DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMALOGIC DRUGS

ADVISORY COMMITTEE

Friday, December 2, 2005

8:00 a.m.

Hilton Hotel
The Ballrooms
Gaithersburg, Maryland

PARTICIPANTS

Wayne K. Goodman, M.D., Chair
Cicely C. Reese, Pharm.D., Executive Secretary

MEMBERS:

Jean E. Bronstein, R.N., M.S.,
  Consumer Representative
Andrew C. Leon, Ph.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.
Barbara G. Wells, Pharm.D.
Bruce G. Pollock, M.D., Ph.D.

CONSULTANTS (VOTING):

Barbara Geller, M.D.
Richard Malone, M.D.
Cynthia Pfeffer, M.D.

PATIENT REPRESENTATIVE (VOTING):

Deborah L. Dokken, MPA

FDA STAFF:

Robert Temple, M.D.
Thomas Laughren, M.D.
Paul Andreason, M.D.
Robert Levin, 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 Opening Remarks

DR. GOODMAN: Good morning. This is the Psychopharmacologic Drugs Advisory Committee. All committee members have been provided with copies of background materials from both the sponsors and the FDA, with copies of letters from the public that we received. The background materials were posted on the FDA web site yesterday morning. Copies of all these materials are available for viewing at the FDA desk outside this room.

FDA relies on its advisory committee to provide the best possible scientific advice available to assist them in making complex decisions. We understand that issues raised during the meeting may easily lead to conversations over breaks or during lunch. However, one of the benefits of an advisory committee meeting is that the discussions take place in an open and public forum so, in the spirit of the Federal Advisory Committee Act and the Sunshine Amendment, we request that members of the committee not engage in

private off-record conversations on today's topic during breaks or lunch. We also ask that the press and the audience assist the committee by not asking them to participate in such conversations. We are confident that everyone is sensitive to these issues and hope you appreciate that these comments are intended as a simple reminder.

We look forward to a productive and interesting meeting. Today we have been asked to render advice on a new drug application on a transdermal delivery system for methylphenidate. We are going to be asked to review issues of both efficacy and safety.

Let me start--I think most of us here--by going around and introducing ourselves. To start off with, I am Wayne Goodman. I am a professor at the University of Florida College of Medicine, Department of Psychiatry. Why don't we start at this end of our committee, over here, Dr. Mehta?

DR. MEHTA: I am Dilip Mehta. I am a retired physician. I worked with Pfizer. I am the industry representative on the committee.

DR. POLLOCK: Bruce Pollock. I am a geriatric psychopharmacologist.

DR. WELLS: Barbara Wells. I am the Dean

of the School of Pharmacy at the University of Mississippi.

DR. LEON: I am Andrew Leon. I am professor of biostatistics at Cornell University Medical college.

DR. PFEFFER: I am Cynthia Pfeffer. I am a professor of psychiatry at Cornell University Medical College and a child psychiatrist.

DR. MALONE: I am Richard Malone, a professor of psychiatry at Drexel University College of Medicine and I am a child psychiatrist.

MS. Dokken: I am Deborah Dokken. I am the patient family representative on the FDA's pediatric advisory committee, and have been asked to serve temporarily on this committee.

DR. REESE: Good morning. I am Cicely Reese, executive secretary.

DR. GELLER: Barbara Geller. I am a physician, a child psychiatrist at Washington

University in St. Louis.

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

DR. ROBINSON: I am Delbert Robinson. I am a psychiatrist at the Albert Einstein College of Medicine, in New York.

DR. PINE: Danny Pine, child and adolescent psychiatrist at the NIMH Intramural Research Program.

DR. LEVIN: I am Robert Levin, medical reviewer in the Psychiatry Division at the FDA.

DR. ANDREASON: Paul Andreason. I am the Acting Deputy Director, Division of Psychiatry Products at the FDA.

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

DR. TEMPLE: Bob Temple, Director of the Office of Drug Evaluation I.

DR. GOODMAN: Thank you, everyone. I am going to turn the microphone over to Cicely who has an important statement to read.

Conflict of Interest Statement

DR. REESE: Good morning again. I will read the conflict of interest statement. 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 a conflict of interest at this meeting with the following exceptions:

Dr. Andrew Leon has been granted a full waiver under 21 U.S.C. section 355(n)(4) for owning stock in a competitor, valued from $5,001 to $25,000. A waiver under 18 U.S.C. section 208(b)(3) is not required for this interest under 5 CFR 2640.202(b) de minimis exemption for matters affecting non-parties applies.

Dr. Bruce Pollock has been granted a full waiver under 18 U.S.C. section 208(b)(3) for

consulting on an unrelated matter for a competitor, for which he receives less than $10,001 a year, and for serving on a speaker's bureau for a competitor, for which he receives less than $10,001 a year. His speaking is unrelated to the product at issue and the competing producs.

Dr. Wayne Goodman has been granted a full waiver under 208(b)(3) for his employer's contracts with a competitor, funded between $100,001 and $300,000 per year. His employer also has a contract with a firm that is a sponsor and a competitor, funded for less than $100,000 per year.

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.

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.

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.

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

DR. GOODMAN: Thank you, Cicely. We have another member who just joined us. I wonder if you could introduce yourself? Use the microphone, please.

MS. BRONSTEIN: I am Jean Bronstein.

DR. GOODMAN: And say something about yourself.

MS. BRONSTEIN: I am the consumer representative. I am a retired psychiatric nurse.

DR. GOODMAN: Just to give you an overview

of the agenda, we are going to start off this morning with formal presentations from the FDA. Although it doesn't show time for questions, that is what I would like to do, and I think it would be useful for the committee to have an opportunity to ask questions of the FDA, and then probably take a brief break. That isn't on the schedule. I find it is better to take some brief breaks so everybody stays fresh, right before the set of presentations from the sponsor. All right? So, I would like to introduce Dr. Tom Laughren, who will be presenting on behalf of the FDA.

FDA Introductory Remarks

DR. LAUGHREN: Good morning. I just have a few brief comments. I mostly want to welcome you back to the Washington area for this meeting, and then I am going to make a few general comments about the topic for today's meeting. As you know, we are going to be discussing this patch formulation of methylphenidate for the treatment of ADHD. This is the first patch formulation we have seen for methylphenidate and we thought it would be

useful to bring this to the committee and have your thoughts on this.

Now, as you will hear, this is the second review cycle for this application. It received a non-approval action the first time around and the reason was primarily our concerns about unacceptable adverse events with the 12-hour wear time that was utilized in the initial program. Subsequently, the sponsor conducted a second program using a 9-hour wear time and they feel that they have demonstrated effectiveness and reasonable safety using this shorter wear time.

From FDA, you are going to hear first from Paul Andreason, the deputy, who is going to give you some additional background information and outline the issues that we would like you to focus on. Then you will hear from Bob Levin, the clinical reviewer, who is going to focus mostly on safety issues. In addition, there are several other members from our review team who are here, who will not be making presentations but they are available to answer questions that might come up.

Is Dr. Kong here? I guess he is not here. In any case, Dr. Kavanagh and other members from the Biopharmaceutics group are here to answer questions. Is Dr. Zeldes here? He is here from the controlled substances staff to answer questions in that area should they come up.

Now, in the clinical review that you received in the package, obviously you are aware that Dr. Levin in that review concluded that this product is not sufficiently safe to be approved. You are going to hear from Dr. Levin today. I believe he has reconsidered that conclusion. In any case, the point that I want to make is that the Division has not yet reached a conclusion about this application and that is why we are seeking your advice on this.

Finally, I want to mention that we are going to ask you to vote on the two general questions of efficacy and safety for this product, but I also want to let you know that you, obviously, are free to raise other questions and issues that you think need to be discussed. As I

pointed out, we have some other review staff from other disciplines who are here to help answer those questions.

Next, I would like to invite Dr. Andreason to come up and make his comments. Thank you.

FDA Overview

DR. ANDREASON: Thank you very much, Tom. I would like to thank the committee for the opportunity of speaking today. As part of my presentation this morning, I would like to go over a little bit of the history of methylphenidate. This is a drug substance that has been on the market as long as I have been alive and, unfortunately, that is a fairly long time.

[Laughter]

It was approved in December of 1955 for an indication which we know today as attention deficit hyperactive disorder but which was called minimal brain dysfunction at that point. Just to give you a little bit of perspective on how far drug regulation has come since that time, it was not until 1962 that Congress amended the Food Drug and

Cosmetic Act to require that drugs demonstrate effectiveness prior to their approval as well as safety.

The basis of approval of the stimulants in general, and methylphenidate specifically, is that they treat patients with an established diagnosis of attention deficit hyperactivity disorder, and that is by whatever the current standard might be. At this point it is the DSM-IV criteria. Improvement on classroom measures of attention and behavior in a double-blind, randomized, placebo-controlled trial, and instruments that are used to measure that are commonly the SKAMP, or the Swanson, Kotkin, Agler, M-Fynn and Pelham, laboratory school rating scale, or another one that is commonly used is the inattention/over-activity with aggression, or IOWA Conners scale.

Over the time that I have been alive and professionally active we have seen many changes in the methylphenidate drug formulations. Methylphenidate was commonly used in an immediate release formulation where children had to receive a

dose early in the morning and then receive a second dose at school. Since it is a Schedule II controlled substance, this required that a separate prescription be filled and kept probably in a safe--literally a safe lock-box at the school and be administered by a school nurse. This also required children to visit that school nurse at some point during the day.

With the extended release formulations, this obviated the visit to the school nurse in the middle of the day and the extra prescription and the logistical problems that were caused by this treatment, and it was worth doing it because, as I will comment again later, clinical trials with the stimulants in general, and with methylphenidate specifically, are uniformly positive, most often positive at every measured time point and these are not only statistically significantly better than placebo but they are clinically better than placebo.

Just to highlight some of the changes in formulation over the years, Ritalin SR was approved

in 1982; Concerta in 2001; Ritalin LA in 2002; Focalin, a dex-methylphenidate extended release formulation, in May of this year. Other formulation changes for non-tablet or not swallowable tablets of capsules--there is the solution that was approved in 2002 and the chewable tablet in 2003. There have been some drug substance changes in that Focalin is the dexmethylphenidate formulation, as well as Focalin XR.

Again, studies with the stimulants in general, and methylphenidate specifically, are uniformly positive. The measurable treatment effects are both statistically and clinically significant. In short, the stimulants are a very reliable mainstay in the treatment of ADHD.

Stimulants are also an archetypical model of a performance-enhancing drug. They not only help people with ADHD, they pretty much help anyone who takes them improve in attention. If these medications are taken in too high a quantity, then they can cause fairly uniformly adverse events,

both psychiatric and cardiovascular. Each individual may vary in their sensitivity to getting these adverse events but, if given enough of any of these stimulants, almost anyone might have them if given a high enough amount.

The methylphenidate patch that we are meeting on today is a change in the route of methylphenidate administration. The regulatory history of this particular formulation is that it was first brought to the FDA as a new drug application in June of 2002 and we issued a not approved letter in April of 2003. The major reason for this decision was that we believed that it significantly over-medicated children at inappropriate times of the day and led to unacceptable adverse events not associated with other once a day products available. The complete response to our not approved action was received in June of 2005, and the due date for our action on this application is December 28 of this year.

Particular questions that I have, in addition to the general question of is the drug

formulation safe and effective as labeled, are the following: Some of the clinical issues that we had with the previous formulation that we did not approve were that efficacy was achieved at the expense of excess drug exposure and an unacceptable incidence of adverse events. Some of these adverse events were insomnia, anorexia and significant weight loss in the short term.

We were also afraid that the higher exposure might lead to other types of adverse events down the road that we would not necessarily see in short-term studies, such as growth retardation and other long-term effects of higher exposure to amphetamine or stimulant drugs. We felt that other products approved for once a day dosing in that population were not associated with that level of exposure or incident risk. We also thought that patients could benefit from decreasing the wear time of the patch.

This is the graphic. It is really not real data. This is not a true comparative study that we looked at with the 12-hour formulation.

This was the 50 cm2 patch compared against a hypothetical Ritalin 10 mg BID dose, which is in blue, and this gives you an idea of what the peak time was during the day. The red graph represents the 50 cm methylphenidate transdermal patch. You will notice that the peak is at about 10 hours and that potentially therapeutically effective doses were in the bloodstream all the way out to 20 hours after the patch was applied.

This is a graph of real data. This is the pharmacokinetic profile of Concerta at three different sizes of the methylphenidate transdermal patch. You can see from the legend the lower curve with the boxes, the 12.5 cm2 patch; the diamond 25 cm2; and the triangle, the 37.5 cm2 patch. I am not exactly sure what that shape is. The open boxes are the Concerta 54 mg sustained release capsule to give you some idea of what the time versus concentration function is for this drug.

I would like to also bring to your attention that the patch should be applied 2 hours before its intended use begins so that would bring

the steep part of the curve for the patches closer to the zero time point. This, again, is a single dose pharmacokinetic profile for d-methylphenidate. I would like to say that the human body differentially takes up the methylphenidate over l.

Here are the numbers. Cmax for the 54 mg Concerta tablet, 24.2 ng/ml, and for 37.5 cm2 the patch 27.2--not the same but roughly equivalent, and you will see that the area under the curve is slightly greater for the 54 mg capsule at 262 versus 255 for the largest patch--again, single dose d-methylphenidate concentrations.

L-methylphenidate reaches the plasma in measurable concentrations with the patch where this is not the case with oral formulations of any kind, even though the oral formulations do contain l-methylphenidate, again due to our preferential processing of d-methylphenidate--particular uptake, I should say.

Here are the numbers for that. For the 54 mg Concerta tablet concentration the maximum is 0.8 versus 17.4 for the 37.5 cm2 and the area under the

curve is about 9.5 for the Concerta tablet and about 105 for the 37 cm2 patch.

Now, for the repeat dose studies at samples that are taken 9 hours after application we see a difference in the Concerta versus the transdermal patch. In these studies, these are average Cmax values that are taken during the Phase III controlled trial. This Phase III controlled trial was titrated to effect and tolerance in a blinded fashion so clinicians were basically prescribing and using these drugs as they would in the clinic. Doing so, generated these differences in plasma peak concentrations.

We are not exactly sure why this difference exists. Is it a difference in tolerability between the patch and the oral formulation? Is it a difference in the presence of l-methylphenidate? Or, is it merely something as simple as the difference in the peak time measurement values? For example, the sample was drawn 9 hours after the patch was administered. The oral formulation peak time occurs somewhat

earlier than that. So, that can also explain the difference. What we would like to be able to discuss is perhaps some of the reasons behind this difference and, if this is a real finding, what this might mean for patients.

Just to review, these are the mean scores by time point after administration of the methylphenidate patch, again showing that with methylphenidate preparations in general, and this one specifically, it was statistically significantly positive at all of the predetermined time points over placebo.

The differences that we see in l- and d-methylphenidate concentrations are not necessarily additive because the l-methylphenidate does not particularly contribute to the efficacy of the drug. In animal models of the effect of the racemate, for example in rats, rats do not metabolize the l-methylphenidate the way we do and it is present in their circulation. In animal models of d-methylphenidate it appears that it is 3.3 times more potent than the l-methylphenidate.

Now, if this was just a gram for gram difference in potency between the d and the l, the l not being active at all, then it would only be twice as potent. This author concluded that perhaps the l had some kind of inhibitory effect on the d form in efficacy but one could argue that the mean values here might not necessarily be significant. Nonetheless, this is one argument as to why its presence might lead to higher concentrations of d-methylphenidate in regular prescribing practices.

Another clinical issue, which is completely different, is that with the skin patch there was a signal for possible skin sensitization. Part of the complete response is that the sponsors performed a skin sensitization test and in that test it showed that somewhere between 13 and 22 percent of the patients developed skin sensitization to the methylphenidate when using the patch. Our dermatology consultants have recommended that if patients did develop skin sensitization to methylphenidate, then in the future they would not be able to take

methylphenidate by any route of administration.

The difference in the adverse event profile of the oral and the patch formulations are roughly equivalent, except perhaps for tics--which you will see towards the bottom in the second to the last box under psychiatric disorders. The bottom line shows that with the methylphenidate transdermal patch approximately 7 percent of the patients developed tics versus 1 percent for the oral formulation and zero for placebo.

Now, in the studies of longer wear time with a larger patch there were no reports of tics. However, there was a report of twitching at a rate of 5 percent versus zero for placebo. Only one of these patients, of 202, dropped out of the study because of twitching. So, it is difficult to say whether twitching was coded correctly, and whether or not there were patients in there that truly had tics or whether perhaps tics may have been over-coded, and we will hear a presentation on that today.

Some of the points of discussion, again in

addition to the general comments that we have about safety or the general comments that we seek about general safety and efficacy of this formulation, is that the total methylphenidate exposure appears to be greater for patches. However, this may largely be due to the presence of the l-enantiomer and we don't know exactly what the long-term effects of this might be. Again, the difference between tics is something that we will hear further discussion on today and we would like you to comment on as a committee.

Finally, and possibly the thing that I have the biggest question about is that the patch must be applied 2 hours before school and removed 9 hours after the application. This makes it so that if a child has a school start time of 8:30 the patch must be applied at 6:30. Then the end of the school day with an 8:30 start time would be 3:00. That is 8.5 hours into the wear time so the patch would have to be removed at 3:30 in order to comply with the labeled use. In other words, the use is more complicated. The patch may be removed

prematurely either on purpose or not--when I say "not" I don't mean accidentally but as an act of non-compliance, or it may be left on in error.

Generally, our regulatory question is can the methylphenidate patch be safe and effective when used as labeled? But, in addition to that, can the methylphenidate patch be used as labeled in the population for which it is intended? Thank you very much.

DR. GOODMAN: Thank you. Dr. Levin?

FDA Presentation

DR. LEVIN: I reviewed the safety issues for both the initial two pivotal studies as well as the new studies for the resubmission. I won't have any slides on efficacy but, as Dr. Andreason and others mentioned, we agree with the sponsor that the pivotal studies in the resubmission were clearly positive.

I will describe the initial studies. One was study 18. This was a multi-center, randomized, double-blind, placebo-controlled dose titration study in children aged 6-12 with a diagnosis of

ADHD. It was a 6-week study with a 4-week double-blind period and the dose initiated was 12.5 or 18.75 cm2 for the patch. Clinicians could titrate the patch size weekly and they could titrate down as well. The range of the patch used was between 6.25 to 50 cm2. In both the pivotal studies the wear time was 12 hours. As you will see, in contrast, in the newer studies the time was 9 hours.

The other study, study 10, similarly was a multi-center, randomized, double-blind, placebo-controlled trial, a dose titration study which was 3 weeks, somewhat shorter than the first study. Again, it was the same population and the dose was started at a lower patch size of 6.25, titrated weekly and the wear time was also 12 hours.

Again, the initial safety issues that we had were that the patients were experiencing excessive drug exposure at inappropriate times, meaning in the evening, and it was determined that the safety profile was unacceptable. In

particular, the concerns were a high proportion of subjects with anorexia, weight loss, insomnia, excessive skin irritancy and the potential for skin sensitization.

Here is a table that shows some of the common adverse events of concern in both studies 10 and 18. So, you can see that anorexia was fairly high in study 10 and quite high in study 18, a study of longer duration--I am sorry, I think I had that backwards but in both studies the proportions were high, as were the proportion of patients with insomnia and twitching, which we will go into later. We had a question about whether some of those might or might not be tics. We will discuss that later.

The recommendation by the Division for the initial studies was that the sponsor consider decreasing the patch wear time from 12 hours, as was done, to 9 hours. We recommended that the sponsor conduct a classroom study looking at PK/PD relationships and study the time course of effect of the methylphenidate patch in children with ADHD,

age 6-12.

Also, it was recommended to prospectively monitor insomnia with a specific scale that would be appropriate for this age group, and that was done as we will discuss. Since there was a possible signal for skin sensitization with periods of use longer than 6 weeks, the Division recommended that the sponsor conduct a skin exposure study of longer than 6 weeks duration to investigate the potential signal. Also, another major recommendation was that the sponsor use an active comparator in subsequent trials of the methylphenidate patch.

The first new study, study 201, was a multi-center, randomized, double-blind, controlled, dose optimization and analog classroom crossover study with 2 phases. The first was a 5-week open-label methylphenidate treatment phase in which subjects were treated open-label with patch sizes ranging from 12.5 to 37.5. I should mention that in addition to the change in the wear time, the new studies used a maximum patch size of 37.5 as

opposed to 50 cm2 in the first set of pivotal studies. The patch sizes are listed below. Wear time was 9 hours. During the studies the main feature was assessing PK and efficacy measures frequently during the study.

The second new pivotal study was study 302, which was an outpatient multi-center, randomized, controlled trial with an active control, Concerta. It was also a dose optimization study with patch sizes ranging from 12.5 to 37.5 cm2 with the same wear time. The Concerta doses used ranged from 18 to 54.

To summarize the safety findings, in both new studies there were no deaths and no serious adverse events. There were several discontinuations due to adverse events. In study 201 8 percent of the open-label group and 1 percent of the placebo group discontinued due to adverse events, and all those patients were being treated with the methylphenidate patch. Two of those discontinuations were due to tic; two due to rash at the application site; two due to anorexia; one

patient had prolonged QT interval and one had both elevated blood pressure and mood lability.

Here is a list of the discontinuations due to AEs in study 302, the second study. Again, there is one patient with tics; two with reaction at the application site; headache and irritability, crying and confusional state. In the Concerta group adverse events thought to be possibly or probably due to Concerta were syncope, abdominal pain, aggression, anger and headache.

These are the adverse events commonly reported--this is actually all the adverse events reported in the open-label phase of 201. As in the initial studies, anorexia or decreased appetite was fairly high but of a lesser degree than in the initial studies. Insomnia had a fairly high proportion of subjects, and that was 16. There was also a similar proportion of headache as in the earlier studies, as well as nausea and vomiting. Again, tics were reported in 2 percent of the subjects in the open-label phase, as was weight loss; and there were 3 percent of patients with

application site reactions. In contrast, in the placebo-controlled phase of study 201, the reported adverse event rates were relatively low. You can see those listed below.

In study 302 with placebo control and Concerta control, again, there is a fairly high incidence of decreased appetite and anorexia, which were higher than both Concerta and placebo. Headache was roughly similar. Insomnia was slightly higher in the methyl patch group than the Concerta group. Other than tic and possible affective lability, the adverse event profile was fairly similar between methyl patch and Concerta.

One important subject, as we mentioned, was the concern about weight loss. In both studies 201 and 302 there was a trend for weight loss in both studies, for both the methyl patch group and the Concerta group. At least in one of the studies there was a trend towards increased weight for the placebo group. For the methyl patch group for both study 201 and 302 the mean decrease in weight was negative 1.3 to negative 2.2 lbs., comparable to

that in the Concerta group, of negative 2.1. In addition, there are decreases in the mean z-scores for both weight and BMI. For study 201 the decrease was from negative 0.08 to negative 0.15. For study 302, for the methyl patch group the mean z-score decreased from 0.05 to negative 0.21 and in the Concerta group it decreased from 0.28 to 0.04. Although these are decreases, in a short-term study it is difficult to interpret the importance or meaning of these findings.

Another important concern by the Division in the first set of studies for which the application was considered non-approvable was the fairly high proportion of subjects reporting insomnia as adverse events. To gain further information, the Division recommended that the sponsor use a directed scale to investigate sleep more thoroughly and prospectively, and they used the well-accepted scale which is the Children's Sleep Habits Questionnaire. It is a directed assessment with 33 items with appropriate categories, including sleep quality, sleep latency,

duration, sleep disturbance, as well as other features of sleep.

In study 201 in most dosing groups, meaning most patch size groups, sleep ratings actually improved in the open-label and placebo-control phases. So, an improvement of sleep was indicated by a decrease in the CSHQ score. Similarly, in study 302 the sleep ratings improved in the methyl patch group and the Concerta group, as well as the placebo group.

One concern I initially had was that since there were so many items--33 items, some of which did not tap into what we might be most concerned about which is sleep delay onset, sleep duration and sleep disturbances, I was concerned that there may be possibly a dilution of potential effect of the methyl patch or Concerta on sleep. But, in fact, when one looks at the sub-scales that the sponsor provided, the scores for bedtime resistance, delayed onset of sleep--scores improved in all three treatment groups so it was more reassuring that there was less of a concern with

insomnia.

Another important issue was a concern about tics and twitching. In studies 10 and 18 the proportion of subjects with tic is as listed below versus none in the placebo group. As far as I remember, I think there was one case of tic reported in the initial studies but I am not quite sure. Maybe the sponsor might be able to comment on that. In some cases of the twitching reported in the initial studies, whereas the investigator termed these as either facial tics, buccolingual tics and mouth movements, those terms were coded to the preferred term twitching. So, it seems at least possible that in some cases--it looks fairly clear that in some cases what was coded as twitching was, in fact, tics. In study 201 the proportion of patients with tics was 2 percent; in study 302 it was 7 percent, and in Concerta it was 1 percent. There were several discontinuations due to tic and twitching in all four studies.

There were dermatology findings in the pivotal studies. In the skin sensitization study,

which was actually done in adults with a 6-week duration, sensitization occurred in 13.22 percent of adult subjects. Thus, as Dr. Andreason mentioned, sensitized patients should not or could not take methylphenidate by any route again after sensitization. In studies 201 and 302 investigators looked at dermal response, meaning erythema or irritation or discomfort, and there was an increase in all three types of events or observations in the methylphenidate group compared to the placebo patch group. In 201 the percentage of subjects was 24-30 percent versus 3-6 percent in the placebo group. In study 302 the mean dermal response score was higher than other groups at all visits.

As Dr. Laughren mentioned, initially I recommended that the Division take a non-approvable action for the NDA for methyl patch in the treatment of children age 6-12 with ADHD. However, I have reconsidered this recommendation for a number of reasons. I think that some of the same safety concerns remain but they seem to appear to a

lesser degree, for example anorexia and insomnia. Problems like tic remain. In some cases the AEs have occurred in reduced proportions compared to the initial studies and may pose less of a concern.

In addition, another reason for considering recommending an approvable action is that the frequency of AEs with the methyl patch is roughly comparable to the active control Concerta in one of the new trials. Also, all these AEs are in labeling for methylphenidate products and they are generally manageable. There were no unexpected or unusual side effects in these trials and no serious side effects or deaths.

So, at this point I would recommend that the Division consider an approval action for the methyl patch in the treatment of children with ADHD.

Questions from the Committee

DR. GOODMAN: I wonder if you could stay at the podium and allow the committee members to ask you a few questions. Thank you. Just to clarify, it would appear from your statements today

that you may have changed your recommendation from what we have seen in the report.

DR. LEVIN: Right.

DR. GOODMAN: Again, could you just explain what new information or considerations led to your change in recommendations?

DR. LEVIN: Sure. Well, first let me explain the reason for recommending a non-approvable. I had the feeling and impression that the same types of adverse events and safety problems that were seen in the first two studies remained in the second studies, not necessarily to the degree or frequency but the same quality of events. While there are numerical differences in proportion of such side effects--insomnia, anorexia, decreased weight with methyl patch versus placebo and methyl patch versus Concerta, on further review, I judged that the differences in numbers are really not as significant as I initially had thought. They are, in fact, known adverse events seen with use of methylphenidate products. One of the primary reasons is that the

adverse event proportions were not significantly different from those of Concerta in a direct head-to-head trial with Concerta.

DR. GOODMAN: Other members of the committee would like to ask questions? Dr. Pfeffer, do you have your mike on? No? Dr. Pollock?

DR. POLLOCK: The concern about the skin sensitization, is this actually the development of a true allergy to methylphenidate? This is a reaction not just to wearing the patch but an actual allergic phenomenon that is created by exposure to methylphenidate and, therefore, it is in the label, if this develops, it sounds like in a substantial number of individuals taking this, up to 23 percent, that they can no longer take methylphenidate?

DR. LEVIN: That is right.

DR. POLLOCK: It is a true allergy?

