, so I think in the real world, there might also be some issues there.

DR. GOODMAN: I don't think I heard anything today, and I don't remember anything from my past when I used to pay attention to this, that baseline hypertension predicts hypertensive reaction, and that is why I thought probably that

even looking at blood pressure as a continuous variable, it is probably not pertinent, it's in relationship to a meal.

I mean if you look at what is contributing the variance, it is not probably even baseline parameters, it is probably your intake, and there are some other factors I guess we need to talk about, but I don't think that baseline hypertension is going to turn out to be that powerful a predictor. I may be overstating the case.

Carol.

DR. TAMMINGA: I just wanted to clarify a minute what you said, because when I was listening to the presentation, I didn't hear that anything bad happened to hardly anybody, let alone 9 percent.

So, why don't we clarify that? Why don't you say exactly what you heard?

DR. McGOUGH: In the one study, the 45 study, in which 12 subjects, 12 healthy subjects--this is Slide 39--12 healthy subjects were given the pressor test and 1 required, I think with a TSF

of 50, required rescue with labetolol. So, I was just quickly figuring 1 out of 12 is about 8 or 9 percent.

DR. SHAROKY: The study design was such that the endpoint was a 30 mm rise in blood pressure. So, we were, in a sense, giving as much tyramine to get that as endpoint.

Labetolol was there because it allowed the investigator, in a very subjective way, that once we reached endpoint, if you wanted to lower the blood pressure, he could do so. In the study that you are pointing to where Dubitsky put labetolol next to that patient, out of those 12 subjects, 11 of the 12 at some point during the study got labetolol based on the investigator's sense that that blood pressure just should be lowered.

So, in this study design, in general, over however many years it has been used by whatever companies to study this, it is a subjective thing. It's we are giving time to raise blood pressure, and interestingly enough, in those 12 subjects, many of those subjects had the labetolol given in

the nonmedicated stage where we give a lot of tyramine. The blood pressure rises in relationship to whether labetolol was given or not was not consistent.

So, it someone had a diastolic of 160, where they may have started at 130 and got 30 mm, that may have been used. If it was 170, so it was not in relationship to a hypertensive crisis at all. It was a part of the study design.

DR. GOODMAN: Please remind us what the dose was of tyramine that produced that 30 mg increase in that one subject.

DR. SHAROKY: Fifty milligrams, it says on the slide.

DR. GOODMAN: So, it was 50. So, it was in excess of what you would ever expect from--

DR. SHAROKY: But let me make it clear that on the front side of that study, that subject--and I can look at it--many of the subjects were also being given that for 400 and 700 mg. It is not related to how much tyramine you are giving, it is related to once you have met endpoint,

regardless of who you are, what dose, medicated or not, the investigator had the option, instead of watching the blood pressure continue--

DR. GOODMAN: I understand that. I just want to focus on that one individual. What was the dose that you said it was, 50 mg of tyramine that produced the--

DR. GROSSMAN: That was 50 mg in the fasted state, and Somerset showed data that the difference between fasted and fed is approximately 2.5 or more, so that is the equivalent of 125 mg in the fed state, which is a realistic situation, and that is why the conclusion was that one couldn't eat that much.

I also, if you would like, we have a slide on those that entered the study with hypertension.

DR. McGOUGH: No, that's okay. Just one last question. The last point that was raised, I think you said overall, there was a 46 percent response rate on drug, is that right, the last slide, compared to placebo?

If that is the case, most people are going

to end up going up in dose, and this quickly becomes a moot point, because unless it is a magical miracle cure for depression, where they respond in 8 days, virtually, everybody is going to go up, or many, many people will go up, so this quickly becomes a moot point.

Conversely, there is sort of a perverse incentive to stay on sub-therapeutic doses. They may actually be a great reluctance to go up to the next step, because you don't want to deal with all this other stuff, and then you have a lot of people going around with a drug that may not cause them any benefit.

DR. GOODMAN: Dr. Pine.

DR. PINE: I guess I want to stay on this point, although I am going to respond to the last thing that Jim just said. I do think even if we are only at the 20 mg dose, and even if, you know, half to two-thirds of the patients ended up going above 20 mg, that would be a meaningful clinical advantage to have a non-dietary restricted 20 mg dose. That is my feeling, just clinically, in

terms of what we need.

On the other hand, the thing that I am really struggling with, and it was your first point, you know, is this one subject who on 50 mg, you know, met the criteria for a blood pressure change that, if not dangerous, at least everybody would agree is noteworthy, and I guess the thing that I am struggling with, as I listen to these guys, and as I listen to you, is that we are kind of harping on, well, one was in fasting, the other was not in fasting, but in reality, it does sound like there is a huge amount of variability in terms of many factors besides just fasting or not fasting, and unless the same subjects are put in the same studies with randomly assigning them to every condition, I am not convinced that it is just the fasting that accounts for the fact that it's 50 mg in one study and much higher dose in the other.

I guess the other thing related to what Wayne was saying, that I am really struggling is it's only 12 subjects, and how do we weigh this very important data, because it's experimental and

it is really nicely controlled, on the one hand, on the other hand, you know, versus 2,500 patients plus 16 years of marketing plus the need for a non-dietary restricted agent.

I guess I am feeling more stuck than you were, but I am struggling with this one patient.

