DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE

NDA21-645, MT 100, (naproxen sodium and metoclopramide hydrochloride) Tablets, Pozen, Inc. for the proposed indication of acute treatment of migraine headache with or without aura

Thursday, August 4, 2004

8:00 a.m.

Advisors and Consultants Staff Conference Room
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

Karl Kieburtz, M.D., MPH, Acting Chair
Anuja Patel, MPH, Executive Secretary

MEMBERS

Michael D. Hughes, Ph.D.
Carol L. Koski, M.D.
Roger J. Porter, M.D., (Industry Rep, Non-Voting)
Ralph L. Sacco, M.D., M.S.

SPECIAL GOVERNMENT EMPLOYEES (VOTING)

Larry B. Goldstein, M.D.
Lily K. Jung, M.D., MMM (Acting Consumer Rep)
Stanley Fahn, M.D.
Marc E. Lenaerts, M.D.
K. Michael Welch, M.B., Ch.B., FRCP
Sheila Weiss-Smith, Ph.D., FISPE
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Robert Temple, M.D.
Russell Katz, M.D.
Eric Bastings, M.D.
Mary Ross Southworth, Pharm.D.

C O N T E N T S

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. KIEBURTZ: Good morning. This is the Peripheral and Central Nervous System Drugs Advisory Committee. We here to discuss the New Drug Application 21-645, proposed trade name of MT100 Tablets, from Pozen, Incorporated for the proposed indication of acute treatment of migraine headache with or without aura.

I would just also take the opportunity to refer people to the agenda. Incorporated in the agenda are the questions which are posed to this committee which will be discussing and voting on today. We won't be discussing or voting on prior actions of the FDA including the non-approvable letter or any issues about a approvability of the product. That is not our remit or discussion for today.

So I would hope that the presentations are focused on what the committee will be discussing and deliberating about today.

When people speak, please speak into the

microphone and turn the microphone on. If you are interested in speaking, raise your hand or you can turn the microphone on. Anuja, the Executive Secretary, will keep track and will get to people who want to speak from the committee.

Just to the committee members, the voting committee members, please keep in mind that, to vote, you need to be here. So there is no leaving of votes. Hopefully, there is no leaving until the meeting is adjourned which is scheduled to be at 5 o'clock. Please plan your travels accordingly.

In a second, I am going to introduce Mary Ann Killian. There is a new procedure--I think we are the inaugural run of it--for disclosure of conflicts of interest where Mary Ann Killian reads a statement and then each individual member of the committee reads their conflict statement. When that is concluded, Mary Ann has some concluding remarks and then we will move on with the rest of the agenda.

The only individual who does report conflicts of interest is Dr. Porter as he is the

industry representative.

So Mary Ann Killian, the Program Integrity Advisor from the Ethics and Integrity Staff.

Conflict of Interest Statement

MS. KILLIAN: Thank you very much. The FDA is convening today's meeting of the Peripheral and Central Nervous System Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. The advisory committee meeting provides transparency into the agency's deliberative processes.

With the exception of the industry representative, all members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict-of-interest laws and regulations.

Consequently, in the interest of transparency and the spirit of disclosure, the following information on the status of this advisory committee's compliance with federal ethics and conflict-of-interest laws covered by but not limited to those found at 18 U.S.C. 208 and 21

U.S.C. 355(n)(4) is being provided to the participants in today's meeting and to the public.

FDA has determined that members of this advisory committee are in compliance with the Federal ethics and conflict-of-interest laws including but not limited to 18 U.S.C. 208 and 21 U.S.C. 355 (n)(4). Under 18 U.S.C. Section 208, applicable to all government agencies, and 21 U.S.C. 355(n)(4), applicable to FDA, Congress has authorized FDA to grant waivers to special government employees who have limited financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Members who are special government employees at today's meeting, including special government employees appointed as temporary voting members, have been screened for potential financial conflicts of interest of their own as well as those imputed to them including those of their employer, spouse, minor child related to the discussions of

today's meeting. These interested may include investments, consulting, expert witness testimony, contracts/grants/CRADAs, teaching/speaking/writing, patents and royalties, and primary employment.

Today's agenda involves a review of New Drug Application 21-645, proposed trade MT100 Tablets, proposed for acute treatment of migraine headache with our without aura sponsored by Pozen, Inc. MT100 is a combination of two approved drugs, naproxen sodium, manufactured by the Albemarle Corporation, and metoclopramide hydrochloride, manufactured by Cosam S.p.A, a member of the CFM group. This is a particular matters meeting during which specific matters related to the NDA will be discussed

Copies of each acknowledgement and consent-to-disclosure statement signed by each participant at today's meeting who received a conflict-of-interest waiver along with this statement will be available for review at the registration table during this meeting and will be included as part of the official meeting

transcript.

A copy of the written conflict-of-interest 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.

At this time, each member will be asked to state his or her name for the record and announce whether his or her participation in this meeting is based on a conflict-of-interest waiver.

Please state your name and whether you have received a waiver from the agency to participate in today's meeting. If you have received a waiver, please describe the details of the interest or interests for which the waiver has been granted. If the agency has reviewed your reported interest and determined that you do not require a waiver, please indicate that for the record.

I guess we will start with you.

DR. KIEBURTZ: I will be the exemplar. I am Dr. Karl Kieburtz. I am a neurologist and on

the faculty of the University of Rochester in Rochester, New York. Based on the agenda for today's meeting and the information regarding my financial and other interests required to be reported to the agency prior to my participation today as a committee member, I have not received a conflict-of-interest waiver to participate in today's meeting. That means I don't need a waiver.

Next is Dr. Porter.

DR. PORTER: Pass.

DR. KIEBURTZ: If you would just introduce yourself for the record.

DR. PORTER: Sure. I am Roger Porter. I am a neurologist twenty years at the NIH, ten years at Wyeth. I am now a consultant.

DR. HUGHES: I am Michael Hughes. I am Professor of Biostatistics from Harvard University. Based on the agenda for today's meeting and the information regarding my financial and other interests required to be reported to the agency prior to my participation today as a committee member, I have not received a conflict-of-interest

waiver to participate in today's meeting.

DR. KOSKI: I am Dr. Carol L. Koski. I am a Professor of Neurology at the University of Maryland School of Medicine. I have received a waiver for ownership of stock in two competing firms. The first is valued between $5,001 and $25,000. The second is valued between $25,001 and $50,000.

DR. SACCO: Hi. Ralph Sacco. I am a Professor of Neurology and Epidemiology and Director of Stroke and Critical Care at Columbia University. I have received a waiver for my service as a consultant for a competing firm. I also serve on the Data and Safety Monitoring Board for a competing firm and I receive less than $10,001 per year from each firm.

DR. GOLDSTEIN: I am Dr. Larry Goldstein. I am a Professor of Medicine at Duke University and Director of the Duke Center for Cerebrovascular Disease. I have received a waiver for consulting for four competing firms and I receive less than $10,001 per firm per year from three of the firms

and between $10,001 and $50,000 per year from the fourth firm. In addition, I serve as a member of two advisory boards and two steering committees for competing firms and receive less than $10,001 per year from each firm.

DR. JUNG: Hi. My name is Lily Jung. I am a neurologist with the Seattle Neural Science Institute and Swedish Medical Center. I am also a Clinical Associate Professor at the University of Washington. I have received a waiver for ownership of stock valued from $5,001 to $25,000 in a competing firm.

DR. FAHN: Good morning. I am Dr. Stanley Fahn. I am a Professor of Neurology at Columbia University subspecializing in the field of movement disorders. I have received a waiver for serving on steering committees for two competing firms. In addition, I also serve as a consultant for two competing firms. I receive less than $10,001 per year from each firm.

DR. LENAERTS: Good morning. Marc Lenaerts, Assistant Professor, University of

Oklahoma, Department of Neurology, a headache specialist. I have received a waiver for serving on three speakers bureaus. One is between $10,001 and $50,000, and two are $10,000 or less.

DR. WELCH: Good morning. I am Dr. Michael Welch. I am a Professor of Neurology at Rosalind Franklin University of Medicine and Science. I have received a waiver for serving as a consultant for two competing firms and I am also an advisory board member for two competing firms and serve on the steering committee for a competing firm. I receive less than $10,001 per year for each firm.

DR. SMITH: Good morning. I am Professor Sheila Weiss Smith. I am an Associate Professor at the University of Maryland Schools of Pharmacy and Medicine. I have not received a conflict-of-interest waiver to participate in today's meeting.

DR. JESTE: Good morning. I am Dr. Dilip Jeste. I am Professor of Psychiatry and Neurosciences at the University of California, San

Diego, and the San Diego V.A. Healthcare System. I have received a waiver for advisory board activities for a competing firm for which I receive less than $10,001 per year.

DR. GREEN: I am Dr. Mark Green. I am a Clinical Professor of Neurology at Columbia University and Director of the Columbia University Headache Center. I have received a waiver from my employer's contracts and grants with three competing firms. My employer receives less than $100,000 from one, between $100,001 and $300,000 from a second and more than $300,000 from a third.

MS. KILLIAN: Thank you very much. Lastly, Dr. Roger Porter is the Industry Representative on the committee today and he will be acting on behalf of all related industry.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant may have a financial interest, all meeting participants are reminded that they are required by 18 U.S.C. 208 to exclude themselves from such deliberations and

announce their exclusion for the record.

Finally, in the interest of public transparency, with respect to all other participants, we ask that they publicly disclose, prior to making any remarks, any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you very much. This concludes my statement.

DR. KIEBURTZ: Thank you everyone for doing that. For an inaugural run, I think that went pretty well.

I would just like to point to the agenda before letting Dr. Katz begin which is, some people know, the sponsor will have approximately an hour and fifteen minutes, up until the 9:45 break, to give their presentation. We will then break and then there is a presentation from the FDA.

There will then be the opportunity for the committee to ask questions about the content of those presentations to the presenters. Then we will break for lunch. There will be a public

hearing after that and then a discussion amongst the committee members after that.

During those discussions, the committee members may ask questions of the presenters regarding details of their presentation. Presenters may not interject or contribute to that discussion voluntarily, just so people know the rules of the game here.

If you have questions that arise during presentations, the FDA's presentation slides are numbered. You may want to note them. You may want to note the slides of a presenter so that you can refer back to them with reference when you pose a question.

On the FDA side of the table, I would like to introduce four people. It looks like it flows from right to left from my sitting. Dr. Robert Temple, Dr. Rusty Katz, Dr. Bastings and Dr. Southworth.

Dr. Katz?

Overview of Issues

DR. KATZ: Thanks, Dr. Kieburtz. I want

to be very, very brief. I just have a couple of points I want to make but, first, I want to add my welcome to the committee. Thanks for coming. Particularly we have several new members. I would like to thank them for agreeing to serve on the committee.

I would also like to thank Dr. Kieburtz for agreeing to chair the committee. It can be a tough job. I would also especially like to thank our invited guests, of whom we have quite a few, who are experts to help us deal with this interesting issue. In particular, I would like to thank Dr. Jinnah who has graciously agreed to actually be part of the presentations this morning. So thanks very much to everybody for coming.

As you know, we are here to discuss NDA 16-145 submitted by Pozen for the use of MT100 which, as you have heard and which you know, is a combination of naproxen and metoclopramide for the treatment of acute migraine.

Actually, we are asking you today to address a type of question that is actually fairly

unusual for the committee to deal with and that is because many of the questions that we are going to be asking you to consider are hypothetical in nature.

Those of you who have been on the committee or have seen previous committee meetings know that, in a typical case, when we bring you a new drug application, we would ask you whether or not the application contains sufficient evidence of safety or effectiveness in order to support marketing approval.

But, today, as Dr. Kieburtz has already stated, we are not primarily interested in the question of whether or not the sponsor submitted substantial evidence of effectiveness for the treatment of acute migraine. We have already decided that they have not done so, in particular because we are unsure that they have presented sufficient evidence of effectiveness for the combination, itself, as a treatment for acute migraine.

But, perhaps, more importantly for today's

discussion, we have determined that they have not demonstrated a contribution of one of the components to the overall effect of the drug and that component is metoclopramide. I think we will have a lot of discussion about that particular question today.

You will, though, of course, hear some more or less detailed presentations of that effectiveness data that we have already ruled on in a sense. You will hear from the company and you will hear, to some extent, from us as well, from Dr. Bastings. We would hope that you would primarily consider those data in the context of helping to inform your answers to the series of hypothetical questions that we are going to ask you.

In particular, we would like you to think about the previous effectiveness data in the context of giving us your advice as to whether or not, if the sponsor does perform an additional study or additional studies in a particular population which you will hear about, whether or

not the results--if the results of these new studies or new study are more or less of the same magnitude as what has been seen already, whether or not you would think that would justify approval of the combination given the potential risks of the treatment.

Of course, the potential risks of the treatment are the underpinnings for the second serious of hypothetical questions we want to ask you. Specifically, we are interested to know your views about the likelihood of occurrence and, perhaps, even estimates of the frequency of particular adverse events that we are concerned about which, as you know, are tardive dyskinesia, primarily, but, in additional, other tardive movement disorders and possibly neuroleptic malignant syndrome associated with the chronic intermittent use of metoclopramide as it would be presumably used in the treatment of acute migraine.

This series of questions is hypothetical because the current data on the risks for these adverse events associated with metoclopramide, such

as they are, don't speak directly to the question of what the frequency of--what they might be when the drug is given in the regimen that the sponsor proposes; namely, chronic intermittent use, as is typical for an acute-migraine treatment.

As difficult as those questions might be to answer, we would like you to go even further and venture an opinion about what sort of possible dosing recommendations, if any, actually could be adopted that might reduce the risks to an acceptable level and then ask you to discuss what you think that possible result and level of risk might be. So these are all, obviously, questions for which we do not have adequate data.

That is what makes it difficult. We know these are difficult questions, but partly because they are so difficult, and partly because we think these questions are very important to try to answer from the perspective of public health, given the large prevalence of acute migraine in the population, that is why we have come to you today.

So, again, thank you for coming. I want

to thank you in advance for all the hard work that you have done already in reading the documents and in today's discussion. So thanks again and I look forward to an interesting and productive meeting.

Thanks.

DR. KIEBURTZ: Thank you, Dr. Katz.

Actually, I realize I was a little remiss in introducing all of you. Maybe, as we have all had the chance to introduce ourselves around the table, Dr. Temple, maybe you could start so that everyone knows who you all are.

Also, to follow up on Dr. Katz' comments, just before you do that, Dr. Temple, these are difficult questions and they are unusual questions. I hope the committee members feel comfortable voicing if they are uncertain about that and I will be happy, as chair, to direct back to the FDA questions about clarifying as to whether we are answering the questions they had in mind and getting clarity that we are providing them the advice that they are seeking from us because it is a little bit unusual.

So, if people are a little uncomfortable about that, that is how we can do that. We can ask questions of them to be certain we are addressing the issues at hand.

So, Dr. Temple, please.

DR. TEMPLE: Good morning. I am Bob Temple. I am the Director of ODE I. That is office in which the Division of Neurology Products lives. I have not received a waiver.

DR. KATZ: I am Russ Katz. I am the Director of the Division of Neurology Products. I, too, am not allowed to have a conflict of interest.

DR. BASTINGS: I am Eric Bastings. I am a clinical team leader in the Division of Neurology.

DR. SOUTHWORTH: I am Mary Ross Southworth, a safety evaluator in the Office of Drug Safety.

DR. KIEBURTZ: Next on the agenda is presentations from the sponsor.

Sponsor Presentation, Pozen, Incorporated

Introduction and Summary

DR. REESE: Good morning and thank you.

(Slide CC-1-2)

Pozen wants to thank the FDA for assembling the Peripheral and Central Nervous System Drugs Advisory Committee today to review our naproxen-metoclopramide combination product called MT100 for the acute treatment of migraine with and without aura.

(Slide CC-3)

Let me briefly review an outline of Pozen's presentation for this morning. Following my introductory comments, Dr. Schapira, Professor and Chair of Neurology at the Royal Free and University College Medical School in London and Professor of Neurology at Queens Square, will present an overview of tardive dyskinesia with metoclopramide use.

Dr. Alexander, Senior Vice President and Chief Medical Officer at Pozen, will briefly review the efficacy data for MT100 as contained in our NDA. Dr. Matchar, Professor of Medicine and Director of the Center for Clinical Health Policy Research at Duke University, will discuss the

potential role of MT100 in migraine therapy and the benefit-to-risk ratio of MT100.

Dr. Silberstein, Director of Jefferson Headache Center in Philadelphia and the current President of the American Headache Society, will review clinical considerations in migraine treatments. Then I will close our presentation of this morning.

(Slide CC-4)

A bit of history. Pozen filed the IND for MT100 in 1997 and undertook a preclinical, clinical and pharmaceutical development program. There were several discussions in meetings with the FDA over the next six years which culminated in the submission of the NDA in July, 2003. Pozen believed that the totality of the data in the NDA supported approval of the fixed-combination product. However, the FDA did not agree with Pozen and issued a not-approvable letter in May, 2004.

A critical-path meeting was held in late October, 2004 with the Division Director, Dr. Katz, and the Office Director, Dr. Temple. As a result

of that meeting, the FDA suggested an advisory-committee meeting be convened to address the potential risk of tardive dyskinesia with MT100 before we undertook any additional work.

(Slide CC-5)

That brings us to today's meeting which really revolves around one central question; does the potential risk of tardive dyskinesia preclude the ultimate approval of MT100, whether for all patients or for a readily identifiable group of patients who receive the maximum benefit.

(Slide CC-6)

MT100 is a patented pharmaceutical tablet formulation which is basically a pill inside a pill. The core consists of the 500 milligrams of naproxen sodium that is sprayed with an insulating coat followed by a spray coating of 16 milligrams of metoclopramide hydrochloride, which is equivalent to 13-and-a-half milligrams of metoclopramide base, then followed by a color coat.

The tablet is designed to release metoclopramide immediately into the stomach to

alleviate the gastroparesis often associated with migraine following the release of the long-acting drug, naproxen, after it leaves the stomach. Please note that the doses of both components are well below the maximum daily doses approved for these two products for other indications.

(Slide CC-7)

In May, 2004, the FDA issued a not-approvable letter for MT100 citing both efficacy and safety concerns. The FDA concluded that the efficacy data for MT100 provided only modest benefit over naproxen at 24 hours and that this benefit, coupled with the possible risk of metoclopramide-induced tardive dyskinesia, did not warrant approval of MT100.

The not-approvable letter also stated that the data submitted in the NDA did not provide a significant benefit for all of the migraine-associated symptoms at two hours versus placebo in two well-controlled studies. The FDA did agree that one study was considered to have met all the endpoints necessary for approval.

Therefore, the FDA felt that the potential risk of developing tardive dyskinesia was not outweighed by the 4 to 6 percent benefit of the MT100 over the active control, naproxen, at 24 hours.