DR. LEVIN: Right. This, again, was in normal adult outpatients.

DR. POLLOCK: Right.

DR. GOODMAN: Let me just ask a follow-up to that same question. How do those rates of sensitization compare to other transdermal

applications with different medications? I know that is a very broad question but, again, I think it is driving at the same point as to how much is it specific to the drug versus just a property that frequently occurs with these vehicles.

DR. LEVIN: Yes, I am not sure about the sensitization question but just sticking with these studies, a fair proportion of subjects taking the placebo patch also had irritation, local application site reactions. I don't know the numbers for that but it wasn't zero and it seemed clear that there were reactions to the placebo patch as well.

DR. GOODMAN: Dr. Leon?

DR. LEON: Bob, could I ask you to clarify the z-scores that you report for weight loss? Maybe the sponsor would have the detail--

DR. LEVIN: Yes, I don't have a detail slide.

DR. LEON: But it is somewhat general--to me it is general. Anyhow, the z-scores represent a standardized deviation from the mean, and it was not clear from either of these documents that we have that it is a standardized deviation from what mean. Is it the baseline mean of the pooled

sample? And what standard deviation was used. Was that, again, the baseline standard deviation? I am not clear on that. It is difficult to interpret this metric without knowing what went into the calculation.

DR. LEVIN: I actually wasn't sure either. I considered the general population versus the study population and I wasn't actually clear on what was used in this study.

DR. GOODMAN: Dr. Laughren?

DR. LAUGHREN: The company can comment but I am quite sure that it was the population mean. It was adjusted for age and gender. That is the standard deviation. So, you are looking at the standard deviation units by subject, how much they varied from that population mean.

DR. LEON: Okay.

DR. LAUGHREN: That is a way of tracking over time what happens to a group of kids if you look at their standard deviation from the mean.

DR. GOODMAN: Dr. Robinson?

DR. ROBINSON: Yes, I would like to get back to the dermatologic findings because that is the one group of side effects that obviously isn't applicable in terms of the oral. You said now you

decided that the formulation should be approved. Can you talk a little more about how, if we have a formulation for maybe a fifth of the subjects, may sort of not be able to take other versions of the standard therapy for the disorder, how you sort of factor that in versus the benefits of the patch?

DR. LEVIN: Yes, that is certainly a large concern for us. One way to look at it is that it might be partially handled by labeling. For patients, for example, who do have trouble swallowing pills or have other difficulties taking oral medications, the product might be reserved for use by them. They still may be at the same risk,

undetermined risk compared to patients taking oral. But, you are right, it is clearly a safety problem but at least in patients who cannot take oral formulations the benefit/risk profile may be favorable.

DR. ROBINSON: So, you would see the labeling as for people who failed on oral only?

DR. LEVIN: That is one possibility. We haven't discussed that internally yet but that is one thing I have thought about.

DR. ROBINSON: Thank you.

DR. GOODMAN: This issue is important enough that I hope the sponsor will address it in some detail because I think we are going to want to go back to it. Dr. Malone?

DR. MALONE: I had one question but I don't know how this would be handled with labeling because if one-fifth of the population couldn't take a major treatment for ADHD that would be a big concern. Why would you have more allergy to methylphenidate because it came through a patch than if you took it orally? Is there any idea

about that? I mean, is it truly a methylphenidate allergy? I mean, it wasn't clear to me why you would decide that.

DR. LEVIN: We don't have details currently about the mechanism but, as I said, first of all, the patch itself looks like it can cause irritancy and inflammation. I guess in a sense it is partly a conclusion that since there is a pattern of this sensitization that it is due to methylphenidate.

DR. GOODMAN: Dr. Pine?

DR. PINE: I guess two issues, one, in that the patch itself, it seems, in the placebo group had some desensitization, that really--I mean, that couldn't be attributed to methylphenidate so I don't know how you came up with these big numbers for methylphenidate allergies.

DR. GOODMAN: My sense is that I think you are not the only one with lingering questions and that is why I was suggesting to return to this after the sponsor, hopefully, will give us some

more details. I agree too, I want to discriminate between how much of it has to do with the vehicle and the drug reaction and how clinically significant it is. Dr. Geller?

DR. GELLER: I have a practical question. The reason that the long-acting stimulant medications were so sought after by clinicians and families was that you could do something once a day in the morning and then you were done with it. Here the patch has to come off. If it is given two hours before school it means it is given at 6:30 or 7:00 in the morning, at the latest. Nine hours later it comes out in the afternoon when parents are at work. So, it is not clear to me who is there to take the patch off. And, can you address what happens if it is left on? Does it then act as if it is the 12-hour patch? And, are you then having the problems that were of concern when the 12-hour patch came through?

DR. LEVIN: In the PK studies of children taking the patch, even when it was removed at nine hours for at least several hours there were

considerable exposures to the drug. It certainly did not drop off quickly. Theoretically, yes, it is possible that continued exposure could increase the risk of insomnia and the other adverse events.

DR. GOODMAN: Dr. Andreason?

DR. ANDREASON: I think you are exactly correct, if the 9-hour patch is left on for 12 hours it will look exactly like the 12-hour patch because it is basically the same patch--smaller size; shorter wear time. So, if left on longer it will produce the same results as the 12-hour patch if it is left on for 12 hours.

DR. GOODMAN: Deborah Dokken?

MS. DOKKEN: This may be a question for later with the sponsor too but I am curious, if one of the principal reasons or advantages of the patch is for those children who cannot easily take other formulations, I mean, what is the size of that population? If you answer it later, that is fine.

DR. LEVIN: Yes, I am not sure of the numbers. For some reason I am thinking of the number 10-15 percent but maybe that occurs to me

from some source.

DR. GOODMAN: Dr. Pollock?

DR. POLLOCK: This may be more properly a question for the controlled substances people but I was concerned if you had had a concern, further to Dr. Geller's point, that if all these kids are taking their patches off in school at 3:30 what the disposal of these patches is, and if there is a concern of diversion from that.

DR. LEVIN: Let me give it a shot here. Obviously, the recommendations in labeling currently are for the child caregiver to remove the patch, fold it and flush it. That is the idea with the standard recommendation. Dr. Zeldes, would you have a chance to discuss that? Is Dr. Zeldes present?

DR. GOODMAN: I need you to come to a microphone, and please introduce yourself.

DR. ZELDES: I am Dr. Zeldes. I am a medical officer with the controlled substance staff. We agree with Dr. Levin that if the patch is removed according to the labeling and disposed

of properly it should not be a problem.

DR. POLLOCK: But if it is not flushed, then there is still an awful lot of drug left in these patches after 9 hours of exposure, or is there?

DR. ZELDES: There would be but even if the patch was picked up and put on by another child, or something, there would then be that 2-hour lead-in time. So, we didn't really think it would be a problem. The formulation of the patch is such that the drug itself--and the sponsor can answer this more fully--is actually attached to the adhesive properties so there is no reservoir component at all.

DR. GOODMAN: Dr. Malone?

DR. MALONE: It seemed from what I read in the packet that instead of putting it back on you could just put it in your mouth and you would have a better absorption time.

DR. ZELDES: The sponsor did a study and I will let them answer that.

DR. GOODMAN: Maybe we can return to that

later then. Dr. Pine?

DR. PINE: I guess three points very quickly. One is the issue that came up a couple of times about, you know, is there really a need and, again just speaking as a clinician, there are a lot of kids who either can't or won't swallow pills and who hate to orally take stimulants. So, I do think that there is a legitimate need, number on.

Number two, like a lot of other people have said, this whole issue of sensitization in general but specifically the idea that even if it is 13 percent of the kids who take this could potentially no longer be suitable candidates for other forms of methylphenidate, that is a very big issue obviously.

Then, number three, I also got the sense in terms of my reading of the materials, the presentation of the data and your final comments that you are backing off somewhat from the tic issue as well and that you are not really concerned about the 7 versus 1 percent. Is that right, that you think there really isn't a difference in terms

of potential to either produce or exacerbate tics with the patch versus Concerta?

DR. LEVIN: In the study, as you mentioned, the proportion was 7 percent to 1 percent. We first asked ourselves was there a relatively high proportion of tics reported in the initial studies. Our answer was no until we recently noticed the difference in twitches, some of which--I am saying roughly half--may have been mis-coded and should have been considered tics. Maybe the best answer to that question is, well, there is concern definitely but it is not an unexpected, unknown adverse event with methylphenidate products and it is in labeling as well.

DR. GOODMAN: Dr. Temple?

DR. TEMPLE: Considering that the initial concerns with this drug were about side effects, one might have thought there would be some attempt to define dose response, but this program appears to be devoid of any dose-response information. Nonetheless, one might have taken the data that

they produced and looked to see whether side effects were related to the dose they were titrated to. Did you or the sponsor do that?

DR. LEVIN: Yes, there were tables. As you said, there were no fixed dose studies so I think it would be hard to interpret the adverse event profile for each individual dose but, yes, I would have liked to have had those here but I don't have them and don't recall them.

DR. TEMPLE: Maybe the sponsor could show it. You are right, they are not randomized to those doses but it might provide some information.

DR. LEVIN: Yes, I think it would.

DR. GOODMAN: Dr. Levin, you said earlier that you were in agreement with the sponsor in their conclusions about the efficacy but I remember reading in one of these reports--it might not have been prepared by you--that there were some questions about the crossover study and some of the difficulties in the statistical analysis because there wasn't a baseline to co-vary for. I wondered if you would just comment on that and whether you

have come to some resolution on that issue and no longer recognize it as a concern.

DR. LEVIN: It was a relative concern but not enough to reach a different conclusion about efficacy. Yes, you are right. The issue was that in study 201 there was no adjustment for baseline score before the placebo-controlled crossover period. We thought that that was not enough of a concern to determine that the study was not efficacious.

DR. GOODMAN: Dr. Wang?

DR. WANG: Yes, my questions are also about what potential benefit you see relative to, say, Concerta both in terms of a population that might particularly benefit, but also, I think it was trial 302, there was a difference. Did you see that difference as reduction in the ADHD rating scale between Concerta and the patch to be clinically important? Is there an additional efficacy advantage to this?

DR. LEVIN: Not obviously. It is not easy to extrapolate from the statistical significance to

clinical. I don't think it was a really huge difference in effect size. Again, it is hard to know what the equivalent doses are between Concerta and the patch, and being flexible dose studies it is a little bit more difficult--it is an additional complication in trying to make conclusions about that.

DR. GOODMAN: Dr. Temple?

DR. TEMPLE: I thought that question was about the small numerical advantage that the patch had but obviously it is not statistically significant. It is very small and you don't really know whether it is real or not.

DR. GOODMAN: If there are no other pressing questions at this time, I would like to take a short, less than ten-minute break. Remember the rules of engagement and let's reconvene and we will be ready to hear from the sponsor for their presentation.

[Brief recess]

DR. GOODMAN: We are about to reconvene. We will be hearing from the sponsor for most of the

remainder of this morning, and the committee will have an opportunity to ask questions at the conclusion of those presentations. I would ask the committee members to refrain from asking questions unless they are for clarification purposes because I think otherwise it may disrupt some of the flow, and I am sure that the sponsor has a cohesive presentation that will anticipate a number of our questions. With that in mind, our first speaker is Dr. Douglas Hay, Senior Vice President of Global Regulatory Affairs at Shire Pharmaceuticals.

Sponsor Presentation

Introduction

DR. HAY: Thank you, Dr. Goodman. Good morning, members of the Psychopharmacologic Drugs Advisory Committee, Dr. Temple, Dr. Laughren, ladies and gentlemen. My name is Douglas Hay. I lead the regulatory function at Shire Pharmaceuticals and it is my pleasure to present our data in support of the methylphenidate transdermal system, for which we have proposed the trade name of Daytrana. As was previously

mentioned, it is also known as methyl patch but Daytrana is the proposed trade name.

For today's presentation we refer to the full generic name, methylphenidate transdermal system or simply its abbreviation MTS. MTS was originated by Noven Pharmaceuticals. It has been co-developed with Shire and submitted for the treatment of children with attention deficit hyperactivity disorder, representing an important alternative in ADHD therapy for those patients and their caregivers that can benefit from the transdermal application of methylphenidate.

With us today we have several external consultants. Let me briefly review their backgrounds and their expertise: Dr. Stephen Faraone is a professor of psychiatry and director of child and adolescent psychiatric research with the SUNY system, Upstate Medical University. His expertise is in drug effects on growth in ADHD.

Dr. Marc Lerner, from the University of California at Irvine is a clinical professor of pediatrics. His expertise is developmental

pediatrics and ADHD.

Dr. Judith Owens, associate professor of pediatrics at Brown University School of Medicine. Dr. Owens has expertise in sleep disorders in ADHD.

Dr. Sharon Wigal, associate clinical professor of pediatrics with UC, Irvine. Dr. Wigal's expertise is clinical trials in ADHD.

Dr. David Heal, director of RenaSci Consultancy, who has expertise in methylphenidate pharmacology; Dr. Jack Henningfield, an adjunct professor of behavioral biology at Johns Hopkins, also vice president of Pinney Associates and an expert in risk management.

To briefly review our agenda for our presentation following my introduction, Dr. Marc Lerner, of UCI, will present a brief overview of ADHD and its current treatment. Dr. Liza Squires, of Shire, will review the clinical data on the efficacy of MTS in treatment of ADHD. Dr. Raymond Pratt, of Shire, will provide an overview of the clinical safety. Dr. Sharon Wigal, of University of California at Irvine, will then give us a

clinical perspective of MTS and its use in the clinical environment. Dr. Pratt will then return to summarize with the benefit/risk of MTS. Again, with the Chairman's agreement and the committee's agreement, we ask that you keep your clarifying questions to the end of each presentation.

The rationale for development of MTS was to provide an effective and well-tolerated therapy that could potentially address several concerns for ADHD patients and their caregivers. As has already been mentioned, an obvious alternative would be provided for those that have difficulty with oral medications and particularly difficulty with swallowing. The literature of this concern is not well developed. Our own market research suggests that something on the order of 15 percent of patients have extreme difficulty or high difficulty in swallowing, and this is from a survey of 250 mothers of ADHD patients.

The transdermal drug delivery also avoids the food effects present with many of the marketed oral ADHD treatments. A patch could provide a

means of visible compliance, important in a hectic environment getting kids off to school. A sustained transdermal methylphenidate release could also supply adequate drug therapy for control of clinical symptoms throughout the daily period, where the need is most necessary, without the need for supplemental medication. Finally, a patch could be useful in altering, and particularly at times abbreviating, the length of exposure and period of treatment.

MTS is formulated for the transdermal once daily extended delivery of methylphenidate. Placebo samples of the patch have been passed out to the committee prior to the presentations. You have in front of you a patch with its protective covering and wrapping, as well as an open patch. The patch consists of three layers. The outer surface is an occlusive laminate film backing. The inner surface is a polyester liner which, upon removal, exposes the middle layer which consists of Noven's proprietary DOT Matrix technology, a silicone and acrylic based pressure-sensitive and

adhesive mixture that is in direct contact with the skin. The methylphenidate is concentrated in acrylic cells that are dispersed in the matrix of silicone. The same technology is used in two marketed second-generation hormone replacement patches.

The MTS patch is both thin and transparent. The proprietary DOT Matrix technology provides concentrated drug and consisted drug delivery in a reasonably small patch, without the need for penetration enhancers that can be in themselves irritating to the skin. The patch has excellent adhesion performance upon first application. We will give you data on that later in the presentations.

The patch is manufactured in four sizes. These are the recommended sizes for the market. These patches, over a 9-hour wear time, targeted 9-hour wear time, deliver nominal methylphenidate doses of 10, 16, 20 and 27 mg based on the amount of methylphenidate remaining after 9-hour use. This is a range of doses that is therapeutically

similar to marketed sustained oral formulations of methylphenidate.

The NDA, as you have heard, was originally submitted by Noven in June of 2002. In April, 2003 the FDA issued an action letter which, while acknowledging the effectiveness of MTS therapy, did identify that there was an unacceptable incidence of insomnia and decreased appetite in particular. Clinical investigation of a shorter wear time was recommended. Following this action letter, Noven and Shire worked with FDA to identify further clinical development that would address the issues in the action letter. These studies were included in a resubmission of the NDA submitted in June of this year.

The NDA includes 12 studies that investigate the pharmacokinetics and biopharmaceutics of the MTS patch, including four studies in patients, and these studies investigate several different endpoints but, importantly, dose proportionality is included, pharmacokinetics with different wear times, and the potential for skin

irritation as well as skin sensitization and, finally, abuse potential. Initial dose-ranging studies were investigated in the early Noven formulation. The core of this submission then is in the controlled Phase II and III trials of the MTS in its final formulation.

These include studies investigating, as you have heard, 12-hour target wear times as well as 9-hour target wear times. The presentations that follow will focus on the highlighted studies. These are SPD-201 and 302. These studies investigate the 9-hour target wear time which is being proposed in labeling. Finally, several long-term open-label studies were also included in the NDA. These include investigation of both 12-hour wear time and 9-hour wear time. The 9-hour wear time 303 study is ongoing.

At this time I would like to introduce Dr. Marc Lerner, of UCI, who will provide an overview of ADHD and its current therapy. Dr. Lerner?

ADHD: Current Treatment

DR. LERNER: Thank you, Dr. Hay. It is a

pleasure to be here to address the committee. By means of self introduction, I am a pediatrician at the University of California, Irvine and, although I do development on behavior pediatrics, I also do general pediatrics actually for the majority of my time.

I wanted to discuss a little bit about attention deficit hyperactivity disorder as an orientation to this important condition from our view as pediatricians. ADHD is an issue which really affects nearly every classroom. Typically, there will be one to two children in each classroom who have a concern in this area. Often children are diagnosed when they get to school age because it becomes clear that they are having difficulties meeting the expectations for their performance for creating work or for meeting the behavior requirements of a classroom.

There is a tendency for boys to be diagnosed more commonly with ADHD, although we have concerns in part that this is due to the nomination process that teachers and parents may be willing to

nominate the kinds of ways that boys show difficulty with hyperactivity or attention in a fashion somewhat more quickly than their sisters who may have ADHD as well.

In a primary care setting we see many children with ADHD. If we look at the most common reasons for children to pediatric offices, ADHD is in the top ten diagnoses that lead to pediatric office visits. In fact, it and asthma are the two most common chronic health conditions that bring children into pediatric care. It is important to recognize that this is a condition, again, which is going to be seen often over many years so we have to be prepared to manage with the issues of an ongoing or chronic illness in distinction to an acute medical condition.

On the next slide you can see some of the risks that are associated with attention deficit hyperactivity disorder. I wanted to emphasize the last "D" and ADHD. Again, this is a disorder so we are talking about significant impairment. This impairment impacts children in a variety of

settings. Again concentrating on school, we see that there is clearly a difference in the nature of the academic performance that these children are producing although their capabilities may be at a higher level. This often then interacts with behavioral expectations in the classroom and these children may be suspended or even expelled from school much more commonly than their peers. Overall, this can lead to a lower level of academic attainment as children reach the end of their formal schooling.

Children not only have problems with the academic curriculum, but they are at risk in regards to the social experiences in school as well. We hear about this at school as we ask how their behavior is perceived by their class mates and certainly by their teachers. Alternatively, we hear about it at home from their siblings and their parents. Children with ADHD often grow up to become adults with ADHD, and their important relationships can be negatively impacted at that time as well.

Part of the work of childhood is to become

prepared to be able to handle adult responsibilities and to be productive as an adult, and when we take a look at how adults with ADHD function we see that there are differences in regards to their ability to be successful in the workplace. These individuals are commonly unemployed; have more frequent job changes. Sometimes that affects the inter-generational impact of ADHD where a parent with ADHD is taken from their workplace to manage the academic and behavior concerns of their children when we look at trying to then say, gosh, your child is having a problem at school; we need to have meetings; we need to start to set up programs to impact the children. An additional important burden are the co-existing conditions or the co-morbidities that may involve aspects of behavior or mood for individuals with ADHD.

We have the opportunity to turn to some of the guidance that has been offered us as practicing clinicians by our national organizations, specifically the American Academy of Pediatrics,

the American Academy of Child and Adolescent Psychiatry, as we attempt to organize a treatment plan on behalf of these children. This slide presents a number of the comments from these general standards.

We sometimes will pick out target outcomes. We want to not only treat a child's activity level but we really want to say what are the struggles that a child is having within the context of their life, their classroom, their day. And, we want to try and challenge any treatment we give them to improve those specific targets.

The treatment guidelines state that stimulant medication should be considered one of our first-line options along with behavioral therapy. So, it is up to the clinician and to the family and to the individual to sort out the priorities for a starting point in treatment. But we then look to see how that starting treatment works to improve the behavior and functional challenges, and if it is not helpful we move on to other treatments.

As you have heard in a series of the presentations, methylphenidate does reduce the inattention, impulsivity and hyperactivity linked

to ADHD. Typically, any individual stimulant preparation that is chosen will positively impact approximately 70 percent of the group of patients for whom we start treatment. But it is very important to me as a practicing clinician to address that remaining 30 percent. So, I can turn to the literature which shows me that many children who fail to respond to my first treatment may, in fact, have a positive response when I change to another treatment.

The treatment guidelines suggest that stimulants are generally safe and well tolerated. So, what I am trying to accomplish is to reach a therapeutic goal important improvement in addressing behavior problems and attentional problems, to show good efficacy and to have few or manageable side effects.

I believe the last slide was a series of references that I will skip.

Again, the American Academy of Pediatrics, in 2001, specifically addressed treatment guidelines for this condition, and these are some of the important issues in those guidelines. First, that stimulants are generally considered safe medications, with few contraindications to

their use. It is my job as a pediatrician to make sure an individual child doesn't have one of those uncommon contraindications and that is one of the areas that I have to address.

Second, that side effects occur commonly early in treatment and tend to be mild or short-lived. Next, the common side effects are some of those that you heard about in the earlier presentations--again, decreased appetite, or stomachache, or delayed sleep onset. What we do in our offices is we monitor for those as part of our ongoing care. We bring children in, for example, and check how they are doing with their weight; how they are doing with their height. That allows us to make decisions for the adjustment of treatment as appropriate for an individual child.

Again staying with our pediatric guidelines, children who fail to show positive effects or who have intolerable side effects, we are encouraged then to seek an alternative medical treatment. We can, in fact, try a different stimulant. The guidelines go on to state that even children who fail two stimulant medications can be tried on a third.

There are specific comments in the area of

habit movements. Whereas a substantial minority of children are recognized to have motor tics, pediatricians see this in children who don't have ADHD, although to a somewhat lesser degree. And, when children are being treated with medications commonly we see that these habit movements are transient. Children who have habit movements linked to their ADHD medical treatment generally do not have a big functional impairment linked to those habit movements, and there is a tendency for many patients to show improvement over the course of treatment through a series of years or decades. Thus, the guidelines state the presence of tics

before or during medical management of ADHD is not an absolute contraindication to the use of stimulants.

I am trying to do well for all of my patients and I do still see that there are gaps in the available ADHD treatments. I am certainly happy to have some of the new tools that have been approved by the FDA that are available to me and to my families, but I think there are still some gaps. I think that we are looking to try to meet the requirements of particular children and particular families and flexibility helps us in that regard.

Some of the areas would include opportunities to provide families to address the issue early in the day. Another would be to be able to have an ability to shorten afternoon function. If a child's impairment is really only an issue in school and there is no homework that night, there may not be a requirement for later treatment. Children have different days based on their schedule, their academic and social schedule of the week. In fact, managing that variability

leads me and many other physicians to put families in a circumstance of having multiple different stimulant prescriptions in their home and then to try and match the prescription to the day or multiple prescriptions to the day. This adds complexity as well as price in terms of multiple co-pays.

An important consideration for any management of a chronic condition is issues of compliance or adherence to treatment. The least effective ADHD medicine, of course, is the one that doesn't get used. So, again, I feel it is very important that I be able to reach a high level of satisfaction as I work with families, not only addressing efficacy in terms of some of my clinical targets but working with families' perceptions of acceptability of treatment because it allows families to use the medicines more regularly.

These are some of the concerns that I hear still in regards to treatment compliance from some individual families. Some of the kids are complaining "I don't like the taste of the

medicine." I even hear that sometimes from kids who are taking a sprinkle preparation where a capsule is opened and put into apple sauce and kids complain about these tiny sprinkles but some of the kids are sensitive, or kids who say I don't like taking medicine, or taking medicine orally. We see refusals. We see children who gag when taking the medicine. Sometimes this reflects the child's behavior disorder, their oppositional behavior and a variety of other concerns. But all of this, again, can sometimes lead to a battle between the child and the parent in the morning.

So, in conclusion, attention deficit hyperactivity disorder is an important impairing disorder with potential long-term implications at home, at school and in the community. Methylphenidate as a treating compound is clearly a first-line treatment for ADHD. Some patients respond preferentially to one in comparison to another ADHD treatment, and having different treatments offers me flexibility to be able to help the largest portion of families. It is my view

that currently there is still a group of patients that are not receiving optimal therapy and families would benefit from new therapeutic options.

Next I will be introducing Liza Squires who will be discussing the clinical efficacy of the MTS in children with ADHD. Thank you.

Clinical Efficacy of MTS in Children with ADHD

DR. SQUIRES: Thank you, Dr. Lerner. Good morning. I will be presenting the efficacy data from our two clinical studies which utilized the 9-hour MTS wear time.

Study 201, the analog or laboratory classroom study, demonstrates the efficacy of MTS and characterizes the onset and duration of therapeutic effect. Study 301, the pivotal trial, demonstrated the efficacy of MTS in an outpatient setting.

The rationale for the 9-hour wear time was based in part on pharmacokinetic study 101. This was a 4-arm, single dose, crossover PK study which used an intermediate dose of MTS 25 cm2 and an intermediate dose of Concerta 36 mg. The 25 cm2

patch was worn for 6, 8 or 10 hours. Twenty-four children with ADHD between the ages of 6 and 12 participated in this study.

This is the concentration time curve, with concentration of d-methylphenidate on the Y axis and time on the X axis. It is important to note that this was not a bioequivalence study and, in fact, the PK curves for Concerta and MTS, whether worn for 6, 8 or 10 hours, do look quite different. The Tmax for Concerta, in orange, occurs earlier than that for the MTS system and the MTS wear time Tmax occurs at the point of patch removal, 6, 8 and 10 hours respectively.

Looking at the latter part of the curve or the offset part of the curve, MTS worn for 10 hours showed slightly higher levels of d-methylphenidate when compared to Concerta. The MTS worn for 8 hours showed slightly lower levels of d-methylphenidate when compared to Concerta. And, because we were interested in approximating the offset time and obtaining more information on offset time, we thought that the 9-hour MTS patch

wear time would approximate the offset time of Concerta or long-acting methylphenidate products.

The 9-hour patch wear time was investigated in the laboratory classroom study. This is a simulated classroom setting in which the children were assessed at multiple time points throughout the day. The goal of the study was to assess the efficacy as well as the time course of treatment.

Two of the primary efficacy outcomes that were measured in the study were the SKAMP Deportment scale, mentioned by Dr. Andreason, and the PERMP or math productivity test. Both of these assessments were developed for use in the laboratory classroom setting. The SKAMP Deportment scale is a measurement of ADHD classroom behaviors and is rated by trained observers. The PERMP or math productivity score is a pencil and paper test which is given at an ability appropriate level for each child. It is a timed test and children are asked to answer as many questions as possible, and they are scored on the number of problems they

answer correctly, as well as the number of problems that they attempt. This is considered an objective measure of the child's ability to concentrate and stay on task. The study was designed as a double-blind, placebo-controlled, crossover study and 93 children with ADHD between the ages of 6 and 12 were enrolled.