DR. GOODMAN: Go on to somebody else, but I want to ask a question. In that one case, and maybe others that experience the 30 mm rise in systolic blood pressure, how many of them are symptomatic? In other words, how many of them would know that their blood pressure is increasing?

DR. BLOB: I performed many of these studies myself, so I was there and watched it. To answer the first part about that one subject, he had no symptoms that were significant in any way, but the majority of the patients would have a feeling that their heart was beating faster, it really was stronger, they could feel that. That was the major symptom they would notice.

No one really in any of these studies had any really serious or significant symptom.

DR. GOODMAN: Really, what I was getting at is the question of how much of asymptomatic transient increases in blood pressure may have been

missed in Eldepryl, in other words, how many patients have been elevations in blood pressure without them knowing it.

It goes back to the question that Dr. Dubitsky raised, about the surveillance.

DR. SHAROKY: If we are talking about the Eldepryl data, if you recall, we presented, with its weaknesses, the AERS database, 1997 to 2005, 250,000 patient years with an incidence of, when we broke it down in our study, 0.4 per 100,000 patient years in an elderly patient population, where a Parkinson's patient's average age is 72.

Then, we look at, because of the weaknesses in the AERS database, then, we looked at the DATATOP, the largest controlled clinical trial, placebo controlled, looking at selegiline over a 10-year period, and there was no increase in morbidity and mortality.

Do patients on oral selegiline have their

blood pressure go up? They may very well have their blood pressure go up for a number of different reasons, but if you look at morbidity and mortality, if you look at hypertensive crisis, it is just not occurring with oral Eldepryl.

Then, we established that EMSAM 20 has the same tyramine sensitivity factor as oral selegiline, and then you look at their 2,500 patients, and there is just no hypertensive crisis going on.

Then, we go back and we look at our data, and you see no progression or increase in blood pressure, if anything, you see a lowering blood pressure.

When you look at AEs of hypertension, there is no difference between placebo and active, and when you look at 278 cases that may in any shape or form in our trial be associated with anything you are worried about in terms of hypertension, meaning not you, but as the company sponsoring the studies, we were not able to see anything related to tyramine, but I do want to make

sure that we are talking about the tyramine studies, because I have a sense of maybe I am just wrong about confusion.

The tyramine sensitivity studies is challenge studies, are done to raise the blood pressure at least 30 mm of mercury on three consecutive things. It is the closest surrogate we can get to what might happen out there. It is clearly short of a hypertensive crisis.

It is an experimental model that allows us to compare one MAO inhibitor to another, but I want to make sure that everybody understands we are inducing a rise in blood pressure on purpose.

DR. GOODMAN: I think we all understand.

DR. SHAROKY: Okay. Very good.

MS. BRONSTEIN: I want to throw out to my fellow committee members some concerns I have about patient issues that I think we need to think about.

It is my experience that patients are going to increase their own use of a medication. I can imagine a patient wearing two patches and having a three-month supply, because many people

are getting their medications through mail order sources and having a large supply.

I think we have to look at this drug usage as possibly people being prescribed at a safe level of 20, but actually receiving 40 mg.

DR. GOODMAN: So you are saying you don't think that the safeguards and packaging are sufficient to prevent that error from occurring?

MS. BRONSTEIN: I think the packaging looks very good, but I think between what is explained to the patient and the infrequency of visits to physicians, there is a lot happening in the public that I don't think that the safety factor is represented well with this first question. I would vote no.

DR. GOODMAN: Gail.

MS. GRIFFITH: I share some of Jean Bronstein's concerns. I think that these two questions are so interrelated that in some ways it would make sense looking at the second one first, but I would like to hear from some of the people who are involved in clinical practice, because from

the patient perspective, I think it is too confusing.

I am not sure that patients can handle that in spite of the very good materials that may go into the packaging. But if it is the case that you are going to titrate a patient up rather rapidly to 30, are docs really going to be able to handle this given all that we know about the current state of practice.

DR. GOODMAN: Dr. Winokur. Did you have a question, Dr. Winokur?

DR. WINOKUR: I have some other comments, I am not sure I am qualified to comment on in general.

DR. GOODMAN: You don't have to.

DR. WINOKUR: I had an earlier question and interchange with Dr. Dubitsky kind of building on, Dr. Goodman, your earlier comment about some of the reassurance from the experience over the years with the Eldepryl. We did have the safety data and the lack of hypertensive crisis and the 2,500 subjects in the clinical trials, and he kind of

reflected it back to us as a committee in terms of how do we feel about that as enough of a signal of safety.

So, to me, I am kind of combining three different datasets - the overall experience with Eldepryl, the safety data that we heard, which described the lack of hypertensive crisis or other suggestive problems in the clinical trials, and then these experimental models, which I think are interesting and help provide a little more fine-grained analysis of either a surrogate marker, which is not hypertensive crisis, but might indicate a vulnerability, and we also heard about encouraging people to eat a lot of cheese to have a high tyramine intake, which was also another approach, that's actually what initially led the FDA to go along with taking away the dietary restrictions.

Personally, I was fairly satisfied with the level of analysis of the variability. I think we got away from just looking at the mean values. So, I didn't see a high degree of concern that the

variability translates to a high likelihood for infrequent, but serious consequences.