(Slide CC-8)

Now, regarding tardive dyskinesia, the not-approvable letter states, "The absence of any detected cases among 300 patients is consistent with the true rate of TD of about 1 percent, an unacceptably high risk in the absence of any advantage of the product."

The FDA's mathematical calculation of 1 percent is derived from the upper limit of the 95 percent confidence interval around zero which we believe is based on the 300 subjects in the long-term safety study. Any implication that the true rate approaches 1 percent is unfounded based on the available scientific data in the literature, the spontaneous case reports from the U.S. and the U.K., national safety databases and our own clinical-trial experience in treating over 3700

patients with MT100.

We feel that the risk of tardive dyskinesia is very low and, certainly, much less than 1 percent. While approximately 2700 of these patients treated only single attacks, our 12-month safety data that we conducted was actually three times larger than the FDA had requested.

This study exposed over 1000 subjects to MT100 for three months, over 600 subjects for 6 months and over 300 subjects for 12 months treating over 23,000 individual migraine attacks and there were no reports of tardive dyskinesia in these studies.

(Slide CC-9)

Now, metoclopramide had been on the market for over 20 years when Pozen submitted the NDA and there were never any concerns raised by the FDA as far as I am aware regarding tardive dyskinesia during the development of MT100. Even though we saw no cases of tardive dyskinesia during the development program, to be conservative, Pozen mimicked the current metoclopramide labeling found

in Reglan, from the Warnings Section of the approved label, regarding any possible risk of tardive dyskinesia.

The Reglan label states, regarding tardive dyskinesia, that both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose. Less commonly, the syndrome can develop after a brief treatment period at low doses. In these cases, the symptoms appear more likely to be reversible.

I would like to stress, again, that the use of MT100 in the migraine population exposes patients to both a low dose, 16 milligrams, of metoclopramide hydrochloride and to an episodic use of about three to six times per month.

(Slide CC-10)

Based on the available scientific evidence, Pozen submits that the risk of tardive dyskinesia associated with metoclopramide use is very low and should be even lower with the episodic

use of MT100. The therapeutic dose of metoclopramide hydrochloride, as I said, in MT100 is only 16 milligrams. The data from the long-term safety study indicates that the expected use of MT100 is only about four doses per month.

Dr. Schapira will review the spontaneous national safety databases from both the U.S. and U.K. and the scientific literature. There have been very few cases of tardive dyskinesia reported from the chronic use of metoclopramide as a single ingredient over the past 40 years and, to our knowledge, no cases of tardive dyskinesia have been reported with the episodic use of metoclopramide.

As I said, there were no cases of tardive dyskinesia seen in our clinical-trial program either. Therefore, to the best of our knowledge from the literature, the national safety databases and experts in the field, the risk of developing tardive dyskinesia from the episodic use of MT100 should be lower than currently approved metoclopramide-containing products. Therefore, Pozen feels its potential risk of tardive

dyskinesia should not preclude the ultimate approval of MT100.

(Slide CC-11)

Since MT100 is a fixed-combination product, it must also satisfy the FDA combination policy as shown on this slide which simply states that, "Two or more drugs may be combined in a single form when each component makes a contribution to the claimed effects and the dosage of each component is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling."

We believe MT100 satisfies this policy.

(Slide CC-12)

Dr. Alexander will review the efficacy data for MT100 in a few moments, but I would like to share a few highlights of what he will show you.

There was a significant improvement in the primary endpoint of sustained pain response over 24 hours in five of six studies versus placebo or the pseudoplacebo metoclopramide. One study did not

achieve significance and the p-value was 0.054.

The data from the two component studies both demonstrate that each component of metoclopramide makes a significant contribution to the claimed effects for all patients but an even greater effect in a significant patient population experiencing migraine attacks without nausea.

In addition to the primary 24-hour sustained pain endpoint, the FDA requested that we evaluate migraine efficacy endpoints at two hours versus placebo. In all six efficacy studies, MT100 was always significantly better than placebo for pain at two hours. We also showed improvement over the associated symptoms of nausea, photophobia and phonophobia at two hours.

Although these studies were not powered to show a difference in these secondary symptoms, in most cases, MT100 was numerically, if not statistically, superior to placebo.

(Slide CC-13)

In conclusion, I believe that the potential risk of tardive dyskinesia should not

preclude the ultimate approval of MT100.

(Slide CC-14)

Next I would like to introduce Dr. Schapira, Professor and Chair of Neurology at the Royal Free and University College Medical School in London and Professor of Neurology at Queens Square, who will summarize the available information on tardive dyskinesia associated with metoclopramide use.

Thank you.

DR. KIEBURTZ: Dr. Reese, before you--does anybody have just a quick clarification or--okay. Thank you.

Overview of Tardive Dyskinesia

DR. SCHAPIRA: Thank you, Dr. Reese, and thank you, Dr. Kieburtz, and thank you to the committee for the opportunity to come and speak to you this morning.

I guess I am coming here wearing two hats. The first is of a neurologist, a general neurologist, in the U.K. who, in outpatient clinic, sees a spectrum of neurological disorders, a

significant proportion of which, of course, includes headache and a significant proportion of that, in turn, includes migraine.

The second hat is that of a neurologist with a specific interest in movement disorders. So it is with those two hats, if you wish, that I am going to cover some specific areas this morning.

(Slide CC-15)

The first is to address the issue of why use metoclopramide in migraine and the second is specifically to address the risk of tardive dyskinesias, or TD, with metoclopramide use. I would like to divide my comments on this into three areas; the chronic, intermittent and episodic use. I will come back each of those in turn.

(Slide CC-16)

Just to begin with why use metoclopramide in migraine.

(Slide CC-17)

I will cover this only briefly because others will also comment on this, but we know that it enhances absorption of orally administered

analgesics. It is an anti-nauseant and anti-emetic. A meta-analysis indicates that parenteral metoclopramide seems to have a specific anti-migraine activity on its own.

(Slide CC-18)

The advantages, if you wish, of metoclopramide in migraine have actually been used in the U.K. because we have, for 25 years, actually had access to three drugs, all of which are metoclopramide analgesic combinations. The first is MigraVess. The second is Paramax, and MigraMax. MigraVess was available between 1980 and 1999 and was then withdrawn in favor of Migramax because of the higher dose of aspirin compound in the latter.

All of these three compounds, as I say, contain 10 milligrams of metoclopramide per dose and the maximum recommended dose in the U.K. is three dose per 24 hours, so a 30-milligram-per-day dose of metoclopramide.

There is no restriction in the U.K. on the number of times a patient may take this compound per week, per month, et cetera, so long as they do

not exceed the three-times-per-day, 24-hour, dose. I should also point out that, for general use, metoclopramide has been available in the U.K. since 1964.

(Slide CC-19)

The use of these metoclopramide-analgesic combinations in the U.K. have been found useful. In fact, they have now been incorporated into the U.K. Guidelines for the management of acute migraine. The first step is a simple analgesic. The second step is, then, the metoclopramide-analgesic combinations given orally or, if necessary, given by suppository. The third step is the use of a triptan.

We have found, in clinical practice in the U.K., that that middle step, that Step 2, is a very useful practical intermediate step between the use of simple analgesics and the use of a triptan.

(Slide CC-20)

Now, I would like to come on specifically to address the issues of tardive dyskinesia. In terms of the use, I will focus first on chronic

use. This I am going to define, really, as the most frequent, most common, use in the U.S., particularly, of Reglan, or metoclopramide, for its gastrointestinal uses, and also in the U.K. we have an equivalent drug which we call Maxolon, again with the same range of uses for gastrointestinal disturbances.

(Slide CC-21)

Let me, first of all, though, before moving on to the surveillance data, begin with a view of tardive dyskinesia. There are several different definitions of tardive dyskinesia, so what I have tried to draw out is some of the commonalities between them.

I think we could say that it is a syndrome consisting of potentially irreversible involuntary dyskinetic movements which can affect any part of the body but which predominantly affect the orolingual-buccal region. It has traditionally been associated with chronic, and that is 30 days or more, use of a dopamine antagonist, generally speaking, at the higher dose ranges of the those

antagonists.

But some definitions of TD also include daily use for three months, or daily use for one month if the patient is 60 years or more, onset during use or, alternatively, onset with four to eight weeks of cessation.

The pathogenesis of tardive dyskinesia is not fully understood but it is thought to include the development of supersensitivity of the dopaminergic system. The prognosis of TD, once it develops, is variable and, again, the precise handles on this can vary. Two studies, for instance, quoted in the helpful FDA submission, suggest that 33 percent of patients may resolve spontaneously in two years and another 29 percent over six months.

But, certainly, TD can be irreversible and can be extremely distressing.

(Slide CC-22)

I would like to just now move quickly to some of the surveillance data that is available on TD, the first of which, looking at the association

between TD and metoclopramide came from Scandinavia. Between 1977 and 1981, there were established 11 million doses and they identified 11 cases of TD.

Then the first of two U.K. studies. The first was a retrospective analysis of the Committee of Safety of Medicines. This is a yellow-card system whereby medical practitioners will send in a yellow card to the CSM when they identify an adverse drug reaction.

Looking at the years between 1967 and 1982, so about 15 years, of Maxolon only--so this is looking at the use of, if you will, the Reglan equivalent in the U.K.--it established 15.9 million prescriptions over this 15-year period, so just over 1 million per year. They identified four cases of TD.

Then there was a prospective study by the same author looking at a time point in 1986 over a six-month period where they prospectively looked at prescriptions, again for Maxolon, the Reglan equivalent, not for the metoclopramide-analgesic

combination. So, for this Reglan equivalent, they identified just over 2-and-a-half thousand prescriptions or patients who were given prescriptions and found 25 extrapyramidal events with 12 dystonias, eight akathisias, five drug-induced Parkinsonism but no case of tardive dyskinesia.

It might be helpful just for me to set in context the dosage issues of metoclopramide in the form of Reglan or Maxolon and that suggested for MT100.

(Slide CC-23)

Reglan, here, I understand, is used at a recommended dose of 10 to 15 milligrams per day, in some cases up to 20 milligrams, but the general recommendation is for 10 to 15, up to four times a day. So the maximum dose would be 60 milligrams a day. Then the course of the medication varies according to the indication it is used for, up to eight weeks or up to 12 weeks.

If you look at the maximum calculated recommended exposure for one course, you come to

just over 5 grams of metoclopramide. But, if you take a conservative estimate of usage--let's say if you half that recommended maximum--you would come out with, let's say, 10 milligrams four times a day and for eight weeks rather than 12 weeks.
You come out to about 2.24 grams, so that is 45 percent of the maximum recommended dose on that schedule.

Just to put this in context, that half-exposure, if you wish, half of the maximum recommended exposure, is the equivalent to treat 166 doses of MT100, 166 migraine attacks, or, if a patient were to take MT100 at its maximum recommended dose of 6 tablets per month every month, they could take 2.3 years of MT100.

In fact, the median number of doses per year of MT100 in the 302 study was 22, so if you translated this into practical MT100 usage, this would be the equivalent to seven-and-a-half years of Reglan at half its maximum recommended dose or 15 years of practical use of MT100 at the maximum exposure of Reglan in one specific course.

So that just sets the sort of dosage issues in context.

(Slide CC-24)

I would like to now come to this very helpful review by Shaffer, Dr. Shaffer, who was--he and two other colleagues from the FDA and another from Duke published a paper looking at the U.S. reporting system for the period 1968 to 2003, so over 35 years.

Now, just for the 10-year period between 1994 and 2003, they estimated that there were about 42 million scripts for metoclopramide. They identified in their database 87 cases, 40 of which made that predetermined definition of TD. But I will talk about this in a little bit more detail.

(Slide CC-25)

This is a 35-year review. Interestingly, just when they looked at all the scripts for patients who were given metoclopramide, 62 percent of those were intended for women and 24 percent, almost a quarter, were intended for patients who were age 70 or over. The authors actually didn't

include the use of migraine in their estimations but I understand from the FDA submission that they have now calculated that 2 percent of this use was for migraine and, no doubt, they will address that issue specifically themselves.

Now, the predetermined definition of TD that these authors used to identify their cases was metoclopramide exposure for 30 days or more and documented involuntary movements or symptoms. As I say, they identified 87 separate reports but 60 of these had involuntary movements and 53 had duration of use of 30 days or more.

In practice, 40 of the 87 met the predetermined criteria of TD. I note that, in the FDA submission, their number is 68 and, again, no doubt, they will address that separately.

Of those that did develop TD, the mean age was 60 with a range of 11 weeks to 95 years, and 65 percent of the TD patients were women which corresponds, actually, quite well with the 62 percent women that were given the scripts in the first place.

The mean dose was 33 milligrams per day, the duration 753 days although, again, the FDA submission, I note, identifies the median as 180 days. Six of the patients were on anti-psychotics as well as metoclopramide and 22 of them were considered to have permanent disability, eight of whom needed a visit to the emergency department or hospitalization because of their TD.

(Slide CC-26)

I would like to now move from what I have considered in terms of the Reglan or Maxolon type usage in the U.K. and the U.S. to the intermittent or episodic. Here I would like to draw my own distinction between these.

In my understanding, intermittent pharmacotherapy is a course of treatment separated by a period of treatment followed by another course of that same treatment so, over a prolonged period, intermittent doses with periods in between without the medication. I contrast that with episodic PRN or as in "when required" use such as, for instance, as used in acute migraine attacks. That is what I

am going to refer to as episodic use.

(Slide CC-27)

Let me just remind you that, in the U.K., we have, for the last 25 years, had access to these metoclopramide-analgesic combinations for the treatment, the episodic treatment, of acute migraine the dosage of which, in any 24 hours, is 30 milligrams. Looking at the equivalent, incidently, in MT100, the maximum daily dose is 13.5 milligrams in terms of the base of metoclopramide which is the equivalent in these combinations.

In the U.K., it is estimated almost 100,000 patients receive a total of about 8 million doses of these combinations per year. In the five-year period 1999 to 2003, there were estimated to be a total of 40 million doses. So these are drugs which are used relatively commonly for the treatment of acute migraine in the U.K.

(Slide CC-28)

Now, the ADROIT database is a physician database. It records physician-identified and

reported adverse events to a central, now computerized, database and it records prescriptions as well as adverse events, so it is particularly helpful.

In the period 1964, when metoclopramide first became available, to 2005, so about a 40-year period, they were able to collect data on metoclopramide. But what is, I think, of particular interest this morning is that this database is able to discriminate between the Maxolon-Reglan type use in the U.K. and the use of metoclopramide-analgesic combinations for acute migraine. So the database discriminates between those two uses.

They found almost 3000 adverse-event reports by any route of which 156 were related to the acute-migraine metoclopramide-analgesic combinations of which 69 were neurological over a period from 1980 to 2005 which is when these combinations have been available to us.

(Slide CC-29)

Just to look at little bit more closely at

these 69 neurological events over that 25-year period reported to this database, there were 26 dystonias or oculogyric crises, eight extrapyramidal disorders not specified, three dyskinesias which were not classified as TD--they were reversible after the patient stopped their medication--one of Parkinsonism, one of akathisia but no reports of choreiform movements and no reports over this 25-year period of tardive dyskinesias.

(Slide CC-30)

There were a collection of other neurological events; acute extrapyramidal disorders were numbered 14 and this may well include things like oculogyric crises, and then a variety of other neurological features. So that totals a number of 69 none of which were TD.

(Slide CC-31)

Just to make a comparison between acute episodic use of metoclopramide-analgesic combinations for acute migraine and the other general use of metoclopramide, I have listed there

the adverse events. You will see that there have been reports, of course, of a variety of neurological events including the dystonia/oculogyric crises with the more chronic type of metoclopramide use, the sort of Maxolon-Reglan type use, and 24 cases of tardive dyskinesia with the non-migraine use of metoclopramide compared to the zero for the migraine use.

(Slide CC-32)

I would just like to very briefly cover the MT100 experience; nine phase 3 studies, 3,700 subjects, over 25,000 doses and a study which took just over a 1,000 patients to follow them up over a period of up to 12 months.

In the MT100 studies, there were two patients that experienced acute dystonic reactions but no patients that experienced tardive dyskinesia.

(Slide CC-33)

Just looking at the longer-term study, 1,000 patients recruited, 621 were followed over

six months, 329 over 12 months, treating 23,000 migraine attacks. As I mentioned before, the median number of doses per patient over the 12 months was 22 and the mean number of days between each dose was almost 10.

(Slide CC-34)

So just looking at the--one has to accept somewhat limited MT100 data. We haven't seen any cases of TD. But just looking at the U.K. data where we have got data now for over 25 years, and there is that period 1999 to 2003 where specifically, just for that period, they have estimated 40 million doses, we haven't had any reports to the ADROIT database of any cases of tardive dyskinesia over that period.

(Slide CC-35)

I would like to summarize. I think we have to accept that the MT100 experience is insufficient to exclude a small risk of TD with its usage. But, moving to the larger U.K. experience, I think we have had no reports of analgesic-metoclopramide combinations causing TD

and that is use for migraine over 25 years and at a very conservative estimate, over 100,000 million doses.

This, remember, is using a dosage and a frequency for these analgesic-metoclopramide combinations in the U.K. which is greater than that which is proposed for MT100.

(Slide CC-36)

The FDA briefing documents raised some important topics and I would just like to address three of those specifically. The first is the question that they asked, is there sufficient evidence that the chronic intermittent administration of metoclopramide does not carry the same risk of TD as the chronic administration.

I can say that the experience from the U.K. over the 25 years that we have had them of these metoclopramide-analgesic preparations, the answer is yes. Yes; we do have sufficient evidence that the chronic intermittent administration of metoclopramide does not carry the same risk of TD as the chronic administration.

(Slide CC-37)

So, if the answer is yes, what is the maximum number of recommended monthly doses to avoid the risk of TD? Well, the answer to that is not known. But I have to come back to the U.K. experience just to mention that, over the 25 years, there have been no cases of TD using the metoclopramide-analgesic combinations at their recommended dose and schedule which exceeds that for MT100.

(Slide CC-38)

Finally, this is an issue which will be addressed by other experts specifically and that is on medication-overuse headache, but the question is posed, do you believe that, based on the existing data on medication-overuse headache, there is evidence that the proportion of patients prescribed MT100 will likely take a number of monthly doses higher than that recommended.

Well, I can't answer this question specifically, of course, but I can only say that if this does happen, even if it does happen with this

type of combination, the U.K. data don't indicate that it should lead to TD.

Thank you very much.

(Slide CC-39)

I would like now to pass to Dr. Jim Alexander who is Pozen's Chief Medical Officer. He will review the data on the efficacy of MT100 in migraine.

DR. KIEBURTZ: Same thing. Anyone have a point of clarification?

DR. SMITH: Could you go over with me, on Slide CC-21, the definition of tardive dyskinesia, please--the definition. My question is, you say some definitions include the duration of exposure. When do the definitions include that? In other words, is that a common use definition?