This is a diagram of the 201 study schedule. Following screening and washout of prior ADHD medications, the children entered a 5-week open-label dose optimization period. All children were initiated at the lowest dosage of path, 12.5 cm, and were evaluated weekly for tolerability and efficacy. Efficacy was determined based upon the ADHD rating scale scores. Children whose ADHD scores had not decreased by a threshold of 25 percent were titrated to the next highest dose or patch size. Children who had demonstrated 25 percent or greater improvement in their ADHD rating scores were maintained at their current patch size, however, they were allowed to be titrated upwards if the clinician felt that they could gain

additional therapeutic benefit.

Following the 5-week dose optimization period, children participated in a practice classroom session while being treated with their optimal patch size. This classroom session gave the children an opportunity to become familiar with the classroom schedule and for teachers and students to become familiar with one another.

Following the practice classroom session, children were randomized with respect to treatment sequence for the 2-week double-blind laboratory classroom period. There was a laboratory classroom assessment done at the end of each week during the 2-week classroom period, and the children who completed the 7-week study were eligible to enter an open-label follow-on study.

This is an example of the daily schedule of a laboratory classroom. As you can see, the children have a long day. They arrive at 6:15 in the morning and are dismissed at 8:00 p.m. at night. The classroom schedule is a repetitive cycle of class time, free time and meals, and

physical assessments including vital signs and blood work. There are 9 analog classroom periods within the day. The first one is a baseline prior to medication dosing. The subsequent 8 classroom sessions occur at 60-90 minute intervals.

The primary efficacy outcome for this study was the mean SKAMP Deportment score for the 9 hours of patch wear time. For SKAMP Deportment scores, the lower scores indicate fewer observations of ADHD behaviors and higher scores indicate more observations of ADHD behaviors. The mean score for the MTS-treated subjects was 3.2 compared to 8.0 for the placebo-treated subjects. This difference of 4.8 was highly statistically significant.

This is a graph already shown by Dr. Andreason that demonstrates the SKAMP Deportment score during the analog classroom day. The mean score is on the Y axis and time in hours is on the X axis. The MTS subjects are represented in yellow. The MTS-treated subjects show an improvement in SKAMP Deportment scores at every

post baseline assessment and this difference was statistically significant when compared to placebo.

The MTS-treated subjects also showed an improvement in their PERMP or math performance score. This graph shows the mean number of math problems on the Y axis and time again in the analog classroom on the X axis. The MTS subjects, demonstrated in yellow, show an improvement in both the number of math problems attempted, with the dashed line, and the number of math problems answered correctly, with the solid line. This difference becomes significant when compared to placebo at the 3-hour time point and then continues throughout the remainder of the post baseline assessments.

DR. GOODMAN: I have a question of clarification. I wonder if you could go back to the previous slide. Have you combined or pooled the data from both phases of the crossover in this slide?

DR. SQUIRES: Yes, we have.

DR. GOODMAN: Would it look any different

if you separated it out?

DR. SQUIRES: We did an analysis for treatment sequence and there was no difference noted.

DR. TEMPLE: Before you leave that, that usually means that there is no statistically significant difference but they might look different.

DR. SQUIRES: They don't look different.

DR. GOODMAN: Dr. Leon?

DR. LEON: Can we see the slide of that, of the two separate sequences?

DR. SQUIRES: Other secondary efficacy endpoints in study 201 included assessments by the clinician with the ADHD rating scale; the Conners parent rating scale and global assessment scales done by both parents and clinicians. The MTS-treated subjects showed significant improvement when compared to placebo on all secondary efficacy endpoints and their sub-scales.

In summary, study 201 demonstrates the overall efficacy of MTS in reducing ADHD symptoms

and this improvement was apparent to trained observers, clinicians and parents. Statistically significant improvement was demonstrated for all primary and secondary efficacy endpoints. The 9-hour target wear time shows an onset of effect within 2 hours of application and a duration of effect through the 12-hour analog classroom day.

I will now move to study 302, which was the pivotal outpatient trial. The role of the study was to evaluate the efficacy of MTS when compared to placebo and did include a reference arm to Concerta. This is a Phase III randomized, double-blind, placebo-controlled study and 38 centers throughout the United States participated and 274 children with ADHD between the ages of 6 and 12 were enrolled.

This is a diagram of the 302 study design. Following screening and washout of prior ADHD medications, the children were randomized for a 7-week double-blind study. The first 5 weeks were dose optimization and the second 2 weeks were a dose maintenance period. The study utilized a

double-dummy design in which each child, whether assigned to placebo, MTS or Concerta, received a patch and a pill every day. Subjects were initiated at the lowest doses of MTS and Concerta and were titrated weekly based on clinical response, similar to that described for study 201. Following week 5, subjects entered a 2-week dose maintenance period. Subjects who had completed through at least week 5 were eligible to enter into an open-label follow-on study.

The primary efficacy outcome measure for study 302 is the clinician-rated ADHD rating scale score. Secondary outcome measures included assessments by teachers with the Conners teaching rating scale score and, in this case, this is the child's regular classroom teacher; the Conners parent rating scale scores, which were assessed on the weekend hours; and global assessment scales including the clinical global impression in improvement completed by the clinician and the parent global assessment reported by the parent.

The children who participated in study 302

are rather typical for an ADHD child. The mean age was between 8.5 and 9 years of age, and the majority of subjects were male. Most subjects were Caucasian, however, there was a fair representation of African-American and other races.

The primary efficacy endpoint for study 302 was the ADHD rating scale score change from baseline to endpoint. For all 3 groups the baseline scores were above 40, suggesting that these children had moderate to moderately severe ADHD. The MTS group demonstrated a 24 point change in ADHD rating scale score compared to a 10.3 change for placebo. This 13.9 point difference was highly statistically significant.

This is a plot of the ADHD rating scale change score on the Y axis and the study visit week on the X axis. The MTS group, demonstrated in yellow, shows an improvement in ADHD rating scale scores at each post baseline assessment, and this difference is statistically significant when compared to placebo, beginning at week 2 and continuing through each subsequent post baseline

visit.

You will note that for the placebo group between weeks 5 and 6 there is a significant improvement, or improvement is noted in the ADHD rating scale scores. This was the time in which children were eligible to enter into the open-label follow-on study and almost half of the placebo-treated patients opted into the open-label follow-on at that point in time, suggesting that perhaps the less affected children were remaining in the study. However, statistical significance was maintained for the MTS group versus the placebo group for the final 2 weeks of the study in the maintenance phase.

Secondary efficacy endpoints for study 302 included the teacher-rated Conners teacher rating scale and the parent-rated Conners parent rating scale. Both of these scales and their sub-scales showed that MTS patients had improvements in behavior which were statistically significant when compared to placebo.

Global assessment scales, reported by the

clinician, showed that 72 percent of MTS-treated patients were rated as much or very much improved by their clinician compared to 24 percent of placebo-treated patients.

Parents of MTS-treated subjects rated their children as much or very much improved 68 percent of the time compared to 25 percent of the time in the placebo group.

To summarize study 302, MTS, worn for 9 hours, reduces symptoms of ADHD based on assessments by clinicians, teachers and parents. Statistically significant improvements in all primary and prespecified secondary efficacy endpoints were achieved.

In conclusion, MTS, with the 9-hour target wear time, demonstrates significant efficacy in the laboratory classroom and outpatient settings. Improvements in behavior are present within 2 hours of patch application and persist for 3 hours after patch removal. Improvements in ADHD symptoms and behavior are reported by trained observers, teachers, parents and clinicians.

That concludes the efficacy portion of our presentation. I would now like to turn the podium over to Dr. Ray Pratt who will present our safety

data.

MTS Safety Evaluations

DR. PRATT: Thank you, Dr. Squires. Members of the committee, I would like to cover the safety evaluations that we conducted during the MTS programs, and discuss some of the issues that you have already heard about.

The safety evaluations that were conducted were conducted at each of the clinic visits when patients came into the clinic for their visits and assessments in both the laboratory classroom study, as well as in the large outpatient study. Overall, in the entire program there were no deaths reported and very few serious adverse events in the whole program, so we won't discuss those any further today as those have been reviewed adequately previously by the agency.

However, we did collect both spontaneous and elicited adverse events at each visit. We also

collected clinical laboratory evaluations, physical examinations, vital signs and ECGs. There were no relevant findings in children at any of the time points here, so we also will not be discussing those during this presentation.

What we did note, as you have already seen, is that the adverse event pattern was similar in the 2 9-hour wear time studies, studies 201 and 302, that occurred, and the predominant effects that were observed were methylphenidate related. I am primarily going to concern myself with the description of the events and what was happening in study 302 today because it was a large double-blind, placebo-controlled trial, conducted with a double-dummy design and it actually had an active comparator group of Concerta included in the design.

Finally, I would like to return in part of my discussion to some of the long-term observations that we have made in study N-021, which is a long-term open-label follow-up of patients who were treated with the MTS system for up to 3 years.

This is a very important study which actually allows us to make some assessments on the exposure and the patients receiving MTS for long-term on their growth effects that were observed.

The structure of my talk is that I am going to go back and overview a couple of things about the adverse event profile in the 12-hour studies, which you have already seen. Then I am going to turn to an overview of the 9-hour wear time study 302, and pay particular attention to a little bit more detail concerning individual adverse events that we have listed here. Then I will come back at the end and deal with a little bit of the dermal evaluations that were conducted during the course of the study.

As we have seen before, this is the adverse event table in the 12-hour methylphenidate studies. Importantly, Noven used the COSTART dictionary for coding terms in that study. It is important to note that there is no COSTART term for tic. So, tics that occurred during the early studies were coded to twitching just simply by

virtue of the COSTART dictionary term that was used.

We took the opportunity of actually recoding these into MedDRA which we were subsequently using and most of the industry is using now for coding adverse events, and we find that, again, while there is a higher incidence of anorexia, the important difference between MedDRA and COSTART here is the recognition that anorexia is considered as a different term than decreased appetite and probably reflects more severity to the decreased appetite perhaps in terms of the terminology that is used by the investigator.

So, what you can see here is that there are still increased numbers of decreased appetite as well as anorexia that are reported along the way, and the number of tics actually, when you recode them using the verbatim term in MedDRA, is exactly the same as the numbers that were presented earlier.

To turn to the 9-hour wear time study, again, you have seen this graph before which shows

that in the 9-hour 302 study the percentage of subjects reporting any of the adverse events--and we define them here as the most common being 5 percent in the methylphenidate transdermal system group compared to placebo and occurring at least twice the rate of placebo to eliminate the background of childhood illnesses and adverse events that may be typically picked up during the course of the study. The majority of these events that we are reporting are methylphenidate-related adverse events and, as has already been alluded to, there is a slight numerical increase in the number of adverse events in the MTS group compared to the Concerta group.

Importantly again, we see the incidence of tic being reported as 7 percent compared to 1 percent, and we will turn to that a little bit later in the course of this talk.

Looking at the discontinuations, we have already seen that 7 percent of the patients discontinued due to adverse events in the MTS group; 3 percent in the Concerta group and 1 in the

placebo group. Again, we have already alluded to the reason for patients leaving the placebo group in the study due to the availability of an open-label follow-on after 5 weeks of participation in the 302 study.

Importantly, these are again the individual patients who discontinued to adverse events in our 302 study. As you can see, 2 of them, on the top, are patients who had viral infections with no plausible biological relationship to the treatment. We have 2 application site reactions which were mild erythema that were reported by the investigator who decided to remove the subject from the study. Then, there were 3 patients in the MTS group that discontinued due to adverse events that could be related to methylphenidate and 3 patients in the Concerta group that discontinued due to adverse events that could have been related to methylphenidate, and 1 patient in the placebo group who discontinued was coded as an adverse event because their symptoms of ADHD changed during the course of participation in

the study.

I am going to go through very quickly a couple of the minor issues of adverse events but I think it is important for us to realize that, again as Dr. Lerner has alluded to, the incidence of adverse events may not necessarily tell the full story concerning what is happening with these subjects and patients. This slide will sort of cover all the remainder slides that we have for individual adverse events.

What we have presented here is for each of the MTS, Concerta and placebo groups the number of subjects who experienced that event; the number of events that were actually experienced because some of these subjects my have experienced more than one event during participation; the number of subjects whose events were ongoing at the end of the study, and these could have been ongoing for one day or one week at the end of the study but they were present at the end of the study and were, therefore, considered as ongoing when the patients finished their controlled trial; again, the mean

duration of the adverse events that resolved in days, again, indicating that most of these events that we are looking at are going to be short-lived over time.

For abdominal pain, vomiting and nausea, you can see that again in some cases there is an increased number of subjects in the MTS group that experienced these events, but the number of events that were ongoing at the end of the study, the ones that clinicians may be concerned about for long term with patients, are the same whether you are in the Concerta group or the MTS arm of the study, and these are both slightly higher than observed in the placebo population.

Again, headache and affect lability and other CNS-related are similar. In this case, the number of events in the MTS and Concerta group for headache are similar. Most of them are transient, as would be expected for headaches occurring in the childhood population and last not a very long time. Affect lability, again an issue that came up at twice the rate of occurrence in the MTS group

compared to the Concerta group, there were 6 subjects versus 3 subjects. The majority of them were short-lived, for a short period of time, and very few were ongoing at the end of the day and these, again, may have been symptoms related to the underlying condition of ADHD.

We would like to now turn to the issue of tics. Again, there was a mention made about the issue of the coding terms for tics. These terms were coded prior to breaking the blind of the study, an evaluation in a totally blinded fashion when we reviewed the safety findings in the study. A decision was made by us to code abnormal movement disorders whether they were classically defined as tics or any other type of treatment emergent disorder as tics. However, I think it is important to look at what the verbatim terms and what the outcome of the patients who experienced these tics in this study actually are.

What we see is that of the 7 patients in the MTS group and the 1 patient in the Concerta group that had tics, 5 of them in the MTS group had

actually either miscellaneous type of mouth movements that occurred or other events that could be coded to compulsion or stereotypy. Repetitive tongue movements--and as we heard from Dr. Lerner, some of these things are commonly observed in the pediatric population whether they are treated or not. Again, most of these resolved within a short period of time. There were a very few of them that were ongoing. However, the ones that were ongoing did not result in any change in medication administration and they were typically mild in intensity and did not interfere in the patient's activities.

These are the 3 cases where actually the term tic was used, which indicted that there was a motor disturbance that arose during the course of the treatment and participation in the clinical study. There is 1 patient in the Concerta group who developed a tongue tic, as described by the investigators; 1 patient in the study who developed a motor tick and was discontinued from the study. The interesting fact about this patient is that

after he was discontinued from the study his behavioral problems persisted and he was started again on an alternative stimulant medication, an amphetamine-based product, and his tic did continue and did not abate even on the amphetamine-based product but his behavior certainly did, and his tic was ongoing at 30 days after discontinuing from the study. The other subject in the MTS group who experienced the tic had it resolved after 9 days and no effects on dosing were noted.

Now, what I would like to do is put the incidence of tics in the context of what we know about tic disorders, and I borrowed this forest plot from our friends in evidence-based medicine to try to present a large volume of data in a very short, single graphic. These are studies that are controlled clinical trials employing oral methylphenidate products and our two studies which used the MTS system, both the MTS product and the OROS Concerta group of that.

Plotted here are the number of subjects in each group who experienced tic on each of the

doses, whether it be MPH or placebo, and it is experienced as a rate difference which, for those of you who are not familiar with the way these things go, is simply the difference in proportions of the patients in the MTS group compared to the placebo group experiencing the number and it is expressed as the decimal equivalent. If you would like it as a percent, just multiply it by 100 and you will get there. So, the scale ranges from 0-50 percent increase or decrease in tics.

As you can see, with all of these studies tics are not an uncommon phenomenon. In fact, overall it is about 6 percent incidence of tics occurring in methylphenidate-treated groups in the controlled clinical studies, and there is about 4 percent occurring in the patients in the placebo groups. Again, the MTS group there--again being a little bit higher and we are still counting all the movement disorders as tics here--shows that we are similar in frequency across the way. The bars indicate the 95 percent confidence intervals around the estimates for these disorders.

Again, in the open-label studies tics are a frequent observance that is observed. If you look at the Concerta package insert, there are 2

studies that are referred to which are long-term open-label follow-up studies which provide important safety information. And, tics occur at a very widely differing rate in those studies. There is no control group to make an absolute comparison, however, the rate ranges from 1.3 to 8 percent over a period of time of about 8-10 months.

In Wilens 2005 paper which looked at 400 subjects treated open-label Concerta, he found an incidence of 9.8 percent of tics throughout his follow-up of the patients. If we look at our long-term 021 study which followed patients for up to 3 years, we have about a 1 percent incidence of tics that emerged during the course of that study, as well as in our ongoing 303 study which is a 9-hour wear time study that enrolled all the patients who were willing to follow-up into an open-label follow-on period 2 percent of tics actually occurred in this follow-up with durations

up to approximately 8 months.

So, I think that for the adverse events coded as tics, they do occur. Most of the MTS events were transient and 4/7 actually resolved with continuing therapy with MTS. Only one patient discontinued from the study, and the symptoms were mild and, again, typically did not interfere with activity. The verbatim descriptions were not all clearly tics, however, they were coded that way because of the conservative nature of trying to describe and put a label together that would explain what type of disorders you might see during the course of therapy with MTS. And, the overall frequency of the tics in our MTS studies is actually consistent with the published data for not only methylphenidate products but other stimulants. Again, as we have heard from Dr. Lerner, tic is not a contraindication to stimulant therapy.

I would like to now turn to the other issues which is of extreme concern, particularly for pediatricians and people following these patients, which is the effects of methylphenidate,

and particularly MTS, on appetite, and then we will follow that up with effects on weight and growth.

Again, this is a similar graph that indicates the effect of anorexia, decreased appetite and weight loss during our clinical program. There were very few events that were ongoing at the end of the study. Most of them were short term, resolved on continued therapy, and did not lead to discontinuations due to adverse events. Again, there were similar numbers of patients in both of the active treatment groups that continued to have the adverse event at the end of the study.

Turning to the effects on weight and growth, again, this is the effects on weight loss that we have already heard alluded to in our study 302. On the left-hand part of the graph is the overall effects in the study population, showing that over the 7-week participation in the study placebo patients tended to gain a little bit of weight and patients who were treated with either Concerta or MTS methylphenidate delivery systems lost a little bit of weight. When you look at the

patients who experienced any appetite-related AE, there was, again, a slightly larger weight decrease but really no difference between the group of MTS or receiving Concerta.

Again, if you looked at those patients who reported anorexia, which we would consider as a more severe form of appetite decrease, there was a slightly greater decrease in weight in the MTS patients but, again, within the same range that we have observed overall in the study and, again, patients who had decreased appropriately tended to have approximately the same type of weight loss experienced and, again, it was mild over the course of the short term of this study.

I think it is always useful to look at individual patient data to get an idea of exactly where patients fall in the course of the study and which groups of patients actually lose the most weight. I think this is very important. As we can see here, on the Y axis here we have the change in patient weight by individual patients so this is a change over the course of the study. On the X axis

is the weight at which the patient started the trial.

So, what we can see is that patients who were the smallest ones, on the far left-side of the graph, while they do lose a little bit of weight, they don't lose proportionately a greater degree of their body weight. Whereas, the patients who are at the heavier weight tend to be the ones experiencing the most weight loss. This, again, is very similar to what has come out of the stimulant literature for weight loss in general and is observed also within all the other classes of stimulants that are on the market today for ADHD.

Looking at the incidence of anorexia in the controlled methylphenidate studies, we see that anorexia, as a complication where it is listed, occurs not infrequently in these studies, and in decreased appetite, again, being a not infrequent occurrence in reporting overall in controlled clinical trials with various rates, depending on the ascertainment bias that is present in the study, again, being present.

So, to conclude on issues of appetite and weight, we did have a higher observed number of appetite-related adverse events, however, most of

these were mild and transient; did not persist; and the number of ongoing adverse events was similar in both the Concerta as well as the MTS groups. The actual weight loss was, again, similar and the effects are, again, typical for other oral methylphenidate products on the market today.

I think importantly, what are the consequences, possible consequences of the long-term use of this drug? For that, we have to go to study N-021, which was a study started by Noven and actually enrolled patients who had participated in the 010 and the 018 study, and employed the 12-hour target wear time and, again, the larger patch size, the 50 cm2 patch size. So, these had patients that were experienced to higher patch sizes, as well as longer durations of study. Patients were followed for up to 3 years during this time frame. This was an important study to assess the continuous use of MTS on growth

parameters .

I will summarize what we found and then I will show you a couple of slides that illustrate the findings we have, and we do have Dr. Steve Faraone here, who actually conducted these, who can address some of the issues during the question and answer period. But we did find that subjects who were treated with MTS over the 3 years of follow-up did continue to grow during treatment. There were some growth deficits present, and growth deficits were defined as the observed weight or height that we actually recorded compared to those that would be expected from the CDC tables that were put out in 2000 for the population on normative data for the United States.

The deficits were small after 3 years. In the short term we did have weight deficits predominantly related to the dose that was administered. However, these did not persist over the long term--

DR. GOODMAN: Excuse me, I think Dr. Leon has a question.

DR. PRATT: Yes, sir?

DR. LEON: To provide a little bit of context, you said this is follow-up up to 3 years.

Well, can you tell us more about that? Maybe what is the median or what some of the quartiles were? Because. no doubt, not all of them got followed up.

DR. PRATT: No, not all of them got followed up. We had approximately 50 patients that continued on in the study for the 3-year period of time, and we actually analyzed the data, which I will show you in the next slide, by bins in terms of how long patients were actually followed. So, we are not just looking at one group that is a small number that looks at the time. We are looking at all the data over the period of time. We can have Dr. Faraone address that in the question and answer period a little bit more specifically to answer your question.

Again, prior stimulant therapy--patients who were previously treated with stimulants tended to have smaller deficits over the time than patients who were starting therapy for the first

time and were followed for a similar time, although the difference was not great. These results, again, were similar to those reported for other stimulants.

This is just a graph of the actual growth that we observed in the various bins. The numbers of patients in each of these bins changes over time. However, when you look at the mean height, weight and body mass unit index of the patients who were participating in the study for 6, 12, 18 or 36 months of follow-up, you do see that the patients grow. Actually, the population itself actually continues to gain weight and there is not much change in the BMI, which indicates that the growth that is occurring is probably proportional.

I think when you look at this as growth velocity, the short-term effects as well as the long-term effects of how much you had grown in a year over how much you would be expected to grow in a year, when you look at the groups that look at it across the half years in the study, we see again the typical pattern with the short-term effects on

body mass index and weight being apparent in the first 6 months of the study. However, by the second, third, fourth and fifth for the groups that are there the weight velocity tends to catch up and actually exceeds that, and there are very little effects on growth velocity as expressed as height reported over the time frame of the patients followed in this study.

Again, how does this compare to other products that are on the market where long-term studies have been conducted? This is a listing of a number of different studies that have been presented with both amphetamine-related products, methylphenidate and amphetamine treatment of patients, as well as methylphenidate, and you can see that males and females for one, two, three years of follow-up study the results that we are showing here for height in our patient group are very similar to what has been expressed. These numbers here, in terms of mean z-score deficits translate into very, very small actual growth deficits.

Sleep effects was another issue that was noted in the original NDA which we attempted to evaluate. We evaluated them in two ways. We took

our traditional spontaneous reporting of events by parents and patients coming into visit, and if they had insomnia it was recorded as an adverse event. Again, we saw that there was a slightly increased number of subjects in the MTS group that experienced the sleep-related insomnia. There were a few more events than in the Concerta group. However, most of these, again, were short-lived; resolved; were typically mild and didn't interfere with activity.

Again, looking at the overall effects of sleep reported in controlled clinical trials with methylphenidate, we see a similar pattern as we have seen in other studies. There is a wide range of differences in terms of effects on insomnia reported in clinical trials from some patients who actually get improvements to some studies that actually show fairly large effects on insomnia, depending on the size of the study. Again, these

are very common events that occur in this patient population.

We used the Children's Sleep Habits Questionnaire, not as an adverse event reporting tool, but as a tool to assess the effects of sleep in the population. The Children's Sleep Habits Questionnaire is a questionnaire that is useful for children ages 4-12, the exact group that we were trying to study, and it asks the parents to assess the behaviors and sleep habits that occurred in the previous week that the patient was there. It assesses a number of different scales, as was already alluded to by Dr. Levin. It consists of 33 questions which receive a score of 1-3 on each question, and 1 basically is a frequency count in terms of has this occurred rarely or never in the one week, or has this occurred 5 or more times or continuously?

Also, there is one other interesting aspect to this study, that it does ask a subjective question for each of these sleep-related frequency counts that the parents are asked to fill out.

That is, whether you scored 1 or 3 on the frequency count, do you consider that this behavior was a problem for your child during that time? So, again, it gives both an objective as well as a subjective assessment of the population's effect.

Surprisingly, as has already been shown here, when you look at the overall total scores on the CSHQ by the time in which patients are followed, we see no differences from placebo and no separation of effects of patients receiving either form of methylphenidate on the CSHQ and, again, similar results were seen when we actually looked at the number of sleep problems. There tended to be a slight decrease in the number of problems identified by parents over the course of the study, but that was the same in all of the groups.

So, I think to summarize our sleep-related findings, insomnia is known to be associated with methylphenidate. The observed incidence was higher in the methylphenidate-treated group but, again, the events were transient and they resolved on continuing treatment. We really didn't have any

discontinuations or dose changes due to these adverse events in the short term, and the MTS and Concerta have been demonstrated, using the CSHQ, as having little effect on sleep habits overall.

Finally, I would like to turn a little bit to the dermal evaluations that we conducted at each of the visits. At each of the visits the patient coming in was assessed by the clinician using 3 separate scales: an adhesion scale which was referenced to how well is the patch attached to the child. In other words, is the patch, you know, sitting on there very well with a little bit of edge coming up or dirt around the edge, or is it almost completely detached? We also asked them to assess the dermal response scale which actually is one that looks at primary skin reactions and is the one that is the most evident for skin irritation. Finally, there is a dermal discomfort scale in which you ask the subject is this uncomfortable? What are you experiencing at the time that you have this patch on?

This is different from the sensitization

study that was conducted, which was an entirely different study and an entirely different population, which we will return to in the question and answer period to present some of that information and clarify some of the thoughts on that.

Now, these are the results. The results were pretty similar across all of the weeks so I chose week 7 of the 302 study because this is where patients had been wearing patches for 7 weeks continuously. The recommendation was that they alternate the patch site every day, and this assessment included the number of the patch that was worn on the site at the day that they came into the clinic. Importantly, on the adhesion system scores of 0-1 indicate very, very good adhesion with just little bits of the edges of the patch coming up from the skin. Most of the subjects fell into the category of scores of 0-1. Very few patients had disconnection of the patch from the skin during the course of the study. There was no difference between the patients who had the active

MTS patch, which is in yellow, or the placebo MTS patches, which are in the orange and the white bars.

Now, as alluded to earlier, there was a higher incidence of minimal to definite erythema that was observed at the time that this patch was examined in the clinic and over 50 percent of the patients had evidence of minimal to definite erythema. Very few individuals had more than just simply erythema that was noted on the patch site. There was a very small number in the active group, actually one patient, I believe, that had erythema and papules in the study at the site that was observed. There were very few patients who withdrew from the study. Again, this is very consistent. It is only seen in the active MTS group and is not seen in the placebo group and may be actually related to the known effects of methylphenidate itself as a mild skin irritant.

The experience of discomfort that was expressed by the patients at each of the times, again, showed very little discomfort that was

experienced at the time that the patient was wearing the patch and, again, these numbers didn't change much over the course of the study. The majority of patients experienced no discomfort at all. Those who experienced any discomfort typically said it was mild, and the worst complaint we got was that it was typically itching. There were very few severe or moderate but tolerable effects that occurred.

So, I think in our dermal assessment scales--and we will return to the sensitization issue during the question and answer period--MTS was associated with slight to minimal erythema that was present in about 50 percent of the patients and, again is a known effect of methylphenidate as a mild skin irritant itself. Most subjects experienced no discomfort. The ones who did typically experienced mild itching. There were excellent adhesion properties of the patch to the child, which is important for an active child going swimming and participating in sports. And, there were few discontinuations overall in the program

due to application site reactions.