But I would like to hear other people's comments about the main body of the safety data that we have, which is the 2,500. To me, that is an important additional information on top of the early experience with Eldepryl.

DR. GOODMAN: Dr. Wang.

DR. WANG: I have been through enough of these meetings including yesterday that I should know the answer to this. Are there any options--this is for Tom and Dr. Dubitsky--to help provide quality assurance for whatever decision we vote for, because obviously, we are all uneasy with the possibilities.

Specifically, is there any way to more than just plead for some pharmaco-epi studies both one quickly on the--a formal one, not sort of case reports or case series--but on the Eldepryl experience, so we have some sense of what are the risks for hypertensive crisis, and then one shortly thereafter, a post-approval one for the patch, is

there anything beyond just sort of asking for a promise which may or may not be kept?

DR. LAUGHREN: In terms of post-approval, what we are talking about, a Phase IV commitment, and as we discussed yesterday, there is no really firm leverage we have to ensure that.

In terms of getting a study done prior to taking an action on this NDA, that is very unlikely.

DR. GOODMAN: Tom, what would the sponsor have to do postmarketing to lift the dietary restrictions for the 30 and 40 mg doses?

DR. LAUGHREN: Well, that is actually something we were hoping that the committee would help us with, you know, what would make you comfortable that the 30 and 40 can be safely used without dietary restrictions.

DR. GOODMAN: I think that really correlates with your question to Dr. Wang, doesn't it? Let's assume we knew what--how long would it take, I guess is the--once we come up with the design, what is your usual experience with how long

would it take for the regulatory body to change the labeling, would it come back to committee? I guess it could be done internally at FDA.

DR. LAUGHREN: There are a number of ways of doing it. How long it would take to do a study depends on what it is that we want done.

DR. GOODMAN: Dr. Tamminga.

DR. TAMMINGA: I guess one of the reasons why we are spending a good deal of time talking about this is because of the reputation of MAO inhibitors and of the serious health implications in the past, and that is why we are all looking very carefully at the initial pressor studies that were done.

I think just for me, those initial pressor studies made me very interested in looking further to see what kind of safety outcome effects there were in the larger study, so when I saw the N of 2,500 patients safety database presented, I thought that the analysis not only of hypertensive crisis, but of all of the symptoms that would be associated with hypertension itself were looked at a number of

different ways, and I don't think that any of us saw a signal there, and Dr. Dubitsky can clarify this or respond to this, if you want to, but at least to my eye, I didn't see a signal there in the 2,500 database.

Then, in the Eldepryl database, there seems not to be a signal, and while we could believe that perhaps there was underreporting, because we all know that there is underreporting with side effects, clearly, this is within the context of people using an MAO inhibitor and both physicians and patients knowing what the set of side effects is.

So, in the larger safety database, I am having trouble seeing any kind of a safety signal at all.

DR. DUBITSKY: I would agree that I don't see a signal there either, however, let me step back a minute and just look at this from a slightly different angle. If you look at how hard the data are, I think in the tyramine challenge studies, one thing that I saw before my eyes for certain was a

variability, very large variability, both between subjects and within subjects.

That, to me, is a very hard, concrete finding. What you can learn from postmarketing data with Eldepryl, what you can know from the 2,500 patients in Phase II/III studies is a little bit softer. Therefore, I can't disregard it, but I am more concerned about the hard data there in front of me that suggests that there is a lot of variability here and that the 20 mg, in terms of tyramine sensitivity may not be much different from 30 or 40.

DR. GOODMAN: I agree with Dr. Tamminga. I don't see a harm concern in any of the formal studies, and more importantly, with the Eldepryl data. No one has given me a rationale for thinking that there would be any difference. in safety or incidence of hypertensive reactions between this formulation and the oral.

I think then it really does come down to variability and to individual variability, and whether the population that is going to be exposed

to this, is there anything that anybody around the table, any special population where we think that it would pose a higher risk. You mentioned before the eating disorder population, bulimia.

Is there any concerns that we have that in this population of depression, that there may be a higher incidence of hypertensive reactions?

DR. McGOUGH: You know, a patient who wants to kill himself or herself can do it, and I think we put the warning on it. If a borderline wants to go out and take 100 tyramine tablets, he or she can do that, but I think that's --

DR. GOODMAN: Or Octoberfest.

DR. McGOUGH: I am comfortable that if the risks are clear, people are going to do what they are going to do, we can't control all that.

DR. GOODMAN: Carol.

DR. TAMMINGA: The other thing that I wanted to add about weighing against the kind of variability risks that Dr. Dubitsky has really outlined is that we are not talking here about a simple me-too compound. This is not our 9th SSRI

or something. This is really a new--it's not a new mechanism of action, but it's a mechanism of action that any psychiatrist would say is really woefully underused.

At least the argument that we have heard today is that the freedom from a dietary restriction would really encourage the use of this. I was really struck in the first report really of the Sardi [?] program, that the antidepressant response of people with depression to SSRIs is really remarkably low, 25 percent, or it was like it was under 30 percent.

Everybody cries out for novel compounds. This isn't novel, it's not even new, but it is a new formulation that might make an alternative mechanism of action drug more broadly utilized. So, I think, for me, this carries some weight in connection to the safety data.