DR. SCHAPIRA: The definitions vary. As I say, some definitions, looking at the case studies that have been published on TD and metoclopramide have required that the patient has been taking metoclopramide continuously for two months, others for three months. Some of the other studies like

the Shaffer review have said that the patient should be taking it for 30 days or more.

So there is some variation in how people define the requirement of metoclopramide exposure before they will associate it with TD.

DR. SMITH: I see. So, if it doesn't meet the duration of use, it would be dyskinesia, not TD? Is that correct?

DR. SCHAPIRA: I think that would depend on the individual study and the interpretation of the authors. For instance, in the Shaffer paper, they identified that they would use the definition of 30 days or more. But they also recognized--for instance, I think they reported on three juvenile cases, two infantile and one adolescent case, that developed tardive dyskinesia, I think the two infants following an overdose of metoclopramide and the adolescent also had some other features.

So I think it depends clearly how strictly you want to define and whether you will comment on other cases that fall outside your definition.

DR. SMITH: Okay. Thank you.

DR. KIEBURTZ: Let's hold on that because we will hear more about definitions. If the question is about TD definitions--no? Go ahead.

DR. LENAERTS: Dr. Schapira, in sharing your U.K. experience, what is your estimate of the prevalence of specifically migrainers either overusing metoclopramide-analgesic combinations or staying frequently or constantly at the maximum recommended dose, because you mention--

DR. KIEBURTZ: Excuse me. I am just going to stop. If you have a clarification on what he presented, that is one thing. Additional questions about something he didn't talk about, not yet.

DR. LENAERTS: Thank you. I will hold.

DR. KIEBURTZ: Just clarifications of the presented material. Dr. Katz?

DR. KATZ: A couple of questions. On Slide 22, the second Bateman study, just for clarification, what the design was. That was a prospective study?

DR. SCHAPIRA: No; that is a retrospective study. The CSM, yellow-card system.

DR. KATZ: The second one is the yellow-card system. I thought you said it was a prospective study.

DR. SCHAPIRA: No. I'm sorry. The second Bateman study that you see on the slide there, the one published in 1989, that was a prospective study.

DR. KATZ: Right; I am talking about the second study.

DR. SCHAPIRA: I'm sorry. I thought you said second on the list.

DR. KATZ: Oh; I'm sorry. The second Bateman study, the 1989. So that is prospective, so those patients were followed and their adverse events were recorded contemporaneous with their occurrence.

DR. SCHAPIRA: Yes.

DR. KATZ: It was a true prospective--

DR. SCHAPIRA: Yes.

DR. KATZ: Okay. Thanks. One other question. Slide 28, which looks at the reports of these events over a 40-year period, do you know

anything about the temporal pattern of those reports? In other words, were there more reports earlier on and then reports started to wane over time which sort of happens all the time, we think, with spontaneous reports? Do you know anything about that?

DR. SCHAPIRA: No; I can't comment on those. I can only say that the system has been in place, of course, for all of that time. More recently, over the past years, it has been computerized. So the ADROIT system is a fairly responsive system which is linked to primary-care computers throughout the U.K. But I can't tell you about the pattern of those over the years.

DR. KATZ: Just one other, if I can, question. The previous slide, 27, which looks at the combination, the actual acute-migraine treatments, do we know the actual doses that people took? As you say, the maximum dose, I guess, is 30 a day. Do we know? I don't know. Maybe we figure it out from the numbers, but do we know what people actually took?

DR. SCHAPIRA: No; we don't know precisely how many they took, only how many were prescribed. As I say, it is estimated as an average of 85 per person, but that doesn't tell you how many they took in an individual dose. So I don't have the data on that.

DR. KATZ: Dr. Fahn?

DR. FAHN: If we can go back to slide 22, again, for a clarification, the second Bateman study, the 1989 study, zero cases of TD, do you know what definition of TD they used to come to that number?

DR. SCHAPIRA: No. They did not specify their definition of TD.

DR. KIEBURTZ: Dr. Goldstein?

DR. GOLDSTEIN: I am not all that familiar with your drug-reporting system. Two questions about it. One is how compulsive is the use of this? In other words, how often do you think you are actually getting reports about things that are actually happening.

The second question related to it is does

the system allow for validation somehow of these reports because, especially with primary-care physicians, it is not clear to me how accurate these reports may be about particular types of problems.

DR. KIEBURTZ: It is a little evaluative. It is a good question. Can we hold on it because I am conscious that the sponsor only has a certain amount of time to present. I don't want to infringe on that.

One last question about the second Bateman study that you have already had questions about. Was that only new prescriptions?

DR. SCHAPIRA: Yes.

DR. KIEBURTZ: Thank you.

DR. SCHAPIRA: I'm sorry; can I just clarify. That was the number of prescriptions that were given during that six-month period. So it didn't specify whether that was a renewed prescription for that individual or not.

DR. KIEBURTZ: Oh; I see. Okay. Thank you.

DR. SCHAPIRA: Thank you. I will now hand over to Dr. Alexander.

Review of MT100 Efficacy

DR. ALEXANDER: Thank you, Dr. Schapira.

Although the potential risk of tardive dyskinesia is the primary focus of this meeting, when Pozen and the FDA discussed the meeting, we agreed that the committee should have the opportunity to review data described in the efficacy of MT100.

(Slide CC-40)

My presentation will, therefore, summarize the results of studies designed to evaluate the efficacy of MT100 using two different trial designs which evaluated the acute treatment of single migraine attacks.

First, I will show the results from the phase 3 studies which evaluated MT100 versus placebo or metoclopramide as a pseudoplacebo. These studies examined the efficacy of MT100 as a migraine drug using those endpoints that are usually required for the approval of new migraine

therapies.

Secondly, I will review the data from the two component controlled trials which I will call the factorial studies. These are the trials that compared MT100 to its two individual components. Now, as you have heard, the efficacy of naproxen sodium as a component of MT100 is really not in question. So my focus in discussing these data will be on comparisons between MT100 and naproxen sodium which directly address the contribution of metoclopramide as a component of MT100.

(Slide CC-41)

The MT100 phase 3 program was quite extensive and almost 6,000 subjects were enrolled in six controlled trials treating single migraine attacks. Four studies directly compared MT100 with placebo while, in the two factorial studies shown below, 301 and 304, metoclopramide was considered a pseudoplacebo.

2,355 subjects received single doses of MT100. Did these studies provide evidence that MT100 was an effective migraine drug? Well, Pozen

believes that the data clearly showed this.

(Slide CC-42)

This table lists the six studies in the left-hand column. It is arranged to show the 30 individual different primary and secondary endpoints in the five columns to the right. Study 306, which is at the top, is the study that was accepted by the FDA as demonstrating the efficacy of MT100. The two columns on the far left show the key pain endpoints--that is, sustained pain response at 24 hours, which was the primary endpoint in four studies, and the two-hour pain response in the second column was a key secondary endpoint in five studies.

As shown now on the slide, in 11 of 12 comparisons, MT100 was significantly superior to the comparator for each of these pain endpoints. In Study 303, which had an unbalanced randomization with a smaller number of placebo recipients, the p-value for sustained pain response was 0.054.

But in all six studies, the efficacy of MT100 over the comparator for the two-hour pain

response, shown in the second column, was significantly superior. These results provide clear and compelling evidence that MT100 provides effective two-hour pain relief, the usual regulatory endpoint in migraine trials, as well as providing sustaining pain responses at 24 hours.

I will provide a better definition of sustained response in a few minutes. I want to mention the efficacy on the associated symptoms. Efficacy for the associated symptoms of nausea, photophobia and phonophobia, are also for a migraine drug. But, in contrast to pain, these symptoms are not always present in migraine attacks and, in fact, none of the Pozen studies were powered to detect differences for these endpoints but all were specified as secondary endpoints in our studies.

Nevertheless, significant differences in the incidences of these symptoms were seen among a number of these studies at two hours after dosing, as shown now. In additional comparisons, shown in yellow, the p-values were between 0.05 and 0.1.

The p-values, finally, in orange, are above 0.1.

As is reviewed in your briefing document, by three or four hours after dosing, significant benefits on all of these associated symptoms were usually present with MT100 treatment.

So, to summarize, the totality of the evidence from these six studies clearly shows that MT100 is an effective acute treatment for migraine.

(Slide CC-43)

I will now show the comparisons of MT100 against naproxen sodium. These comparisons, again, reflect the direct assessments of the contribution of metoclopramide within MT100 in order to satisfy the combination drug rule.

The two phase 3 factorial studies were each performed at sites in the U.S. Subjects were randomized to treatment with either MT100, naproxen sodium 500 milligrams, or metoclopramide 16 milligrams, the identical doses of these component drugs that are contained within MT100.

Subjects treated a single migraine attack of moderate of severe pain intensity and symptom

assessments were performed at baseline and hourly for 24 hours. Rescue medication was permitted after at least two hours had elapsed after dosing.

(Slide CC-44)

I would like to take a second and explain the pain assessments in these trials, the primary endpoint as well as the secondary endpoints. Sustained pain response at 24 hours was agreed by Pozen and the FDA as the appropriate measure to use to assess the efficacy of MT100 versus each of its two components.

Sustained pain response is a composite measure of efficacy and is defined as pain relief at two hours--that is, no pain or only mild pain--and no relapse or moderate or severe pain and no need for the use of rescue medication over the next 22 hours after the two-hour assessment. The efficacy of this endpoint is judged by how many subjects meet this definition at 24 hours.

I would like to stop at this point and explain why Pozen and the FDA agreed that the use of the two-hour pain response endpoint would not be

acceptable for the comparison of MT100 with naproxen sodium. This was because both treatment are active due to the presence of naproxen in each drug and should, in fact, produce very similar pain responses at the time point of two hours after dosing.

Two-hour pain response was a secondary endpoint in these studies and was used to evaluate MT100 versus metoclopramide as a pseudoplacebo, as I have previously shown.

In contrast to the sustained pain response and two-hour response rates which measure the number of subjects responding, at the bottom of the slide, you will see three secondary endpoints that were also evaluated in these trials. These are the Pain Intensity Difference score, PID, the Sum of Pain Intensity Difference scores, SPID, and the TOTPAR scores, or Total Pain Relief scores, over time.

These are the measurements of how much pain relief is obtained, not of how many subjects have a specific pain response at a given time.

These are the accepted general endpoints for analgesics within the FDA. They are recognized as very sensitive for detecting differences between individual active analgesic drugs.

But let's first look at the agreed primary endpoint and that was sustained pain response from these two studies.

(Slide CC-45)

Shown here are the data from these studies with a percent of responders plotted. First, note that the metoclopramide-alone treatment produced sustained pain response rates of 19 and 20 percent which are similar to what might be expected of a placebo.

The responses to naproxen sodium alone were 9 to 10 percent higher than metoclopramide and the rates were actually 28 percent and 30 percent in the two trials. These were significant differences over metoclopramide. The sustained response rates for MT100 were 6 percent and 4 percent higher than those for naproxen sodium in these two studies.

I am sure you have noted that Pozen and the FDA arrived at different p-values for these comparisons. But both parties agree that the absolute differences are 4 and 6 percent for this endpoint. Are these differences confirmed by other analyses? The secondary endpoints provide support for these findings.

(Slide CC-46)

The mean SPID scores at 24 hours show significant differences for MT100 versus naproxen sodium in both studies. So these analyses of a secondary endpoint, a valid measure of pain relief, support the findings of the sustained endpoint. I would also note, and not shown, but the fact that the differences were significant in the SPID scores at two hours after dosing in both studies.

(Slide CC-47)

A third dataset, the 24-hour TOTPAR scores, is also supportive with mean TOTPAR scores at 24 hours for these two studies showing significant differences between MT100 and naproxen sodium. So these additional analyses, which were

secondary, support and confirm the results seen with the sustained pain-response endpoint and substantiate the contribution of metoclopramide to the effect of MT100.

But, even if this were not the case, there is a subgroup pseudoplacebo that seems to respond much better to MT100 than the naproxen sodium. Now, the reason that we can discuss this subgroup is the following: at the outset of the phase 3 program, Pozen theorized that metoclopramide might contribute not only to better pain relief but might also contribute to the relief of nausea that may accompany migraine attacks.

(Slide CC-48)

For this reason, one of the three pre-planned analyses that were used in all of the phase 3 studies include analyses of pain endpoints within two subgroups of migraine attacks--that is, those with nausea and those without nausea at the time of treatment.

(Slide CC-49)

These are the results for subjects whose

migraine attacks were not accompanied by nausea. This type of migraine attack made up one-third of the attacks treated in Study 304 and one-half of the attacks treated in Study 301. The number of subjects in each study is shown with the figure on the left being 301, the figure on the right, 304.

In these subgroups of attacks, the differences between MT100 and naproxen sodium for sustained pain responses were essentially doubled to 9 and 10 percent. In this instance, the differences were highly significant, with p-values less than 0.01 in both studies. This was seen in both studies and, therefore, is not likely to be a chance occurrence.

Pozen took a further step of providing its phase 3 data to Drs. Richard Lipton and Ken Kolodner who conducted independent analyses of these data and confirmed these findings. The odds ratios and the significant p-values are provided in your briefing document in Table 11.

(Slide CC-50)

As additional confirmation, the mean SPID

scores in these subjects with attacks without nausea also showed significant differences in these sensitive measures of pain relief for MT100 versus naproxen sodium at 24 hours. When Pozen met with the FDA in late 2004 and the data for this subgroup of attacks were presented to the agency, Pozen was asked if the same effect was seen for MT100 across the phase 3 studies.

The answer is definitely yes. Pozen performed a pooled analysis of phase 3 trial data and these results were obtained.

(Slide CC-51)

These studies were conducted in the same time period. They all treated subjects with migraine attacks of moderate to severe intensity and there were similar entry criteria and evaluation criteria. The comparators included placebo, metoclopramide and naproxen sodium.

As you can see, there was a significant difference only in the treatment with MT100 for the comparison of the treatment of attacks with and without nausea, again, highly significant.

So why would these effects be present? The only plausible explanation is the 16 milligrams of metoclopramide contained within MT100.

(Slide CC-52)

Therefore, the unique contribution of metoclopramide may be described as counteracting the gastric stasis associated with migraine, enhancing the rate of absorption of naproxen, providing better pain relief in the overall treatment population and, finally, enabling maximum benefit to be obtained in migraine attacks without nausea.

(Slide CC-53)

So where does this leave the efficacy of MT100? Pozen believes that the data show that MT100 is an effective migraine treatment, that MT100 provides an absolute 4 to 6 percent improvement in sustained pain response over that for naproxen sodium, that MT100 provides absolute 9 to 10 percent improvements in sustained pain response over naproxen sodium in migraine attacks without nausea.

Secondary endpoints, SPID and TOTPAR, confirm the superiority of MT100 over naproxen sodium. Finally, the contribution of metoclopramide to the primary endpoint of sustained pain response is demonstrated in two studies.

Thank you for your attention.

(Slide CC-54)

I would like now to introduce--it is my privilege now to introduce Dr. David Matchar, Professor of Medicine at Duke University School of Medicine. Dr. Matchar is Director of the Duke Center for Clinical Health Policy Research and, over the past two decades, he has made significant contributions in the field of evidence-based decision making in medical care. In the migraine area, he has been a member of the U.S. Headache Consortium and was lead author of the group's evidence-based guidelines for the treatment of migraine, a collaboration among eight professional societies.

Dr. Matchar was invited by Pozen to provide his perspective on the potential role of

MT100 in the treatment of migraine and his view on the balance of benefits and risks of this treatment.

DR. KIEBURTZ: Just real quickly, any last clarifying questions? Dr. Welch?

DR. WELCH: The nausea versus the non-nausea studies. Was that a prospective nausea versus non-nausea?

DR. ALEXANDER: The studies were both designed to have a preplanned analysis of the subgroups of attacks with nausea and without nausea.

DR. WELCH: So you didn't look for separate populations.

DR. ALEXANDER: I'm sorry; I didn't understand.

DR. WELCH: You didn't look for separate populations. It was all in the same study.

DR. ALEXANDER: Oh; I'm sorry. It was the same study. It was certainly not randomized between nausea and no nausea.

DR. WELCH: Did you look at the time from

the start of the pain to the onset of the nausea in the nausea group?

DR. ALEXANDER: No; we didn't.

DR. KIEBURTZ: Dr. Temple.

DR. TEMPLE: Maybe you will think this is too much discussion, but when you separated out the nausea people, my assumption always was you thought the drug would work better in people that had nausea, not less.

DR. ALEXANDER: That is exactly right. I mentioned that--I may not have emphasized it enough because initially Pozen believed that metoclopramide would have an anti-nausea effect in migraine. The thought was, we will look at those with nausea and those without nausea.

We did that. As it turns out, if there is an anti-nausea effect, it occurs after two hours--

DR. TEMPLE: No; I don't even mean that. You have said that the effect on pain is better in people with nausea.

DR. ALEXANDER: That's correct.

DR. TEMPLE: And you did, as you showed,

have groups with and without nausea separated for analysis. But what happened was the opposite of what you expected. Maybe that is not a major point.

DR. KIEBURTZ: Dr. Koski?

DR. KOSKI: I assume that your patients within this study had more than one attack of migraine.

DR. ALEXANDER: That's not correct. This was a single-attack study.

DR. KOSKI: It was single attack. Thank you.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: You may also want to defer this question for later, but the preparations that you used in these comparator studies, you went through, or somebody went through, in the beginning talking about how the MT100 is put together. You have a core. Then it is sprayed and sprayed again, and then there is another spraying on top of that.

In these studies, how is the metoclopramide put together? Was this done with a

blind core that was then sprayed in the same way so that the pharmacokinetics would be the same?

DR. ALEXANDER: Yes; they were identical in visual appearance and the placebo--excuse me; the comparators were identical and the metoclopramide was around a core, a blank core.

DR. GOLDSTEIN: Thank you.

DR. KIEBURTZ: Dr. Katz, did you have something?

DR. KATZ: No.

DR. KIEBURTZ: Just to remind the sponsor, we will stop in half an hour. Just if you want to think about your presentations, we will be stopping at ten of the hour.

Potential Role of the MT100 in Migraine Therapy

Balancing Benefits and Risks

DR. MATCHAR: Good morning. I think, in addition to the introduction that Dr. Alexander gave me, I would just like to comment that I am also a principal investigator of the three-city study of headache management that is funded by the Agency for Healthcare Research and Quality and that

is in an effort to link the evidence-based guidelines that have been developed to actual clinical practice. So it is in that context that I will make my remarks this morning.

I guess, also parenthetically, I should mention that I am the husband of a migrainer and the father of a migrainer so I guess I have both a clinical, a research and also a personal interest in this topic.

(Slide CC-55)

My task that I have been asked to fulfil today is to talk about the clinical trials and the safety studies in a clinical-practice context. In thinking about this, three questions really arose in my mind that I felt were particularly salient.

The first is is there really a role for a new migraine therapy above and beyond what we have available. We have seven triptans that are out there, for example. Do we really need something else?