So, I think that we can conclude for our approach to the MTS safety conclusions that the patch was generally well tolerated and there were no related serious adverse events that occurred. We did have a few discontinuations due to adverse events and those were typically due to methylphenidate-related adverse events. The common adverse events that we observed, again, were due to the stimulant effects. They were mild and transient. They tended to occur early during the course of treatment and there were very few persisting adverse events during the course of the study. Our target wear time of 9 hours appeared to reduce the incidence of the two adverse events that could be considered as related to time of wearing the patch, which are anorexia and insomnia. The skin reactions that we observed were mild, and the long- and short-term growth effects were really similar to those observed with other stimulants on the market today. Again, the results of our studies here are consistent with those of other

approved methylphenidate products.

I would like to now call Dr. Sharon Wigal up. Dr. Wigal was the director of our child classroom study but she is going to talk today a little bit about the clinical perspective and use of the MTS patch. Dr. Wigal?

MTS: Clinical Perspective

DR. WIGAL: Thank you. It is a pleasure to be here today and speak with the committee. I should say that in my position at the University of California, Irvine, I have opportunity to direct a number of clinical trials, typically in the pediatric age group and typically in ADHD. During the last 12 or so years I have worked with my colleagues in the development of a number of different measures, as well as extensions to the laboratory school protocol, and I appreciate Dr. Andreason as well as Dr. Squires speaking to some of those data.

Today I will give a little bit different talk and that is that I won't be presenting actual scientific data to you. Really what I would like

to do is give you some of my observations from my experience with MTS over these few studies and give you some of the clinical perspective.

As far as how we enrolled patients in these studies, obviously we go through an institutional review board for recruitment and our recruiting is through electronic advertising, through the web, e-mail, newspaper print, fliers, as well as radio advertising, and I just thought it might be helpful to have the actual language that we use for these studies: an investigational medicinal patch to treat ADHD. Again, this was in 6-12 year-olds. The sorts of families that responded to this through phone calls were those with treatment-naive children as well as those who had prior exposure to stimulant treatment. I should say that I really thought that we would see predominantly kids who had trouble with swallowing. Actually, we had about one child who fit into that category. A number of the other families were simply looking for other treatments that might be beneficial to their child whether or not they had

been exposed to treatment in the past.

So, some of the experience in this novel laboratory school environment I thought may be helpful in terms of how the MTS is applied, its removal and those kinds of issues. What we typically will do--you saw this schedule earlier--is bring these children in at the same time and we are actually simultaneously dosing the kids. So, you can imagine a large room where there are screens for privacy, and we actually involve the parents in the dosing because they are actually the experts on doing this, having gone through dose optimization clinic visits and having already learned how to apply the patch.

I don't think it was mentioned that it is actually applied to the hip area and that was rotated each day. Pressure would be applied for about 30 seconds. So, once our medical director would give the signal parents would apply the patch. It was already cut open. You have samples. I don't know if anyone tried to actually apply it, but they would apply it to the child and the

children oftentimes actually assisted in the process and they would hold it for that 30-second interval. Then we allow the parents to exit. They didn't stick around for the removal of the MTS. We actually had our nursing staff involved with that. It is very simple and pretty much like removing a band-aid and just moments to remove. So, parents did comment in the clinic visits as well as during the study that it was very easy to put on; very easy to remove; no struggle with their child to do that, and for those hectic mornings of getting their child out in the morning to school, they found it very easy to use.

What I would like to do is go through some of the comments from the parents. They were sort of direct informants in these visits. As you may know, with ADHD it really requires that there be symptoms that are severe in at least two settings, so the home setting and one other setting. When we are talking about school age kids, typically that other setting is the school setting. So, we have here the parents sort of relaying comments from

teachers during these clinic visits.

One such comment is, "the teacher reports the change is like night and day." That is not an unusual comment for methylphenidate type treatment. We have heard that actually for years. For these families it was something new. Some of their kids may have been on other preparations prior to the study, whether they were short-acting, intermediate-acting and also other longer-acting preparations.

We also heard, "his teacher noticed a big difference...like a different kid." Then, finally, "much more focused and accomplishes work." You know, for school age kids that is their job. They are supposed to be performing their school work; paying attention to the details in their day. So, we thought it was really critical to have this comment.

At home we heard parents remark, "everybody comments on her improvement." Again, to sort of visit an ADHD family, which is what we do in our clinic, what we find is that oftentimes a

parent may meet with a lot of resistance from other family members as far as seeking not only a diagnosis but treatment for their child. So, everybody in this particular case referred to a spouse, siblings, even grandparents who may provide after-care for kids when parents are working.

"My child listens, follows through on directions." On first hearing this you might think, well, what is so special about that comment? You know, if you are a parent that is what your expectation is for your kids the majority of the time. But for parents of ADHD kids, they are not seeing this without this sort of treatment or some sort of treatment that is effective. So, what they find is that the kids are actually showing these hallmark symptoms on a regular basis of not listening, not following through.

Then, "I can tell when the meds wear off because" --this is the child's name--"pesters her brother." I think it is really important to note not just that the medication works but also that I think for parents it is consoling that they have

recognition as to when does the medicine seem to stop working. Whether it is behaviorally or attentionally, they want to know that information. I will say that the parents that we work with--it has changed over time--they are getting more and more savvy, more and more articulate and more and more educated about what their expectation is not only about a treatment but how it should work and how it should help individually for their kids. I think a lot of that may be due to the fact that various companies have put a lot into educational resources for families so they come to a doctor's visit or appointment really armed, knowing information and knowing what they want for their child. Maybe not knowing what medications they want, but knowing what kind of relief from symptoms their expectation is.

So, I have a quote here that is quite lengthy but I thought it was valuable because I think it really does highlight for you some of that risk/benefit type analysis that parents go through, as well as that they are partnering not only with

their child but whoever it is that they are seeing in the office as far as what they expect from treatment.

This is from the long-term usage study, so the one-year follow-up study: "The three side effects that I have noted, loss of appetite, sleeplessness and skin irritation, have all been acceptable trade offs...After several weeks, his appetite returned in the evening either by acclimation or by modifying our removal time to 3:30 p.m."

I will pause there for a moment. We filed a research protocol where it was outlined with 7:00 a.m., for instance, application time of the MTS and the removal time 9 hours afterwards would actually be at 4:00 p.m. So, this parent took it upon themselves to adjust that removal time during the week or during clinic visits, not actually during any sort of lab school type study day.

"The earlier removal time also assisted in eradicating sleeplessness at bedtime. Lastly, I have noticed far less reddening of skin, barely

any, as time has passed and have not had any complaints of skin irritation for some time."

So, to conclude, from these studies what I have seen is that MTS is a viable treatment option for kids with ADHD. It is very easy in terms of its use. The families are compliant to the treatment. We saw the Hippocrates quote that Dr. Lerner used in his presentation about adherence. You might think one more medication to treat ADHD? Why? But if families and the children aren't really being compliant with medication treatment, then it doesn't matter how many treatments are out there, and if this a treatment that parents will adhere to its use, which is what we have seen in our studies, I think that really is significant.

We saw a positive parent perception, and I will tell you that as far as entering the study parents weren't necessarily responding because of the novelty of the MTS. I went back and looked at our data and our phone screens, and that wasn't necessarily the reason but by the end of the study we saw a number of parents who were very, very

receptive to the use of the patch and wanting to see it as a treatment, and thinking that this is actually something that is preferential for some kids for oral medication.

I mentioned that we didn't have that many kids who had problems swallowing taking the MTS, but for some reasons some of the parents who hadn't had their kids on treatment before, stimulant treatment, they were actually less reticent about using a transdermal system than using an oral system. Somehow, they saw it as being more holistic in some way, and those are the comments that we heard from parents.

I will say for myself that I was actually a skeptic going into this research. I live in southern California. It is a heavy beach community--swimming, water polo and swim team, that sort of thing with your kids, and exercise is really promoted heavily in the schools, playing baseball. I mean, sit at a lot of baseball games for one child, and a lot of our kids in this environment are very heavily into physical fitness.

So, I really thought that between the outer elements, and sweat, and all these things, how are these kids ever going to keep a patch system on? It was real interesting seeing that we had no problem with that in the study as far as kids' activity levels or their normal engagement in terms of sports during the week. It didn't impact the patch and its adherence. So, I thought that was very significant.

Then, the flexibility of the treatment period, the fact that families could adjust what time they actually put the MTS system on. I know there was a comment made earlier about not seeing it work' what do you do early in the morning if it is not working for at least two hours? You have to keep in mind that these data are from the lab school setting, which I do value because I am part of that creation, but when we looked at other methylphenidate type products as well as amphetamine products in that setting, we typically don't see a positive significant effect for about 60-90 minutes after dosing. That is not to say the

medication is not working, but as far as seeing the significance, we are not seeing it until that time period. Parents do remark for the flexibility in terms of removal time as well.

In terms of side effects, you have seen that the side effects can be manageable, and I think that parents, again, are very astute as far as being a practitioner or paraprofessional at home, working with their kids.

Thank you for your time, and Dr. Pratt is going to come back to talk about the benefit/risk summary.

Benefit/Risk Summary

DR. PRATT: Thank you, Dr. Wigal. I would like to briefly just summarize what we believe to be the benefits and the risks associated with this, and then, with the Chairman's permission, after I finish this, we do have a couple of additional things. We would like to answer some of the questions that have been left hanging at the moment. So, with your permission, I will go into that next.

I think for the benefits of the MTS system we have seen that a once daily application, which indicates a behavioral response occurring within

two hours of applying the patch, and clinical benefits persisting for over three hours of patch removal is the prime efficacy parameter that we have investigated both in our laboratory classroom study, as well as the data overall from the 302 study.

The benefits of the transdermal dosing system--again, there is no oral dosing involved so, again, perhaps for those patients who have difficulty or resist taking medications in the morning this might be a very useful alternative and aid in compliance.

We did have excellent adhesion properties of the patch. It stayed on during the day when it should have. There was minimal irritation that was noted and, again, very few individuals had to discontinue the study due to application site reactions.

The 9-hour methylphenidate exposure

through the MTS system in the single dose study resulted in similar exposure to other oral methylphenidate products, and you can control the exposure of this compound by two parameters instead of the usual administration of a pill and then taking the consequences of the pharmacokinetics of the pill as it occurs during the day. You can manipulate the patch size and you can manipulate the wear time. As we have heard, drug delivery does stop upon removal of the patch. So, if there is an adverse event that perhaps is occurring or is time dependent that is recognized by the parent or clinician and adjustment in terms of patch removal, as we have heard Dr. Wigal allude to, may be a very useful property for a patch that is not present with a pill.

Finally, there is a decreased risk of accidental ingestion of overdose. I hope some of you have tried to open up those packets that we have had in front of you. The primary packaging is very child resistant. It is very difficult for a child. You know, again, with the issue of younger

children in the household who may find patches that are not secured, the ability to get into those patches and actually apply them is very difficult. You need to have at least a period of time of pressure to put on there to actually get maximal adhesion. So, we believe that the patch in this situation may actually decrease the risk of accidental ingestion or overdose.

Plus, the patch being present actually reminds the parent that perhaps the therapy was given. In the hectic time of getting kids to school in the morning, I don't know how many people have experienced, you know, did I give the pill or did I not give the pill? Did the child take the pill? What is going on? And, you don't want to inadvertently overdose with two or three pills in the morning. With this one, you can always check on the patch. So, again, it may be a benefit for some patients in this situation.

The risks of the MTS system--again, we are predominantly talking about the adverse events with MTS and they are the same as those with oral

methylphenidate products. The MTS wear times, if you wear them for greater than 9 hours it might lead to a higher incidence of insomnia and anorexia. However, as Dr. Lerner had alluded to, most of these events occur early in the course of treatment and that is what we saw when we looked at the pattern distribution of when most of these adverse events occurred in our short-term and long-term clinical trials. They all occurred during the time when the patients were being titrated up. Once they were titrated to the effective dose and maintained on that, the number of the adverse events incidences decreased over time.

There are longer-term effects of MTS on growth parameters, but these are similar to those with other approved psychostimulants on the market for ADHD today. We will come back a little bit to talk about the potential for sensitization and irritation with MTS. Needless to say, it does exist, however those sensitization studies were conducted with a very unusual wear time paradigm.

They were patients who wore the patch for 21 consecutive days in the same location, at the highest patch size so that it was a very, very unusual exposure. When patients wore the patch by the typical recommendation by alternating sites during the course of our clinical trials and removals we did not see quite as much of the effects on irritation predominantly and/or sensitization.

Finally, this is a controlled substance. We recognize that, and it does have a potential for abuse and diversion and we have a comprehensive risk management plan that we are planning to put into place to deal with these issues that may potentially arise.

So, to conclude, I think the MTS, the methylphenidate transdermal system is a new and effective delivery system for the once daily treatment of patients with ADHD with methylphenidate. The onset of effect that we have seen when patients apply the patch is within two hours of application and, importantly, the duration

of the effect covers the school day and also covers time into the early evening when homework would be particularly important.

There is a potential for further customization of treatment. We do believe a positive benefit/risk balance occurs, and the incidence of adverse events is similar to those of other methylphenidate products. Thank you very much for your time and attention.

Questions from the Committee to the FDA and Sponsor

DR. GOODMAN: If you would start with the sensitization issue, I would appreciate it.

DR. PRATT: Sure. I think we will do that. Can I have the slides on the results of the sensitization study? The study, as I said, was conducted in adults. There were two studies. They were conducted according to the guidances from the FDA developing skin sensitization. These were adult subjects. They were brought in and they wore the patch, and it started out with a 50 cm2 patch that was applied to a site in the back, with a control patch that was a placebo patch, as well as

a saline thin chamber that was put on the back as sort of an irritant control which used SDS.

The patients came in. They wore the patches for three days or two days at a time. They were changed every two or three days depending on whether it was a weekend. The patch was reapplied to the same place, and they were doing this for 21 days. After the first week in the study, the latest study that was done, we had to cut down the patch size to 25 cm because too many patients were experiencing methylphenidate-related adverse events in terms of the euphoria that they got from having the patch on for such a long period of time continuously. So, the study was done with the 25 cm patch size for the remainder of time.

When patients came back after the induction period, therapy was stopped for a 2-week period of time. Then patients were brought back for a primary challenge. The active patch was applied to a different site again for a 72-hour period and the assessment at that time was done for irritation as well as for potential sensitization.

Potential sensitization was scored as the presence of erythema and edema or worse at the site. In other words, you had to have at least

those two components in order to be scored for potential sensitization. Again, the irritation levels were also scored.

This is the result of the irritation analysis that was done in this study. Again, looking at the negative saline controls, you can see that the mean score that was done was very, very low for that; that the MTS group had a higher score of irritation overall in the patient population, and the placebo transdermal system, while a little bit greater than the negative saline control, again was still higher than the negative saline control.

Now, these are the results of the actual sensitization analysis that was conducted. We had 133 patients who actually went through this 21-day induction period. Of those patients, based on the original challenge, only one patient was determined to have sensitization. However, because of the

high number and high amount of irritation that was noted, and the difficulty in attempting to establish whether there really was a sensitization signal or not, 36 patients were brought back for another challenge two weeks later than that. So, a third site was chosen to apply the patch. Of those 36 patients who participated in the rechallenge period, 16 of them had only irritation that was present in that rechallenge period. So, the total number of patients who had sensitization based on the challenge and rechallenge periods were 17 subjects overall out of the 133.

Now, there was a potential sensitization that was noted in 8 patients who needed rechallenge but they didn't come back to participate in the rechallenge period. They must have had enough with the exposure that they did have. But, again, there was one other subject with sensitization based on an incomplete challenge period.

So, if you look at the percentages here you have 17 out of 133 patients potentially being able to be sensitized under these extreme

conditions of wear. Now, how does that translate into our clinical program here? Again, as you have seen from Dr. Hay's presentation over the entire Noven program as well as our clinical program, we have probably over 900 subjects that have been exposed to various time frames of wearing the methylphenidate patches. We have found one subject only that has developed what could be considered an allergic reaction to methylphenidate. This was a child who participated in one of our studies for approximately three weeks and developed a rash; was discontinued; was started on oral methylphenidate. The rash actually recurred at the site where the patch had been applied so it was determined that this patient had an allergy and was started on another stimulant product.

DR. GOODMAN: Dr. Pine?

DR. PINE: I am a little confused, given how important this issue is, why a study was done where the parameters of exposure, at least based on what you just said, are not really relevant to the parameters of exposure that would occur when the

agent is clinically used, number one.

Number two, at the least it would be nice to see data from a study that did use the appropriate parameters, similarly to what you just presented for an exposure duration that was not appropriate.

DR. PRATT: Perhaps Dr. Andreason would like to answer that question.

DR. ANDREASON: We consulted this to our dermatology staff who suggested the design of the study since the number of patients needed to detect a signal and the amount of wear time needs to be higher--well, let me start the sentence over. In order to detect a signal with standard wear time, they anticipated you would need many more subjects. As a matter of fact, for this type of study they said that you would need a minimum of 200 patients in order to detect a signal, if the signal was there, with this design of wear time. That number was not reached in the study, however, they were able to assess the sensitization in the study because the signal was present.

DR. PINE: So, the rationale there was that this extreme acute exposure was supposed to mirror a more chronic exposure that would occur?

DR. ANDREASON: No, the extreme exposure is supposed to be able to detect a signal for skin sensitization if one exists. This percentage is not necessarily representative of usual wear time but it does say that there is a potential for skin sensitization. What that rate would be with normal wear time is not known.

DR. PRATT: And, again, there are rare but confirmed reports of methylphenidate allergies that do occur in individuals administered oral methylphenidate products as well.

DR. PINE: One more question--

DR. PRATT: Sure.

DR. PINE: So, basically the conclusion from this is that there is a potential for skin sensitization. We have no idea what the point estimate is with regular use, let alone a confidence interval around that point estimate.

DR. ANDREASON: No. No, not necessarily.

What we can report on are the results of the study. That study says that compared to the placebo system there were somewhere between 13 and I think 22 percent of patients who had a skin sensitization reaction. It is hard to say, you know, if those 8 other patients would represent the difference between 13 and 22 because they didn't return and that was a signal that this was not just skin redness; that it actually represented a contact sensitization above just the patch itself.

DR. GOODMAN: For further clarification then, how many of those subjects showed evidence of systemic reaction? I think you said it but I just want to hear it again and understand how you would define it.

DR. PRATT: I am not sure whether you mean, you know, by a systemic reaction. I mean, did they exhibit signs of being exposed to methylphenidate in terms of the effects that were observed, or systemic reactions that occurred--they were not rechallenged with oral methylphenidate, if that is the question that you are asking.

DR. GOODMAN: That is one of the questions. So, your definition of sensitization is that it is defined by the reaction at the local

site, qualitative and quantitative changes at the site of contact?

DR. PRATT: At the site of contact only.

DR. GOODMAN: But you didn't see any other evidence of a rash elsewhere on the body?

DR. PRATT: Not that was reported in this study, I believe.

DR. GOODMAN: Dr. Laughren?

DR. LAUGHREN: Yes, I think it might be of some importance to figure out what the right denominator here is for the clinical program. You mentioned, as I recall, one instance of sensitization--

DR. PRATT: Yes.

DR. LAUGHREN: --out of 900.

DR. PRATT: We would have to look at the total number of patients, adults and children that were exposed over the time.

DR. LAUGHREN: Right. The question is of

those 900, how many were exposed for a reasonable period of time to have expected the possibility of sensitization? I mean, obviously it is a smaller number than 900.

DR. PRATT: Yes, it is. I mean, if you just look at it in terms of the number of patients who participated in the large controlled clinical trials, it is somewhere probably in the range of up to 500 who have been exposed for that period. I don't have the exact numbers at the top of my tongue here but it is somewhere in that range. You know, about 200 in the Noven 12-hour wear time studies; about 100 in our studies here but then, again, we have another number of patients participating for longer periods of time in open-label follow-up that could be exposed.

DR. LAUGHREN: Then one follow-up question, our consultants in dermatology recommended that if sensitization did occur, that individual should never be exposed to methylphenidate in any form. Do you agree with that?

DR. PRATT: I think that that is a very logical follow-up for a general statement. I believe that, again, when you look at the

literature for methylphenidate allergies, sparse though it may be, when you look at the individual cases that are reported, the majority of them are actually very mild and, again, that one patient that we experienced developed this mild rash; was given a dose of methylphenidate and the rash returned at the site. The doctor discontinued the therapy and switched them to another one. I think that is a very reasonable recommendation.

DR. GOODMAN: Dr. Temple?

DR. TEMPLE: Are you going to be able to explain to people the difference between a little local irritation and sensitization?

DR. PRATT: Well, I think that may be a little difficult. Again, the definition of sensitization was erythema plus edema at the site. As you see, our scales there indicate that we did have places where you could actually report erythema, edema, papules, extension beyond the

site. I think, again, for labeling that would just have to be clarified with language with the agency.

DR. TEMPLE: Yes, but it is a matter of some importance. You wouldn't want ten percent of the people who get this drug never be able to get methylphenidate.

DR. PRATT: No, of course not.

DR. TEMPLE: That would be a disaster.

DR. PRATT: Of course. Again, I think the severity of the reactions needs to be considered. We are certainly willing to work with the agency on defining language to define this.

DR. GOODMAN: Do you have any photographs of these cases for us to see?

DR. PRATT: We don't have any cases of desensitization to show you. The pictures were not done of these individuals at the site.

DR. GOODMAN: Dr. Pollock?

DR. POLLOCK: Yes, if you could clarify how many individuals in your open follow-up--like, what the length of exposure is; how many people; because your trials were, like, 4-6 weeks in the

pivotal studies so we know that is the length, you know, among several hundred people that participated. But how many people have gone beyond that 6-week period?

DR. PRATT: I think perhaps one way to sort of address two questions would be to give you the number of patients in one of the long-term open-label studies that we followed, as well as to perhaps address one of Dr. Temple's questions earlier about the incidence of adverse events across the way with time on exposure.

May I have the slide that actually looks at our open-label, the long-term open-label adverse event profile?

DR. POLLOCK: For further clarification to Dr. Laughren's point, what is the denominator for real exposure? We can't say it is 900.

DR. PRATT: No, it isn't.

DR. POLLOCK: It is maybe a few hundred. So.

DR. PRATT: If you will give me maybe one second here--in the interest of time, how about if

I take that off and answer that question at the end of the period here when we can actually get you a reasonable number--here we go, this is one that I think will help you out.

Again, this is the number of patients that are followed--this is a portion of them in our long-term pediatric population. So, for patients that participated for greater than 6 months on therapy we had 117, starting up from the 322 that were originally enrolled. We do have an ongoing open-label study right now that has enrolled approximately, I would have to say, about 300 patients that are being followed for at least a year or as long as they want to participate in the study. So, we can have some numbers that come together.

DR. POLLOCK: The bottom line here, the 18 out of 117 had some form of reaction at the site which may, you know, lead to them not taking methylphenidate--

DR. PRATT: Well, no, again, these are studies that have not employed the dermal

evaluation scale so this is 18 out of the 117 that had some type of irritation response. It doesn't mean that they stopped therapy. It doesn't qualify the extent of the injury.

DR. GOODMAN: Dr. Robinson?

DR. ROBINSON: Yes, if you could go back to the slide that we have in our handout, number 85, which was week 7 dermal response evaluation?

DR. PRATT: Sure. Is that the graph?

DR. ROBINSON: Yes, it is the graph.

DR. PRATT: Yes, sir?

DR. ROBINSON: I am trying to understand what your recommendations for clinicians would be. At what level on this scale would you want to tell them that they should stop the treatment? Is it 1, 2, 3 or greater than 3?

DR. PRATT: It would probably be greater than 3 and when the reactions occurred. Because it is a transparent patch you can see some erythema at the time that it is there. When you remove it, the erythema typically dissipates very quickly. If the erythema is persisting the next day or it is

concerning to the parents, or if you have reactions that are more than just simply the erythema so you have papules, vesicles, edema that is present at the patch site, those should be brought to the attention of the clinician for potential evaluation. Again, there are certain children out there that do have sensitive skin and certain adults also that do have sensitive skin and these need to be taken into consideration also. This may not be the appropriate product for somebody who has other topical sensitivities that have already been manifest.

DR. ROBINSON: Well, let me just make sure I understand. So, even at a level of 3 you would say that clinicians could continue the person on MTS?

DR. PRATT: Yes, because, again, you should be rotating the sites and only if they are persisting perhaps for longer periods of time and not abating would that be a problem. Again, that has to be left to individual clinician judgment across the way.

DR. ROBINSON: Also on this scale, at what level of this response would clinicians have to take it off and say I am also not going to give

this child methylphenidate oral?

DR. PRATT: Well, if you look at the definition of what contact sensitization was, it included erythema plus edema and/or papules. So, that is a score of 5 on this dermal response scale.

DR. GOODMAN: Why wouldn't it be 4?

DR. PRATT: You could have it 4. Again, it would have to be observed directly in terms of being there at the patch site.

DR. POLLOCK: Could you just elaborate because it might be relevant to the warning--oh, sorry.

DR. ROBINSON: I am sorry, but did anybody have a score of 4 at all?

DR. PRATT: Not in the 302 study that we had and I don't believe that we had scores of 4 in any of the others, but I would have to look that up. I don't have that information.

DR. GOODMAN: Dr. Leon?

DR. LEON: This is a week 7 slide, if you could keep that up.

DR. PRATT: Certainly.

DR. LEON: It is just week 7.

DR. PRATT: Yes.

DR. LEON: So, I mean, no one during the

course of the prior 6 weeks, including those who might have dropped out, had a higher score than 3?

DR. PRATT: No, that is why we chose to show the week 7 data because it had the longest time in which patients were participating in the study and would have had the highest potential for showing an effect.

DR. LEON: What was the N here? How many people dropped out from baseline until they got to this point?

DR. PRATT: At week 7, again, I would have to go back to the slide but, again, in the methylphenidate-treated group we had about 70 percent of the patients who were completing at the end of that time frame.

DR. TEMPLE: No, he is asking how many

people dropped out for dermal reactions before week 7.

DR. PRATT: Two patients.

DR. LEON: Thanks.

DR. PRATT: But they were, again, very mild dermal reactions.

DR. GOODMAN: Dr. Wang?

DR. WANG: Are you saying erythema is sort of generally non-specific and just due to having a patch on and it resolves when you remove it?

DR. PRATT: Actually, methylphenidate itself is classified as a mild skin irritant. So, you know, if you took an oral methylphenidate or methylphenidate solution and put it on your skin you might actually get some irritation from it. So, as you can see, the orange and the white lines here are actually the patients who received the placebo patch with no methylphenidate in it.

DR. WANG: That was my point because if it is a non-specific patch effect you have a definite difference in the percent achieving a score of 2--

DR. PRATT: Correct.

DR. WANG: --between the placebo patches.

DR. PRATT: Yes, yes.

DR. GOODMAN: Dr. Pfeffer?

DR. PFEFFER: While we are talking about the benefits of the patch, and it is easy and children who can't swallow might be able to do this, do you have data on children's perceptions of wearing the patch; children's compliance with wearing the patch; children's cooperation in applying the patch; children coming home still wearing the patch?

DR. PRATT: Well, obviously we don't have any data particularly on the satisfaction. What we do know is that we had very good compliance in our clinical trials program with patch wearing. Again, patch compliance can be defined in two parameters here, not just how many patches were actually applied and/or returned to us but how long were the patches actually worn. One of the things which we actually did was we sent a diary home with the parents at each visit that they had and we collected those diaries at the end of each week,

and we tried to look at how long were the patches actually applied.

Can I have that slide, please? This is an example of the mean patch wear time in our safety population that we found over the time, again by the size of patch and by the visit, and we are very close to the 9-hour mean patch wear time as determined by the diary data that was returned to us. Given that it was diary data, we have no way of absolutely checking, we did not have patch policy going out and examining these children outside of the clinic, but the parent reported that they wore them and there was enough variation and enough diaries returned that actually gave it.