DR. GOODMAN: Dr. Pine.

DR. PINE: I am still struggling with a lot of the issues. On the one hand, I hear what you just said, Carol. On the other hands, it is

not like we are saying you can't use it, and it's not like we are saying it's not going to be available, and it is not even like we are saying we are going to put a black box on it.

It is more like we are saying do we want to err on the side of maybe being a little overly cautious and discourage use, on the one hand, or do we want to err on the side of, you know, that the overwhelming weight of the evidence suggest that there is no risk or minimal risk, therefore, we should not necessarily scare people.

I guess I am still on the fence, number one. Number two, just talking about some of the patient concerns, I think that those are legitimate and important to consider, on the one hand.

On the other hand, there are all kinds of dangerous things that we do with patients all the time where the border between doing something that is therapeutic and acceptable, on the one hand, versus potentially fatal, on the other, is very slim.

Lithium, for example, has a very narrow

index in terms of what is appropriate versus what is potentially dangerous, and while it is important to acknowledge that and deal with it, I think the fact of the matter is that for the average physician in the community, they can be taught how to manage appropriately in that situation to the point where a treatment can be delivered safely. So, that is the second thing.

The third thing is I would say the one thing that still really bothers me is the experimental data, and it is not even so much the fact that there is this one patient, what really bothers me is there is so little data, and really, from an experimental standpoint, so thinking of Tom's thing of what would you need, I would feel just a lot better if the N's in those 30-day fasted states were 60 or even 40 instead of 8, and if the confidence intervals were just a little tighter on some of those data, it just leaves me in a state of not really knowing what--you know, when you are basing something on 8 subjects.

DR. GOODMAN: Dr. Rudorfer.

DR. RUDORFER: A couple of observations. First, I do want to second the idea that we are really considering the benefit to risk ratio here,

and we should not underestimate the benefit side of having a different type of antidepressant available.

I think one concern that we all have on the clinical end is that the history of these types of medications is that many clinicians in practice trained either learning that these were dangerous historical artifacts or if they had experience in the past, many abandoned the use of MAO inhibitors out of concern that they were simply too dangerous to use.

One concern I would have is that introducing all doses with dietary restrictions might have this drug be seen as just a new Nardil that maybe some specialist somewhere might want to use, but isn't for regular practitioners. I think that would be a loss if, in fact, safety was not of concern.

I don't see the harm signal at the 20 mg

dose. I have to say I wish that the pivotal studies had been done differently, so that we could have a great greater sense of the dose-response relationship, because I know what has happened with some medications where there seems to be a dose-adverse effect relationship is that people get reassured at low doses.

There is even an example that comes to mind where the FDA said there is an absolute ceiling on the dose you can use, but the trouble is then people have difficulty making those low doses work, so that we would be in a real conundrum if, in fact, it turns out that the 20 mg dose is safe, but it didn't seem to work in enough people.

Having said that, what we saw with the higher doses, I also see didn't enough cause for concern to make me thing that was a limiting factor, but a final point, I do agree with Jean. I had the same thought in terms of we are used to thinking of raising dose by taking more, usually, it's pills or tablets, and this is an unusual scenario where the dose would be raised by taking a

totally different version of the product.

I would hope, though, that that could be addressed with maybe further attention to the packaging, I am thinking, since these I assume would be individually packaged, essentially, a warning to the patient, as well as the educational program that people need to be instructed if you miss a dose, don't take an extra patch, and, you know, education to pharmacists.

At the further extreme, which I don't think would be necessary, but I wonder if one could consider this as an option and, if need be, even the kind of packaging as with oral contraceptives, where a month's supply is literally labeled by day, that it is to be used one a day, and that would make it clear in terms of staying with the one.

DR. GOODMAN: I think it's abundantly clear from the data, although it is not a large N, that the 20 mg, for that matter, all the doses of the transdermal are safer, have a lower risk of the hypertensive reaction than tranylcypromine. I mean that is abundantly clear. Nobody around the table

would disagree with that.

That, to me, is the most important benefit of this medication, and if I think back on my clinical practice and why I don't prescribe MAOIs, it is not because of the diet. I think certainly the diet has a factor in terms of patients being less willing to take the medication, but I have plenty of patients, and I have plenty of patients still that would be willing to adhere to the diet.

The reason I stopped using it is because despite the dietary restrictions and good adherence, occasionally, a patient would have a hypertensive reaction. In fact, it got to the point where I would have them carry an antidote with them. Initially, that was thorazine, and then it was a calcium channel blocker, and after enough unexplained hypertensive events occurred, I became very shy of prescribing.

I wouldn't feel the same way with this medication probably at any of the doses, and, in fact, no matter how we vote, and whatever the FDA decides, I probably would still encourage my

patients not to take a chance, and I would probably apprise them of some of the dietary concerns, because I don't want to do the experiment in clinical practice.

DR. PINE: Even at 20 mg, if you had a patient, based on everything that we have heard today, you would tell the patient to follow the diet? That is what I took you to just say.

DR. GOODMAN: I would make them aware of it. I would probably still make them aware of it.

Dr. Winokur.

DR. WINOKUR: I agree with everything you said, but I would just add one additional point from my clinical experience. I absolutely have some patients highly treatment refractory, who I would love to try an MAO inhibitor for whom the dietary restriction is the deal breaker.