The second question is, when we look at clinical differences in clinical-trial results of 4

to 6 percent, what, really, does that mean to patients. Is that something really worth pursuing? Then the third question is how should we be thinking about benefit to risk in the particular scenario of an acute migraine treatment.

So, in talking about these three questions, or in addressing these three questions, I am going to follow the following outline which is first describing just some context of the clinical burden of migraine, efficacy in clinical trials focusing on the relationship between the measures and the meaning those measures might have in a clinical setting, and a little bit about available oral treatments including something about adverse effects of available treatments, and then, finally, talk a little more about this issue of balancing benefits and risks and a clinically useful conceptual framework that I have, I use, and I find useful in thinking about benefit and risk.

(Slide CC-56)

Not to really belabor the obvious to a group of neurologists about headache, headache is

about pain. The definition from the International Headache Society places pain as key. It is an episodic disorder lasting 4 to 72 hours with two of any of the following pain characteristics; unilateral location, pulsating quality, moderate or severe intensity and worsened by movement.

In addition, there are the associated symptoms which were described earlier, specifically photophobia and phonophobia together or nausea and/or vomiting. So that constitutes a definition. But, again, the key element from a clinical perspective, and from the diagnostic perspective, is pain.

(Slide CC-57)

It might go without saying that migraine is not a homogenous disease. While pain is nearly always present, what is less consistent is the presence of associated symptoms. Here the phonophobia or photophobia, the punch line, basically, is that most people typically do have these symptoms whereas, in the case of nausea, most people typically don't have nausea. So the data

here is only 38 percent reported nausea or vomiting in more than half of attacks and only 32 percent reported nausea in all attacks. So that is just, again, the point. The nausea is not uniformly present and that migraine really is a syndrome with a variable syndrome cluster presentation.

(Slide CC-58)

The question I am moving on to now is the issue of the unmet need. I don't know if anyone cited the statistic of 25 million people in the United States having migraine. That is based on a very high-quality epidemiologic study done by Richard Lipton and colleagues.

Of those 25 million, 53 percent of these individuals describe a disability, significant disability, or the need for bed rest. Now, I think this is going to be described a bit later, but there needs to be some understanding of the true magnitude of a migraine for most migrainers. These are very severe headaches. They are very disabling. In fact, a day is sliced out of that person's life.

In addition to there being a lot of migrainers and the disability being quite severe, patients tend not to be satisfied with their treatment. We will go into that a little bit later. I will mention--I will expand a bit on the issue of adverse effects, in particular, but there is good evidence that patients are not getting effective care in their early visits, that physicians are finding it difficult to take the medications that are available to them and create a mix that is useful to a large majority of patients.

One of the issues at the bottom here that is cited, and I realize it is not a FDA concern, per se, but it certainly is a concern for our patients, is that the medications available are very expensive and often interfere with patients' willingness and ability to take them regularly for their severe attacks.

(Slide CC-59)

What do patients need? What patients need, effectively, is what they want. What do they want? They want pain relief. Again, this is from

a survey done by Dr. Lipton and colleagues. Patients surveyed with migraine, they say the most desirable outcomes in an acute migraine therapy are rapid onset of pain relief, their freedom from pain and there is no recurrence of pain. So it is the notion of a sustained response to pain and sustained response that goes into the definition of what patients are asking for from a migraine therapy.

(Slide CC-60)

Do clinical measures, or do measures used in clinical trials, address what patients want? Now, the standard measure that is used in clinical trials is the ordinal rating system in which pain is rated 3, 2, 1, 0 from severe to none. It is important to point out that 3 to 2 is not especially valuable for patients but going from 2 to 1 is something that patients would clearly desire and, therefore, the criteria for entry into clinical studies would be having severe or moderate pain and the criteria for response is going from severe or moderate to mild or none.

So the measure that is typically used, the standard measure that has historically been used, is pain response rate. It is the proportion of subjects who achieve mild or pain-free status two hours after dose when pain was either moderate or severe at baseline and no rescue medications were allowed in that period. But it is a two-hour measure.

(Slide CC-61)

Let's turn to that other issue about sustainability of the response. Let's start with the measure I just mentioned which is a good measure. It is a two-hour pain relief. It is a good start. Historically, it is what has been used as the regulatory endpoint. Triptans, for example, were approved on the basis of the two-hour response.

But a better response takes into account this time-course issue that patients care about. Sustained pain response at 24 hours includes mild or no pain at two hours, so it is what the preceding measure includes, but also includes to

relapse to moderate or severe pain and no use of rescue medications. This means you get relief. You continue to have relief.

Again, from a clinical perspective, the notion that you are not going to have a recurrence is extremely important because the possibility of having a recurrence is a very ominous concern for patients. If you know that there is a good likelihood that this is going to come back again, you are not going to be able to experience your day in a normal way.

This also raises this concern about, well, is 5 percent more people having this response really worthwhile. I would suggest, well, if we were only talking about 5 percent of people, or 5 percent of pain, being better, going from 100 to a 95, or going from 95 to a 90, that would not be particularly worthwhile.

But what we are talking about is 5 percent more people, so we are talking about people, in this case, they get relief and they continue to have relief. Again, this is a point of

differentiation that distinguishes MT100, potentially, here.

At the bottom, I have here what would be considered the best outcome which would be sustained pain-free at 24 hours. I think this constitutes our vision for what we would like to see in migraine therapy and I think we are moving towards that as a more standard measure in future clinical trials.

(Slide CC-62)

Briefly, on the issue of associated symptoms, we talked about the three photophobia, phonophobia and nausea. In clinical trials, these symptoms tend to be more commonly reported than they are in community samples of migrainers. But, again, even in trials, these symptoms are associated only with a fraction of the patients.

They are recorded as present or absent so the all-or-none measure is a relatively crude measure of response to treatment. Again, efficacy is assessed at two hours which has a concern from a clinical perspective that some of these patients

who won't have nausea at the outset will start to have nausea after and will have nausea two hours, but then might have it relieved at three hours after their pain is relieved.

So I think the point here really is that the measures of associated symptoms--it is not that associated symptoms aren't important. They are important. But the measures that tend to be used and are standard in clinical trials are relatively crude and more so than the measures used for pain.

(Slide CC-63)

So what do we have currently for migraine therapy that is oral and FDA-approved for migraine indication? What is currently available includes, on the left side, the over-the-counters, which are ibuprofen, which are two products, acetaminophen, aspirin-caffeine combination. That is one side.

On the other side, and I would say, actually, far on the right side, are, then the prescription medications. There are seven triptans currently FDA-approved for migraine and the point here is there is a paucity of approved oral drugs.

I don't know any clinicians who would say they are particularly happy with the variety of medications that are available.

In light of the fact that most patients presenting to a doctor have failed over-the-counter medications for at least their worst headaches, then there really, truly, is a big gap in what is available when a patient presents to you. In effect, the only thing you have available, as a migraine-specific therapy in this case, is going to be the triptans.

I will mention in a moment that that is not always a satisfactory solution for patients. Unfortunately, what happens clinically, when this gap is not filled with another more useful medication, physicians are tending to use--continue to use--narcotics and barbiturates which are undesirable for lots of reasons, three of which are that they have not been studied in clinical trials. They are not FDA-approved, so that is a concern. And they, obviously, have undesirable adverse effects.

(Slide CC-64)

This clinical impression that there is a therapeutic gap is supported by empirical evidence. This is a couple of studies in which, they point out, in the real world, half of patients will often delay treatment with prescribed medications. They will have a prescription in hand and 69 percent of them will wait and see if the headache is really a migraine. About half of them will want to take their medication only if the attack is severe.

This is not the sign of a very healthy environment, that people have prescriptions and they are not wanting to take them even though they are having, in this case, at least moderate to severe pain.

As a consequence, I would presume, that four out of five migrainers have expressed an interest, a specific interest, in trying a novel product with similar efficacy to what they have in hand, the prescription they have in hand, but has fewer adverse effects.

(Slide CC-65)

This then turns us to the issue of bothersome adverse effects. Why don't migrainers like what we have available?

On the right side, you see the non-triptan products which include the over-the-counters I mentioned, nonsteroidals, but also include opioids and barbiturates. As one would expect, the side effects are sleepiness, nausea, difficulty thinking, inability to function, and so on.

Not too dissimilar, even, are the triptans on the left side. But one syndrome which is particularly bothersome to many of my patients--I know it is extremely bothersome to my daughter--is this chest-pressure phenomenon.

Yes; there are coronary effects of the triptan. Some patients--and, indeed, it is contraindicated with patients with coronary-artery disease--but, for the vast majority of people who are having these chest-pressure syndromes, they have no coronary disease. These are not coronary symptoms. What they are, again, is a bit of conjecture, but they are extremely frightening and

most people who experience them find them sufficiently disturbing that, even if you try to convince them endlessly that they are not having cardiac ischemia, they are frightened and they won't want to take the medication.

So that is a concern and, as I say, other symptoms are sufficiently aversive for patients that they will delay their therapy or not take the medications prescribed at all.

(Slide CC-66)

Now let's turn to the issue of balancing benefits and risks of acute therapy. To think about this, I would like you to imagine, first of all, another scenario entirely. This other scenario entirely is a stroke-preventive medication.

A stroke-preventive medication might work and it might not work. How do you know that it doesn't work? For the most part, you know it doesn't work because the patient has a stroke. Okay; you lose. And that is how you know that your drug is a failure.

Well, we have a very lucky circumstance with migraine in that migraine lends itself to tailoring. There are multiple episodic attacks over many years. You get immediate feedback on the efficacy of the acute treatment. Tailoring here, then, is specifically aimed at maximizing the chance that the therapy will work for a given attack.

The idea, basically, is patients don't like to take medications that don't work, especially if they don't have any other effect that you kind of like. So an opioid you might take even if it doesn't really--well, not me, personally, or you, personally, but, certainly, some people will take them just because they have another effect that they like.

Consequently, with this tailoring occurring, the benefit-to-risk margin actually improves over time for each of our individual patients.

(Slide CC-67)

Recognizing that some people don't like

words as much as they like pictures, I have here a picture that basically raises this concept as the filter of clinical experience. We start out basically saying, look, from population studies, from clinical trials, we realize that not all patients are going to respond. But we are going to try it. We are going to treat all these patients within some set of characteristics.

We have some set of characteristics and, of course, it wouldn't have been approved if we hadn't considered the benefit-to-risk to be acceptable. Now, after some period of time, patients decide this works under this condition, this doesn't work under this condition, and they pick and choose, and what we end up with is patients taking medications for which they tend to respond.

Consequently, the clinical benefit-to-risk ratio improves over time and is ultimately maximized. Again, the point I want to make is that patients don't take drugs that don't work for the most park.

(Slide CC-68)

As suggested earlier, from the experience in the U.K., as Dr. Schapira mentioned as well as using the components in the United States, the notion is that MT100 would fill in this gap that is currently basically being filled with opioids and barbiturates which is a bad scenario. The notion, again, is that, amongst the various options, what we allow by making this new drug available is to fill in the gap and to offer an opportunity for patients to create a mix for themselves that makes the most sense for them.

Not all patients, certainly, will respond to this. Those who will respond to it will take it. The benefit, again, as I mentioned earlier, or the risks, will only accrue to those people who achieve benefits.

(Slide CC-69)

So, in summary, I am going to just cover those three questions real quickly. Is there a role for a new migraine drug? I believe the answer is unequivocally yes. Migraine is a common

disorder. Patients have significant unmet needs. The available oral medications are very limited and, unfortunately, the gap that exists is now being filled by undesirable drugs.

The second question is what is the meaning of the clinical-trial difference, this 4 to 6 percent everyone is talking about. Well, not quibbling over whether you buy the 4 to 6 percent statistical significance or not, what does 5 percent mean. Let's just say 5 percent. 5 percent is not 5 percent of pain. It is 5 percent of people. That is an important point from a clinical perspective. That is meaningful.

Now, the last point, or the last question, is what is the meaning of a benefit-to-risk ratio in clinical practice. I just want to mention again this concept of tailoring. Migraine treatment lends itself to tailoring. Patients don't take drugs that don't work and thus, in clinical practice, we have the lucky circumstance that benefit-to-risk ratios can be optimized.

Thank you very much.

DR. KIEBURTZ: Any--Dr. Sacco?.

DR. SACCO: Dr. Matchar, just a clarification, maybe, on Slide 63 for part of your talk. I assume most of your talk has been indicated for acute migraine attacks. You haven't dealt with any of the FDA-approved medications for migraine prevention, of which there are some.

DR. MATCHAR: Oh, sure; yes.

DR. SACCO: That would just be a clarification.

DR. MATCHAR: Right. These are oral products for acute indication, acute migraine.

DR. KIEBURTZ: Dr. Lenaerts?

DR. LENAERTS: Thank you. I have a question regarding Slide 57. Could you confirm the 38 percent of patients reporting nausea and then 32 percent, actually, reporting in all attacks. I have some other information that says up to 90 percent of people have nausea occurring. So migrainers have up to 90 percent.

DR. MATCHAR: Right. The point that I am making here has to do with the patterns, the

typical patterns, for patients, not the average for all migraines. So having nausea is a typical pattern in a minority of patients. Actually, Dr. Silberstein did one of these studies and he might be able to clarify that later.

DR. KIEBURTZ: Dr. Jeste.

DR. JESTE: I have a similar question. If you look at your Slide 62, you said nausea incidence is 40 to 70 percent.

DR. MATCHAR: Right; and this is in clinical trials. So the population you are going to see in clinical trials is going to be different. So this says, basically, as a patient enters into these trials, the presence of nausea is going to be more likely than it was going to be when you are asking the question, what is the typical pattern or cluster of symptoms among migrainers. So, yes; patients who are in trials will typically have the symptoms more commonly.

DR. KIEBURTZ: Thank you.

DR. MATCHAR: I am going to turn to Dr. Silberstein.

(Slide CC-70)

Dr. Silberstein is actually a colleague working on one of the clinical trials that I mentioned earlier and he is the Director of the Jefferson Headache Center and the Department of Neurology and is the President of the American Headache Society.

DR. KIEBURTZ: We see your number of slides in the book, but just so you are--

DR. SILBERSTEIN: I have cut them.

DR. KIEBURTZ: Perfect. Thank you.

Clinical Considerations on Migraine Therapy

DR. SILBERSTEIN: I want to thank everybody for having us here today. Looking at the time, I have tried to cut and I will try to talk reasonably quickly.

(Slide CC-71)

I am going to talk a little bit about the rationale for the use of metoclopramide. I am going to briefly talk about attacks without nausea. I am going to spend most of my time talking about medication-overuse headache of which I have a

particular interest and then summarize a possible benefit of MT100.

(Slide CC-72)

We learned about metoclopramide and migraine many years ago from, actually, our colleagues in London. Marshall Wilkenson and Nat Blau who run the City of London Migraine Clinic made it part of their everyday treatment and it got introduced, like many things do, on the basis of anecdote.

Many of us continue to use it in the absence of trials until you saw the evidence today. It is used to prevent nausea. It enhances the absorption of nonsteroidals. Many headache experts continue to use metoclopramide for those reasons.

(Slide CC-74)

I think you have seen the evidence to show that MT100 is more effective than placebo. One can argue about the statistics, but you see in the evidence that MT100 is more effective than naproxen sodium and clearly more effective than metoclopramide.

(Slide CC-76)

One of issues is its 4 to 6 percent response, clinically significant. I think, in part, it depends on how seriously you view migraine as a disorder. If you had a patient who has had cancer of the brain and you had a survival rate of 10 percent and you went to 14 percent, nobody would argue that that is clinically significant. So take into context what migraine is to the sufferer and take into context that migraine is often considered not a serious disorder.

One of the ways of looking at it is to look at all attacks and look at the absolute and relative differences. If the 4 to 6 percent really means in patients getting 14 to 20 percent relative increase, and if you look at the subset of attacks without nausea, you are assuming that the data is correct because the subset analysis was not the primary endpoint, you are talking about a third improvement.

This, to me, is clinically significant.

(Slide CC-78)

I would like to spend a little bit of time talking about the concept of medication-overuse headache, for that was one of the questions. What is it? First, many patients have chronic daily headache which, by definition, means nothing more than headaches occurring more than 15 days a month.

In the clinic, it is the most common cause of chronic daily headache. I was fortunate enough to be the head of the International Headache Society Classification Committee on Chronic Daily Headache. The criteria we came up with were the following: headache has to be there more often than not greater than or equal to 15 days per month; regular overuse for more than three months of acute medication; the headache is actually developed or worsened coexistent with overuse; lastly, you stop the overuse medication and the headache reverts to its previous form.

(Slide CC-79)

The next issue is how much medicine. First, triptans, ergots, opioids or butalbital-containing analgesics taken on a regular

basis ten or more days per month. What we don't mean is ten days in a row. We mean ten days divided up. Two, other analgesics 15 or more days a month for a total exposure of 15 or more days a month. That is the definition of medication-overuse headache.

(Slide CC-80)

The next issue is which are the drugs that are most likely to produce medication-overuse headache. The first caveat is there are absolutely no placebo-controlled, well-designed clinical trials of medication-overuse headache in the world, yet. High probability based on a series of anecdotes, opioids or narcotics, ergotamine and butalbital-containing compounds.

Chris Diener from Germany said the best thing he ever did was get butalbital-containing compounds removed from the market in Germany. That is his legacy.

Caffeine is associated with medication-overuse headache. Lower probability; aspirin, acetaminophen, and triptans. Unlikely and

controversial, other non-steroidals, DHE or neuroleptics are even associated with medication-overuse headache.

(Slide CC-81)

In summary, MT100 in migraine therapy. I think it could be a primary therapy when simple analgesics fail. By the time patients come to the physician, they have failed simple analgesics and, as Dr. Matchar showed, there is an area in between. Triptans can't be used, don't work or are overused.

The reason for this is, we believe, that nonsteroidals and neuroleptics, metoclopramide, in particular, are unlikely to produce medication-overuse headache. It is common among clinicians who are interested in headache--we use this class of drugs to prevent medication-overuse headache or to treat medication-overuse headache. Lastly, we believe it can fill the gap between simple analgesics and triptans that is now being filled by opioids and by butalbital-containing compounds.

(Slide CC-82)

I think it is important to realize the World Health Organization has said that migraine is one of the four most disabling disorders know to mankind and that a patient with a severe migraine attack has the same degree of disability as somebody who has quadriparesis, dementia or acute psychosis.

Thank you.

DR. KIEBURTZ: Thank you.

Any clarification questions? Dr. Temple?

DR. TEMPLE: One of your slides, and a number of people have shown the same one, was the attractiveness of oral metoclopramide in migraine.

DR. SILBERSTEIN: Correct.

DR. TEMPLE: Counteracting gastric stasis.

DR. SILBERSTEIN: Correct.

DR. TEMPLE: Treating or preventing nausea, enhancing absorption of NSAIDs and a lot of people use it.

DR. SILBERSTEIN: Right.

DR. TEMPLE: I guess what are you saying about those things? Are you saying that is part of

the evidence? Or what?