This is an example of a diary that we actually employed, and which is also going to be part of any marketed product that we are actually putting out because we found it very good. The parents were very pleased with using it. It reminded them that they actually had it; reminded them that they actually had to take it off; and sort of allowed them to keep track of where it was

applied, at what time during the week; and, again, the disposal message. Again, it is important to make sure you secure these patches and dispose of them properly. Yes?

DR. GOODMAN: Remind me, if you will, how you were monitoring any possible rash at the site of the patch, how systematic that was, who was observing it and, finally, can you actually see any problems through the patch itself.

DR. PRATT: The answer to that is that the clinician evaluated the patients' patch sites when they came in to clinic visits so that we had a doctor looking at them at all the times.

Yes, if i could go back to that one picture, I think it is probably worthwhile--a picture may be worth a thousand words here. We do have a couple of patients who complied and actually allowed us to take a picture of their patch so we do have one here that I think we can demonstrate to you.

This is an example of a child who had what appeared to be a definite erythema, if you look at

it. Again, you can see that there is no involvement of the surrounding area but you can see right through the patch and you can see that it is there. When it is removed the erythema typically dissipates in a short period of time. This was the smallest size patch that the patient was wearing here, the 12.5 cm2 patch.

DR. GOODMAN: Deborah Dokken?

MS. DOKKEN: Dr. Pfeffer, to me, went beyond the dermal reactions to the broader issue of compliance, and I would like to go out a bit further to the issue of benefit because I can only speak from the point of view of a consumer, not a clinician, but it seems to me that the debate about ADHD treatment has always been about risk and benefit, and there is no treatment that doesn't carry risks with it and parents are always juggling that.

But as I have sat here this morning, I am getting confused--I often get confused about some of the highly technical information but right now I am confused about how benefit is being described,

and to whom would this patch be particularly recommended? It feels to me a little like the description of benefit is evolving. Dr. Lerner's slide on compliance came back to that issue of difficulty in swallowing and the difficulty with oral medications. But Dr. Wigal talked about only one parent who reported that as why they thought this would be effective for their child and, in fact, really other parents were coming up with their own definition of benefit, namely, that it would be more holistic to have a patch.

So, I would like someone, probably from the sponsor, to say who is the target of children with ADHD and to whom would it be marketed? Are you talking about the kids with the swallowing issues, or is it becoming more broad and it is, well, this is another thing we could try but it is non-specific to audience?

DR. LERNER: I thought I would start the response, if I could, to first think about when you talk about the benefit who was seeing the positive change. What are the targets? What are the things

that are a challenge for a particular child? In these studies we have reports from the clinicians who were seeing the children as part of their evaluations in double-blind, as well as continuing treatment; the parent reports; in the analog classroom so those are specially trained teachers who work with children with ADHD all the time; but then teachers in the community who were the regular teachers that worked with these kids Monday through Friday. So, we are hearing, from the various environments where children with ADHD struggle, positive, statistically significant and clinically significant changes. These children are doing better.

What is interesting in all of that is how much do the kids notice the change? And, it is fairly common that young children don't pay attention to their own attention. They just do things. It depends on the individual child and the age. Many teenagers, for example, start to become aware not whether or not they are in trouble but whether their focus changes. So, I would say the

information here was from parents and from teachers in a variety of settings, as well as from clinicians, saying this was changing ADHD behavior. That may or may not be addressing the issue of why this should be used in distinction to a pill. I think that is the second question.

MS. DOKKEN: The second question was my question. I am not asking whether children with ADHD should be treated. I don't think that is what we are addressing today. I am talking about the specific formulation or vehicle. So, my question was the second one which hasn't been answered yet.

DR. PRATT: I think the question is what patient populations do you think would be most benefited, how would you, in your clinical practice, employ this patch as opposed to a pill? Is that the question in terms of where do you think this would be the most useful? Because I don't have any data that says, you know, what the child's perception of the treatment is, other than that we have very good compliance and they seem to enjoy participating in this, just from what we have

heard, but we didn't collect any specific data concerning that.

DR. GOODMAN: I think we can probably go back to this discussion. This point is a very important one and we can take it up as a committee in our discussion this afternoon. I want to make a comment first but I have a list of people, Pfeffer, Pollock, Mehta, Pine and Wang so you are on my list.

Going back to the skin sensitization issue for a moment, it seems clinically sensible that if you are seeing evidence of urticaria at the site you are going to worry about sensitization and decide not to give oral methylphenidate because of the concern that you are going to have a systemic reaction. I want to know from somebody who knows better than I how well founded is that risk. Basically, it is a skin test, as I see it. It is an allergy skin test. How well founded is that as a predictor of systemic reaction? No one knows? Dr. Temple knows.

DR. TEMPLE: No, I don't know, but the

contention is that you can get some sense of irritation just because the drug is a local irritant so that not everybody that gets a little red is sensitized in that sense. But I share your concern, how are you going to know and how are you going to communicate to a non-dermatologist population just how to figure this out? And, might you make an unacceptably large number of people ineligible for the treatment? Maybe you need to show pictures or--I don't know. I think that is a very good question.

DR. GOODMAN: Now we have Dr. Pollock and then Drs. Mehta, Pine, Wang and Pfeffer.

DR. POLLOCK: Yes, there was a comment that kind of flew by. You said that, well, you shouldn't perhaps use this in kids who are sensitive to atopic reactions. I wondered if that could be better defined. I mean, kids with asthma, kids who are sensitive to environmental--I mean, how large a group are we talking about? Would there be specific warnings about that?

DR. PRATT: Well, I think I can answer the

question from our clinical trials perspective. We excluded patients from participation who had known dermatologic reactions to topical--those patients who had sensitive skin syndrome already. You know, it didn't make any sense to put a potential irritant on a child who already was showing events of other non-specific irritations that occur. We had many subjects in our studies here who did experience much in the line of allergic type reactions otherwise, a lot of patients with asthma, a lot of patients with seasonal allergic rhinitis that didn't seem to impact on the reactions that were there or their continued participation in the study. Again, these were conducted during the school year time so we had it during allergy times and we had a lot of allergic rhinitis that was reported also.

DR. GOODMAN: Dr. Mehta?

DR. MEHTA: Actually, this is a question for Dr. Pine. The solution of methylphenidate has been on the market and it is given to young and older children, and when you try to give anything

to a young child almost invariably things go around the mouth and there will be local irritation. Has that been a problem? If so, how significant is it? In any case, that exposure would be in several thousand or several hundred thousand children compared to the few hundred with the MTS system.

DR. GOODMAN: Dr. Pine?

DR. PINE: Are you asking me to speak to their data because I can't speak to their data.

DR. PRATT: We don't have a solution that is marketed.

DR. MEHTA: I am asking in general, you know, as a safety review officer, would you know anything about the solution problems of skin irritation around the mouth with children given methylphenidate solution?

DR. PINE: I have never seen that. I have never seen irritation around the mouth and, you know, I don't know how many children I have seen--more than 500, so for what that is worth.

DR. GOODMAN: Dr. Wang?

DR. WANG: I actually want to follow up on

Miss Dokken's comment. We need to sort of understand or it would help me understand what the kind of complete accounting of what the potential benefits might be. Then I have a couple of questions about a couple of risks that maybe you could just put to rest.

Actually, Dr. Levin's comment was that one of the potential advantages is that there is no food interaction that you see with an oral, and I thought the sponsor was going to comment on that. What is the food interaction with oral agents? What is it? Is this a potential subgroup that might benefit from the patch?

DR. PRATT: Well, there are food effects that are recorded in the package insert of a number of both methylphenidate as well as amphetamine products. They tend to be either affecting the time to Cmax if you are giving the drug with a typical high fat meal or with breakfast. There is a potential advantage. Most of them are just aware that there are these potential food effects and, again, they need to be taken into account when you

are prescribing but don't tend to affect the efficacy overall.

DR. WANG: So you could just overcome them by dose?

DR. PRATT: You can overcome them by dose or just adjusting the time at which you administer the drug before breakfast or a little bit after breakfast, etc.

DR. WANG: Thank you. The question about risk, just to sort of get a complete accounting, someone mentioned that this is the same matrix delivery system as hormone replacement therapy, and I recall a story in the news a few weeks ago, I think, about HRT having some infrequent breakdown and people getting large boluses of doses. Is this the same system? And, is there some reason to believe it is not affected--again, I don't know what that problem was but it sounded like it might be something that would be sort of generalized to this kind of delivery system.

DR. PRATT: To answer that question, Dr. Mantelle from Noven Pharmaceuticals can at least

help clarify some of this for you.

DR. MANTELLE: Good morning. The two products that are involved with this particular matrix formulation are Reveldoc [?] and CombiPatch. None of those has been involved in the press that you have heard. The press that you have heard about is primarily on the birth control product, and it is a totally different matrix adhesive system.

DR. GOODMAN: Dr. Temple?

DR. TEMPLE: There have been some stories about more delivery of hormone than had originally been thought with the existing product. It isn't a sudden burst of activity, it is just a larger area under the curve.

DR. WANT: Okay. The third thing, just to put this to rest, is did you assess for emergence of suicidality and is it potentially in that affect of lability?

DR. PRATT: Yes, as part of a request by the agency to all sponsors of products for ADHD with stimulants, we did go back into our database.

We don't have as extensive a database on MTS because we don't have it on the market so we don't have the long post-marketing surveillance, but when you look at our program that we have conducted, this slide actually summarizes the events that came out of interest with that request along the way.

This covers the entire program, including the 021 study which followed patients for a longer period of time. For those of you who can't see, down at the bottom it breaks it down by what arm of the study they actually were in, and the events they were interested in were events of psychosis and mania that were reported, suicidal events, and the one event that occurred in the 021 study was a suicidal ideation, not actually a suicide attempt but they were classified together, and then the events of aggression overall. This, again, shows that with our program here, at least to date with the limited follow-up that we do have in exposure, we don't have very many of these events that have emerged.

DR. GOODMAN: Dr. Pine?

DR. PINE: This comment relates a little bit to the question of need but then also how it relates to the issue of skin sensitization. So, in

terms of need and what would the role of a compound like this be, clearly it is the case that there is a group of kids who just cannot take medications or won't take medications. On the one hand, it is not a large issue. The company gave a figure of 15 percent. I could believe 15 percent. I don't think it is any bigger than 15 percent, but there clearly is that group of kids.

The problem really has kind of two forms. There are some kids who just will not take any medicine or stimulant at all, and then there are some kids who will take liquid medicines or medicines that you crunch up. In the first case, kids couldn't get any stimulant whatsoever because it is just not feasible to get it into their bodies. In the second case, they can't take long-acting forms because the long-acting forms have to be chewed. Again, it is not a big group of kids but it clearly is a group of kids that

clinicians see.

On the other hand, as a lot of people have said, it is a big deal if you would not be able to tell for kids who were taking this product if they would be disqualified from ever getting methylphenidate. So, maybe the way to think about it is, you know, how relevant is it for kids who would have no other way of getting methylphenidate because they just could not take it orally, and the choice there would be doing nothing, or trying another therapy which is not effective, or waiting three, four, five years until kids can swallow.

So, for me, the thing I am struggling with is if that is really the niche or if that is really the group of kids, again, the group of kids who cannot take it orally what is the better thing, to have a compound like this available where there is a risk that we haven't really quantified yet, or to have a child who just cannot take methylphenidate, period, or has to take methylphenidate multiple times a day which often means that they are not going to take it?

DR. GOODMAN: Dr. Pfeffer?

DR. PFEFFER? My question has to do I think more with the pharmacokinetics. I am very

interested in the graphs you have shown in terms of the onset of the MTS patch where it takes about two hours, you feel, before you begin to see an effect or blood level effect. Given that, I am wondering about the metabolism because one of the other comments was that a value of this is that it avoids digestion. Yet, the onset seems to be faster in terms of getting a blood level for those taken orally, for the Concerta at least taken orally, than use of the patch. So, I was curious if you can explain a little bit more about the onset of blood levels using the patch.

DR. PRATT: Well, I think that there are two aspects to that. What we showed were the single dose studies in which children had been washed out completely. They did not have any evidence of methylphenidate previous to that. In that case there was a lag time of approximately two hours before you got a detectable blood level along

the way.

Now, in the multiple dosing study, it is interesting that the lag time--again, this was the PK graph which you are referring to and where we actually saw the d-methylphenidate, and this happens to be in our Caucasian population here, where you actually have detectable levels within an hour of that going up. Again, you see it is a difference. The oral formulation of Concerta is a different formulation. It has a coating on the outside that is immediate release, followed by sustained release on the inside. It is interesting that we find statistical onset of effect in the classroom study to be approximately two hours. Now, that was the first time point at which we actually measured the statistical effect. As we heard from Dr. Wigal, statistical effect does not necessarily always correlate 100 percent with when the parent or observer is going to be seeing a behavioral effect. It is just that that is the time we actually chose.

I think that in the multiple dosing study

the lag time tended to disappear as patients were dosed on a daily basis to steady state. As you see here, at the 24-hour time point, at which point you would be getting ready to apply a new patch, there are low but still detectable levels of methylphenidate that are present. So, with time you may get a little reservoir within the skin that actually eliminates that and probably accounts for some of the changes that we see in our multiple dosing as opposed to our single dosing.

DR. PFEFFER: Does it make a difference also in relation to children who were drug-naive when they started the study? I wonder if you have data on differences between those children versus children who might have been already on some version of methylphenidate?

DR. PRATT: Actually, it turns out that in the studies we conducted that about 60 percent of the patients were actually drug-naive; 40 percent had been on other stimulants or other treatments beforehand. We did not do separate analyses on the response of one group versus the other group. We

could do those eventually but we did not do them for this determination because all subjects were withdrawn if they were on a previous therapy. Okay? They were withdrawn and washed out for that therapy for at least one week, if not longer, before they were actually enrolled in the study so, to all intents and purposes, they were back down to their base level of what response they might get.

DR. GOODMAN: A related question about the delivery system versus oral ingestion, if I understood correctly, Dr. Andreason, you mentioned earlier that there would be more of the l-enantiomer with the transdermal application. Were there any clinical safety implications of having a high proportion of that enantiomer versus what you might see with oral ingestion? Either of you can answer.

DR. ANDREASON: The only clinical implications that we would be able to see would be those seen in the short-term trials versus the oral preparation where the l-enantiomer would not be present. The differences that we saw could be due

to dose or, you know, theoretically could be due to the l-enantiomer, for example tics. I don't necessarily think that that is true but we don't know. As far as animal studies go, if you look at the animal studies the d- and l-enantiomers are there and in tox. studies, carcinogenicity studies that l-enantiomer has been evaluated in animals even though the d is what is seen usually by humans. So, that is why we didn't necessarily need new data from animals.

DR. GOODMAN: Dr. Wells?

DR. WELLS: My question is about slide number 27, which is a plasma concentration time curve. It shows a comparison of plasma concentrations over time for the 6-hour, 8-hour and 10-hour wear times compared to Concerta.

DR. PRATT: This one?

DR. WELLS: Exactly. That is offered, as I understand it, as at least a partial rationale for the 9-hour wear time. But, of course, this is single dose data. Correct?

DR. PRATT: Yes, it is.

DR. WELLS: The multi-dose data is actually quite different and, in fact, in the briefing document there was mention that after

repeated doses of MTS 9-hour plasma concentrations were approximately double those for the corresponding dose of Concerta.

DR. PRATT: Yes.

DR. WELLS: So, that makes me wonder about the rationale for the 9-hour wear time.

DR. PRATT: Well, again, we felt that we needed to at least make some attempt to say why--the concern was that adverse events that were reported in the 12-hour wear time studies could have been related to peak plasma concentrations which, with the patch system as we know here, occurs at the time in which you take off the patch so at approximately 12 hours you would have had the peak. Again, these were predominantly the anorexia as well as the insomnia, and it is plausible that this could be related. We were searching for at least a rationale to say, well, what time could we take off the patch and, you know, let elimination

take over so that, if these were actually related to the plasma concentrations at the time in the majority of the patients, we would be able to at least lessen those concentrations and make sure that by the time the children went to sleep at night they would actually be getting plasma concentrations down there.

The logistics of the child school day also played a very important part in terms of selecting a wear time. It would not be sensible to require a wear time that would be six hours or seven hours. That would require it to be taken off during the course of the day. We were searching for a time that would sort of maximize, you know, the lowering of the plasma levels at the end of the day with coverage during the time that the patients were going to be in school, which is an important time, and they wouldn't have to remove it along that time. So, this was only a partial reason.

Yes, there are higher plasma concentrations but, again, when you look at the distribution of when the adverse events occur that

were of interest concerning anorexia, they occur during the earlier parts of the study when patients are on the lower doses and titrating up. Once they get to the dose that they are optimized at and continue on therapy those events tend to go away and they, again, tend to be mild and moderate. So, we were trying to balance a number of different variables in coming up with a wear time that would fit the parents and school children's day, as well as try to address the issues of plasma concentrations in the later daytime periods.

DR. GOODMAN: Dr. Andreason and then Dr. Temple.

DR. ANDREASON: To address the table I think you are looking at, those are mean plasma concentrations in the Phase III study. Those plasma concentrations are not necessarily matched dose per dose or time per time. What you are not seeing there--and correct me if I am wrong--is an equivalent dose so that if the patch is somehow tolerated better--and there are several scenarios that would produce this--if the patch is tolerated

better, then the 37.5 cm2 would be maintained. But in the oral group, if they were taking a lower dose, it would be reflected in that mean plasma concentration.

DR. PRATT: Yes. The data were collected--again, this is not every single child that completed the study; this was a subset of patients who actually could come into the clinic so it was a sparse sampling paradigm that we used to obtain the data. We tried to get it at the time because we were mainly interested in what the plasma levels of the MTS patch were. The Tmax for Concerta, which was the comparator arm, is an earlier time frame. Because the study was blinded, we did not know which children were on MTS or Concerta so we just collected sparse sampling for all of the children that came in, including those in the placebo group, that were willing to do it.

DR. ANDREASON: Nevertheless, on page 38 of the briefing document you do seem to concede that with repeat dosing the exposure to d-methylphenidate from the patch is roughly double

what you would see with, I guess, an equivalent dose of the Concerta.

DR. PRATT: They are higher in terms of--

DR. ANDREASON: That is what you say, you say doubling--

DR. PRATT: Yes.

DR. ANDREASON: --within the 9-hour value. Now, if the Cmax for the Concerta occurred earlier--

DR. PRATT: That would impact that and we are not able to model the Concerta AUCs as well as we would have liked.

DR. GOODMAN: Dr. Temple?

DR. TEMPLE: I want to obsess further about dose response. Could you put up slide 41? I probably mis-spoke in saying you didn't have any dose-response information. You actually do, and it shows that you don't need the high dose, or at least one can read it that way. If I understand the study design, by week three nobody is on more than--what?--the 25 patch. Right?

DR. PRATT: Yes, by week three, yes, that

is the 25 cm2 patch or the equivalent 36 mg of Concerta.

DR. TEMPLE: Yes, I am only interested in the patch placebo difference. You know, you don't want to make too much out of pictures, but it is fairly obvious--you can see the asterisk there--that the difference between drug and placebo is as large at week three as it ever is. Okay? That is the 25 patch. There doesn't seem to be any further effect from further titration. You worry about these things in case a lot of patients are dropping out, but in this case actually you did very well on that because pretty much the entire patient population is still there.

DR. PRATT: Yes.

DR. TEMPLE: So, I guess I would ask you what makes you think anybody needs 37.5?

DR. PRATT: Well, again, this was individual titration. In the mean population--you know, those numbers are correct but, again, these were titrated to the effect in terms of the clinician. We did not get information, which

complicates this analysis and, again, if the patients--we defined a rather minimal response for the ADHD RS which was a 25 percent reduction. Again, many of these patients had much worse scores and the clinicians felt the goal of therapy today--and my clinician counterparts can correct me if I am wrong--is to attempt to normalize behavior. So, there was allowance for trying to get to normalization of behavior.

DR. TEMPLE: No, I understand that. Since there is a gradual fall in all groups over time, probably everybody thought that their increased drug dose was doing a lot of good. That is what people always think and they are always wrong, which is why titration studies always lead to an overestimate of the dose you need, which this one does too. Really, consider the question of whether there is any hint that the further titration to the larger patch did anything at all in this titration study. It doesn't look as if it did, which could have something to do with, you know, side effects and a lot of other things. Maybe you don't really

need to give that much.

DR. PRATT: Side effects, interestingly, were not limiting at those top two doses there in terms of the number of events that were occurring additionally. The majority of events occurred by the time you reached that third titration level and very few additional recruitment as you went on up on either of the other doses there.

DR. TEMPLE: Okay. So, we may not have terrible consequences but still, you know, in general you don't want to give more than is useful.

DR. PRATT: Yes.

DR. GOODMAN: Dr. Geller?

DR. GELLER: I still have a few practical questions. This is my area of obsessing. It is 3:30 in the afternoon. The child's parents are at work. The child may be home; maybe with the latchkey group; maybe in an extracurricular activity. Who is allowed to take the patch off? And, how does that person communicate to the parent so the parent can chart what time the patch was taken off?

DR. PRATT: I don't know if I have a completely good answer to that because I think that, again, in our clinical studies we did not

have that raised up as a major problem. I mean, if that was considered a major problem I would have anticipated seeing a lot of patients dropping out of the study because of that. We really did not have that listed as, you know, inability to comply with instructions. Now, does that translate into the real world? I don't know that for sure.

DR. GELLER: If I can just follow-up, who took the patch off in the afternoon? Did you have only families where the mother was there at 3:30?

DR. PRATT: No, no, no. Actually, maybe Dr. Wigal can help us on this a bit.

DR. WIGAL: We certainly did encounter that practical issue in the lab school study on the non-lab school days, and what we found was that parents could designate another adult. Whether it was a spouse, a grandparent, babysitter who was an adult, they could designate someone else who would actually do the removal and ensure that it was

disposed--I guess we were retaining it and bringing it back to the site for accountability so we would have information about that.

DR. GELLER: Let's just say that the child goes to latch key. The latch key adult agrees to take the patch off. How does the patch then get back to the parent? Or, are you going to assume that it is going to be flushed by the latch key?

DR. PRATT: It should be disposed of appropriately. Dr. Andreason, you had a comment?

DR. ANDREASON: Yes, I was just going to say that according to your use information, it should be thrown away. It shouldn't be saved and passed on.

DR. GOODMAN: Dr. Pollock?

DR. POLLOCK: Going back to the pharmacokinetics, I was also puzzled why the exposures to the l-enantiomer were so much greater and if it at least has some inhibiting effect on the long-term clearance of d-methylphenidate and potentially, you know, in the long term whether it accumulates to an extent where it inhibits actually

the action of the d-methylphenidate.

DR. PRATT: We will have Dr. David Heal come up to help address part of that question for you.

DR. HEAL: Good morning, ladies and gentlemen. Yes, you raise a very, very interesting question. Let me just tell you a little bit about methylphenidate and its enantiomers, just to help answer these questions.

You can see here the structure of methylphenidate. It contains two chiral centers which are shown by the asterisks here. That actually means that it exists as four isomers, the erythro and threo isomers. But for purposes of methylphenidate products nowadays, we are really only interested in the d- and l-threo isomers, and they are shown here on the bottom of the slide.

Now, what you can see is that structurally they are identical and, in fact, if you want to think about the structures in very simplistic terms, they are the equivalent of your left and right hand. In other words, they are mirror images

but they are not superimposable. In fact, in terms of the way that these drugs act as reuptake inhibitors, they will both act as reuptake inhibitors, as I will show you in a minute. But obviously your right hand fits in your right glove much better than your left hand, which is why the d-isomer is so much more potent than the l.

Now, if we are talking about what actually happens in man between oral and transdermal application--not to make too much of this point but, in fact, the amount of the l-isomer that you will actually see will vary according to the Ritalin preparation that is given. What actually happens is that, obviously, racemic methylphenidate is a 50-50 mixture of d and l and, in fact, when you take that orally the presence of d actually prevents the stereo-selected metabolism of the l.

So, with the instantaneously released formulations you see much higher ratios of l to d than you do in the slow release formulations. In fact, although we have figures here of 1.6 and 1.9 to 1.0, there is a large inter-subject variability

on this and, in fact, with instantaneous release you can actually get as little as a 3-fold difference between d and l. Actually, for all instantaneous Ritalin products patients are now getting quite high exposures to the l-isomer.

If you think about what they are actually going to have, when you think about these products you have to think in terms of what are their pharmacological modes of action because all of the effects that we are talking about, whether they are on the efficacy side or on the common side effects on the other side of the equation, they are actually all driven by a very, very common pharmacological mechanism. So, whether it is noradrenaline selective reuptake inhibitors like atomoxetine, or dopamine selective inhibitors like bupropion, or mixed products like methylphenidate there is exactly the same pharmacology driving these effects.

Now, the way that you can look at the contribution of these isomers to efficacy and side effects is to actually consider their potencies as

reuptake inhibitors. If you look at the racemate on the top, you can see that it really only has effects on two neurotransmitters. The data are shown as a Ki or IC-50 value and the smaller the number, the more potent the action.

So, you can see here that the racemate is more potent as a noradrenaline reuptake inhibitor than is dopamine. With Ki's up in the 22,000 nanomolar, really no effect at all on 5HT. Now, if you look at the d- and l- isomers, what you see is an identical pharmacology, except one is only a very weak mirror image of the other. So, the Ki for the d-isomer is 150; the l-isomer is 10-fold lower, at 1200. You see exactly the same for the dopamine uptake inhibition. What you are seeing here is exactly the same pharmacology across these two isomers.

This actually shows you some data performed in our own labs. This is micro-dialysis performed in freely moving animals. What you can actually see here, shown on these graphs are the noradrenaline and dopamine concentration in the

brains of freely moving animals, norepinephrine in the frontal cortex, dopamine in the striatum. What you can see here is that this 10-fold difference that you see in vitro is translated in vivo because you can see that the dose of d-methylphenidate at 1 mg/kg here is approximately equivalent to that of 10 mg/kg of the l-isomer. If you look at the behavioral data you see exactly the same thing happening. The same pharmacology but just 10-fold weaker.

So, what about clinical studies? There was mention of the Srinivas work. Well, of course, this work did show that the l-methylphenidate was inactive but you have to consider the dose that was used. It was only 5 mg and to show efficacy, as the authors acknowledge, you would have needed to have given at least 50 mg of this isomer. Again, the same applies to the other study which was published by Dr. Wigal, who is here today.

So, if you think about efficacy and side effects as being the two issues associated with the isomers, what you can see is that really the same.

There is just a 10-fold difference in terms of potency. Obviously, the amphetamine and racemic mixture is going to be the predominant driver of efficacy and side effects. With the lower potency and plasma concentrations you can actually run a rough estimate to find out what the contribution will be. In fact, at most it is going to be 5-10 percent of your efficacy, 5-10 percent of your side effects because 10-fold less and half the concentration.

Actually, the clinical data support the hypothesis that while l-methylphenidate delivers no discernible benefit in these low dose trials, actually, its presence did not adversely impact on the side effect liability of such products. In fact, the side effect profiles of the single enantiomer products like Focalin, are exactly the same as those of all the racemic products.

DR. GOODMAN: Is the l a competitive inhibitor of the r so that it might interfere with the potency of the d?

DR. HEAL: In fact, with the difference,

you know, if you look at those clinical studies there was no difference in efficacy between the d/l and the single d-isomer. So, with a potency difference of 10-fold I don't believe that would be a positive contributor.

DR. POLLOCK: I am still left with the initial question I asked. Why are the l concentrations so much higher than for Concerta? You know, you say that it is minimal compared to the d but for your product, if you compare the two kinetic curves acutely you have, say at your highest dose, 25 ng/ml for d and you have 16 ng/ml for the l at the same dose. So, you are almost getting 50-50 as opposed to with Concerta where it is actually, as you said, maybe 10-fold less.