Now, if we were to discuss this, we would still have to discuss the need to follow a diet in higher doses, but I see a major difference in being able to present them with the option that at least starting, they could do it without the extreme diet

restriction.

DR. GOODMAN: Any other comments? Dr. Mehta.

DR. MEHTA: During clinical trial, one uses certain dose, but when the drug gets on the market, almost invariably, not only for psychotropic agents, but for other areas, the mean daily dose is much lower.

If there was a less than 20 mg dose of the dermal patch, I would think that it will be used more commonly, so there will be some patients who would use more than 20 mg, but the majority of them will probably will remain at 20 mg.

DR. GOODMAN: I want to see if we could move to a vote. One of the reasons, Dr. Tamminga has to leave soon, and I want to have her be able to participate in that vote.

Go ahead.

DR. RUDORFER: This is just a very quick observation because of your point, Wayne, about the spontaneous hypertensive crises that have been reported for tranylcypromine.

DR. GOODMAN: I am sorry, I missed that, Matt.

DR. RUDORFER: You had referred to the

spontaneous hypertensive crises that have appeared in patients adhering to the diet, taking tranylcypromine.

DR. GOODMAN: I wouldn't call them spontaneous. I would say inexplicable. They went to the Chinese restaurant or the barbecue place, and they don't know what was in the sauce.

DR. RUDORFER: Because that has been reported, though, the literature has usually used the term "spontaneous" in quotation marks, but I was reassured by Dr. Preskorn's comments that selegiline does not have active metabolites, which I interpreted as meaning that the drug won't autoproduce complications.

DR. GOODMAN: Other comments from around the table? Let me just say that if you feel that we need more discussion before taking a vote, do it, but I feel we are going to--we are 11, so that's fortunate, so it's not going to be a tie,

but I don't think it's going to be unanimous.

Other comments? Dr. Dubitsky.

DR. DUBITSKY: Just one thing I want to comment on. I know there is a lot been made of the food effect on tyramine sensitivity, and I know the figure of 2.5 has been used as a factor to be used, but I do want to encourage folks, too, and I don't know if the sponsor can address this--I should have the data in front of me, but I don't--how much variability is there in that factor of 2.5? For some patients, it may not be that much.

DR. BLOB: Yes, 3a-20, please.

[Slide.]

These are the 8 subjects in the study that continued. They started at 30, 60, 90 days, and then went to 96 days and completed the fed portion of the study.

The fasted minimum pressor doses are listed. These are the minimum pressor dose, it was obtained at 30, 60, or 90 days, but it was their minimum pressor dose.

The fed column shows you what the response

was when they were fed, that is, the capsule in the middle of a standard meal. You can see what the conversion factors are.

So, actually, in this study, the factor was greater than 2.5.

DR. DUBITSKY: Thank you.

DR. GOODMAN: Any final comments before we take a vote? Have we heard from everybody from around the table? I think we have.

I am going to cast the first vote. It's going to be a yes. I am a database kind of guy. I mean I shared with you some of my clinical impressions, but when it comes down to it, I was convinced that there is no harm signal in either the clinical data, clinical trials data that were presented, or in more extensive database from using Eldepryl, and even in the challenge data, no one met the threshold for having a reaction 40 mg or under of tyramine, and I wouldn't expect any meal to exceed that.

Benefit is clearly an issue here, and as I mentioned, we do have other MAOIs on the market,

but it is clear to me that this is going to produce far less risk than our existing medications of having a hypertensive reaction, and will encourage use, and my own experience, too, has been very positive in the past with use of MAOIs in patients with depression. So, that is my vote.

Why don't we then continue with Dr. Mehta. You don't vote, but how you would vote if you--your vote counts in my heart, but just not for the record.

DR. MEHTA: That is more important. I would vote yes, and I think for some of the same reasons, that this is sort of a different mechanism of action, the safety of the oral drug, the safety of the dermal product, but also that every patient is probably going to get some information on the 30 and 40 mg. Again, as I said earlier, most likely the patient will remain at 20 mg, so I don't think there will be a problem with it.

DR. RUDORFER: I vote yes, as well. I would just add that we discussed a lot yesterday and today about the heterogeneity of depression,

and I think it's clear that the more options we have available, the better.

I, too, was not happy with the 45 percent response rate, but I am thinking that that was probably a fairly unselected group of people with depression. I think what we will learn over time is that as we have seen in the past, there are probably subgroups of people with depression who respond better to MAOIs, so I am convinced that the safety data is reassuring.

DR. GOODMAN: Thank you, Dr. Rudorfer.

Dr. Leon.

DR. LEON: I will vote no. I think the sample size is so small for the safety data, and I just don't find it convincing despite the fact that there may be a need for it, for the treatment, I just don't see the safety data convincing to me.

DR. GOODMAN: Gail Griffith.

MS. GRIFFITH: I am going to vote no. As the patient, you indeed are always weighing the risk and benefit, unfortunately, there is so seldom enough material out there to guide patients and

inform them authoritatively.

I understand, I agree with Daniel Pine, I mean a lot of treatment, course of treatment engenders a certain amount of risk. I have to say I am convinced by the data that it did not show a signal. I am convinced that it's most likely safe, but if it has not been demonstrated at 30 and 40 mg, I don't see how we can fail to indicate certain dietary restrictions at 20. So, I vote no.