DR. SILBERSTEIN: What I am saying is the following. Until these trials were done, we were doing this on anecdote. Physicians continue to do a number of things in the absence of evidence-based medicine. I think what you have seen today is evidence-based medicine. I think the questions are going to be, there are a lot of patterns of behavior. The pattern of behavior in the United States today for taking care of most migraine attacks is to either give a narcotic or opioid or butalbutal-containing in the absence of scientific evidence.

What I am suggesting is this is an alternative and I think it is the job of this panel to see whether it is a good or a bad alternative.

DR. TEMPLE: Okay. But you are not suggesting any of those reasons are the reasons or true or--

DR. SILBERSTEIN: I am suggesting that this is the anecdotal lure and the basis of why this compound has been commonly used in the past in

the absence of good scientific evidence.

DR. TEMPLE: Okay.

DR. KIEBURTZ: Thank you.

We will break now for fifteen minutes. I will just remind the committee members that our discussions only happen in public. During the break, you are not to discuss with other committee members or, in fact, anybody, the presentations or your views on things. The point of having a public meeting is our discussions are public. So, just avoid that in the interim and we will start at 10:05.

Thank you.

(Break.)

DR. KIEBURTZ: Why don't we get started. Dr. Bastings will be our first presenter, the clinical team leader. We will have, just to clarify the agenda, about an hour-and-15-minute presentation from FDA including an invited speaker. Then we will have time to question, for the committee to question, both the sponsor and the FDA.

Some of the questions I kind of suppressed earlier about interpretation, context, and so forth, that is our opportunity to do that.

So, Dr. Bastings, please.

FDA Presentations

FDA Risk/Benefit Considerations

DR. BASTINGS: Thank you. Good morning.

(Slide 1)

I will now present you some FDA risk/benefit considerations for MT100.

(Slide 2)

As you know, MT100 is a combination of naproxen sodium 500 milligrams and metoclopramide hydrochloride 16 milligrams. The proposed indication is the acute treatment of a migraine headache with or without aura.

The division issued a not-approvable action in May, 2004 mostly because the review team determined that the contribution of both active drug components to the claimed effects of the product had not been established.

(Slide 3)

According to the FDA Combination Policy, two or more drugs may be combined in a single dosage form when each component makes a contribution to claimed effects and the dosage of each component is such that the combination is safe and effective for a significant patient population regarding such concurrent therapy.

(Slide 4)

To address the Combination Policy requirements, Pozen conducted two factorial studies of similar design. These were Study 301 and 304. In both studies, patients were randomized to MT100, naproxen or metoclopramide. The primary endpoint was sustained pain response.

(Slide 5)

Sustained pain response is defined as a moderate or severe headache at baseline with mild or no headache at two hours and no relapse and no use of rescue medication between two and 24 hours.

(Slide 6)

This slide shows you the key result of the two factorial studies. For Study 301, the

sustained response rate for MT100 was 35.6 percent as compared to 29.8 percent for naproxen. So the contribution of metoclopramide was 5.8 percent and this was not a statistically significant difference according to the prespecified analysis plan.

For Study 304, which was a much larger study, the sustained response rate for MT100 was 31.8 percent as compared to 27.9 percent for naproxen. So the contribution of metoclopramide was 3.9 percent and this was not a statistically significant difference according to the prespecified analysis plan.

(Slide 7)

This slide shows you the two-hour endpoints in the factorial studies. I must stress that Pozen was not required to show a contribution of metoclopramide on these endpoints. However, these are highly relevant endpoints in migraine studies. These are the ones typically used to approve migraine drugs. Since the primary endpoint did not show a significant contribution of metoclopramide, it is useful to examine these

typical endpoints.

What you can see on this slide is that, in both studies, there was no significant difference between MT100 and naproxen for the two-hour pain response, the incidence of nausea at two hours, the incidence of photophobia at two hours and the incidence of phonophobia at two hours.

(Slide 8)

As you know, sustained pain response is a composite endpoint. To better understand the changes seen with that endpoint, it is useful to look at the individual components which are the two-hour pain response and the use of relapse or rescue medication.

So, in Study 301, you can see that the two-hour response for MT100 was 48.1 percent as compared to 46.6 percent with naproxen. So the contribution of metoclopramide at two hours at 1.5 percent. This was not statistically significant.

The use of rescue medication or the relapse of the headache after a response at two hours was seen in 12.6 percent of MT100 patients

versus 16.8 percent of naproxen patients. So the contribution of metoclopramide there was 4.2 percent and this adds up to 5.8 percent of difference in the sustained response rate.

(Slide 9)

In Study 304, you can see a contribution of metoclopramide for the two-hour pain response of 3.1 percent and you see that the difference in the relapse or rescue-medication use is less than 1 percent. This adds up to 3.9 percent of difference in the sustained response rate.

(Slide 10)

Finally, this slide shows the sustained responses for the associated symptoms. Sustained responses here are defined in a similar manner as for sustained pain response. For example, sustained nausea-free means no nausea at two hours with no relapse of nausea between two and 24 hours and not use of rescue medication.

What you can see is that, in both studies, there was no significant difference between MT100 and naproxen for sustained nausea-free, sustained

photophobia-free, and sustained phonophobia-free.

(Slide 11)

Pozen met with the division in October, 2004, and, at that time, they presented these subgroup analyses which suggested a contribution of metoclopramide in patients with no nausea at baseline. At that time, the division considered to accept the prospective replication of these findings to fulfill the Combination Policy requirements but we assured Pozen that we would need to bring this to an advisory meeting because this is an unusual patient population and we need to make sure the benefits in that population outweigh the risk related to metoclopramide.

(Slide 12)

I will briefly show you these subgroup analyses that Pozen made. You already know that, for the combined patient population, there was no significant difference between MT100 and naproxen for sustained pain response and for the two-hour pain response.

If you look at the patients who did not

have nausea at baseline, you see about 10 percent difference between MT100 and naproxen with a low p-value. But, if you look at the two-hour pain response, there was no significant difference between MT100 and naproxen even in that subgroup.

For patients who had nausea at baseline, you can see that there was less than 1 percent difference between MT100 and naproxen for sustained pain response. For the two-hour pain response, the rate was actually numerically higher for naproxen but the difference was not statistically significant with MT100.

(Slide 13)

Similar findings for Study 304. You know that, for the combined patient populations, there was no significant difference for sustained pain response and two-hour pain response. For patients with no nausea at baseline, again, there is about a 10 percent difference between MT100 and naproxen. For the two-hour pain response, there is no significant difference between MT100 and naproxen for that subgroup.

For patients with nausea at baseline, there was about a 1 percent difference between MT100 and naproxen for sustained pain response and the two-hour pain response. These differences were not statistically significant.

(Slide 14)

I would like to give you some thoughts on an indication limited to patients with no nausea at baseline. In a survey of 500 self-reported migrainers, nausea occurred in more than 90 percent of these patients and nearly one-third of these experienced nausea during every attack.

Less than 10 percent of patients consistently had migraine with no nausea at baseline which is the indication for which MT100 which is being considered today. In line with that survey, there was a 45 to 69 percent incidence of nausea at baseline in the MT100 phase e studies.

(Slide 15)

Migraine patients, in the majority of them, may have some attacks with nausea and other attacks without or nausea may develop during the

attack. Patients would, therefore, need two different treatments based on the presence or absence of nausea or they would treat their attacks with nausea with a combination product containing metoclopramide which has no established contribution for efficacy for the type of attack. Yet, they would be exposed to the risk of metoclopramide.

(Slide 16)

As you know, our main safety concern is tardive dyskinesia. Tardive was originally intended to emphasize a late appearance during neuroleptic treatment. However, there have been a number of reports that TD may appear early during the neuroleptic treatment and there seems to be no fundamental distinction between cases appearing early and those appearing late.

(Slide 17)

In addition, there have been a number of TD variants described and these include tardive dystonia, tardive akathisia, tardive myoclonus, tardive tics, tardive tremor, and it is very much

unclear how well these different variants have been captured in the post-marketing reporting systems.

(Slide 18)

TD is a well-known side effect of metoclopramide. Its exact incidence remains unclear. There was no case reported in the MT100 database but the database was too small to detect rare events such as TD.

(Slide 19)

The current metoclopramide labeling includes a warning which I am going to read to you. "Tardive dyskinesia may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become reversible are believed to increase with the duration of treatment and the total cumulative dose. Less commonly, the syndrome can develop after relatively brief treatment periods at low doses. In these

cases, symptoms appear more likely to be reversible."

(Slide 20)

Because of these safety concerns, the FDA limited the indication of oral metoclopramide for short-term therapy for gastroesophageal reflux for up to 12 weeks and only when conservative treatment fails for the treatment of diabetic gastroparesis for up to eight weeks. The recommended dose is 5 to 15 milligrams up to four times a day.

(Slide 21)

As I mentioned earlier, there have been a number of cases reported in the literature of the relatively short durations of treatment, sometimes as short as one or two weeks. We also asked our colleagues from the Office of Drug Safety to look for cases of movement disorders associated to metoclopramide in the AERS database and you will hear a presentation with much more detail on that topic later in the morning.

In that analysis, the first quartile of duration of treatment for the cases of TD was 19.5

days.

(Slide 22)

This slide show you a breakdown of the treatment duration. You can see that there are quite a few cases with duration of treatment less than the 90-day definition which has been used in some of the earlier studies.

(Slide 23)

We also asked our colleagues from ODS to look at the patterns of use of metoclopramide. Metoclopramide is mostly used for GI indications. Migraine use, up to now, is quite limited. It is less than 2 percent. 13 percent of patients appeared to have received prescriptions for more than 90 days and 7 percent of patients for more than 180 days, so exceeding the labeling recommendations.

Over a three-year period, cumulative therapy was longer than 90 days for almost 20 percent of patients and greater than 180 days for over 10 percent of patients, again exceeding the recommendations.

(Slide 24)

What about the risk of TD associated with chronic intermittent use of metoclopramide as has been proposed in this NDA. This is very difficult to evaluate for a variety of reasons which include that there is no current indication for chronic intermittent use in the United States and that there is no specific capture of chronic intermittent use in the AERS database.

Some animal data suggests that the intermittent use of neuroleptics may be no safer, or even riskier, than continuous use in an animal model of TD. In the psychiatric population, the number of interruptions in chronic treatment--so this is slightly different from chronic intermittent but this may be suggestive--the number of interruptions was the second factor after age in predicting the occurrence of TD.

(Slide 25)

Another concern that we have is the overuse of acute migraine drugs. Medication-overuse headache was recently introduced

in the IHS classification. There is a subcategory of analgesic-overuse headache. According to experts, there is substantial evidence that all drugs used for the treatment of migraine may cause medication-overuse headache and the prevalence of medication-overuse headache in the general population is around 1 percent.

The IHS also said that the overuse of symptomatic migraine drugs is the most common cause of chronic daily headache. We are not that much worried that MT100 could cause chronic daily headache. We are just worried that there could be a similar abuse of the drug as has been seen with the other approved or non-approved migraine drugs.

(Slide 26)

So we have the following questions for the advisory committee. The first one; in a recent submission to the NDA, Pozen estimated an annual incidence of TD of up to 0.038 percent for metoclopramide at a daily dose of 30 to 40 milligrams per day for 72 days per year which corresponds to up to 380 cases of TD per million

patients per year.

Do you think that this is a reasonable estimate? If MT100 were to carry the same risk, would such a risk level be acceptable if the only contribution of metoclopramide is a 5 to 10 percent improvement on sustained headache relief with no effect onto our endpoints? Is any risk of TD acceptable for a migraine population?

(Slide 27)

Question 1; is there sufficient evidence that the chronic intermittent administration of metoclopramide does not carry a risk of TD? Is it possible to define a maximum recommended number of monthly doses of MT100 to avoid the risk of tardive dyskinesia?

(Slide 28)

Question 3; do you believe that, based on the existing data on medication-overuse headache, there is evidence that a proportion of patients prescribed MT100 will likely take a number of monthly doses higher than recommended?

(Slide 29)

Question 4; all currently approved acute treatments of migraine are indicated without restriction regarding the presence of absence of nausea at baseline. Given that patients may have nausea at some attacks and no nausea at others, does an indication limited to the subpopulation of migraine patients with no nausea at baseline represent a clinically meaningful and acceptable indication?

(Slide 30)

The last question; if Pozen shows prospectively in a new clinical study in migraine patients with no nausea at baseline a significant contribution of metoclopramide on sustained headache pain relief of 5 to 10 percent with no contribution at two hours and no contribution on relapse rates or rescue-medication use in the two to 24 hour period, would the demonstrated benefit outweigh the risk related to TD? If not, what additional data or desired primary outcome, or desired effect on sustained relief, could provide evidence of safety and efficacy?

(Slide 31)

Finally, I would like to thank the following FDA colleagues who have contributed to this presentation . Thank you for your attention.

DR. KIEBURTZ: Thank you. Same deal. If there are some clarifying questions. Let me just point out some things about the questions which Dr. Bastings has presented. After the public hearing this afternoon, that will be the time we have to spend a great deal of time discussing these.

We can clarify points of these questions at that time rather than at this time because it will be immediate to our discussion.

I would just add at this point my approach to this, or our approach to this, should be that there are some assumptions made in here. We are not debating whether those assumptions are good ones or bad ones. The question to us is, if that was assumed, how would you think. This is what Dr. Katz referred to earlier in terms of this being somewhat hypothetical.

I think we could spend a lot of time

arguing about whether the assumptions are good ones or not. I don't think that is the meat of the matter here. If one assumed those things, then how would you make decisions about that. I just want to put that out there.

There are some questions that are asked of us about estimates and whether those are reasonable. But, again, much of the clarification on the questions, I think it would be better to do at the time we discuss the questions individually unless you have a burning question about those. Certainly, they are open to questions about the rest of Dr. Bastings' presentation.

Dr. Green.

DR. GREEN: I have a regulatory question about the Combination Policy. It has to do with the contribution of each drug and what is acceptable. Is one drug increasing the bioavailability of another? How would that be interpreted?

DR. KIEBURTZ: Dr. Katz or Dr. Bastings?

DR. KATZ: I think the contribution, as

defined in the reg--it is ill-defined in the reg. It just says "some contribution." So it could be in any one of a number of clinical areas, safety, efficacy. But, in and of itself, increasing the bioavailability probably wouldn't be particularly helpful unless that resulted in some sort of clinical advantage; faster onset, or more sustained onset, or fewer side effects.

So, in and of itself, increasing the bioavailability in a typical case, at least off the top of my head, wouldn't be, necessarily, considered useful.

DR. TEMPLE: But you can imagine cases, and there have been cases, where inhibiting metabolism might lead to a more sustained and less variable blood level. In some sense, what does carba dopa do? So there could be cases. But, as Russ says, you would have to weigh the disadvantage of adding another therapy and, if the alternative is just tasking 20 percent more, you would probably find that not worth it.

DR. KIEBURTZ: Okay. Why don't we go on.

Our next speaker is Dr. Jinnah from Johns Hopkins Hospital.

Overview of Tardive Dyskinesia

DR. JINNAH: Good morning.

(Slide)

Thanks for the invitation to come and speak here. I have been asked to give a brief summary of the clinical condition of tardive dyskinesia.

Normally, my presentation on this topic would be about an hour, but I am going to limit my comments to ten minutes and, in so doing, I am only going to be able to touch on the highlights. I am going to skip a lot of details but I can certainly answer questions later if necessary.

(Slide)

So, with that, let me just proceed to review this topic. The term "dyskinesia" refers to any abnormal movement and the term "tardive" refers to late or delayed. What I would like to do is first address the nature of the abnormal movements and then go on to describe when it occurs.

(Slide)

The movements vary quite a bit depending on different patients. By far the most common abnormal tardive syndrome is the so-called buccolingomasticatory syndrome, which is a bit of a mouthful, but it basically refers to abnormal movements of the face and tongue. I will show you an example of this on videotape in just a second.

Less common tardive movement disorder syndromes include the ones listed there including tardive dystonia, which refers to mainly twisting and bending movements, tardive chorea, which resembles dancing, tardive tourettism which resembles Tourette syndrome, tardive tremor or myoclonus which, simply put, are shakes and jerks.

In addition to this group of broader movement disorders, there are some tardive syndromes that are not necessarily classified as abnormal movements but, rather, psychological or psychiatric manifestations. These include akathisia, which is a sense of severe restlessness that prevents people from sitting still. It

includes unusual tardive pain syndromes which have an unusual anatomical distribution that include the oral or perineal regions, and, finally, respiratory irregularities referred to as tardive respiratory dyskinesias.

Now, most clinicians will recognize the most common form here and that is the top one, the face-and-tongue syndrome. But the less common forms are far less well appreciated.

(Video)

Let me show you an example of two of these, first the most common one. This is a videotape of a man who has two problems. I hope it is not too small to see. If you can see his mouth, it is in constant motion, jaw, lips and tongue. He came complaining that he had trouble talking, he had trouble eating and he was biting his tongue.

You can also see his hand. One of his hands is shaking. He has a tremor that resembles Parkinson's disease. This man got his condition after two years of metoclopramide use. He was, unfortunately, unaware that he was only supposed to

be taking the medication for three months and his doctor was unaware that metoclopramide was on the list of medications that can cause a tardive syndrome like this.

(Video)

Let me show you a second example of the tardive dystonia. You can see this man's problem is much more severe and, perhaps, more disabling. This is an example of dystonia or the bending-and-twisting syndrome. You can see that he has great difficulty standing up straight because of extreme arching of his back and backward bending of his head and neck.

Here you will see a closer view of the nature of this problem. He is like this more than 80 percent of his waking hours, standing or seated. He gets relief only if he lies down. He can only temporarily bring his head to the midline position voluntarily and then it just goes back and it is too much effort to keep straight.

This man got his condition from the use of a classic neuroleptic agent which is a more common

source of this problem.

(Slide)

So what exactly causes these syndromes? It is widely recognized that they are most commonly caused by the neuroleptics. These are the dopamine-receptor-blocking agents that Dr. Schapira alluded to in the initial presentation. Essentially all classes of neuroleptics will cause this syndrome although some are less likely to cause it than others.

These are widely recognized but what is less well recognized is a much longer list of agents that also have the potential to cause these syndromes. On this list include anti-emetics such as metoclopramide and prochlorperazine. Other medications used in psychiatry such as anti-depressants and several others of which I have provided a partial list here.

(Slide)

So when do these problems actually arise? They are referred to as tardive syndromes because they usually require chronic administration of the

offending drugs. They occur with a wide range of prevalence according to different studies from less than 5 percent to more than 50 percent with an overall average being somewhere in the 20 percent range of chronically treated patients.

These numbers here were not derived specifically from metoclopramide use but rather from all neuroleptics and other drugs capable of causing tardive syndromes. The incidence is estimated to be about 5 percent per year during chronic daily treatment. The treatment duration is somewhat arguable and varies from report to report and definition to definition. The most conservative one is that treatment requires at least three months of constant therapy.