DR. HEAL: Let me just clarify that issue for you because I think I can do that. I talked about Ritalin being instantaneous release. There is stereo-selective preferential metabolism of the l-isomer versus the d in the liver. And, the presence of the d-isomer actually slows down the metabolism of the l-isomer, not vice versa. What

happens when you have the sustained release products like the Ritalin SR and Concerta is that d and l are released into the system much more slowly, which means that l gets preferentially cleared out of the system faster. So, that is why on the first slide I showed you, and we can go back to slide 981, that with the instantaneous release--look at the bottom left-hand corner, the instantaneous release has a ratio of 5 of d to 1 of l. For individuals this can be as low as 3:1. Once you start moving into the slow release formulations where there is not so much of the d-isomer being dumped as a bolus through first-pass metabolism, you can see that the ratio drops to 10:1 Ritalin SR and 40:1 in Concerta. That is a specific aspect of the way those drug delivery systems work.

The reason why the concentrations for the MTS patch are greater than those for Ritalin IR is because it is a transdermal application and, because it is applied that way, this largely bypasses first-pass metabolism by the liver. So,

not so much of the l gets preferentially taken out. That is the reason for that.

I guess I probably did not put that clearly enough at the beginning, but what I was trying to explain to you afterwards is that even taking into account the fact that there might be 50 percent in concentration terms, when you take that down pharmacologically 10 times in terms of potency you are left with 5 percent. That is how I got to that figure.

DR. GOODMAN: Thank you. I intend to stay on time and I want to make sure that we break at lunch and get back on schedule. I still have a few people that have questions. I want to see if they still do. Dr. Leon?

DR. LEON: Back to what Dr. Geller was asking, I am curious, I see in these samples that the patch indicates that it is placebo but does the active patch have some identification that indicates what the product is?

DR. PRATT: Yes--

DR. LEON: And, is it something a lay

person would understand?

DR. PRATT: Yes. I mean, once we get the approved packaging and labeling negotiated with the FDA, it will be very clear as to the fact that it is a methylphenidate-containing drug and the packaging will also clearly indicate that it is a controlled substance.

DR. GOODMAN: Dr. Mehta, you didn't have a question? Dr. Malone?

DR. MALONE: I just have two more practical questions about the patches. Can you detach them and then re-attach them?

DR. PRATT: You can detach them. Re-attachment is a little bit more difficult because, again, you pull a layer of epidermis when you remove it, like removing a band-aid. Trying to re-attach a band-aid is a little bit difficult. Importantly, to get the concentration gradient and the delivery of the drug, it is designed that when you put it on you have to have a 30-second period to actually, you know, hold it and bond it to the skin. If you do attach it, it will still deliver

drug if you can manage to get it on there, however, it will deliver drug at a lower rate because if it has been used there is not as much of a concentration gradient there anymore and, typically, you won't be able to attach to be able to deliver a sufficient dose. It would not tend to deliver as much on a second application.

DR. LEON: I guess these patches are additive, so if you wanted to double the dose of any patch you could just put two of them on?

DR. PRATT: You could use multiple ones. Again, we have a wide range of patch sizes that are intended to be prescribed as single patch uses. You know, there may be someone who might wish to abuse it apply multiple doses. We have done abuse liability studies with multiple applications of the patch and it does deliver more methylphenidate if you double the application. Again, its intended use is as a single patch to be applied each day. The doses will be wide enough in range that there should be no need to apply more than one patch in a day.

DR. GOODMAN: I would like to break for lunch. Dr. Laughren, you want a last word?

DR. LAUGHREN: I don't want to open up a

whole new area but I am still a little bit nervous about the time of onset. I know that in study 201 you showed us a statistically significant effect at two hours. We have looked at the plasma levels in individual subjects and at two hours in many subjects they are very low. I am just wondering, in that study did you do any kind of responder analysis so we can get a sense, and maybe Dr. Wigal could speak to this, observing these kids in the laboratory classroom. Are you really seeing in a majority of kids a good response at two hours, given the fairly slow onset of this? And, part of the concern is that if you are not getting a response early clinicians might be inclined to push the dose higher to get that early response and then you are getting a higher dose than you need later in the day.

DR. WIGAL: I can't answer your question in terms of a responder analysis. I don't think

that has been done, which would be really critical to have completed. But I would just remind you that the measures in the classroom that were conducted, including the PK measures, were at pre-dose and then at two hours. There were no measures in between so we don't have any data about that. But definitely at two hours, speaking to our classroom teachers--it was double-blind, but they could see kids who definitely were being much more productive and much more attentive. Their behavior was less disruptive at that time point. So, it was something that they definitely saw at that time point.

DR. LAUGHREN: Then, in the outpatient study you weren't getting any complaints from clinicians or teachers about inadequate response early in the day?

DR. PRATT: No, that were reported to us. Again, we did not have parents coming and withdrawing their children from the study because of complaints from the teacher that they were not actually behaving appropriately when they got into

the school setting.

DR. GOODMAN: At this point, I understand we have only one person signed up for the open public testimony period and we have not confirmed yet if that person is here. In any event, we should have a short amount of time in the public hearing session which will allow us to get started on the discussions among the committee earlier.

I understand there is a room reserved for the committee members within the restaurant. My goal would be to actually get back here before 1:00 so we can get a clean start.

[Whereupon, the proceedings were recessed for lunch, to reconvene at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

Committee Discussion

DR. GOODMAN: We are going to get started in order to be on time. I would like to have everybody return to their seats, please. We have no public representative providing testimony. Somebody signed up but they have not shown so there will be no public testimony for this hearing. Unless it is one of you out there. This is your last chance! That is it!

There is a little bit of leftover business from this morning. We had asked for some additional information. In particular, two of the committee members, including myself, wanted to look in a little bit more detail at your crossover study at the two phases and look to see if there were any differences. As people know who have done crossover studies, sometimes they are hard to interpret statistically, in part because of carryover effects. In this case, also there was some allusion in the briefing document to the possibility of a rebound effect because there was

no period in which there was a gradual titration off of the medication; it was an abrupt change. So, I wonder if you could review that for me.

DR. PRATT: This is the data from both periods of the crossover. Again, remember that in the middle there is a one-week period in which the crossovers occurred. So, the subjects who were on active for the first week then received placebo for the subsequent week, and then came in on the Saturday for their classroom evaluation, and vice versa for the placebo group. This is just run together for convenience. If there are any questions, we will be happy to discuss them. The effect is similar in both groups as they cross over obviously.

DR. GOODMAN: Dr. Leon?

DR. LEON: The magnitude of the effect does shrink somewhat.

DR. PRATT: A little bit perhaps.

DR. LEON: From this angle it does.

DR. PRATT: Okay. Again, it is half the number of subjects when you put the whole thing

together, placebo versus MTS.

DR. GOODMAN: It was mentioned in the executive summary briefing documents that we received earlier that one of the concerns was that the patients in the placebo group did not go through a tapering period before changing to placebo. I am quoting here: "Therefore, it is unclear if the observed treatment effect was real or was due to a sudden change of treatment." I assume that what is being referred to is a rebound effect of coming off the methylphenidate abruptly. Would you just address that?

DR. PRATT: Yes, sure. You can put the slide back up, please, the previous one. Yes, I think that, again, the half-life of methylphenidate is about 2.5 to 3.0 hours so that the subjects who completed the first classroom period, their patch was removed at 9 hours. They went home with a new set of patches and were maintained on placebo for the rest of the week.

Clinically, when you stop therapy with methylphenidate there is no tapering that is

usually employed in these subjects because the next time the dose would come up they are usually at lower plasma levels. Again, this is more than 5 half-lives out from the peak plasma levels that would have occurred during the classroom studies and patients did have an opportunity to be on this therapy for at lease 1 week before they were brought back into the study. So, we don't believe that there is any rebound phenomenon that would be observed in the 2-week classroom studies. Again, this paradigm has been used extensively with all of the other classroom designs that have been employed.

DR. GOODMAN: Dr. Pine?

DR. PINE: Not to beat a dead horse too much, but you can see from the 2-hour point that there is maybe some of this though so that it looks like the placebo and active agent in the second epoch are basically overlapping, if I am reading it correctly. Is that right, that they are basically on top of each other?

DR. PRATT: Yes, but there is a difference

in the pre-dose assessments so when you look at the difference in the change from pre-dose assessment they wouldn't overlap. But on the Y axis is the actual mean SKAMP score, not the change from the pre-assessment SKAMP score but the actual SKAMP score.

DR. PINE: But the fact that they are overlapping at pre-dose number one, something has happened--anyway, it is not that big a point because it is clearly effective both before and after the crossover.

DR. GOODMAN: Anything else, talking about carryover effect, carrying over from this morning?

DR. PRATT: Actually, we do have one other question that we left a little bit vaguely answered from Ms. Dokken. It was the issue about the benefits that can be perceived in populations along the way. Our clinical trials program didn't specifically target any one particular group of patients, for example those who could not swallow pills or not take pills. We actually investigated this in a general population of patients with

attention deficit hyperactivity disorder.

So, while I think that there is a special group of patients on one extreme who may particularly benefit from this therapy, again, we believe that this therapy should be available as an alternative for clinicians and parents to be able to expand their ability to deal with the flexibility that perhaps would be required, and that you won't get with oral medications that are currently available today.

DR. GOODMAN: Thank you very much.

DR. PRATT: Thank you.

DR. GOODMAN: Jean Bronstein?

MS. BRONSTEIN: Thank you. This is kind of a carryover from this morning. I just want to make sure I fully understand the skin sensitivity issue. We don't have data on the number of children who had skin reactions that also developed the true sensitivity to the drug--is that true? Is that a true statement? We do have data on the number of children that developed a true sensitivity to the drug?

DR. GOODMAN: Those data, as I understand it, are from adults.

MS. BRONSTEIN: No, I am talking about

children. I want to know about the children. I understood the adult dermatological study. I am asking in the children data that we have seen, do we know how many of those children that had some skin reaction actually developed the sensitivity to the drug.

DR. PRATT: There was only the one subject that was reported. That subject developed a rash; was stopped on therapy; was restarted on oral methylphenidate and a rash occurred at the site where the reaction was. No other subject--and we have been trying to follow that in our clinical program--has developed any such other reactivity.

DR. GOODMAN: And they were restarted on the patch?

DR. PRATT: Pardon?

DR. GOODMAN: They were restarted on the patch?

DR. PRATT: No, they were restarted on

oral methylphenidate.

DR. GOODMAN: And what was the reaction exactly?

DR. PRATT: The reaction was a mild rash at the site of previous patch application, indicating a contact sensitization.

MS. BRONSTEIN: And then they had to be removed from the drug entirely because of the sensitivity?

DR. PRATT: They were stopped. I don't know if they were continued on amphetamine or not at this point. I don't know what the subsequent therapy was.

MS. BRONSTEIN: Thank you.

DR. GOODMAN: Let me be 100 percent clear here. So, on rechallenge with oral they developed a rash at the site where previously the transdermal patch was placed?

DR. PRATT: That is what we understood.

DR. GOODMAN: And nowhere else?

DR. PRATT: Nowhere else.

DR. GOODMAN: Is that a well-known

phenomenon?

DR. PRATT: Yes, it is.

DR. GOODMAN: What is that called?

DR. PRATT: Contact sensitization.

DR. GOODMAN: Okay, interesting. Dr. Geller?

DR. GELLER: And that is always a reason never to give that drug again?

DR. PRATT: Most clinicians would be uncomfortable continuing to prescribe for somebody who actually evinced that type of skin reaction to an oral drug.

DR. GOODMAN: Jean?

MS. BRONSTEIN: So, what is the percentage of that risk in this population?

DR. PRATT: Well, because we have only had one subject, it is very difficult to quantify that because, again, depending on the agent, obviously you can sensitize some people with a single exposure; other patients may require multiple exposure. We don't really know what the overall incidence is. We can say that in our clinical

trials population where subjects were exposed to various patch sizes for various periods of time in our control population, 300-plus children for between 5-7 weeks, we have not seen any of this type of reaction except in this one subject. I mean, I don't know whether that will translate into a true number overall. It could be much, much less along the way.

DR. GOODMAN: Yes, Dr. Pine?

DR. PINE: Just to make sure that I understand the relationship from a dermatologic perspective, I guess this is for Dr. Andreason. When we combine the one child out of 300-400 with the data from the adult study, the adult study basically tells us that sensitization with this compound is a real phenomenon. It does happen. That is what that was a test of. We don't know what the prevalence is but, to the extent that we can estimate that reliably, the one out of 300 would be a point estimate for what that would be, and to estimate it more reliably we would have to do a much bigger study basically. Is that right?

DR. ANDREASON: That is right.

DR. GOODMAN: Dr. Pollock?

DR. POLLOCK: A further question about

that, does the risk of contact sensitization--obviously one part is dose related, the other is time. When you go beyond six weeks, even if they are at the same dose or a lower dose, does the risk go up? I mean, do your dermatological colleagues have any comment on that? Is it a time phenomenon as well?

DR. ANDREASON: I don't have any particular data on that but, if my memory serves me right from my dermatology rotation those types of things happen within the first three months and then the risk drops off over time. I would be willing to change that if a dermatologist told me otherwise. That is the way I remember it.

DR. POLLOCK: Probably in an acute period of at least 12 weeks for the maximal risk.

DR. ANDREASON: That is what I would guess but I would have to look that up.

DR. GOODMAN: Before we turn to the

questions before the committee and discussion leading up to a vote, I wanted to ask for some clarification, particularly from Dr. Levin and others in the FDA. I want to make sure I can reconcile some of the statements or conclusions that were drawn in the executive summary with what seemed to me a somewhat different set of conclusions or different overall recommendation presented to us this morning. So, if you will allow me, I would like to turn to the clinical review that we should all have that was written on June 28, 2005. If you turn to page 5, it starts off, "I recommend that the Division take a non-approvable action for NDA 25-514." Go down a bit "...was associated with an adverse event profile and potential risk that could pose clinically important risk to a significant number of pediatric patients who might be exposed to MTS." Again I am skipping "...these adverse events were more significantly common in the MTS group than the active comparator compared outcome the placebo group."

Usually when I see that word "significant" I am assuming that is statistical significance but that is no longer clear to me after having seen

some of the data presented today. I will give you a chance to respond but I just want to finish going through a couple more of these points.

In addition, "treatment with MTS was associated with a relatively high risk of developing tic disorder compared to the active comparator, Concerta." Also, "MTS was associated with"--again the word--"significant degree of dermal signs and symptoms at the patch application." Other reasons--these are all side effect reasons--"the subjects experienced unacceptable incidence of insomnia, anorexia, significant weight loss in the short run." That is more based upon earlier trials I think.

Turning to page 8 and study 302, "in cases of tic disorder a proportion of subjects with these adverse events in the MTS group exceeded that of the Concerta group."

Finally, on page 10, "in study 303

insomnia was reported for 8 percent and 5 percent in the Concerta and placebo groups respectively. In my opinion, the proportion of subjects in the MTS group who had insomnia was significant, especially compared to proportions in the Concerta and placebo groups."

If we could kind of take those one at a time and see whether you would change your conclusions at this point, or the way you might word some of these, starting with the initial recommendation which was that you would take a non-approvable action. As we heard this morning, that is a different recommendation.

DR. LEVIN: One of the main reasons for changing my recommendation is because of reviewing the data further and having more data available. I do certainly have concerns about safety and the adverse events that you mentioned, insomnia, anorexia, weight loss, potential skin sensitization. One of the reasons I have changed my thinking is that it is clear that almost all these, if not all other than the skin

sensitization, adverse events are consistent with those labeled for other methylphenidate products. So, there is really no new or unexpected finding, other than the skin sensitization. Also, even though I did say significantly different than Concerta, it was not a statistical difference; it was an impression.

DR. GOODMAN: So, would you correct that now to say numerical?

DR. LEVIN: Yes.

DR. GOODMAN: Numerical differences and not use the word "significant?"

DR. LEVIN: Yes, definitely. Upon further review, I don't think it is a widely different range of adverse events between those two groups, except for tic disorder which is concerning but, again, it is a known adverse event associated with methylphenidate treatment in this population.

DR. GOODMAN: Could you stay with that point for a moment? Upon hearing some more details this morning--and I will see what the other members of the panel think--I wasn't convinced that all

those mapped onto tics. Some of them sounded like buccofacial dyskinesia. But you would still interpret this to say an N of seven in one of those studies has tics?

DR. LEVIN: I agree that some of them seem to be clearly dyskinesia or consistent with dyskinesia rather than tic, maybe one-third at least, roughly, which is still a concern but I think, again, it is something that is a known adverse event with methylphenidate treatment.

One particular example with insomnia, there is still what I would say is a considerable proportion of patients with insomnia. However, when the sponsor did as we suggested or recommended and used the specific sleep rating scale there was no difference in sleep quality or sleep habits compared to Concerta or placebo. In fact, actually there was improvement in sleep among all groups.

Another reason for changing my conclusion is that although there were adverse events to be concerned about, recently in our Division we have discussed a recent analysis that shows that a lot

of the adverse events tend to happen early in treatment and there appears to be a threshold effect, which I think the sponsor has mentioned earlier today.

In the big picture, again, there were no deaths in the studies, no serious adverse events and relatively few discontinuations due to adverse events. Although I do have concerns about some safety issues and logistical concerns such as applying and removing the patch, I think it is a reasonably safe treatment in this population, with a need probably for changing or suggesting changes in labeling for the most safe and effective use of the treatment.

DR. GOODMAN: Other comments from the committee members along these lines? Maybe I am the only one struck with it, but there was a disparity between what I saw as the written recommendations level of concern and what we heard this morning. In fact, that was also reflected in the media's take on this. If you look at the "Wall Street Journal," they had an article based upon

having read the briefing documents that, from a cursory reading, would indicate that the FDA was recommending non-approval, which is consistent with what this executive summary is.

It is fine for you to change your mind. I want to make sure that we agree with your changes and not with what your previous statement was. I want to make sure that as a committee we agree with your final conclusions, as well as address the process. Dr. Temple?

DR. TEMPLE: You need to do that, but everybody should know that if we reached a full and final conclusion within the Division we ordinarily wouldn't bring it to you to ask you a question because that would be sort of wasting your time. So, the fact that we did means that there wasn't full agreement that that initial view was right, and this won't be the first time people have changed their mind along the way as they got more data and looked at other things. So, we consider this just ordinary part of the process. We don't always agree with each other and committees don't

always agree with us, and that is fine.

DR. GOODMAN: Dr. Pine?

DR. PINE: Jut to echo some of the things that Dr. Goodman just said, you know, on the one hand, I too was struck by the fact that when you read the summary it says not approvable here but then when you present orally it is approvable, on the one hand.

On the other hand, I did have a little bit of a sense as I read the document that when you looked at the actual data that was informing that conclusion, you know, the data seemed kind of on the fence a little bit. I guess I was more struck by the conviction of the non-approvable statement which I interpreted, particularly now with what Dr. Temple said, as maybe your initial take on the data after you looked at it, which did not seem to be a slam-dunk just based on the fact that while the rates of the side effects were higher, they weren't dramatically higher and not even statistically higher. So, I guess overall looking at the document and listening to the presentation I don't

think there is quite as striking a disconnect.

DR. GOODMAN: Anyone else? Dr. Leon?

DR. LEON: I have an unrelated question for the sponsor, but given that the analog classroom was used, it would really invite opportunity for site differences. I haven't heard anything about how site was controlled for, especially with 34 sites or whatever that number was in either of these trials.

DR. PRATT: The analog classroom was only conducted at four sites. Dr. Wigal maybe should come up here to help a little bit in terms of how we actually standardized and dealt with those initial training sessions for everybody.

DR. LEON: Before we hear about standardization, could you tell me how in the statistical model site was accounted for, and what the magnitude of the site differences might have been?

DR. PRATT: Dr. Davidson, would you come up and address that?

DR. DAVIDSON: We recognize that, based

upon the ICH-E9 guidance, it is very difficult to look at center in a model that is evaluating a treatment effect. Therefore, we did not include center in the model, nor did we look at a treatment by center interaction.

DR. LEON: Although it wasn't included in the model, did you look at SKAMP scores separately for each site, and can you show us that slide--SKAMP change scores?

DR. PRATT: I would have to get that from the study report. We did look at the individual sites just to make sure there was consistency across the way but, again, there was variability in the number of subjects that were enrolled in each site so the pooled data for the four sites that we used are much stronger. I don't have a slide that actually shows the individual SKAMP data. I would have to pull that up out of the study reports that we submitted to the FDA. We could look at it later on but, as I recall, from looking at it there were consistent effects in all of the sites and, again, we did standardize the training and observations

which I think is important in this type of a multi-center study.

Questions to the Committee

DR. GOODMAN: Actually, I am not sure you need to. Is there a feeling that we need to go into detail about the standardization procedures? I think we can trust that that was done carefully, systematically.

Let's turn to the questions. We have those on a slide. Tom, did you want me just to go ahead and read the questions, or any clarification from you and charge to the committee?

DR. LAUGHREN: They are very standard questions about safety and efficacy.

DR. GOODMAN: It will require a vote on both. Has the methylphenidate transdermal system been shown to be effective for the treatment of attention deficit hyperactivity disorder?

The second one is has the methylphenidate transdermal system been shown to be acceptably safe in the treatment of ADHD?

When you say acceptably safe, is that a

qualifier or is that standard language?

DR. LAUGHREN: Within the usual meaning, as labeled, is the drug safe as it is intended to be used for the population for which it is intended to be used as proposed in labeling?

The other thing I want to add here is these are the standard questions. As a committee, you can add additional issues that you can discuss or vote on if you want.

DR. GOODMAN: Yes, I have done that before. I have no problem.

[Laughter]

DR. TEMPLE: Terms like acceptably safe are used because we all know that no drug is free of adverse effects. So, it usually implies some benefit/risk consideration.

DR. GOODMAN: Dr. Wang?

DR. WANG: Actually, in terms of clarifying these questions, I was wondering--it is an earlier point that came up--what the possible FDA actions are here because that will obviously inform us what the questions are, maybe some

additional supplemental questions. Specifically, is one possibility approvable but in a restricted population, those who failed oral agents? Because we are all struggling with whether in the general population of ADHD patients there are some disadvantages of this patch--desensitization, the two-hour late until onset, it takes an adult to take it off. Meanwhile, it looks like it is unequivocally advantageous in the population that can't take an oral agent.

DR. LAUGHREN: Certainly, it is possible for us to restrict a drug to a particular part of the population. Although it is somewhat unusual for us to do that, it is possible and you can advise us on that if you think that there are concerns about this drug that would lead you in that direction. But it is unusual for us to limit a drug to a particular part of the population.

DR. GOODMAN: I think that is a useful segway for us to have a discussion among ourselves, starting with the advantages of the compound and the formulation. I wonder if we could do that. I

think some of them are obvious in terms of adherence; in terms of duration of action, although I have a question that I want to pose to the committee about the advantages of duration of action or delivery over existing extended release compounds. But perhaps we can hear from members around the table in terms of what they see as the advantages or niche where clinicians might be most likely to use this compound. Jean?

MS. BRONSTEIN: I think it is really clear that there is a group of patients for whom a transdermal patch is going to be better because they don't have to swallow a pill. So, that one is pretty clear.

I personally think that the removal issue is not going to be as difficult as some folks think it is. I have been a working mother my whole life and a working grandmother and my experience in child-care settings of different kinds that I have used or that I am aware of employees of mine using, I don't think that it is going to be difficult to get this thing removed provided there is

child-care. I think if it is truly a latch key kid who doesn't have anybody that they go home to, and I doubt that that is going to happen with an ADHD child, I think that the removal isn't going to be bad because you can destroy it. I think the problem would be more difficult if it couldn't be just pitched. That is my view.

DR. GOODMAN: Thank you. Dr. Robinson?

DR. ROBINSON: Well, I understand that, yes, the parent can put it on, but the flip side is it also means this thing is very easy to take off. So, the kids, either the patient or other kids at school, etc., they can take this thing off. It is not rocket science. So, in some ways you may have different subgroups. You know, we have made the assumption that it is all going to increase adherence. It may for subgroups actually have worse adherence than having them take a liquid or a pill where if they get it down they can't get it up as easily as this thing can be just taken off as soon as you get to school.

MS. BRONSTEIN: On the other hand, we saw

from the data that this works and it can really be seen when it doesn't work. So, if you have a non-compliant kid who takes it off and you still have all the problems as a parent, what do you do? You switch to a drug that they can't take off. So, I think in that way it is kind of not as big a deal.

Now, from the abuse standpoint there is another issue. Although I did play with this silly thing and I tried to put it back on and held it in place pretty firmly, it didn't work really well. I have a lot of dry epithelial cells.

[Laughter]

DR. GOODMAN: Other comments along these lines of adherence? On first blush, that is one of the advantages but now Dr. Robinson has raised a question that there might actually be in some cases decreased adherence because it can be removed.

[No response]

No one else wants to weigh in on this issue? Good.

MS. DOKKEN: I just had a quick comment

related I suppose to adherence but also reality. Because of the two-hour time frame and, at least in this particular geographic area, middle school kids can start school as early as 7:15, 7:20 but that means they have to get on a bus before that. So, I am trying to imagine do parents, you know, creep in at 5:00 a.m. because that age group isn't going to get up extra early.

DR. ANDREASON: My youngest child is now 18 and I have been through that with all of them. She is the one that takes the methylphenidate and getting her up in the morning is not getting any easier. But I imagine one could go in and apply the patch as a way of getting them up in the morning because at that time in the morning either my wife's or my hands are very cold!

[Laughter]

DR. GOODMAN: Let's stay with this issue of practicality. The laboratory classroom certainly seemed to emulate ideal conditions. If I recall correctly, you affixed it at 7:30 and you didn't start class until 9:30. Is that correct?

So, it was designed so it was two hours afterwards. What we are talking about is how practical will it be to affix it two hours before they are actually making it to class. Normally it is not 9:30 that you are starting class; it is more likely to be eight o'clock in the morning. Do you want to respond to that?

DR. PRATT: I think that, again, the first assessment period that was conducted in the classroom setting where we actually examined the behavioral effects was conducted at the two-hour period. In the outpatient clinic setting there was no classroom and it was applied in the morning and children went along their usual day. We did conduct this during the school year. This was not conducted during a summer holiday when you might expect that there would be a little bit more variability and flexibility. Again, we didn't collect information but the teachers scale that was conducted--we sent these to all the kids and had their teachers participating and actually sending it back in. The 11:00 a.m. assessment basically

covered the morning classes. The afternoon assessment covered the afternoon classes. We tried to look at them and the overall assessments that we got from the teachers was that the teachers noticed that these children were behaving better when they were either on MTS on the Concerta arm of the study compared to the patients who were in the placebo arm in the study. So, I think that is the key in terms of the school day, as supported by some of the teachers rating scales that we used.

DR. GOODMAN: Dr. Pine?

DR. PINE: Again, just speaking globally to this issue and at least for now leaving totally aside the question of safety and, again, speaking as a clinician, number one, it looks pretty clear that efficacy data are fine in terms of what we saw, at least to me when I look at the data, number one.

Then, number two, I also think it is pretty clear that there would be a need for a transdermal stimulant medication, and that there is a reasonable number of children that are

encountered for whom taking pills is just not an easy option. Again just to weigh in on this, it seems to me, again as a clinician, pretty straightforward that the need is there and that the efficacy data at least support it.

DR. GOODMAN: Let me stay with that for a moment. How do you see the advantage of this formulation over current long-acting orally administered medications? I would also like input from the other members of the committee.

DR. PINE: In particular for kids who cannot swallow pills, long-acting preparations are not an option because they must be swallowed. You cannot grind them up; you cannot dissolve them; you cannot put them in apple sauce. So, for kids who cannot take pills, the current option now is you give chewable, or you give liquid, or you grind it up, or you do something like that. And, some kids who will not swallow will do that; other kids will not do that. They just say it tastes too nasty. They don't want something in their mouth, whatever. They are just not going to do that.