DR. GOODMAN: Carol Tamminga.

DR. TAMMINGA: For giving the overall risk-benefit ratio to my own assessment, I would vote yes.

DR. GOODMAN: McGough.

DR. McGOUGH: I am going to vote yes on 1. Interpreting the question very strictly, do the current data support that this dose is safe, and I think the signal of risk is within what we see with Eldepryl, and I think since that is acceptable, then I would vote yes. I am actually going to be voting no on 2, because I think in the context of the other doses, it doesn't make any sense.

DR. GOODMAN: Dr. Wang.

DR. WANG: A very uneasy yes and a formal plea to have there be some kind of mechanism

whereby formal pharmaco-epi studies can be a precondition for approval.

DR. GOODMAN: Dr Winokur.

DR. WINOKUR: I vote yes. I think I summarized that I found the combination of the experience with Eldepryl in the clinical trial experience to be reassuring, and I felt the discussion of the more experimental approaches gave enough additional reason to be reassured.

DR. GOODMAN: Jean Bronstein.

MS. BRONSTEIN: I am going to vote no and reluctantly no, because I think it is exciting to have an MAO available for greater use, but I am concerned about the patient interpretation data, and I think the drug company did a very good job on their materials, but my experience is it is going to be misunderstood and misused.

DR. GOODMAN: Dr. Pine.

DR. PINE: I am very much on the fence. I

am going to vote no, and I think it is really based on the paucity of experimental data. I just would like to see more although again it's a very reluctant no.

DR. GOODMAN: Dr. Robinson.

DR. ROBINSON: As everybody, I sort of share the ambivalence of it's a new drug, so to speak, and potentially can help a lot of patients. I think the one thing that we have seen is it is reasonably as safe as Eldepryl. That's the best that we have right now, and since that seems to be safe, I am going to vote yes.

DR. GOODMAN: The final tally is 7 yes, 4 no.

I want to turn to Question No. 2. Dr. Tamminga, are you going to have to leave? Do you feel comfortable voting without further discussion?

I will just ask one question of the sponsors before we do that.

If the outcome is that we said yes to 1, but I don't know, is it possible that you might consider just marketing the 20 mg if that one did

not have dietary restrictions?

DR. DUBITSKY: I don't think they have adequate efficacy data just at 20 mg.

DR. GOODMAN: Please explain that.

DR. DUBITSKY: They have two positive trials. One study was done with just 20 mg. The second study was done using flexible dosing, 20 to 40. Initially, the initial submission contained only the first study at 20 mg, but on the basis of one study, we didn't consider that adequate evidence of efficacy.

DR. GOODMAN: So, they have to market the higher doses.

DR. DUBITSKY: Unless they want to do another efficacy study at 20.

DR. GOODMAN: I didn't realize that. I wish that had come up earlier actually in our discussions.

Any further questions?

Okay. Let me reread it.

If the EMSAM 20 mg patch formulation could be considered reasonably safe--the question is are

you doing this as an individual or as the--the committee voted overall, but I think you have to do this as an individual, not based upon, you know, that we said yes, because we didn't all say yes--it could be considered reasonably safe for marketing without the need for dietary restrictions, would it be acceptable to market the 20 mg patch without dietary restrictions and at the same time require dietary restrictions--well, maybe not.

Tom, I may have that interpretation wrong. I mean maybe we are--we should answer this in the abstract.

DR. LAUGHREN: Yes, I would be happy in the abstract. I think even if you voted no on one, you would still offer an opinion on whether or not it is acceptable to have this drug out there with dietary restrictions on two strengths, but not on the third.

DR. GOODMAN: Is everybody clear that that is going to be the assumptions? Any questions?

Dr. Mehta, do you want to start? We are going to go straight to a vote.

DR. MEHTA: I have no problem as long as it is written in the package insert, the label says very clearly that too high doses there is red line,

and all that, a box saying that you need dietary restrictions, and the lower one doesn't need it.

Just one comment, Dr. Dubitsky. I thought that there were two pivotal studies at 20 mg, and only one study in which 20 to 40 mg was used. At least from the table that I have from Somerset, it looks like that, there are two studies. One was 6 weeks and another one was a 52-week study.

DR. LAUGHREN: We have generally not accepted a long-term trial as evidence of acute efficacy, so that the requirement is two studies at the dose that is going to be used, and they don't have that unless all three strengths are marketed.

DR. GOODMAN: Did you vote?

DR. MEHTA: I did.

DR. GOODMAN: What did you say?

DR. MEHTA: I did, I said yes.

DR. GOODMAN: Okay, I missed that, I am sorry.

Dr. Rudorfer.

DR. RUDORFER: I will vote yes. I was initially, actually, rather troubled by this. The more I think about it, on the one hand, my initial concern that people would get accustomed to taking the medication without the restrictions, and then

be titrated up, and have trouble shifting gears, in a sense, there is a certain protective factor because what I was saying about the fact that you would need to switch to a different product as opposed to increase the number of units per dose, so that would be a very clear qualitative kind of shift.

I think the analogy that Dr. Pine used before to lithium came to mind, which is for certain medications, one needs more active patient understanding and involvement than for others, and this is clearly not a situation of, well, you just slap on a patch and forget about it, that patients do need to be aware of these issues, and clearly, that should go into physician prescribing practices.