But, as noted before, there are lots of cases out there who have developed tardive syndromes with much shorter durations of action, sometimes just a few days. We can then ask whether or not these disorders should be classified as tardive syndromes or not, but that is generally not done in most of the epidemiological reports or

collecting databases.

There are some known risk factors of developing this condition. They include older age, female gender and several other less well-understood phenomena such as duration of treatment, the total cumulative dose of treatment, prior brain injury or other organic problems, diabetes, mood disorders and others.

(Slide)

How are these treated once they arise? In general, these recommendations come from psychiatry where this problem is most prevalent. They refer to all neuroleptics, not specifically to metoclopramide. Generally speaking, the recommendation is to attempt to discontinue the offending agent if possible.

If it is not possible, or if discontinuation does not cause resolution of the syndrome, as it often does not, there are several other things that are often tried, but there is very little evidence supporting a beneficial effect of any of these. Individual patients may respond

somewhat to one or another of the items on this list, but, by no means, can these be considered reliable treatments.

Instead, at least in the psychiatry literature, the belief for the use of neuroleptics and related offending medications that can cause tardive syndromes is that prevention should be one of the key aspects of treatment.

To prevent the disorder, the general guidelines are that the neuroleptics should not be used unless there are no other alternatives. When they are used, they should be used at the lowest dose possible. Some even recommend intermittent withdrawal of the neuroleptic to make sure that ongoing therapy is still needed. Since this disorder is quite difficult to treat, prevention is really quite an important element.

I believe that is all I have here and if there are any questions, I could take them.

DR. KIEBURTZ: Dr. Jeste.

DR. JESTE: One question. Did you imply that antidepressants and antibiotics cause tardive

dyskinesia?

DR. JINNAH: Causation is difficult to establish. If you look in the literature, you will find many cases of tardive dyskinesia reported that are due to a whole variety of different medications. The frequency of some of these other medications--for example, antidepressants or antibiotics, or I should say the frequency of the reports, is quite low. We could argue whether or not the patients who were presented in those reports really were tardive dyskinesia or not.

I am not passing judgement on the diagnosis of those. But I think it is generally well-accepted that tardive dyskinesia does not just come from neuroleptic medications and that was my point.

DR. JUNG: Can you clarify what mood disorders are associated with the development of tardive dyskinesia?

DR. JINNAH: There appears to be a slight epidemiological risk associated with affective and schizo-affective disorders as opposed to, for

example, schizophrenia.

DR. JUNG: So that includes just general depression which is very prevalent in the population.

DR. JINNAH: It does.

DR. JUNG: Thank you.

DR. SMITH: When a case comes up where isn't chronic exposure to a drug, is that typically categorized, then, as a dyskinesia as opposed to a tardive dyskinesia?

DR. JINNAH: It is a very good question. I think different experts would answer you differently here. Some people use a very strict criteria that it has to be at least 30 days or you call it something else, dyskinesia and acute abnormal syndrome. Some people are a little bit less strict in their criteria and say, well, if it looks and behaves like tardive dyskinesia, then, perhaps, one week exposure is sufficient. But these are not generally agreed-upon timetables.

DR. JUNG: You didn't talk about this on your slides, but could you discuss a little bit

about the kindling phenomenon with intermittent use, or is this an appropriate time?

DR. KIEBURTZ: Can we hold that one for the general question session.

Dr. Sacco?

DR. SACCO: On Slide 3, I think it is Slide 3 of yours, can you clarify what you mean by--it is actually blurred on my page--restlessness.

DR. JINNAH: Restlessness is exactly what that sounds like. These patients report that they can't sit still. When you watch them, they often rock in their chair. They stand up. They pace around. They just can't sit still and they describe a severe inner sense of restlessness.

DR. SACCO: Thank you.

DR. KIEBURTZ: Just a point of clarification, a follow up on Dr. Jeste's comment. Linking exposure to a phenomenon or establishing causation is a long road. There are various degrees of that road being established for various agents in tardive dyskinesia.

But, if I understood you properly, would you say that it is generally accepted that metoclopramide, as an agent, can cause tardive dyskinesia?

DR. JINNAH: I believe most would agree with that.

DR. KIEBURTZ: Thanks.

Our next speaker is Mary Ross Southworth.

Post-Marketing Review of Movement Disorders and Neuroleptic Syndrome Associated with Metoclopramide

DR. SOUTHWORTH: Good morning.

(Slides 1 and 2)

As we have heard this morning, MT100 is a combination of metoclopramide and naproxen that is being evaluated for the treatment of acute migraine. The proposed dosing is an a chronic but intermittent matter based on episodes of migraine. The proposed dosing of the drug recommends no more than six tablets be used per month and more than one tablet used per single migraine episode.

We were interested in looking at this

chronic intermittent dosing, whether we could look in our adverse-event database to see whether we could elucidate the risks associated with this kind of dosing.

(Slide 3)

I think we are pretty clear on the fact that metoclopramide is well known to cause movement disorders. In fact, the program labeling is specific on several movement disorders including extrapyramidal symptoms, Parkinsonian symptoms, tardive dyskinesia and neuroleptic malignant syndrome. The labeling for metoclopramide recommends a daily dose of 5 to 20 milligrams QID with a duration of therapy not exceeded 12 weeks.

(Slide 4)

This slide shows number of prescriptions dispensed for metoclopramide over about the last ten years. You can see that it exceeds 7 million in the year 2004. This jump in number of prescriptions dispensed in 2000 coincides with the withdrawal of cisipride from the market.

You have to keep in mind that the numbers

represented here are prescriptions dispensed, not patients. Also keep in mind that, although this usage data slide only extends for ten years, my adverse-event review will extend farther than that.

(Slide 5)

When developing our case series for metoclopramide-associated movement disorders and neuroleptic malignant syndrome, we wanted to focus on several points. First, could we ascertain what the reversibility of the reaction was, whether it be treatment with another pharmacologic agent or withdrawal of the offending drug.

We also were very interested in associating the dose and duration reported in the adverse-event reports, themselves, to the proposed dosing for MT100 which, as you have heard, is in a chronic intermittent manner. We also wanted to focus on any associated risk factors that were apparent in the cases such as concomitant drugs or concomitant disease states that the patients might experience.

(Slide 6)

So the purpose of our review is to characterize the cases of some specific adverse events that were reported in the adverse-event reporting system, or the AERS database, that were associated with metoclopramide.

(Slide 7)

The AERS database is a computerized database which contains reports of adverse events for all U.S. marketed drugs. It contains over 3 million adverse-event reports. The reporting in it is largely spontaneous meaning that healthcare providers are not compelled to report adverse events. However, sponsors, when they become aware of adverse events through a variety of sources, are required by regulations to report those to the agency.

Consequently, the source of the reports, for the most part, come from sponsors. However, there are a good number that come from healthcare providers or lay people like consumers, patients, patient's families or lawyers.

(Slide 8)

The left side of the screen shows the adverse events that were specifically searched for in our database. They included neuroleptic malignant syndrome, acute dystonia, akathisia, Parkinsonism and tardive dyskinesia. For each of these adverse events, we looked at the total number of case reports with specific focus given to daily dose of metoclopramide, the duration of treatment, any risk factors that might be present and the reversibility of the reaction.

(Slide 9)

In order to do this, we ran a search of the database using each of the movement disorders and NMS as a search term plus metoclopramide. We classified the cases into movement-disorder categories based on the diagnosis in the case, itself. I think it is pretty clear that there is substantial overlap between some of the reporting of the different movement disorders and, in order to keep clarity, we just used the diagnosis that was used of the case thinking we could capture the most number of cases that way.

Some points to remember when reviewing our case series were there could be what could be considered case misclassification because some cases might have reported a movement disorder after several doses of drug but may have caused the tardive dyskinesia where it could have possibly been called an acute dystonia. But we used the diagnosis made in the case.

Another thing to remember is that the way cases are reported in AERS, we frequently know dose, duration or frequency of the dose given but we very rarely know whether the dose was given continuously or intermittently.

Obviously, because these are labeled adverse reactions, there is going to be under-reporting of adverse events and also because the drug has been on the market for a long time, we are not going to get a maximum number of reports of adverse events.

The quality of the reports varied, as you might expect. There are several data points that seem to be more inconsistent and some of those

included status of recovery. Some cases may not have reported whether the patient recovered or not, and also time to that recovery.

(Slide 10)

This slide shows the number of reports we retrieved for each of the adverse events we searched for. There were 37 cases of NMS, 203 cases of acute dystonia, 57 cases of akathisia, 35 cases of Parkinson's and 68 of tardive dyskinesia.

(Slide 11)

Using those reports, we developed our case series which I will present to you. The case series is going to include demographics of the patients and clinical characteristics including any information we have on recovery. I am also going to spend some time talking about cases that reported continuing symptoms at the time of reporting. I will present some representative cases and then focus a little bit on cases associated with short-term metoclopramide therapy.

(Slide 12)

The first adverse event that will be

presented is neuroleptic malignant syndrome. We had 37 unique cases. The age represented was a mean of 49. The range of daily dose ranged from 7.5 to 80 milligrams with a mean of 33, mostly I.V. dosing represented here and mostly G.I.-related indications which will be very common in the next few slides. The range of duration of therapy was from 1 to 196 days with a median of three days.

(Slide 13)

In these 37 cases, concomitant medications that were associated with the development of NMS or NMS-like symptoms was reported in 20 and they included anti-depressants, anti-emetics and anti-psychotics.

One thing to remember is that not all cases reported whether there were concomitant medications or not, so I have just provided information on the cases that have.

Drug therapy was used to treat the adverse event in 18 cases and it largely consisted of what would be considered standard of care for neuroleptic malignant syndrome. The symptoms were

reported or resolved in 11 of the cases. The symptom was reported as continuing in one of the NMS cases but the symptom that was reported as continuing was more of a dystonic jaw clenching. In this series, eight patients died.

(Slide 14)

To look a little bit closer to the patients that died, in those eight patients, the daily dose of metoclopramide ranged from 10 to 40 milligrams with a mean of 32, kind of a mix of oral and I.V. dosing used, and the duration of therapy was short and ranged from two days to 15 days.

(Slide 15)

The first movement disorder, in our view, is acute dystonia. There were 203 unique cases. Acute dystonia was reported in a younger population with a mean age of 32. The range of daily dose was 0.6 to 800 milligrams with a mean of 71 milligrams. Largely oral dosing reported here. The range of therapy from one dose to over 2000 days but a short median duration of therapy of two days.

Again, you see mostly G.I. symptoms being

treated here although there were a sizeable number who were getting pre-treatment for chemotherapy with metoclopramide.

(Slide 16)

For these 203 acute dystonia cases, there were 64 cases which reported concomitant medications that were associated with movement disorders, mostly anti-depressants and anti-emetics. Drug therapy was used to treat the adverse event in 115 cases. For these acute dystonia cases, 115 cases reported the symptoms as improved or resolved. But symptoms were reported as continuing in 12 cases.

(Slide 17)

In those 12 cases which reported continuing symptoms, the daily dose ranged from 10 to 40 milligrams with a mean of 25, mostly oral dosing, and duration of therapy ranged from one day to over 2000 days with a median of 2.5 days.

(Slide 18)

We have 57 unique cases of akathisia. The mean age seen in this case series was 45. The

daily dose ranged from 5 to 200 milligrams with a mean of 42, mostly oral dosing again. Duration of therapy ranged from one over 2500 days with a median duration of 17 days. Again, mostly G.I. indications.

(Slide 19)

For these 57 cases akathisia, concomitant medications associated with movement disorders was reported in 23. Drug therapy was used to treat akathisia in 29 cases. Symptoms were reported as improved or resolved in 31 cases but symptoms were reported as continuing in nine cases.

(Slide 20)

In the nine cases that reported continuing symptoms, the daily dose ranged from 8.6 to 40 milligrams with a mean of 25 milligrams, mostly oral dosing. Duration of therapy ranged from 17 to over 2500 days with a median duration of 119 days.

(Slide 21)

We reviewed 35 unique cases of Parkinson's. This was in an older population with a mean age of 60. Daily dose ranged from 10 to 80

milligrams with a mean dose of 36 milligrams per day, mostly oral dosing. The duration of therapy ranged from one to over 1400 days with a median of 60 days.

(Slide 22)

In these 35 cases of Parkinson's, there were 13 cases which reported concomitant medications that were associated with movement disorders. Drug therapy was used to treat the adverse event in 18 cases.

Symptoms were reported as improved or resolved in 15 of the cases but symptoms were reported as continuing in eight cases.

(Slide 23)

In those eight cases that reported continuing symptoms of Parkinson's, the daily dose ranged from 20 to 40 milligrams with a mean of 32, mostly oral dosing, and the duration of therapy ranged from one day to 203 days with a median duration of 81.

(Slide 24)

There were 67 cases of tardive dyskinesia.

The mean age was 57. The daily dose ranged from 5 to 80 milligrams with a mean of 35, mostly oral dosing again. Duration of therapy ranged from one to over 4700 days with a median of 180 days, again G.I. indications for the metoclopramide.

(Slide 25)

25 cases reported that the patient was taking concomitant medications associated with movement disorders and drug therapy was used to treat the adverse event in 19 cases. In 12 of these cases, symptoms were reported as improved or resolved. In 20 cases, symptoms were reported as continuing.

(Slide 26)

In those 20 cases with continuing symptoms, the daily dose ranged from 5 to 80 milligrams with a mean of 53, mostly oral dosing and a duration of therapy from one to over 4700 days with a median of 165 days.

(Slide 27)

After we developed our case series, we wanted to look at a more focused group of these

cases to see if we could approximate the dosing seen in the MT100. So we looked at two further subgroups of our case series. One, we looked at characteristics of cases that specifically reported symptoms as continuing at the time of reporting. Then we also looked at cases with the diagnosis of tardive dyskinesia that were related to short-term metoclopramide therapy.

(Slide 28)

There were 50 cases out of 400, over 400, that reported continuing symptoms. They were represented by eight Parkinson's, 20 tardives, nine akathisias, 12 acute dystonias and one NMS which was actually likely a dystonic reaction. A little over half of the cases with continuing symptoms reported a duration of therapy of greater than 30 days.

(Slide 29)

So 15 cases in our series reported continuing symptoms with a duration of therapy of less than 31 days. Eight of those cases reported continuing symptoms with a duration of therapy of

less than three days, what we would call very short durations of therapy. That included one Parkinsonism case, two tardive cases, four acute dystonias and one NMS. Most of those eight cases occurred after at least three doses of metoclopramide.

(Slide 30)

I have a few representative cases to describe to you. The first one is a 49-year-old female who received two doses of metoclopramide, 20 milligrams orally, over two days for treatment of gastric reflux. Concomitant therapy included cimetidine. On Day 2 of therapy, she developed dystonic reactions consisting of torticollis and trismus. Her dystonic reaction was reversed by diphenhydramine. However, she subsequently complained of left-sided weakness and temporary loosing of the teeth.

(Slide 31)

The second case is a 34-year-old female with nausea who received metoclopramide, 10 milligrams, orally three times a day for three

doses and experienced difficulty breathing, extremity shaking, head and neck jerking back. She went to the E.D. where she was treated with benztropine, after which she started to relax.

However, symptoms still occurred. She was subsequently treated with lorazepam and paroxetine which did not completely relieve the symptoms. She was seen in the E.C. and by neurologists several times for reactions milder than the first reaction. Approximately three months later, she still suffers from head pain, dizziness, tingling, pressure, fatigue, agitation, involuntary shaking, muscle spasm and neck pain among other symptoms.

(Slide 32)

The third case, a 27-year-old male received three doses of metoclopramide, 10 milligrams orally, over two days for diabetic gastroparesis. He experienced a dystonic reaction with psychotic tendencies, agitation and agitation with suicidal tendencies on the second day of therapy.

He was treated in the E.D. with

diphenhydramine and lorazepam. Once discharged, he continued to have symptoms of inability to concentrate, slowed mental processing, difficulty focusing, eye strain, vertigo, loss of equilibrium, fatigue, dizziness and hallucinations.

(Slide 33)

The second subgroup analysis of our case series that we did looked at specific cases with the diagnosis of tardive dyskinesia that were associated with short-term therapy of metoclopramide of less than 30 days. What we were trying to look at here was trying to approximate what kind of dosing regimen would be seen with chronic overusers of migraine therapy because there is a certain population of migrainers who might use this drug prophylactically in a manner similar to other migraine therapies.

We chose tardive dyskinesia as our adverse event because the diagnosis of tardive dyskinesia infers a long-term or permanent adverse event. We also noted that about 25 percent of our cases had a duration of therapy of less than 30 days.

(Slide 35)

You have seen this slide before, but you can see that this is the distribution of our cases based on the duration of therapy of metoclopramide. The large number are reported with durations of therapy of less than 90 days, but there is a significant number with durations of therapy of less than 30. Actually, there are 15 such cases of tardive dyskinesia with a duration of therapy of less than 31 days.

Of these 15 cases, the status of recovery was not reported in nine of them. Symptoms were reported as resolved in one case but continuing symptoms were reported in five of these cases. Some of the characteristics of these cases include two out of the five cases reported symptoms as continuing but improved. Two out of the five cases reported I.V. dosing and four out of five cases reported daily doses of 40 milligrams.

The important thing to remember is, again, we are not really able to discern, because of the AERS data, whether this was chronic intermittent

use of metoclopramide or chronic continuous use of metoclopramide in these cases.

(Slide 36)

In fact, we found no cases in AERS that specifically linked intermittent use of metoclopramide with any movement disorders. There are maybe several reasons for this. First, and probably most likely, is that AERS--the way data is reported in AERS does not make the distinction about intermittent dosing so it just wasn't clearly described in the report.

It could be that intermittent dosing is not commonly used or the adverse events seen with intermittent dose are not commonly reported or that there may be few movement-disorder-related adverse events with intermittent dosing.

(Slide 37)

So, in conclusion, most of the reports that we saw with continuing symptoms of the adverse event involved long-term therapy of greater than 30 days with the caveat, again, that we didn't know whether it was intermittent or continuous therapy.

There were eight cases which reported continuing symptoms with very short-term therapy. There were five cases of tardive dyskinesia that were associated with therapy of less than 30 days. Concomitant medications associated with movement disorders were frequently present in the cases and there were two out of eight deaths from neuroleptic malignancy syndrome that occurred after less than three days of therapy.

(Slide 38)

That's it.

DR. KIEBURTZ: Thank you.

Questions or clarifications for our last speaker?

DR. KIEBURTZ: Dr. Jeste.

DR. JESTE: In these cases of acute dystonia and neuroleptic malignant syndrome, some of the patients have some concomitant therapy as shown, in these cases, the side effects occur after metoclopramide therapy.

DR. MATCHAR: Right; they were temporarily associated with metoclopramide. Yes.

DR. KIEBURTZ: Dr. Porter.

DR. PORTER: Metoclopramide is not widely used in the U.S. You didn't spend a lot of time on the primary diagnosis. I presume that you found no migraine-related movement disorders in this search.