DR. GOODMAN: Let me just clarify for the purposes of people that might be in the audience and not understanding this. The reason you can't

crush or dissolve it is because then you defeat the purpose of the long-acting formulation. Is that correct? Is that what you are saying?

DR. PINE: That is correct.

DR. GOODMAN: Dr. Malone?

DR. MALONE: Actually, the child rep. always comes to my office and says you can take the capsule apart--and we have Shire here--you can put the capsule apart and put it in apple sauce and it is the long-acting formulation.

DR. GOODMAN: Is that an FDA-approved delivery method?

DR. MALONE: I think it is in the insert.

DR. LAUGHREN: Yes, there are different kinds of long-acting formulations. Some can be handled that way; others cannot. It depends on the particular long-acting mechanism.

DR. GOODMAN: But with Concerta you could.

DR. MALONE: But I would like to say there

are other possible advantages for having a patch, like the control you have over when you are going to end the medication effect is there with the patch but not with the pill. Once you take a pill you are going to have to go through the whole action of the pill. If you had a child who had various times where you wanted to end medication effect during the day, you can control that by taking the patch off. For instance, if you had a child who had a lot of anorexia but needed a longer-acting medicine on some days you could leave the patch on, but if you are trying to get them to gain weight you could take the patch off earlier on those given days. So, even though they are talking about it for people who won't take pills, they also mentioned, and it is true, probably a bigger advantage is the control of the length of action that the drug would have.

DR. GOODMAN: Dr. Pfeffer?

DR. PFEFFER: I also agree with both Dr. Pine and Dr. Malone. I just want to add that I think in medicine if we have various potentials for

administering medicine, even if just two children additionally are able to use this where they couldn't take medicine before, I think that is a potential gain.

But one other issue is that some children who might have other conditions, let's say medical conditions where they take medications that may disrupt their GI tract in some way, and then if one needed to also administer a stimulant, that might inhibit the effects of the stimulant. So, this route that avoids that approach may have very great value for certain children with certain medical conditions who might require a stimulant. So, it does add to the armamentarium.

DR. GOODMAN: I am not sure I understood your last point.

DR. PFEFFER: The last point is let's assume, for example, a child with ADHD, a simple example, has a bacterial infection and is taking an antibiotic which will disrupt the flora of the GI tract. It may also then disrupt the use of stimulant medicine if a child is taking that as an

oral medication. By using a patch format that avoids that issue and the child gets the appropriate dose of medication. Now, that is a simple example and that is an acute example, but there may be other children who have, fore example, other GI tract problems--Crohn's disease, ulcerative colitis--who have ADHD and this may be a way also of administering a medication in a way which avoids disrupting the other problem.

DR. GOODMAN: Dr. Malone?

DR. MALONE: Are we still able to ask questions about--

DR. GOODMAN: You can ask any questions you want.

DR. MALONE: It has been mentioned that there are other patch forms of medications. For instance, clonidine has been used in child psychiatry. It is not labeled for that. But of these patch medications that get used, how many of them really cause desensitization and you have to stop taking the drug and never take that drug again? Is that even reported or has it become an

issue?

DR. TEMPLE: I can't actually think of it having come up often. It is hard to imagine that it wouldn't happen sometimes. On the other hand, for a lot of drugs if you couldn't take them again, you would take something else and it wouldn't be such a big deal. Maybe it is a bigger deal here if that happens, but it doesn't seem to happen very often.

DR. GOODMAN: Is the group satisfied with the data they have seen today on efficacy to come to a vote on that first question? Any further discussion? Dr. Temple?

DR. TEMPLE: I just wanted to mention that to the extent there is anything about efficacy that people need to be reminded of, that would go in the labeling. For example, if you don't really expect an effect for two hours, that will be prominently placed so that people will factor that in, and anything else of that nature that is important. Labeling would include those things. If you have thoughts about what to include, you should probably

tell us.

DR. GOODMAN: Yes, we will be glad to do that. I still think we are going to have considerable discussion about number two. I want to get through 50 percent of our questions if we are ready to take a vote. Dr. Leon?

DR. LEON: How will the label deal with the different doses when there is not comparative data on the different doses? I mean, right now it has all been pooled.

DR. TEMPLE: Well, it is a good question but it is not unusual. More and more drugs are being studied in these titration designs that give you no good information about the individual doses. You describe what you have and you put your areas of uncertainty in there. We sort of argue about it probably with ourselves and the company.

DR. GOODMAN: So, let's turn to a vote on question number one on the efficacy of the MTS. I would like to start with Dr. Mehta, whose vote doesn't officially count but it counts a great deal in my mind.

DR. MEHTA: Thank you, again. I would vote yes for efficacy, mainly because you can stop the effect of the drug within a couple of hours if

you want to do it, that is, by taking it off. Secondly, the number of children with GI diseases where absorption would be affected when you give it orally. My last comment is that in this particular NDA I don't even know why efficacy studies were done because it is the same formulation, same dosage and the same number of time points that you are observing. So, from the previous NDA one could have assumed that there is efficacy so there is no reason to do efficacy studies in this NDA.

DR. GOODMAN: Dr. Pollock?

DR. POLLOCK: I would vote yes for efficacy.

DR. GOODMAN: Dr. Wells?

DR. WELLS: Yes for efficacy.

DR. GOODMAN: Dr. Leon?

DR. LEON: I vote yes for efficacy.

DR. GOODMAN: Dr. Pfeffer?

DR. PFEFFER: I vote yes for efficacy.

DR. GOODMAN: Dr. Malone??

DR. MALONE: I vote yes for efficacy.

DR. GOODMAN: Deborah Dokken?

MS. DOKKEN: Yes.

DR. GOODMAN: I am voting yes for efficacy.

DR. GELLER: Yes.

DR. WANG: Yes.

MS. BRONSTEIN: Yes.

DR. ROBINSON: Yes.

DR. PINE: Yes.

DR. GOODMAN: Let's tally that up! It is a unanimous vote in favor of efficacy. No surprises there.

Before we take a vote on number two let's return to some of the issues that came up about safety concerns. Some of the ones that I have on my list have to do with the sensitivity issue. We spent a lot of time on it but I want to see if we could review what the salient concerns are. However, the vote turns out, I am going to say that this is an area that needs some post-marketing

surveillance. I am not sure exactly how to design that kind of study but I think one of the problems troubling us is that we are having a hard time estimating the risk.

On one hand, we have data from adults which was really more of a toxicology study than it was clearly reflecting what we might experience in clinical practice. I think Dr. Pine expressed it very well earlier. It is very hard to extrapolate from those data in terms of what the risk is going to be when you use it as prescribed.

I am glad we had the clarification. Jean Bronstein, you made us go through that and I didn't appreciate the first time around that there was one case where rechallenge with oral administration did not seem advisable. I am not sure whether from that we can estimate some risk. Let me pose that as a question for the FDA group. Based upon that one case, do you have an estimated percentage of risk of sensitivity? I am not sure what the denominator is. What was it, 300?

DR. LAUGHREN: We will have to think about

how to define the denominator and we are going to talk with our own dermatology consultants. The issue is how long would one need to be exposed to have a risk of having sensitization, and does that differ from one type of drug to another? But, you know, we have one case. That is not a lot from which to get a good point estimate.

But just in terms of the other part of your question about what one might do post-marketing, there are lots of things one could do, ranging all the way from asking the sponsor to submit, in an expedited manner, any reports of sensitization to doing something more formally, looking at a cohort to see if we can estimate what the incidence is. There are a number of epidemiologic type studies that one might do to try and get a better fix on that and we can have discussions with the company and get a commitment to do that post-marketing.

DR. GOODMAN: I will get to you in a second, Dr. Pine. I just want to clarify for the rest of the members, not just around the table. I

don't think it is that we are concerned about allergic reaction or high rate of allergic reaction; we are concerned about the implications of developing sensitivity, specifically that if somehow there is an increased risk of inducing sensitivity to methylphenidate by the patch, then it is going to deprive these individuals of future exposure to methylphenidate and that will then influence your clinical decision-making. Once you know what that risk is, where do you start? Do you start with the oral or start with the transdermal? And, the concern might be don't start with the transdermal because then you might eliminate one of your most important options in a small group of patients. Dr. Pine?

DR. PINE: I wanted to ask either Dr. Wang or Dr. Leon if we were to take 1/400 as a point estimate, kind of like a pilot study, if you were to calculate a confidence interval given that we got 1/400 in this one study, obviously the lower bound would be zero, how high would that go? I mean, are we talking 10? Are we talking 20?

DR. WANG: The rule of thumb I think is 3 over N as the upper bound, if I remember correctly.

DR. PINE: That is if there are no cases.

The confidence interval obviously would be zero because there is only one case. I was wondering what the upper bound--

DR. WANG: If you have one case?

DR. PINE: If you have one case out of 400. I mean, is it about 10?

DR. TEMPLE: You want the upper bound for how high the rate should be.

DR. LEON: If you want to go through the math of variance of a binomial so 1/300 or 1/400 times 299/300 and you get the square root of that and multiply it by 1.96. It is not going to be very big but I don't think there is a lot of data even to base this discussion on.

DR. POLLOCK: But the exposure period is only--I mean, assuming that Dr. Andreason's initial estimate that you need 12 weeks and this is 6 weeks, you know, we might need a longer exposure period for that group of 300 or 400.

DR. PINE: But it is not likely to be real high. Right?

DR. LEON: I think I would rather be quoted as saying the data is inadequate to make that estimate.

DR. TEMPLE: Right, but even from that one

the chance could be as high as one percent and I am sure it is going to turn out that way. So, that might be something to think about.

DR. LAUGHREN: If there were no cases the upper bound would be one percent out of 300, 3 over N. With one case it is going to be something bigger than one percent. I don't know exactly where it is going to fall but it could be a pretty good sized number.

DR. GOODMAN: Dr. Pfeffer?

DR. PFEFFER: I have a question that maybe can be clarified again by Shire. That is, you mentioned that the most side effects, adverse effects, seemed to be early on. I wasn't quite sure how you got that and maybe you could re-explain it. My concern is as follows, as a

clinician if I needed to tell a parent to watch for things and if I told the parent, well, we would expect that if we are going to see adverse events it will be early on, and I am still not sure that is a clear statement given the data. For example, in the two controlled studies there was an escalating dose first of all, and then there was really only one day [sic] on the medication in the first study when you reached peak, maybe two weeks in both studies when you reached the right dose that the child would be on, first of all.

Then, in the long term with longer duration of exposure it almost seems counter-intuitive that there would not be continuation of potential adverse effects. So, I would like to have it clarified a little bit more.

DR. PRATT: Sure, I would be happy to try to clarify that.

DR. PFEFFER: Thank you.

DR. PRATT: First of all, in the two studies, the 201 and the classroom study there was a 5-week dose escalation period, open-label, and

then 2-weeks double-blind in which patients who had reached their level were then continued at that level and then were crossed over.

In the large pivotal study it was again a 5-week dose escalation. When you start looking at when do these adverse events occur--do they occur predominantly at the same rate across all the weeks that you are there? I don't have the distributions. It is very nice when you actually sit there and you look at, you know, at what visit do you see the adverse events occurring. You see that the majority of them in our MTS studies occurred during the first one week, two weeks, three weeks of visits when you are starting to titrate up. You don't get additional recruitment in the last four or five weeks because patients are already moving up or they have reached their optimization period and they are staying along the way there. There are always a couple of additional adverse events that come in as you bring up the dose so that at week four, if you get somebody at the highest dose level size, they may have an

adverse event that occurs along the way.

So, when we talk about early in therapy, particularly clinically, when you are in the process of finding the optimal dose and figuring out where the child is, that is when the majority of events occur. We see this, again, in our open-label studies where when you are titrating back up from patients who come in from the previous studies, whether they are on placebo or whatever other arm they were in, and they re-titrate back up you can sometimes see an increased number of events in those people who were in the placebo group along the way. But as they stay on, they tolerate to the effects and these effects tend to go away. Some of them do persist and some of them do come up at various times along the way, but the majority of them, again, occur early in the course of titration.

DR. PFEFFER: Do you have any data on the differential effects of early versus later, especially as you just mentioned that there may be some adverse effects a little bit later as the

child is on a dose that is the best dose?

DR. PRATT: Typically with the stimulants, and with our MTS system in particular, the typical ones that you see coming on early are the ones that are related to methylphenidate so you get, again, typically some insomnia early. It can occur at any time you change the dosing. We haven't really done numbers there but when you just look at the distribution it is shifted to the early part of the titration scheme rather than, you know, having additional recruitment as you get higher up and the longer you are on therapy. So, I hope that clarified your point. Thank you.

DR. GOODMAN: Dr. Pine?

DR. PINE: This might be more of a dermatological question for Dr. Andreason and you might not be able to answer it, but I am also a little concerned about this issue of the clinician in the field who is going to see a skin reaction and they are trying to tell the difference between just a non-specific erythema versus the development of sensitization. Would it be the case that if I

am a clinician in the field and I give a child the patch and they develop erythema and I am not sure if this is sensitization or just erythema, and I took the patch off and I gave the child a test dose of oral methylphenidate and nothing happened, would it be such that then I could conclude that, you know, this was not a sensitization but this was just a non-specific reaction?

DR. ANDREASON: I will defer. I am not a dermatologist by any stretch of the imagination but I can read to you the labeling that they suggest.

DR. GOODMAN: That would be useful. I think the erythema is not enough. It seems reasonable that there needs to be some qualitative differences in that dermatological reaction to be truly concerned.

DR. PINE: But just for a clinician in the community, I mean, how comfortable would you be that people are going to reliably going to be able to tell the difference?

DR. GOODMAN: I am not so worried about the clinician as I am about the parents. I think

most clinicians can tell the difference between erythema and urticaria. You know, I think they can make that diagnosis. But I agree in terms of the early warning system. I think getting the caregivers to recognize the difference is more of a challenge.

DR. TEMPLE: People would certainly need to be apprised about the different implications of those two things, which I think would not be obvious to everybody. So, that is a labeling challenge to make sure that they know what you do. Otherwise, you get the very thing you are worried about, namely, making ten percent of the population unfit for methylphenidate.

DR. GOODMAN: Dr. Geller?

DR. GELLER: I just want to take what Dr. Pine is saying a little further. Ordinarily, once the kids are on the medication and have the good effect they are seen very infrequently in practice, and I am thinking that for families who can't really differentiate it could be weeks or even months before a clinician would look at the area

again. So, that might be something that will have to be taken into account.

DR. ANDREASON: I think the erythema was fairly common in the clinical trial. Contact sensitization would probably get worse and have some blistering. Let me read to you the section that they suggest under contact sensitization, and this would be in a warning section: Use of--and then trade mark--should be discontinued of contact sensitization is suspected. Patients sensitized from use of this, as evidenced by development of an allergic contact dermatitis may experience systemic contact dermatitis, and in parentheses, systemic eczematous reaction, parentheses closed, or other systemic reactions if methylphenidate or related drugs are taken via other routes, e.g., orally. This would be in bold. Individuals who develop contact sensitization to--trade mark--should avoid exposure to methylphenidate and related drugs in other dosage forms. This would be the operative instruction here, diagnosis of allergic contact dermatitis should be corroborated by appropriate

diagnostic testing.

DR. GOODMAN: What do they mean by diagnostic testing? A clinician looking--

DR. ANDREASON: Skin testing.

DR. GOODMAN: Skin testing?

DR. ANDREASON: Yes, that is what they usually have done in the past.

DR. POLLOCK: What are related drugs?

DR. ANDREASON: What are the related drugs? Anything containing methylphenidate.

DR. POLLOCK: It says methylphenidate or other related drugs. So, are we talking about something structurally similar in some way?

DR. ANDREASON: Methylphenidate, dex-methylphenidate. I would have to ask them but I don't think that they imply amphetamine.

DR. TEMPLE: It has to be fixed, that whole section has to be fixed. It doesn't tell a person who is not a dermatologist what to do.

DR. GOODMAN: Dr. Malone?

DR. MALONE: I think Dr. Temple just settled that. I was going to say both as a

clinician and as a parent what it means so I wouldn't know what to do.

DR. GOODMAN: Deborah?

MS. DOKKEN: I was searching through our two notebooks. Do we have a copy of the insert, and is there a patient or parent piece like there sometimes is?

DR. LAUGHREN: There is in what the sponsor has proposed. It wasn't in your package but it is something that obviously we will spend a lot of time thinking about.

MS. DOKKEN: Well, it would be easier for us to comment on it if we knew what was already there. I am particularly concerned about the consumer piece.

DR. LAUGHREN: You are certainly, again, free to give us advice about what you think needs to go in there.

DR. TEMPLE: We have a long history of finding that it takes a very long time to go through the exact words of labeling. It doesn't mean we couldn't send it to you later.

DR. GOODMAN: Could the sponsor remind us what the incidence was of erythema at the patch site in your studies?

DR. PRATT: Sure. At the patch site about 50-55 percent experienced either minimal or definite erythema.

DR. GOODMAN: So, you could have a lot of false positives by parents or kids that they are having allergic reactions.

DR. PRATT: Again, this was at the site at the time that it was evaluated. If it is a persisting problem that persists after they take the patch off and it is not going away, is becoming urticarial or having even some edema or vesiculation occurring there, those are the types of things that would bring them to the attention not only of the pediatrician but perhaps a dermatologist who would be able to recognize this type of reactivity.

DR. GOODMAN: Dr. Malone?

DR. MALONE: Do you ever include pictures? If you had a picture of urticaria--I mean, if you

had various pictures, two of them, one just redness and one of an allergic reaction, it would do more than all these words I think.

DR. GOODMAN: Dr. Leon?

DR. LEON: I am confused about what is being discussed. Can someone clarify this? Have I heard that some patients will develop a sensitivity to the oral administration? If initially they have the patch on, they will develop sensitivity to oral administration and that is a sensitivity they wouldn't have had if they started with the oral? It is something that can't be tested empirically, I don't think.

DR. GOODMAN: That is the concern. The concern is not an acute allergic reaction. It is of the patch inducing sensitivity to methylphenidate in any form.

DR. LEON: How do we know that they wouldn't have had the sensitivity with the oral administration in the first place had they not had the patch? We don't know that. DR. GOODMAN: That is a good point. That is correct.

DR. LEON: That is my question.

DR. GOODMAN: And it is conceivable that they could have developed that sensitivity in

response to repeated oral exposure. It is beginning to come back to me, I think that probably is a different phenomenon being induced through the skin.

DR. PINE: And it is not one in 400.

DR. TEMPLE: Skin is a good way to sensitize people to things. So, it is probably more common, not that you couldn't do it orally.

DR. POLLOCK: Especially if you have a pharmacologically irritating agent.

DR. GOODMAN: What I would actually like to do, I would like to circle back on this before we take a vote but I would like to cover some of the other ones that may be easier to resolve, some of the other concerns that came up. Let me doing it by the different symptoms. Let's start with tics. When I saw the data earlier and the actual verbatim descriptions I wasn't convinced many of those were bona fide tics. They sounded more like

dyskinesia. I think though that we should have some discussion about the issue of stimulants inducing tics. It has been a while since I have reviewed that literature. It continues to be controversial. I think we saw a very nice evidence-based slide that was a nice review of the literature. I think really the bigger concern has been not so much transient induction of tics, but inducing, and irreversibly inducing tics, and if others around the table could help me in terms of where that stands.

A related question, and I didn't hear this answered this morning, is I assume that you assessed for tics at baseline. Can you say anything about how many of those patients where tic-like movements were induced already had a preexisting tick disorder?

DR. PRATT: Actually, the patients who had a diagnosis of Tourette syndrome were excluded from participation in this study. We did not particularly assess previous history of tic disorder or exclude patients who might have had an

occasional tic that was present. So, it was not part of the inclusion criteria to examine a history of a previous tic disorder.

DR. GOODMAN: And did you exclude chronic multiple motor tics?

DR. PRATT: The investigator was free to exclude patients. We didn't enroll anybody that had tics that were present at baseline.

DR. GOODMAN: But what you are saying is that you didn't exclude ones that might have had a history, but these are young kids. Are there other comments on this issue?

DR. POLLOCK: Just a diagnostic nuance, dyskinetic movement induced by the medication--why do you think that is better? Because it is transient? I am asking.

DR. GOODMAN: I don't know if it is better or not, but I think it probably signifies less specificity and stimulants often induce a range of dyskinetic hyperkinetic movements that don't indicate that you have unmasked or exacerbated an underlying condition of TS, Tourette syndrome, or

another chronic multiple tic disorder. So, I think it is less specific. I don't know if others can weigh in on this. Dr. Pine and Dr. Malone.

DR. MALONE: I think it is safer to call them involuntary abnormal movements because there is always an argument about whether it is a tic, dyskinesia or stereotypy. I think that actually amphetamines are the drugs that are used in the animal model for inducing stereotypic, or whatever you want to call it, behaviors in rats and other animals. So, it is not surprising that in clinical use you do get some incidence of tics. I don't think there is clear evidence that you will develop--you can induce abnormal movements in animals by giving the right dose of these drugs. You probably could induce tics in most people, or many people, but as far as permanent, irreversible movements in patients who develop them, I think most people think that they probably had an underlying propensity that allowed them to then go on to have permanent abnormal movements.

DR. GOODMAN: Dr. Pine?

DR. PINE: I would actually be interested to hear what some of the officials say about labeling, but as far as kind of clinical practice,

as was said in the presentation by the sponsors, clinically tics are not a contraindication for stimulant use. Stimulants are used in kids with tics, number one.

Number two, I think most clinicians and clinical research as well shows that, without question, psychostimulant medications can worsen tics, no question.

Number three, it is also very clear that it is not uncommon--you know, less than 10 percent but not that much less--to see in kids given stimulants the first spontaneous occurrence of a tic. So, that is not that uncommon a situation.

Last of all, whether you ever see the permanent occurrence of a tick following the use of stimulants, that has been a very controversial topic. In the late '70s and early '80s there was a lot of concern that that was, indeed, the case and that concern has waned but it has not gone, and it

is one of those situations where you can't really prove a negative. So, my take on the data, actually before the presentation, was that, you know, 7/100 is not that far out of line from what I would expect.

DR. GOODMAN: But the question is versus the comparator. That is really the question. We are not surprised to see it but, again, on an initial reading of the summary there is a suggestion that it was more than you might expect.

DR. PINE: But when asked, Dr. Levin said it was not statistically different. Right? That the rate of tics was not statistically significant in the MTS versus the Concerta. Right?

DR. GOODMAN: Dr. Malone?

DR. MALONE: I know that the sponsor has shown some of this but before the meeting I did pull some articles to look at incidence of side effects because we really only had one comparator. Actually, one of the articles was I think once daily oral, which I think was Concerta, but I looked at this last night and something like six

percent of the patients--I think it was an open long-term study, but six percent who never had tics developed them on Concerta in this study. So, I think if you look at a variety of studies you always get a different estimate of how many people develop tics from stimulants. That has been part of the whole controversy of trying to decide whether stimulants cause permanent tics in people, because every study gets slightly different numbers. So, the numbers from this trial, for me at least, were within the range that could occur with stimulant medications.

DR. GOODMAN: So, to summarize, one expects with stimulant medications in an ADHD population to see the induction or masking or exacerbation of involuntary movements which may represent tics, and that you do not see any evidence that the rate seen with the MTS system is significantly higher than an active comparator. Is that a fair statement? Can we move on from tics then?

How about insomnia? We divided that up a

little bit differently, problems of sleep and insomnia. It wouldn't hurt if you could show that slide. One of you did a very nice presentation going by organ system or group of the different side effects. If we could just have that slide up there? You had one on effects on sleep.

DR. PRATT: In terms of the persistence of insomnia?

DR. GOODMAN: You had it divided in terms of incidence, duration.

DR. PRATT: Yes. Is this the one you want?

DR. GOODMAN: Well, we can do without it for the moment.

DR. PRATT: It will be one second. Is this the one you were referring to, Dr. Goodman?

DR. GOODMAN: Yes. Nothing there. How about anorexia and weight loss? Maybe you can put up the corresponding slides for us to look at.

DR. PRATT: Yes, this one for anorexia, and then, again, weight loss reported as an adverse event.

DR. GOODMAN: Thank you. Any discussion about those side effects and whether we have any concerns about the medication under review compared

to active comparator? No? All right, any other safety concerns that we haven't touched upon in our discussion?

DR. POLLOCK: If it is not specified in the label or recommended that this medication be reserved for those who cannot take oral medication then, clearly, it can be advertised direct-to-consumer and pushed fairly widely for ease and convenience of use. So, I just wanted to be sure at what level--I mean, this recommendation has to be specific in the label that it is reserved for this? I mean, it has to be that strong. They police what is in the label, right?

DR. LAUGHREN: Right, they would be guided very heavily by what is in the label and, as I said before, the agency has on occasion restricted the use of a product to a particular subset of the population, but that is a fairly unusual move to take and there has to be some very compelling

reason to do that. A case in point might be a drug like Clozapine which is limited to treatment refractory patients because of the risk of agranular cytosis. If there is some comparable reason here to restrict it, but there would have to be a compelling reason.

DR. TEMPLE: Do you have all your questions about advertising? I mean, advertising has to reflect and be comparable with the labeling. So, if there is a restriction in labeling, that would need to be featured prominently. If there isn't, it wouldn't.

DR. GOODMAN: Jean?

MS. BRONSTEIN: I just stepped out so I may be out of order in this discussion, but we heard this morning that some families saw this as a more holistic approach and that concerns me because it isn't. I mean, it is just another drug delivery system and I think we have to be careful--well, I know we haven't finished the sensitivity stuff but I think it could be advertised as appealing to people who are not wanting to take drugs when,

indeed, this is taking a drug every bit as much as popping a pill in one's mouth.

DR. GOODMAN: Who said it was holistic? I don't remember that comment.

MS. BRONSTEIN: It was in the presentation on the model schools.

DR. TEMPLE: This will not be advertised as a non-drug. Trust me!

[Laughter]

DR. GOODMAN: Dr. Malone, did you have a question?

DR. MALONE: No.

DR. GOODMAN: Deborah?

MS. DOKKEN: I wanted to go back to the comment that was just made about marketing and labeling because that is where I was earlier today. We heard before in Dr. Pratt's response to me, he said something about this therapy should be available as an alternative to provide flexibility. I think it is a statement like "to provide flexibility" that is troubling for me in terms of down the road. I mean, does that mean flexible for

those patients for whom there aren't other good options, or is it flexible in situations where it appears to people that it might be handier to just slap on a patch? You know, I don't know where we go with that. You put it in pretty stark terms about how you can define the subset and we are probably not there but I still feel uncomfortable sort of having it be flexible.

DR. GOODMAN: You didn't ask my opinion but I would tend to agree with that characterization. It seems to be that flexibility shouldn't be the adjective. If anything, a short-acting one would offer more flexibility in titration, but it doesn't offer convenience. But I will let somebody else comment on that.

DR. LAUGHREN: What we try and do in labeling is, as accurately as possible, give the characteristics, you know, the benefits of a drug and the risks of a drug and leave it to clinicians to decide how to use the drug. We try not to interfere with the practice of medicine unless, as I mentioned, in certain cases where a drug is so

toxic that we feel compelled to limit it to a particular population. But ordinarily we don't do that. If you look at almost any drug, you find different formulations that are available to give clinicians and patients more options, and you might view this as a similar situation. But it would be unusual I think to try and narrow that use in labeling to a particular subset of the population unless there is a very good reason to do that.

DR. POLLOCK: What if the toxicity, as we have been discussing, isn't fully established? That is basically I think the issue we are struggling with. Unless there is a rigorous post-marketing surveillance in kind of a defined group, the concern is the potential--not to belabor it but the potential is that this is used very freely and by the time that there is a course correction you might have a substantial percentage of children with serious ADHD who can no longer take methylphenidate, and then there will be a huge outcry.