DR. GOODMAN: Dr. Leon.

DR. LEON: I will vote no.

DR. GOODMAN: Gail Griffith.

MS. GRIFFITH: I also vote no.

DR. GOODMAN: I am going to vote yes only to be consistent with my previous vote, because otherwise we create kind of a dilemma or paradox. I am more ambivalent about this question than the first, because I am concerned about implementation.

I think you took some excellent steps to try to differentiate the products at all levels in the packaging. I wish there was a way to write the dietary restrictions directly on the patch, so that they could be reminded which one they are wearing, and maybe you could do something, I don't know, creative along those lines.

Again, I am going to vote yes, as I said, but I can bet that clinicians in the field, before they embark upon even starting at the 20, even is there are no dietary restrictions, will engage in a conversation with the patients, that they may need higher doses, and if they do, they need to be aware

of the dietary restrictions.

So, I think that conversation is going to occur whether it's in the label or not. In fact, I would prefer it occur earlier.

Dr. McGough.

DR. McGOUGH: I actually don't see a paradox, because I think they are two separate questions. What I would really like to see is the company get data showing that 30 and 40 mg are safe, and it sounds like given the experience with the 2,500, it may very well be, but it would be nice to be sure enough of that, so that we could lift the restrictions generally across the class, because I believe, in truth, I believe that it is much lower than what we have with traditional MAOIs.

But I think absent that, I suspect Dr. Goodman is an incredible clinician. I have very little confidence in physicians or impaired patients to follow the rules and to do as they are told. I think this is really an invitation for lots of confusion.

I honestly think most patients are going to go up in dose, so this becomes a moot point, and I think, again, I am concerned that there may be a

lot of people who remain on a low dose inappropriately, cannot enter these muddy waters.

So, I think in the context of the other two still having the restriction, it doesn't make any sense to market this. So, I am going to vote no.

DR. GOODMAN: Dr. Wang.

DR. WANG: A very reluctant yes.

DR. GOODMAN: Dr. Winokur.

DR. WINOKUR: I will vote yes. I already commented that, to me, the dietary restrictions for MAO inhibitors, which I consider vastly underused at the present time, has been a deal breaker frequently, so at least having an option to get people started, I think will be clinically very important.

I also, as Dr. Goodman suggested, am sure that I will start discussing with patients doing some dietary modifications right at the get-go with

the 20 mg, at least in part to prepare for going up.

I think it will be very important for the sponsor to follow through faithfully on the commitment for education, and I also agree that it would be extremely important to follow through to get to the point where 30 and 40 mg could also be judged by the FDA to not require the restriction.

DR. GOODMAN: Jean Bronstein.

MS. BRONSTEIN: I am going to vote no, and I would ask the sponsor to consider the same labeling that they have on the outside of the box for the 30 and 40 mg, also be repeated on the patch internal sleeve for each of the patches. Until and I really hope that you can prove that it is not necessary because I think its use would really be enhanced by the public if there is no restriction for the 30 and 40 mg patch.

DR. GOODMAN: Dr. Pine.

DR. PINE: I am going to take a very literal reading of the question just because I voted no to the last one, and so I am going to read

this very narrowly, and I am going to assume--and maybe you will tell me I shouldn't assume that--that, you know, the "if" statement is true.

So, given that, if we all accept that, and I am forced to agree with that, then, I would vote yes for this, that I see no major problem with the fact.

DR. GOODMAN: I accept the assumptions. That's a yes?

DR. PINE: Yes, oh, yes.

DR. GOODMAN: Dr. Robinson.

DR. ROBINSON: I think given also the fact that any MAO inhibitor is mostly going to be considered for patients who haven't responded to other treatment and/or have special sorts of symptoms atypical.

So, I think, you know, given that sort of physician-patient interaction, there is going to be education, and in that context, I think you could easily say, okay, there is one dose where you have to do this, and there are two other doses where you can't do this, and you have got to do something

totally different.

In that context, I think patients could be educated about the differences. So, I am going to vote yes for this.

DR. GOODMAN: We are down one member, so our total is 10 for those who are checking the arithmetic.

We have 6 yes, 4 no.

Tom.

DR. LAUGHREN: Before you wind up for the day, could we have some discussion about what would make people more comfortable. Those who voted no on 1, and those who voted no on 2, what would make people more comfortable with either, you know, having this out there without dietary restriction at the 20, or I guess having, in the absence of sufficient evidence for the 30 and 40, you know, having this different advice for the 20 and 30 and 40.

DR. GOODMAN: I think that is fair and I think that we should review that. Are you looking for help in design of studies that would provide

irrefutable evidence of safety at all doses?

DR. LAUGHREN: I think just generally, the kinds of data that you would find convincing.

DR. GOODMAN: Dr. Pine, do you want to start?

DR. PINE: Sure. I will just reiterate what I said after my no vote, that I would like to see more experimental data with tyramine challenge, extreme case scenarios with bigger N's, just basically, the kind of studies that have been done, but just triple or quadruple the N.

DR. GOODMAN: Even though I voted yes, I concur with that.

Jean Bronstein.