DR. MATCHAR: There were very, very few cases that reported adverse events related to migraine. As you saw from the indications, they were mostly G.I.-related indications.

DR. KIEBURTZ: Dr. Welch.

DR. WELCH: Were there any different characteristics of the patients who had the T.D. after the short-term as opposed to the long-term? It is almost like a biphasic population response there.

DR. MATCHAR: No; it was a very heterogeneous population. There were different presentations, different durations of therapy, so I am not really sure whether you could say those that experienced it earlier had similar characteristics than those that presented after 90 days of therapy.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: Just one point of clarification which I think is true. Maybe you said it and I missed it, but, obviously, we focused on the patients with continuing symptoms, at least in part. As a general matter, I think, for these reports, and correct me if I am wrong, what we don't have which would be nice to have in terms of information about those cases is sort of the latency between the onset of the event, the movement disorder, and the time of the report.

So it could be that an event happened on Day 1 and the report is made on Day 2, in which case, it might be continuing. But if the report had been made on Day 47, after the drug had been discontinued, for example, it might be that they were discontinued. So I think, as a general matter, we don't know this duration of continuation of symptoms because we don't know the link between when the event happened or stopped and the time of the reporting.

There were a few cases, I think, where we do have that but I think, in many cases, we don't.

DR. MATCHAR: Right.

DR. KIEBURTZ: Dr. Hughes.

DR. HUGHES: You mentioned under-reporting in the AERS database, a well-known problem. But when you have an adverse event which is labeled, what sort of characterizes the types of adverse events that might then be reported? We are looking at a very peculiar set here.

DR. MATCHAR: Probably. There were a lot of reports from lawyers. I mean, that is one. Looking at other case series that I have done, it seemed like there were a lot of reports from lawyers. But we looked at, actually, quarters of years, the reports, and there really didn't seem to be any change, like an increase in reporting after cisipride came off. It seemed to be fairly steady so I am not sure that I could say that there was one specific thing.

DR. KIEBURTZ: Good. Thank you.

Questions from the Committee to the Sponsor and FDA

Now, we have time to ask questions of the presenters without me suppressing you about them to

be about clarifications. We have about an hour to do that. I suggest we start principally with questions to the sponsor and immediately with those individuals who I suppressed.

I recall stopping Dr. Goldstein when you were asking Dr. Schapira a question about the U.K. reporting database, I believe, and Dr. Lenaerts, I stopped you in the middle of a question, too, but I can't remember the context.

DR. LENAERTS: It was in the same context.

DR. KIEBURTZ: Dr. Goldstein, would you--and you can draw anyone from the sponsor or from the FDA if you would like to them to repeat or present material again.

DR. GOLDSTEIN: I guess what I was actually asking for was clarification about the validity and accuracy and reporting rates in the U.K. system, especially now as contrasted to the last presentation we had from data here in the United States which is a similar sort of reporting system, but the numbers seem to be quite different.

DR. SCHAPIRA: Thank you. The U.K.

reporting system to the Committee of the Safety of Medicines, the so-called yellow-card system, is a system by which physicians send in to the CSM documentation of an adverse event. So it is physician-led. It is not spontaneous in terms of including patients. But it is spontaneous in the sense that physicians have to send in the yellow card.

Those that do send in yellow cards often get a response back from the CSM asking for further clarification if all the relevant information is not included in the original yellow form that they have submitted.

As for a proportion of reporting to all potential cases, of course, I can't comment on that. I don't know the data. Obviously, that is not possible to obtain.

DR. GOLDSTEIN: The second part of that question--it was sort of a two-parter--was, in terms of validating the conditions that are being reported, we have this clear problem with categorizing a lot of these movement disorders.

There is this point of definition about how much exposure is enough exposure to be categorized as a given type of condition. Are these validated in any way, or is it just based on individual reporting.

DR. SCHAPIRA: It is predominantly based on physician reporting.

DR. KIEBURTZ: It sounds analogous to what we heard from Dr. Southworth. Dr. Bastings.

DR. BASTINGS: I have a comment regarding the U.K. reporting system. We have a fair idea of the incidence of acute dystonic reactions with metoclopramide. In the Pozen study, it was 0.05 percent. I find it surprising to see that only 26 cases were reported with migraine product, if you consider the exposure, to have so few cases and it suggests that there was a vast under-reporting of these adverse reactions.

Do you have any comment on that?

DR. SCHAPIRA: This, remember, was the number of reported cases with migraine preparations as opposed to those with all metoclopramide

preparations. Do you have the slide number from which that is taken?

DR. BASTINGS: Yes; it is Slide 31, CC-31.

DR. SCHAPIRA: Just looking at all metoclopramide preparations, that is to say the non-migraine ones, there were 478 of those. I don't know how that compares to the U.S. data.

DR. SOUTHWORTH: There were 203 unique dystonia cases.

DR. SCHAPIRA: In the U.S. data.

DR. SOUTHWORTH: Over about the early '80's to present.

DR. SCHAPIRA: So this is actually twice the number here in the U.K.

DR. KIEBURTZ: Over a longer period.

DR. SCHAPIRA: Over a period of 64 to 45. So this is 40 years and the U.S. data was over 35 years, I think. Is that right?

DR. SOUTHWORTH: The earliest reports we have are from the early '80's.

DR. SCHAPIRA: So about 25 years.

DR. KATZ: I think the point is that we

have a good--an estimate, anyway, from the Pozen control trials of a particular adverse event associated with the acute use of the product. It is 0.05 percent or maybe it is 0.1 percent, depending--we have seen those numbers vary.

DR. SCHAPIRA: Yes.

DR. KATZ: But, when you look at, for example, over the 40-year period in the U.K., and if you look at dystonia with episodic use of the combination products, which are the migraine products, there are 26 reports. So I don't know what the percentage of use that is, but it is probably less than 0.1 percent.

I think that is the point from the controlled trials, which are the best way to get an estimate of these events, you see some finite risk. It is relatively low but finite that the reporting rate seems to be, perhaps, orders of magnitudes less than that, the point being that under-reporting may be a sizeable--there may be sizeable under-reporting for these events which are known to be associated with these treatments.

DR. SCHAPIRA: Yes; I agree entirely. It was just the comparison between the U.S. and the U.K. reporting system. It seems that there isn't a difference between them here.

DR. KIEBURTZ: Dr. Hughes, did you have a comment?

DR. HUGHES: A related question. I think you mentioned there were no cases of tardive dyskinesia amongst the combination users. I think you mentioned something like 100 million doses had been prescribed. That was an estimate.

DR. SCHAPIRA: That was an estimate.

DR. HUGHES: But 24 cases amongst those on chronic use.

DR. SCHAPIRA: Yes.

DR. HUGHES: Do you have an idea of how many doses have been prescribed for chronic use? I am trying to get some sense of--

DR. SCHAPIRA: Right. Of course, I am going to have to speculate on this, but the proportion of use of metoclopramide in the U.K. for migraine as a precaution for all of its other uses

is about 20 to 25 percent of metoclopramide prescriptions are for migraine, approximately. So I suppose that one could extrapolate from that.

DR. KIEBURTZ: Dr. Temple.

DR. TEMPLE: Just a comment on reporting rates and spontaneous reporting systems. We spend endless hours and months agonizing about this. It is very clear the rates are different for different kinds of reactions. There is something called the Weber curve that was derived mostly from British data that says reports of any given reaction decline after the first three years because people all know about it. It is in the label.

You can easily imagine that people wouldn't report very much of something like a dystonic reaction which everybody knows about. You would hope that they would be more likely to report TD because it is not as clear that everybody knows about it. But there is just no way to know these things and it is a constant source of difficulty.

The other thing that is going on, in the United States, in the '80s, there were maybe 20,000

reports to us a year. You probably have the number. We are now up over 400,000 a year. So we have a belief that reporting of all things is going up. It is very impossible to reach conclusions that are valid, however.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: I will pass.

DR. KIEBURTZ: Dr. Fahn.

DR. FAHN: Regarding Slide 31 and then 22, where there is no tardive dyskinesia being reported, Slide 22, the Bateman second article there, the Bateman 1989, the second of the Bateman articles, fortunately, and I must congratulate the sponsor because we do have the reprints of these articles so I was looking at that because that came as a big surprise where there were zero TD cases.

But, actually, what this survey was is that they wrote to the physicians who prescribed the drug Maxolon for migraine--I assume it is all for migraine--and got the responses back. But they grouped the responses. They didn't list tardive dyskinesia as one of the responses. They just said

dystonia-dyskinesias and they grouped all that together. So they are listed here in your table as 12 dystonias. But a lot of them--and some of these are older people. It is very likely that a lot of these were persistent dyskinesias and not just acute dystonic reactions or something that this table may imply.

So I just wanted to say that, looking at this, you can't really clearly say how many--there was no zero TD cases. So that was one comment.

DR. SCHAPIRA: Yes; they classified patients as dystonia-dyskinesia which, if you look back at the first Bateman paper here, they also used that classification and separated out from tardive dyskinesia. So, in the first paper they did, they did clearly separate dystonia-dyskinesia and tardive dyskinesia. In the dystonia-dyskinesia they noted that--I think the dyskinesia resolved and made the comment--and this is with respect to their paper in 1985--that this was more likely an acute type reaction.

DR. FAHN: But the other thing on this

table, too, in the second Bateman article, they have 46 other events. So, perhaps, within that, there might be TD. That is what I am saying. From this paper, you can't really say there was no TD because they specifically failed to talk about TD. That is the problem.

If I can also make a comment at this time. The definitions of TD, that is another thing that can confuse people. If you are going to use the definition of TD that you have to be on the drug for 30 days or more or three months, as some definitions have used, I am not sure any neurologist used that kind of definition. We tended to look at tardive dyskinesia as persistent dyskinesia.

The name tardive was given because it wasn't seen until later on after the neuroleptic drugs had been on the market for a while. That is when tardive came on. But, with more experience with this, recognizing what the syndromes are, we sort of consider, now, tardive dyskinesia really should have been properly named persistent

dyskinesia, meaning that it lasts longer than 30 days.

It doesn't matter how long they have been on it for. They can be on it for one day and still have persistent dyskinesia. To us, that is what we now refer to as tardive dyskinesia. So we don't give up the name tardive dyskinesia. We use the definition differently than what was stated here. I just wanted to make sure the concern I would have, as a neurologist, who treats tardive dyskinesia as meaning persistent dyskinesia, that these can be irreversible.

When I heard the comment about how devastating migraine is, and I agree it can be--severe pains can be very bad for people, devastating, but so can severe akathisia including tardive akathisia, I consider that equally as bad. If you ever induce this for a drug you might not have needed, then that is a concern for us that we have to face.

DR. KIEBURTZ: I am going to follow your comment and pursue questions with a couple of

people. Neurologists fall into camps of movement disorders and stroke and headache. I think, just to set tone, I think everyone would agree that migraine is a serious and disabling disorder that needs good treatments. I don't think anyone is debating that. And there are unmet therapeutic needs.

I think everyone also admits, but might not be so familiar with, that tardive syndromes, tardive dyskinesia and other tardive syndromes, are also very disabling, much less common than migraine. The issue before us is how to balance those issues. Neither is more important or less important than the other. They are both very important clinical issues. I don't think anyone is doubting that. So I don't want to have that sort of be on the table, that we are undervaluing one or the other.

Dr. Lenaerts.

DR. LENAERTS: Thank you. In the U.K. experience, could Dr. Schapira possibly--I don't know if it is hypothetical or known

information--the comment on the use of metoclopramide specifically in migrainers and, namely, the frequency of use as that may factor in the relatively low reports of adverse events in migrainers as compared to the U.S. experience.

DR. SCHAPIRA: Thank you. Well, as I mentioned, the combination of metoclopramide and analgesics is the second step in the U.K.-recommended guidelines for the management of acute migraine. The estimate of prescriptions of combinations, of the two combinations currently marketed, is approximately 200,000 per annum. It is estimated that about 95,000 patients are taking these products each year.

DR. LENAERTS: How does that do--in terms of frequency of use per patient because that would be really the relevant issue there.

DR. SCHAPIRA: Of course, that is undoubtedly going to vary from one patient to another depending upon the severity of response, frequency of attacks, et cetera. The sort of bottom-line figure, if you like, that we have is 85

doses per annum. But, between that, there is going to be a substantial range.

For instance, one has patients who will take two doses at the onset of an attack and have a good effect from that. Another proportion of patients will need to take two doses separated by four hours.

But what I don't have is the data to tell you what proportion take just one dose at the beginning, two doses, et cetera. I don't have the data and don't think it is available to tell me how many migraine attacks they are treating per year. I can only give you that bottom line of about 85 per person per annum.

DR. KIEBURTZ: Dr. Welch?

DR. WELCH: Do you have any comment on any difference in prevalence of medication overuse between Britain and the United States?

DR. SCHAPIRA: I think I should pass that to one of my U.S. migraine experts because I think they will probably know more about that in terms of the prevalence of medication overuse.

DR. KIEBURTZ: If you haven't spoken before, just please introduce yourself for the record.

DR. SAPER: My name is Joel Saper. I am a neurologist specializing in headache and Director of the Michigan Head Pain and Neurological Institute in Ann Arbor. Dr. Welch, could you--I got part of that question. I didn't hear the whole question.

DR. WELCH: What is the prevalence of medication overuse in the U.K. and what is the prevalence of medication overuse in the United States?

DR. SAPER: I am not sure that I can answer the question with specific statistics. I think Dr. Silberstein showed a slide, was it 1 to 2 percent, Steve, on the medication overuse in the United States?

DR. SILBERSTEIN: The data is extraordinarily limited. The two studies I know of, population-based studies, in medication overuse headache, Ann Scher's study done in this region.

What Ann and Richard Lipton showed is about 4 percent of the population have chronic daily headache. In the clinic, it is estimated that most of the patients we see with daily headache overuse medication, what Ann and Richard estimated in the population is about 30 percent.

I don't know of any good estimates in Great Britain. I do know that, in other parts of the world where the problem has been studied, all worldwide estimates of chronic daily headache are about 4 percent and half are migraine, and of those patients, about 30 to 40 percent in population-based studies.

Anecdotal experience from Peter Goadsby in National Hospital in Queens Square suggests that is clinic-based population is about the same as here.

Mike, do you know of any population-based estimates? Anyone?

DR. SCHAPIRA: No. So, in other words, we don't know whether the medication overuse is less in the United Kingdom than here and we are being given data on the adverse events in Britain.

DR. SAPER: If I may just finish the point I wished to make when I asked Dr. Silberstein for a clarification, I do know this. In our system, in the United States, medication overuse is a significant problem of the referral base that is referred to us, perhaps 60 to 70 percent of referrals to a tertiary quadrinary will have that problem.

In the U.K., I do not know for other than opioids. In opioids, which is the dominant overuse in this country, in my referral base, which is very large. In the U.K., opioid use is much more limited. So, to the extent that we can compare opioid overuse in the United States to that in the U.K., there would be much more overuse in the United States, but specifically targeting the opioids.

DR. WELCH: Do you think that speaks to the difference in physician practice in the United Kingdom--in other words, major primary-care control of the prescriptions in the United Kingdom as opposed to the United States?

DR. SAPER: There is, I think, a difference in prescribing habits, Dr. Welch. I think, in the United States, opioids, particularly in the last ten years, are being much more aggressively prescribed for non-cancer pain than they were prescribed ten or fifteen years ago.

In the U.K., from my understanding and talking to colleagues, the opioids are restricted much more so for non-cancer pain.

DR. KIEBURTZ: Dr. Hughes, you had a question.

DR. HUGHES: Sort of two related questions. Going back to the Reglan warning label and the comment in that label about risk of TD being increased after relatively brief treatment periods at low doses, is there data available that is underpinning that particular comment?

DR. BASTINGS: We don't know what that was based on. We did not write that label. It is a different division and we don't have that information.

DR. KIEBURTZ: I am not sure it is

data-driven but, even in the comments you saw in the Pozen briefing booklet, I believe, amongst movement-disorder neurologists, there is the impression that even one dose of exposure can possibly cause tardive syndromes.

To answer your question, I am not familiar with data to address the question but the label may have incorporated clinical acumen or anecdote as part of the label.

DR. HUGHES: I guess the related question was the open-label safety study that you have conducted, I was wondering if there were eligibility restrictions or the treatment-management approach within that study was conservative to try and avoid risk of movement disorders.

DR. ALEXANDER: Thank you. This study we call 302 enrolled 1,006 subjects. They were enrolled on the basis of having a history of migraine. But there were no restrictions on previous presence of movement disorders or any persistent neurologist deficits. We had not, at

the time of that study being initiated, anticipated that this would be an issue in the development and so there were no particular requirements.

DR. HUGHES: And there weren't any particular requirements in terms of management of patients?

DR. ALEXANDER: Well, no. This was 54 centers, I believe, headache centers in the U.S., generally, and patients were instructed to take one dose of MT100--this was open label--one dose for the treatment of moderate to severe headache. There was no second use of MT100 as rescue medication, for example.

It was a safety study. Subjects were asked to record adverse events after taking doses within 24 hours and then, when they came back to clinic, at 3-month intervals.

DR. HUGHES: But these patients were taking it on a chronic intermittent basis.

DR. ALEXANDER: Well, I would call it--I would like to make the distinction that we are talking about episodic or PRN use because chronic

intermittent could also include the psychiatric use of neuroleptics in the treatment of schizophrenia, for example.

One thing I would point out is that the episodic three-times-a-month use is probably very different than chronic intermittent time-on/time-off of a neuroleptic used in the treatment of psychiatric conditions. These were PRN intermittent. As Dr. Schapira has shown, the average number of doses per month was 4 and the median number of doses that each subject took over the 12-month period was 22.

DR. HUGHES: So would you characterize the study as mimicking what might occur in clinical practice?

DR. ALEXANDER: Yes; exactly. It was a clinical-practice type study, a real-world study, just looking at the adverse-event collection over the time enrolled.

DR. KIEBURTZ: Dr. Katz, you had a question?

DR. KATZ: No; he answered my question.

DR. KIEBURTZ: Dr. Jeste.

DR. JESTE: Do you have a theory why metoclopramide would work better in people without nausea?

DR. ALEXANDER: Thank you, Dr. Jeste. We believe, and we have phase 1 data to show, that the addition of metoclopramide to naproxen sodium will enhance the absorption of naproxen through accelerating the--well, it brings the T-max closer to the time of dose. We have phase 1 studies showing that the T-max for naproxen is decreased by about 30 minutes, on average.

That is Slide 25.

(Slide EB--25)

Just to illustrate this point further, is that, in the phase 1 studies, when we gave naproxen sodium 500 milligrams without metoclopramide, the T-max was 72 minutes. We added, first, 8 milligrams of metoclopramide and the T-max dropped to 57. With 16 milligrams, which is the dose in MT100, the T-max was 44. So I think I am answering your question about why it speeds the absorption

because it empties the stomach. Naproxen is only absorbed in small bowel as are all the other NSAIDs.