DR. LAUGHREN: Yes, clearly it is coming

down to that issue of the possibility of sensitizing a substantial fraction of the population who might need this drug so that they can no longer take it. I think that is the issue. Again, if a strong case could be made that we know so little about that risk that one cannot reasonably use this drug without restricting it--I mean, you could give us that advice. That would be possible.

DR. GOODMAN: Dr. Wells?

DR. WELLS: I am ready to go on record as saying that I do find it acceptably safe to use in children with ADHD. However, I am not comfortable in going on the record as it being first-line therapy in pediatric patients with ADHD and I would hope that there would be a mechanism within the labeling where we could add that caveat that it would not be considered first-line therapy in unselected pediatric patients.

DR. LAUGHREN: Can you say for whom it would be second-line therapy?

DR. WELLS: I would prefer that it not be

designated as first-line until such time as additional data is provided on the drug sensitization issue. So, I would see it as being acceptable therapy for individuals who have not responded to other dosage forms of methylphenidate and those who can't or won't take oral medications.

DR. LAUGHREN: Of course, we don't have evidence that it works in patients who have not responded to other formulations. We would be flying blind in that area.

DR. TEMPLE: Yes, but you could identify people who can't take things by mouth. For the non-responder it doesn't seem very likely; it is the same drug.

DR. GOODMAN: Or where there are issues of adherence that could be dealt with by giving this formulation.

DR. TEMPLE: I think, as Tom said, we do that sometimes but there should generally be a pretty good reason, one of which could be lack of critical data.

DR. GOODMAN: Dr. Pine?

DR. PINE: Kind of stepping back a little bit and looking at this whole issue, I guess a couple of thing seem at least reasonably clear from

the data that has been presented: Number one, sensitization clearly occurs. Right? That was unequivocally demonstrated with the adult data. Right?

Number two, I mean, we heard from Dr. Leon, whom I would trust, that we cannot really say much about what the prevalence is, number two.

Number three, if the prevalence is even reasonably high it would be a potential disaster if this were widely used, and even a sizeable minority of kids with ADHD could not take methylphenidate. So, just looking at that evidence, that seems like pretty good evidence for an unusual circumstance.

DR. LAUGHREN: Can I just make a comment? We are going to try and do a better job of coming up with what the point estimate might be and what the confidence limits might be. My statistical colleague here advised me that, as I said before, if the right denominator is 300 and there were no

cases the upper bound of that confidence interval would be 1/100. It is not going to be so different with one case. So, depending on what the denominator is, you know, we may be talking about an upper bound of that confidence interval of maybe 1/100. Based on the data that we have, which is very limited data, that is where you would end up with that one case. So, that is sort of what we are working with right now.

DR. TEMPLE: Suppose it was one percent, how would you feel about all this?

DR. GELLER: I am going to play devil's advocate with this a little bit. My experience is that the more restrictions you put on doctors and the way they prescribe--they are very, very intelligent and they will find very good ways of writing down on the chart why they have gone around it. So, I really see that as probably not the most useful way to go now.

I think the issue that came out very clearly here is that child psychiatrists are not good dermatologists, and what has to be emphasized

in some kind of boxed warning so it clearly can be seen is that there is an uncommon or rare, or whatever the number will be, incidence of kids who will get sensitized so that they can never take methylphenidate again and the child psychiatrists have to be very clearly aware that that is a possibility and then it becomes a fact you deal with, with the family. Because I think that that is not something I would have guessed. You can see that from the questions I was asking--you mean you can get a little rash here and then you can never take it again? I suspect I have other colleagues who also would find that new information.

DR. GOODMAN: Dr. Pine?

DR. PINE: Again, as a clinician, if it were one percent, thinking of the child who absolutely cannot take oral stimulants, for whatever reason, I do think that there still clearly would be instances where a clinician would want to give the medication. Again, it would raise concern and I would be worried about all the issues we are talking about but it would not, in my mind

anyway, speaking mostly as a clinician and somebody familiar with the prevalence of ADHD and the problems in treating it--one percent would not make it a useless alternative.

DR. TEMPLE: For that group. What about for everybody else?

DR. PINE: Personally, again just speaking for myself, I am not sure that I would want to use it before a child has failed oral stimulants with a one percent risk. It would matter how reasonable those oral alternatives were, but there would have to be pretty bad options before personally, just speaking as--

DR. TEMPLE: Let's dichotomize it. I mean, what people have said going around is that one thing you might do is reserve it for people who, in the opinion of the investigator, can't usefully take one of the other forms. What you are saying is one percent risk for those people is probably reasonable because they don't really have a choice.

DR. PINE: That is what I am saying.

DR. TEMPLE: But the big question is whether the use of the drug should be directed toward only those people or toward anybody that the

doctor thinks this might be a good alternative for, which is not necessarily people who can't swallow; it could be a larger group. Where are you on that?

DR. PINE: So, if you said in the label--

DR. TEMPLE: At the one percent rate.

DR. PINE: Yes, if you said in the label that it is restricted for people who can't take it orally there is nothing to stop me as a physician from prescribing it off-label anyway. Correct?

DR. TEMPLE: You don't like to put things in that you expect to be ignored.

DR. PINE: Well, but it happens--

DR. TEMPLE: Not that we never have.

DR. PINE: It happens all the time.

DR. GOODMAN: It does seem to me that the considerations go beyond not being able to take it orally. There are other adherence issues so I think it has to be a little bit more broadly defined. Let me go out on a limb now too. If

asked about it, I would vote in favor of safety. I don't see any acute imminent risk. However, I would recommend a warning. I am not saying a black box but we will have to discuss what form it takes and how it would be worded, but until there is more data on the risk I think there needs to be a warning so that could be weighed in any clinical decision-making. Ms. Bronstein?

MS. BRONSTEIN: Have we finished talking about long-term studies? We talked about it very briefly but I think we, as a committee, need to make a recommendation, if this is approved, for some very serious--looking at the prevalence of sensitization in the population.

DR. GOODMAN: Dr. Wang?

DR. WANG: I think there are compelling reasons to do something unusual here. It is not only that there may be this fraction that can be sensitized, but it is also the 50 percent who are going to develop this erythema who might be scared from ever taking stimulants ever again--you know, go to a dermatologist and say I am not going to put

my kid on something like this; I don't care what it is. So, it is actually I think a large public health problem in the aggregate.

Meanwhile, you have a situation that I think as researchers we yearn for and clinicians yearn for too where you could segment the population into those in whom the benefit/risk is positive and those in whom it is not so positive. You have a cheap, accurate and easy to do screen and that is can you take a pill or not? It seems to me that in this situation it may call for something unusual.

DR. GOODMAN: I guess my feeling is that, for some of the reasons other have stated, I don't want to define it that narrowly so that we are telling physicians exactly that you can only prescribe it under these conditions. We can think of some exceptions that have to do with adherence now. There are probably going to be other considerations too. So, I don't think it should be quite that narrow.

DR. WANG: Clinicians will figure out what

it means when a pill is not possible so some of the exceptions you raise--you know, GI problems, interactions with other medications, you know, they will know, or maybe just that the kid can't take pills or doesn't want to. They will know what fits under that rubric and we already know it is 15 percent or higher. Anyway, I suspect if you left it up to the clinician in whom pills are not possible or something like that, they will know who falls into that.

DR. GOODMAN: Dr. Robinson?

DR. ROBINSON: One of the things that I think that makes it also difficult for me is, you know, if it is one percent the problem is we don't have people who have talked to us who have expertise in dermatology and sensitization. Even though I think, you know, you are a very smart guy but basing all of it on--

DR. TEMPLE: He can handle it.

DR. ANDREASON: I am surprised that people keep asking me.

DR. MALONE: You know, obviously there is

expertise within the different branches in terms of the time course to sensitization, etc. Should we really be looking at 12 weeks? Should we really be looking cumulatively over a year? Those sorts of issues. Even what the exact denominator is, is it 300 or 400? How many weeks each subject go? Were people dropping out early who had a rash who might have later gone on to sensitization? I think there is just a huge sort of cloud about the data we have. Also, the expertise to interpret that which is obviously not sort of in psychiatry sort of field, and I think that makes it very difficult to sort of know what level of warning algorithm, although I think all of us have the feeling that, yes, it is not the first-line treatment but I think it is very difficult until for some of these other issues we have any sort of estimate.

DR. GOODMAN: Dr. Laughren?

DR. LAUGHREN: Let me try and lay out a couple of issues. We will take this advice back about talking more with our dermatologists, and I am sure the company is going to talk to theirs as

well, to try and define, as best we can, what this risk is and try and figure out a way to very prominently label that. I think a warning is the right level for this kind of risk, and we can do that and try and lay that out as clearly as possible in labeling.

But the other issue that has been raised that we need to reach some resolution on is whether or not you want us to try and restrict this drug to some part of the population, keeping in mind that that is a very difficult thing to try and define and however you do that, it is probably going to limit the way prescribers--now, maybe that is what you want, but it is going to limit the way prescribers use that drug maybe beyond ways in which you intended if you try and do that.

DR. GOODMAN: We could vote on that question.

DR. LAUGHREN: That would work. I just want to make sure there is full discussion of that before you vote on it, that you fully understand what the implications are of doing that.

DR. MALONE: I am not sure what that means--

DR. LAUGHREN: It is like clozapine,

putting language in labeling that basically tells prescribers that they can only use it in this subset of the population who has ADHD. That is going to inhibit prescribing because they are not going to--and if you can't think of all the possible situations right here, today, where you might want to use it, you know, trying to restrict it in some way could prevent prescribers from using it in situations that you haven't thought of. That is my point.

DR. TEMPLE: There are degrees of this sort of thing. Clozapine is an example of a drug that is explicitly for people who failed on other therapy. Ziprasidone doesn't say that. It just says while you are considering using it, you might want to notice there are some other drugs that don't prolong the QT interval. So, there are gradations of reminders that appear in labeling. It is not out of the question that one could write

something that said when you are thinking of using this remember that if you do get an allergic reaction, which happens maybe this percent, you might not be able to use the drug. So, I am just saying that there are a lot of options, not only second-line/first-line, things like that.

DR. GOODMAN: Also, the analogy breaks down with Clozaril. Clozaril was established as effective in patients who are resistant to other conventional agents and we don't have any evidence that that is the case here. So, it would be selecting a subgroup not based on treatment response.

DR. TEMPLE: No, but you do know that people who won't take a pill can slap this on.

DR. GOODMAN: I would be in favor for us to take a vote on question number two and then go back and see whether we want to compose additional questions, either to vote on or just to discuss, in terms of specific recommendations either about indication restrictions or safety.

DR. PINE: Could we at least change

question two to say something about in some populations so that we can vote on question two and them move on?

DR. GOODMAN: Deborah, go ahead.

MS. DOKKEN: I wanted to ask from someone at the FDA a question of clarification. Again, what is the relationship between labeling and direct-to-consumer marketing? Does it have to be in a black box? Anyway, that is what I want to know before I vote.

DR. TEMPLE: There are not too many rules. If something carries a black box you are not allowed to do something called reminder advertising. That is where you just name the drug and don't say what it is for--probably not a big deal. The general idea is that important warning information, such as that in a black box, needs to be prominently displayed as part of the ad, not just stuck over on the brief summary that is at the end of it but incorporated into the body of the ad, not as the black box necessarily but appropriately prominently.

MS. DOKKEN: What about non-black box?

DR. TEMPLE: Any important warning information needs to be part of the overall body of

the ad and in addition, of course, has to be in the small, invisible print part that follows.

DR. GOODMAN: Dr. Pine, I am not sure what we are going to gain by modifying question two.

DR. PINE: I think it is easier, at least for me--

DR. GOODMAN: It would make it easier to vote, yes, but other than that I am not sure what it does in terms of our decisions.

DR. PINE: I guess if we are going to devote considerable time to question number three, which is, is it or not only restricted to a population, we can vote yes on question two and move onto three and finish.

DR. GOODMAN: That is what I am thinking. It wouldn't affect our decision to then come back and suggest some restrictions. I would like to go ahead and call the vote on question two on safety. I will start this time. I already indicated that I

will vote in favor but also suggest some safety concerns. Why don't we start from this end? Dr. Pine?

DR. PINE: I will vote yes, with the provision that I would want it to be either warned or restricted, and we can talk about which that is, to some subset of the population.

DR. GOODMAN: Dr. Robinson?

DR. ROBINSON: Yes, I would vote yes with the same provision. In general I would have voted no but with the provision that we are going to put warnings or restrictions I will vote yes.

DR. GOODMAN: Jean Bronstein?

MS. BRONSTEIN: I too would vote yes, with some kind of restriction and also the issue of some long-term follow-up study data.

DR. GOODMAN: Dr. Wang?

DR. WANG: Also the conditional yes as my colleagues have indicated.

DR. GOODMAN: Dr. Geller?

DR. GELLER: Yes, with warning.

DR. GOODMAN: Deborah Dokken?

MS. DOKKEN: Yes, with the same conditions that have already been laid out.

DR. GOODMAN: Dr. Malone?

DR. MALONE: I would vote yes, with the provision of warning and some formal post-market surveillance of the sensitivity.

DR. GOODMAN: Dr. Pfeffer?

DR. PFEFFER: I would vote yes also, and I agree with Dr. Malone with the warning and some type of clear, systematic post-marketing surveillance.

DR. GOODMAN: Dr. Leon?

DR. LEON: I agree, yes, and with warnings, restrictions and post-marketing surveillance.

DR. GOODMAN: Dr. Wells?

DR. WELLS: Yes, with warning and post-marketing surveillance.

DR. GOODMAN: Dr. Pollock?

DR. POLLOCK: The same.

DR. GOODMAN: Dr. Mehta?

DR. MEHTA: I would vote yes but with some

recommendation for post-marketing study, as well as figuring out a way by which the patient or the doctor is informed very clearly that this child has received the product and, as a result of dermatitis, the child probably will not be able to take the oral drug again.

DR. GOODMAN: So, you would be recommending a warning too.

DR. MEHTA: Yes.

DR. GOODMAN: It seems to me that there are two issues that we could vote on--I am not saying we will vote on but could vote on. One has to do with restrictions such as saying--I don't know if it can be put in this form--it should not be considered for first-line or considered first-line only in those patients who cannot take oral. I personally am not in favor that. I just don't feel that we are going to be able to articulate all the circumstances in which to indicate those restrictions. So, I think I would rather focus on the safety warnings and the need for surveillance. But I am glad to hear from my

colleagues around the table and then maybe we can take a vote on it.

So, the first question would be should there be restrictions on prescribing, and how would you enunciate those? The choice being those who cannot take oral medication.

DR. TEMPLE: Just to be sure, everybody said there ought to be some warning information so that is not going to be controversial but you mean ion addition--

DR. GOODMAN: Yes, I have this feeling, and maybe I am wrong, that individuals around here would like to add stipulations about what populations.

DR. TEMPLE: Yes, but I am saying assume that there is going to be appropriate warning--

DR. GOODMAN: Oh, absolutely, yes.

DR. POLLOCK: But, again, with the gradations. We are not talking about the kind of restriction with clozapine but more along the lines as you were saying, Dr. Temple, more up front, near the indications, that it is recommended or it

should be considered. Again, I am thinking not just to physicians but also to DTC. If it is not up front, and we are not talking about a black box necessarily but even if the warning is strongly phrased at the end it is kind of like ease of convenience. Then, at the end there is kind of and..., and potential for allergy, and you know, that comes right then. So, it is more if it could be a more up front, stronger recommendation based on the uncertain information.

DR. GOODMAN: Let me give another try about my rationale for focusing on the safety warning rather than under what circumstances to prescribe the medication. Part of what you said is because right now we are not yet in a position where we can clearly know what the risk is and write out an algorithm. So, I think that is going to be a work in progress.

I would rather stress the part that we don't know; what the concerns are and the implications of those concerns will then drive prescribing practices. I think it would be clear

to anybody who follows the logic that this may not be something, until there is further data, that you would want to prescribe as the first choice unless they had problems taking the medication or you are concerned about adherence. I mean, you could add that but that is going to be obvious. And, how you weigh those factors will evolve over time as data starts to come back in on really what the risk is for the sensitivity reaction. I would rather have that the safety concerns be the driver rather than up front us telling where this place is in the algorithm.

DR. POLLOCK: And not just the actual risk but, as Dr. Wang pointed out, the potential hysteria with 50 percent erythema and how that is handled, and if it is a true urticaria how long it persists, and there would be all this uncertainty and cloud over potentially 50 percent of the kids who take this medicine.

DR. GOODMAN: Dr. Pfeffer?

DR. PFEFFER: I am actually still quite concerned about this. Even if we have

post-marketing surveillance, it is almost still like we are trying to gather data experimentally and I just realize I don't know are there any animal models with this patch? Is there a possibility to get more rapid data about risk in terms of ultimately looking at this concern?

DR. POLLOCK: That is what the adult volunteers were.

DR. TEMPLE: Yes, you have human data; it is possible. The question is how often it happens in the kids.

DR. PFEFFER: We don't know about the children though.

DR. GOODMAN: We know about one child who developed it. Dr. Pine?

DR. PINE: I guess two thoughts, first of all--and I am not sure I totally understand your position, what would be wrong with saying--you know, a question or a phrase or a thing that said this medication should only be first-line treatment for children where oral methylphenidate treatment is not an option? I mean, that seems fairly clear

to me and I would vote for that personally. So, that is the first thing.

The second thing is, just again thinking of myself as a clinician in the office and what is the level of concern here, and trying to at least, you know, think somewhat historically in this committee, what would my level of concern be faced with a child where I was thinking about should I use this treatment or not and then thinking about the issue of SSRIs for example in depression. You know, SSRIs are used in depression still despite the warnings that we talked about. I don't know that the concern in a child who could take oral medication is out of the realm of that level of concern. For a child who could take oral medication, again just speaking as a clinician, I am not sure that I would want to do that and I am not sure that I would want the label to not advise against that.

DR. GOODMAN: It sounds like we should compose a question and take a vote. I am not good at doing this on the fly but it would be along the

lines, should the use of MTS system be restricted to patients who cannot take or are intolerant of oral medication? It is that simple, or along those lines.

DR. PINE: It should be first-line--it should only be a first-line treatment for--

DR. GOODMAN: Okay, MTS should only be a first-line treatment in patients who cannot take oral methylphenidate.

DR. TEMPLE: The first-line/second-line doesn't enhance the original proposal. I mean, if you say it should be reserved for people who can't use the other, that captures it. First-line and second-line always seems ambiguous to me. I don't particularly like it. But, you know, I don't think you have to worry totally about the words; you need to get the concept. We understand. You are voting as to whether it should be clearly directed toward people who can't take the oral.

DR. GOODMAN: So, does everybody understand the intent of the question, that MTS should be reserved for patients who cannot take or

will not take oral methylphenidate. That is the question.

DR. PINE: I like the phrase "clearly directed for" because I think that captures it, that Dr. Temple used.

DR. GOODMAN: You agree with him but you won't agree with me but that is okay.

DR. TEMPLE: That doesn't give you the words. That is the concept you are I think talking about.

DR. GOODMAN: Any modification of that question? We certainly should have discussion. Dr. Wang?

DR. WANG: I think we don't have to specify exactly why they are not taking pills. That is not an issue because it is not necessarily a medical condition or an experience of a failure. The clinician or the patient or the patient's family can just decide they don't want pills. So, I like your "in whom pills are not an option," something purposely loose like that, maybe even saying, i.e., patient family preference, making it

clear that they don't have to fail oral medications; they could just prefer it.

DR. GOODMAN: Where does adherence fit into that equation? Because that would be the other circumstance that you might use it for.

DR. WANG: You could put that in as another example. You could say potentially beneficial adherence.

DR. GOODMAN: This is my problem, it starts to become a slippery slope because I am not convinced we are going to figure out every circumstance in which it is appropriate as a second- but not as a first-line. I am not sure we need to define it.

Let's just take the one that doesn't include adherence, should it be reserved for patients who cannot take oral medication?

DR. ROBINSON: But also I think one of the things that was mentioned before is the labeling for ziprasidone, which essentially just says this thing potentially--the original labeling, it could cause QTc changes. The other drugs don't do that.

Therefore, you should really consider them before ziprasidone. I think we are in a somewhat similar situation with this. We have methylphenidate. There is oral methylphenidate and there is this patch form, and if we say up front the patch form comes with a risk--and, unfortunately, we are not going to be able to find out exactly how much--that you will develop sensitivity so that the patient can never take methylphenidate again. Therefore, you should consider oral formulations first.

DR. GOODMAN: That was my point. That is why I was suggesting that you let--

DR. ROBINSON: And it actually influenced psychiatrist behavior at least initially with ziprasidone.

DR. GOODMAN: That said, I still want to go through the exercise now of taking a vote on should this be reserved or directed for patients who cannot take or will not take the oral form of the medication? Let's just go around and take a vote. I will start. I am going to vote against that restriction, again, because I would like to

focus on the severity rather than articulating, delineating the niche. I think that shouldn't be our job.

DR. TEMPLE: So, this is a vote on the explicit restriction. You are not uncomfortable with words you might want to think about other things?

DR. GOODMAN: I am very comfortable with that. I want the vote as an overt restriction. That is how I intended the question.

DR. LEON: And the warning would include the rationale that sensitivity could prohibit use or prevent use of oral.

DR. TEMPLE: I will tell you we are definitely going to have to explain to people how to distinguish between a little erythema and other stuff. So assume that. The labeling is going to have to do that.

DR. GOODMAN: One more time then, I would like to take a vote on yes or no recommending overt restriction on the use of MTS for patients who cannot take oral medication. I voted against that

overt restriction. We can start with Dr. Mehta.

DR. MEHTA: I will vote against it too.

DR. POLLOCK: Well, putting it the way you did, I have to vote no.

DR. GOODMAN: Somebody else can draft it; it is okay.

DR. GELLER: I think you have the concept and people can vote on the concept.

DR. MALONE: Could you change it to recommendation? You are making it sound so restrictive. The spirit of it is to try to channel people. If there is some flippage in either direction, that is okay.

DR. TEMPLE: That is the very distinction he is trying to get at. This first version is "thou shalt not." There are probably some people who think that is the right thing to do. The alternative is, eh, think about it; maybe you shouldn't. This is very helpful to us, I have to tell you.

DR. GOODMAN: Thank you. It does not obviate our being able to make a second vote on do

we recommend that we steer people to consider those who cannot take oral medications. It is a different question, as I see it. Dr. Pollock?

DR. POLLOCK: Yes, as I said, restricted, I have to vote no. We haven't done the second one but if it is recommended, then I would vote yes.

DR. WELLS: I will vote no.

DR. LEON: I would vote no for restriction, particularly as Dr. Temple pointed out, it will contradict the data--we don't have data supporting this efficacy in that restricted population.

DR. PFEFFER: I also vote no for restriction.

DR. GOODMAN: Dr. Malone?

DR. MALONE: I vote no for restriction.

MS. DOKKEN: No for restriction.

DR. GELLER: No.

DR. WANG: No for restriction, but I hope the next vote is not so far--

DR. GOODMAN: You are going to write the next question!

MS. BRONSTEIN: No for restriction.

DR. ROBINSON: No.

DR. PINE: I vote yes.

DR. GOODMAN: Now, Dr. Wang, how would you like to phrase the question?

DR. WANG: Strongly recommend.

DR. GOODMAN: Strongly recommend what?

DR. WANG: Strongly recommend reserving this for patients in whom oral medications are not an option. But it can't just be sort--if it is anymore wishy-washy than that it sort of loses its purpose. I always said yes for the first but maybe one notch below. So, if anyone is a better word-smith, take a shot.

DR. GOODMAN: Can you change that language as the data emerges? You can revise the labeling in accord with emerging data.

DR. TEMPLE: Sure. If it turns out that this hardly ever happens and somehow post-marketing data support that, you can obliterate--you would still warn people about the possibility but you would change whatever the language, which we

haven't heard yet, would be.

DR. GOODMAN: Could you rephrase that, Dr. Wang, just so we are clear what we are voting on?

DR. WANG: Something like strongly recommend in whom oral medications are not an option.

DR. GOODMAN: Have the clinician strongly consider reserving the use of this medication to those in which oral medications are not an option.

DR. WANG: There are a couple of negatives there.

DR. GELLER: Or an alternative, given the current state of knowledge about sensitivity, it is strongly advised at the current time that the medication be limited to individuals who cannot tolerate oral medications.

DR. GOODMAN: That is too close to the first one. Tom?

DR. LAUGHREN: The language that we have for ziprasidone I think goes something along the lines of physicians should generally consider other medications before ziprasidone because of

such-and-such.

DR. GOODMAN: I like that.

DR. GELLER: I think here though there may be reason to be stronger because for ziprasidone there were other marketed medications that might have comparable efficacy. In terms of stimulants I don't see the choice as being that wide and I think, you know, there is some concern about not being able to use methylphenidate for a common illness when there are very few alternatives.

DR. LAUGHREN: But if you use language like "strongly advise," it seems to me that that is really the question that you just voted on.

DR. GOODMAN: Having something along the lines that the clinician should weigh--Dr. Pine, why don't you go for it?

DR. PINE: I like "clearly directed." So, use of this medication should be clearly directed towards patients for whom--

DR. GOODMAN: No, I think we want to leave it in the hands of the clinician.

DR. PINE: Use of this medication is

primarily recommended for--I mean, it is better as a positive as opposed to a negative.

DR. GOODMAN: Given the current concerns about the risk--

DR. POLLOCK: The uncertain nature of knowledge.

DR. GOODMAN: Given the uncertain nature of knowledge about the risk of sensitization, consideration should be given to prescribing oral forms of methylphenidate prior to prescribing MTS, something along those lines?

DR. TEMPLE: We don't think you have to write the exact words but I think we understand what you are saying.

DR. GOODMAN: I am going to start. I am voting yes, affirmative, for that recommendation. Dr. Mehta?

DR. MEHTA: I vote yes, particularly if it is language like ziprasidone. There are more than one reason why I like it.

DR. POLLOCK: Yes.

DR. WELLS: Yes.

DR. LEON: Yes.

DR. PFEFFER: Yes.

DR. GOODMAN: Dr. Malone?

DR. MALONE: I guess I vote yes.

MS. DOKKEN: Yes.

DR. GELLER: Yes.

DR. WANG: Yes, but with the hope that the language is stronger than for ziprasidone.

MS. BRONSTEIN: Yes.

DR. ROBINSON: Yes.

DR. PINE: Yes, but I do think the language is too weak because I voted yes for the last one, and I also think, given the amount of knowledge, that we should err on the side of caution and that is kind of what is informing my votes.

DR. GOODMAN: Dr. Pollock?

DR. POLLOCK: Just to get to the fourth point maybe about the state of lack of knowledge, does the FDA--I mean, once a drug is approved, then it seems you always have to fall back on your MedWatch. You always then have to go into the soft

kind of voluntary reporting, or do you ever require manufacturers, where there is a specific concern, that they more actively gather systematic data in populations? I mean, is that a mechanism?

DR. LAUGHREN: Yes, we have that option. Actually, this question could be answered I think fairly easily by looking at a cohort of maybe a thousand people and following them closely and finding out how many of those patients develop sensitization. I don't think it is that hard. I mean, all you have to do is follow--you have to decide how many patients and at what level you want to rule this out, but it is not that hard.

DR. POLLOCK: But you could require a formal Phase IV study.

DR. LAUGHREN: We can get a commitment to do that, yes.

DR. GOODMAN: Moreover, it would behoove the sponsor to try and get an answer to this question rapidly because that could clearly relax some of the concerns that are being expressed. So, I wouldn't worry about their compliance with that

recommendation.

I think we don't need to compose a question and take another vote on whether surveillance studies need to be conducted or what form they take. I think we will leave that up to the FDA. I am sure there is unanimous agreement that we would like to see such studies conducted systematically and promptly in order to resolve this issue.

Anything else that we need to cover? If not, I am going to adjourn the meeting and thank you all for your attention.

DR. LAUGHREN: And I would like to thank the committee again for very helpful advice.

[Whereupon, at 3:05 p.m., the proceedings were adjourned.]

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