MS. BRONSTEIN: I am not a scientist, so I am not going to speak to the design element at all, but I would like the FDA to be so convinced that the data coming across for all three proves that there isn't a problem, and I am now thinking of the variability of patients out there and how much cheese they would eat.

I would like to see that looked at in

looking at the noncompliant or even looking at the bulimic, because patients come in lots of different sizes, shapes, and forms.

DR. GOODMAN: Dr. Wang.

DR. WANG: Again, I would like to see some epidemiologic studies in real-world, you know, typical practice, because there, you are going to see whether people are getting instructions, not getting instructions, using things improperly, and what kind of risk they have, so I would strongly recommend those.

DR. GOODMAN: Dr. Leon.

DR. LEON: I agree with Dr. Pine, larger sample sizes for the experimental studies, also perhaps an experiment where some subjects are given the dietary restrictions, and some are not given the dietary restrictions, and perhaps followed for six weeks and carefully monitored.

DR. GOODMAN: I am not sure that that design would work, because you would have to--I am just not sure. You would need such a large N, and I just don't know.

DR. LEON: But large N's are needed to study safety, and I think given the severity of the AE, it is worth a study like that.

DR. GOODMAN: That is where the advantage is of the challenge studies, it allows you to really push that dose in a very safe setting and controlling the variables, I think you will get more answers there than you would--that's my opinion.

DR. LEON: But right now the assumption around the table except for a minority is that this is safe, so I feel like we--in patient populations, I would like to see the experiment not only in healthy controls, but also in those who would be using it. I think the healthy controls that were included in those experiments were younger and healthier, of course, and not depressed, and probably didn't have the cognitive impairment.

DR. GOODMAN: Another option along the same lines, though, would it be possible to have a registry in a subset of patients, you know, that would beef up the postmarketing surveillance in

which you are tracking a side effect. Well, I don't know if that adds any value to what you already do.

Tom, you want to comment on that?

DR. LAUGHREN: Andy, what risks do you want to rule out? I mean the expectation now is that this would be quite a rare event. I mean as it is, it's a rare event with the currently available oral MAOIs, the expectation it would be quite a rare event here.

DR. LEON: Well, if it is as rare as the data suggest, we would see no events.

DR. LAUGHREN: But if you saw no events in 1,000 patients, I guess you could rule it out at 1 in 300. That is probably not very comforting. I think it would have to be an enormous trial.

DR. LEON: I do agree with that, that it would have to be large, and it is a difficult question to get at. I mean a lot of it could be gotten at with pharmaco- surveillance studies, as well.

DR. GOODMAN: Other thoughts on this

matter?

Dr. Dubitsky.

DR. DUBITSKY: I just wanted to ask Dr. Leon and Dr. Pine, when you talk about having more tyramine challenge data, are you referring to data at the 20 mg dose?

DR. PINE: I guess you could speak to two issues. One issue is I would have felt more comfortable, and could have been persuaded to vote yes, with those data, but I also agree with what was said about it would be nice to know whether the dietary restrictions are really necessary at 30 and 40.

So, I would like to see both. I mean I would feel better about the 20 mg if we could see the data, and I would feel even better still if we did 30 and 40 mg data and we could look at all of it, and we could say, you know, nobody gets close to the point where we really worry about it.

I mean that would be a really good thing for treatment.

DR. LEON: But given limited resources, I

would focus on the 20 mg, but I agree with Dr. Pine that the 30 and 40 would be very informative, and maybe the dietary restrictions could be eliminated from them with larger sample size.

DR. GOODMAN: Gail.

MS. GRIFFITH: Given that we saw them titrating up rather rapidly, I was really persuaded that that became an issue very quickly. So, I would like to see it across all of the milligrams.

DR. PINE: The data at the 40 mg, I mean again if you read them very conservatively, there were a couple of people at 25, you know, it would be nice to know is that a fluke or is that due to the testing conditions, or, you know, is there kind of like with lithium, a relatively steep increase in the risk as the dose goes up, which I don't think you can speak to, quite frankly, with the small sample sizes and the questions about stability of the response and the like, in between subject variables.

DR. GOODMAN: Any further comments?

I think we have done our work for today.

I think there is a variety of views. I hope it has been helpful to the FDA. I imagine it is usually helpful when there is a unanimous vote one way or the other, but I think that the discussion, the data presented was very thoughtful, and I hope this will help you in rendering a decision.

I also do hope that whatever the final decision, I am glad that there will be another medication available. I think that has been very clear around the table, that we are all excited about the prospect of having a safer MAOI, and I don't think anybody doubted the fact that this is safer than existing agents.

So, I think that no matter what you decide it is going to be good news for the public in giving us another option that is safer.

Karen, do you have anything final?

DR. TEMPLETON-SOMERS: The only thing would be if the committee members could give me their original backgrounder, because that will have to be shredded. There was a lot of redacted material in it, unless you want to keep it, which

is fine.

DR. LAUGHREN: I just want to thank the committee. It was a thoughtful discussion and very thorough, and close votes are more difficult to deal with, but I do appreciate your thoughts on this.

DR. GOODMAN: Let me thank the audience and the sponsors and their consultants, and most of all, to all of my fellow panel members for two days of very interesting and productive hearings.

[Whereupon, at 1:12 p.m., the proceedings were concluded.]

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