DR. JESTE: So you think it would work differently in people without versus with nausea?

DR. ALEXANDER: I have no data for sure. The theory, just to answer that, is that when nausea is present, there is probably more gastric stasis, and 16 milligrams of metoclopramide cannot overcome the gastric stasis present.

There also may be--there is a theory that dopamine has effects in migraine and maybe the dopamine has an effect to increase nausea.

DR. KIEBURTZ: Dr. Sacco is next.

DR. SACCO: I had a question regarding adverse experiences for someone from the company to maybe comment. Looking at the FDA briefing document, in the clinical review section, FDA Clinical Review, there is an overview that puts together all the adverse experiences. I would like someone to just comment for me, as a stroke neurologist, not a movement-disorder neurologist,

how best to be sure that the increased frequencies of restlessness and feeling jittery that are noted with MT100 and MT100 two tablets versus some of the other groups wouldn't be possibly forme fruste or partial TD-related symptoms.

This is on Page 103 of 128 in the FDA document.

DR. KIEBURTZ: Your document may not be entirely the same as theirs. But I am not sure. I believe they would know the table.

DR. KATZ: Could you just repeat which page, which document.

DR. SACCO: The document I have, which is under a section called FDA Clinical Review, it is Page 103 of 128 in the section, I guess, document dated--Table 64. I have a table number. I guess my question just is, again, getting back to that original slide where I asked the clarification, akathisia, restlessness, is possibly a form of tardive dyskinesia. Being, again, a stroke neurologist, I am just trying to understand and be sure that the restlessness and feeling jittery

issues that are listed in that table that are increased--I see 13 in the MT100 group and then, actually, 12 or 4 percent in the MT100 two tablets group, and I see feeling jittery, 13 and 4, also there.

I am just trying to get a better handle, maybe, from the company what some of those adverse experiences were all about.

DR. ALEXANDER: Thank you, Dr. Sacco. I am looking at Table 64, that the data across all the treatment--each treatment arm. I would point out that, if you look at restlessness with MT100, there were 2400 subjects who were exposed to a single dose. There were 13 cases of restlessness there, less than 1 percent.

That was the same percentage relative to the restlessness in naproxen sodium, metoclopramide, sumatriptan and placebo. All were less than 1 percent. You have pointed out that there is a 4 percent incidence of restlessness with the two-tablet dose of MT100. There were 313 subjects who received the two-tablet dose.

Pozen has not, did not, submit the NDA asking for approval of a two-tablet dose of MT100. So, therefore, the 4 percent higher rate of restlessness may not be relevant to our discussions today.

But I would want to say that these were acute events that were seen and they did resolve. The question of restlessness with the use of MT100 could, perhaps, be looked at in the 302 database just to put this in perspective.

Let me have, please, Slide No. 19.

(Slide SA-19)

This is the study, the large study, repeat-dose study, that we have spoken about. I just think it might be beneficial to the committee to see that the most common event in these 1,006 subjects was somnolence, dizziness, 7 percent. Restlessness, overall, was 2 percent. Again, these are 23,000 single doses of MT100 being treated, being used by these 1,006 patients.

Anxiety is 4 percent and nervousness, 1 percent. Fatigue is a little more common.

Perhaps, that would help put this in context.

DR. KIEBURTZ: Thanks. Actually, Dr. Temple and Katz, but we are keeping a list.

DR. TEMPLE: I am still curious about the theory of why the people with no nausea might benefit. You might even think that, if they have delayed absorption, they would benefit more--you might. I guess I couldn't understand what the theoretical basis for expecting a benefit on the sustained response and not on the acute response would be. If you shortened T-max, it would seem more likely to do the opposite, I would have thought.

That is a question to the people who put forth the theory, not to the committee.

DR. ALEXANDER: I'm sorry. I thought you were posing that to committee. I think the question would be what happens when migraine is effectively treated by an analgesic agent. We don't know the effective plasma dose of naproxen that will start the process of analgesia. I don't think we know that.

So we, in theory, if we can bring the time of obtaining whatever that is closer to dosing and start the process of analgesia and the effect on neurovascular leakage or whatever it is that is causing the migraine pain, then we can effect, perhaps, a smaller two-hour improvement. But that improvement then goes on after two hours to 24, and we see less relapse. We see less need for remedication and the pain response, as measured by sustained pain response, may be there.

That is just a theory. But, certainly, the quicker you treat the pain, perhaps the better it will be at 24 hours.

DR. TEMPLE: Plausible. But it doesn't treat it quicker. I mean, that is what the results show.

DR. ALEXANDER: Remember I showed the SPID data. SPID data is used in the analgesic division as the most sensitive tool we have to measure the duration, the onset, the amount of pain relief. And we showed, in both studies, that, by two hours, MT100 was statistically significantly better than

naproxen sodium using SPID scores.

So I would just say we have data that makes it effective. Let's have Slide 83.

(Slide EB-83)

Just to answer this. The SPID scores in Study 301. The pink line at the top is MT100. The blue line is naproxen sodium. The green line is metoclopramide. At one hour, MT100 is significantly better than metoclopramide. At one-and-a-half hours, naproxen sodium is better than metoclopramide. At two hours, MT100 is significantly better than naproxen sodium, p-value 0.044.

The same thing was seen in 304. The next slide would be, I think, 84.

(Slide EB-84)

Importantly, in 304, this effect was seen and one-and-a-half hours. By, by one-and-a-half hours after dosing, you have separation of these two treatments.

DR. KIEBURTZ: Dr. Welch.

DR. WELCH: I would like to pursue the

same issues that Dr. Temple is discussing. There may be other explanations other than just simply absorption from the gut. When you look at the PET studies or MR studies, you find that basal ganglia and a whole network of systems are activated during an acute migraine attack. It could be that it is interfering with that at some stage or other.

But I would really like you to address the issue of the time from the onset of the migraine attack to treatment as another possible explanation. Nausea is very variable. Sometimes it comes on in the middle of the attack and often is associated with the severity of the pain or severity of the attack.

Could it be, can you reassure us, in making this differentiation of a 10 percent difference between nausea and non-nausea and you don't have a population that treated itself at a different time, and if, for example, the group without nausea treated themselves earlier than the group with nausea, then you might expect a differential benefit because you are interfering

earlier with the cascade of events involved in the migraine attack. So there is another possible explanation that may have nothing whatsoever to do with absorption from the gut.

DR. KIEBURTZ: Let me just, to clarify, your question is is there evidence regarding the time that has passed between the onset of headache and the self taking of the medication in those who report nausea versus those who don't as a possible potential explanation.

DR. WELCH: Correct.

DR. KIEBURTZ: Could you address that specifically? Do you have that?

DR. ALEXANDER: First of all, Dr. Welch, I don't have data to answer your question. We did not measure the time from onset to treatment in these studies. I think you are referring to early treatment modalities and perhaps treating when the pain is mild or moderate before nausea may develop in a subject. We just don't have data to support that.

DR. WELCH: It is not necessarily mild.

It is the duration--it is the time when you treat it first.

DR. KIEBURTZ: Thank you. Dr. Jung.

DR. JUNG: Can we go back to Table 19.

DR. ALEXANDER: That is the overall safety data from 302?

DR. JUNG: Can you tell me what the difference is between restlessness, anxiety and nervousness? Was there a specific way of differentiating for the patients or for the providers who submitted the reports?

DR. ALEXANDER: No; there wasn't. These were characterization of the adverse-event reports by the investigators who recorded the data in the case-report form.

DR. KIEBURTZ: Are those WHO-ART coded? Are these verbatim? Does anybody know?

DR. ALEXANDER: They do get coded through the WHO-ART system, or CoStart system--I'm sorry; the MedDRA system.

DR. KIEBURTZ: So these are MedDRA roll-up terms?

DR. ALEXANDER: Yes.

DR. KIEBURTZ: So that means that these are terms, the text was coded into these terms. To be sure, you would have--this is not the actual verbatim; correct?

DR. ALEXANDER: Well, it may be. I would have to look--

DR. KIEBURTZ: It may or may not be.

DR. ALEXANDER: I would have to look at the MedDRA Coding Guidelines to see if these are verbatim. But there are some terms that, as you say, do get coded to something else.

DR. JUNG: Does that mean that there is clarity between the difference between anxiety, nervousness--there isn't?

DR. ALEXANDER: No.

DR. JUNG: So if you take restlessness, anxiety and nervousness and added all that up in terms of adverse events, wouldn't that be pretty close to the primary 108 that was reported somnolence? If you have restlessness, anxiety and nervousness, that is 50, 60--

DR. ALEXANDER: It is a percent. If you look at the bottom of that column, 78 percent of these subjects who were treated for up to a year, at some time or another, reported some adverse event. I don't think it is uncommon to have 78 percent of the subjects reporting something over the course of a 12-month study.

DR. JUNG: I had a second question.

DR. KIEBURTZ: Please, go ahead.

DR. JUNG: Not related to the slide. Going back to Dr. Fahn's comments earlier about the significance of movement disorders on quality of life, do we have--this is for the FDA staff--do we have any data that looks at the incidence of other adverse effects associated with other treatments for migraines, so, for example, cardiovascular side effects, G.I. side effects, just for comparison?

DR. KATZ: The rates of things like chest discomfort and stuff can be read in the labeling for all these drugs. They are not inconsiderable. There is a fair rate in those things. But I don't think we have them on the top of our head at the

moment. Anybody with a Blackberry can probably find it.

DR. JUNG: I guess my point was that, if we are trying to decide whether or not this drug is worthwhile, it would be reasonable to compare that.

DR. KIEBURTZ: Dr. Porter?

DR. PORTER: Back to Dr. Schapira. On your combinations on metoclopramide and analgesics marketed in the U.K. and the 95,000 patients per year that receive these doses which are twice that of the MT dose, the question arises which is in a similar vein to what other people have asked. On the dystonia oculogyric crisis, for example, or extrapyramidal disorders not specified, what is the possibility that a substantial number of those, or even some of those, could be tardive dyskinesias and not just properly classified. That would make a big difference, I think, in our interpretation of this rather impressive database if we thought that that was possible.

DR. SCHAPIRA: The identification of dystonia or oculogyric crisis is a phenomenon

associated with the acute, generally speaking, exposure to a neuroleptic specifically, in this context, metoclopramide. Therefore, they are, I believe, more easily distinguished in terms of an acute dystonic episode from tardive dyskinesia.

Also, acute oculogyric crises or acute dystonia, upon exposure, which may, for instance, occur with the first dose ever of metoclopramide, resolves spontaneously and I think can be more easily, or relatively easily, distinguished from tardive dyskinesia which, generally speaking, involves a different type of movement.

Stan has already--I'm sorry; Dr. Fahn has already alluded to the issue of persistent dyskinesias as opposed to tardive dyskinesias. I would make a distinction between those persistent, brackets, tardive, brackets, dyskinesias and the sort of acute oculogyric, acute dystonic, reactions that we see with metoclopramide.

DR. PORTER: So you don't think that these dystonia extrapyramidal disorders dyskinesia were persistent in the same way that tardive dyskinesia

might be persistent.

DR. SCHAPIRA: Well, I can only speculate, of course, because I don't have the original case reports in front of me. But, as these have come from medical practitioners, I would hope that at least the great majority of them, the vast majority of them, would relate specifically to an acute dystonic reaction. Otherwise, they would have been, I would hope, classified as something else.

DR. PORTER: They had at least the option to check a box that was tardive dyskinesia?

DR. SCHAPIRA: They wouldn't, I believe, have a box to check. They would have a space to include what they thought.

DR. PORTER: Okay. Thank you very much.

DR. KIEBURTZ: Can I have four more people I have no my list. Those are Drs. Goldstein, Jeste, Sacco and Katz and I have a couple of questions. So if we get through those, then we can do more.

DR. GOLDSTEIN: First, just a few questions for clarification just for me, I guess.

The data that you showed very quickly about the difference in time in rate of onset, I guess, for the three treatments that were just shown, the statistics for that. I know there is this whole debate about what is the right statistics to use but, in that particular graph, you were showing repeated measures over time. I was wanting to know whether those were just uncorrected pairwise statistical comparisons or whether that was analysis of variance with repeated measures and then post hoc tests.

DR. ALEXANDER: Dr. Goldstein, are you speaking of the SPID scores?

DR. GOLDSTEIN: Yes.

DR. ALEXANDER: Could we have the SPID score methodology? Just come on over, Susan. Susan Spruill is the Senior Director of Biostatistics at Pozen.

DR. SPRUILL: The answer to your question is that it was an analysis of variance for each time point and it was not corrected for multiple time points.

DR. GOLDSTEIN: So it wasn't corrected. Okay. The second question is, again, just a general question about the trials that were done. You guys must have measured or recorded concomitant medications. Many patients with migraine are also on prophylactic therapy as well as this rescue therapy. This is basically a rescue therapy.

Were there differences in what types of other medications these patients were on?

DR. ALEXANDER: There were exclusion criteria if patients had changed their prophylactic medication within several weeks to a month of enrollment. We did not exclude patients that were on prophylactic medications or anti-depressants, anything that was used for the routine medical treatment. There was no stratification of the randomization by use of prophylactic medications.

DR. GOLDSTEIN: Thanks. The third technical question is, again, related to this whole issue of absorption. The preparation that you are looking at here has the naproxen that is sort of like buried inside this sort of shell. Is there a

difference in the bioavailability of the naproxen alone in that preparation? You said you used that in the controls also in the studies. Is there a difference in bioavailability of that compared to the usual preparation of naproxen if you would get it within that particular formulation?

DR. ALEXANDER: I am really not qualified to answer that with data. My impression is that there is no difference.

DR. PORTER: The point, I guess, is that what you are hypothesizing is that the metoclopramide is improving the absorption of the naproxen in this particular preparation because that is the comparison you have. But you don't know that, if you didn't have it in this particular preparation, that there would or would not be a difference.

DR. ALEXANDER: No; we used the same blinded study medication that was naproxen in the core with a placebo around it in these studies that were conducted. So I would answer to say that it seems that we have controlled for everything except

the metoclopramide component.

DR. KIEBURTZ: Let me just restate it. I think your question is, in the naproxen alone, how does that compare to a standard naproxen preparation.

DR. GOLDSTEIN: Exactly.

DR. KIEBURTZ: Does the formulation here somehow delay the naproxen so that the metoclopramide then just speeds it back to normal?

DR. GOLDSTEIN: That is exactly right.

DR. ALEXANDER: Let me clarify. These two are bioequivalent as far as the naproxen component. I was not familiar with the study.

DR. KIEBURTZ: Dr. Jeste.

DR. JESTE: If people with nausea respond differently to metoclopramide, that people without nausea have greater therapeutic benefit, it is also possible that they may have differential response in terms of side effects. They might have more side effects or less side effects than people with nausea.

Do you have any evidence for that?

DR. ALEXANDER: That is one of the things that we looked at very quickly after seeing this efficacy difference was to see if there was any apparent difference in adverse events. There are none. Again, these were prespecified analysis for the endpoint subgroups so we went back and looked at the adverse events. There is no difference between the two subgroups as far as adverse events.

DR. SACCO: It is a question for, I think, Dr. Schapira maybe to comment on. We heard from Dr. Matchar about this unmet need, about the number of people suffering with migraine, the disability, and how this drug could, perhaps, be an unmet need.

One of your slides talks about the fact that this is available in the U.K. and some of your numbers have been 95,000 patients possibly treated. I guess what I am trying to get an understanding of is in the U.K., using the U.K. as an example, the sponsor provided in their document, Appendix 3, which talks about prescription use in migraine patients.

If anything, at least from my

interpretation of this table, the migraine anti-emetic combinations, of which the main one is this kind of drug out there, is dropping kind of precipitously from November, 1999, about 112,000 to 79,000 in November of 2003.

When you look at the overall proportion of migraine sufferers again estimated in these tables, it is a little lower and dropping, so, just again, a feel for, if we use the U.K. as an experience where this drug was available, we recognize the unmet needs that perhaps are possible in the U.S., can you comment on why this seems to be dropping off as a migraine type of drug.

DR. SCHAPIRA: Yes. I think that the guidelines that have incorporated the use of these combinations into the acute treatment of migraine is in response to a need to rationalize the acute treatment of migraine.

First of all, I think many patients with migraine never even go to a doctor. They just treat a headache, themselves. Those that do go to a doctor, I think are recommended to begin an

analgesic just to see if they have tried that and, if they have and have not responded, then there is a pressure, if you like, from the guidelines, the Headache Society in the U.K., et cetera, to try and build the patient's future management on an appropriate logical step which is, if you like, tailored to the patient because I think a significant proportion of patients are being taken from simple analgesic to triptan without this step in between.

I think, to some extent, this is a response to the introduction and marketing of triptans in the U.K. What we have tried to do is to actually insert this intermediate step between those two.

DR. KIEBURTZ: Which one of you two--you had your hand up before, or would you like Dr. Bastings--

DR. KATZ: Eric has, I think, an interesting question but I just have a few maybe sort of random thoughts. The side-effect profile or incidences that were shown for Study 302, that

is open-label data. It is hard, really, to understand exactly what those numbers mean. There is no concurrent control group.

I don't know. I didn't really understand Dr. Alexander's answer when he said, well, you add them all up, you get 78 percent of people reported some sort of an adverse event, therefore, it is not unexpected.

I think Dr. Jung's point is a very good one. We are well familiar with the distinction between lumpers and splitters when adverse events are recorded and reported. Of course, it is hard to do know what to make of the specific point here about adding up all these things because we have no idea, really, what those terms represent, which is a point, I think, that has been made.

But, certainly, of course, it is possible that the restlessness, anxiety, nervousness, sleeplessness, whatever these things are, it is possible that they are all akathisia or some extrapyramidal symptom. It is hard to know, but I think the point is a very good one that,

generically, these sorts of events are notoriously poorly reported, not in this application specifically, but across applications, and poorly translated from verbatim reports to MedDRA or CoStart.

So that is something to watch out for. It is true individually they are less than what--but, even if you look individually, they are all less than 1 percent more or less across all the groups. But, 0.9 percent is different, perhaps, then 0.2 percent. But if you just list them all as less than 1 percent, they all look the same.

So that is just something to keep in mind. Again, it is hard to know what to make of it specifically in this case.

The only other thing I want to say is there has been a lot of discussion about the rationale of why it should be true that it works in people who don't have nausea at baseline. Anything is going to be somebody's interesting theory. It is impossible to really know what the rationale would be.

It would be nice to know what the rationale was to sort of have a real solid well-accepted rationale in hand because I do think, as Dr. Temple said, that this was probably an unexpected finding. It was probably expected to work better in people who had nausea at baseline. There is going to be a retrospective explanation, but we are mostly concerned about whether or not it is a real effect and, as one of our questions asks, whether or not it is an appropriate, well-defined population.

So just sort of generically, I think we are probably less concerned with the rationale for it than is it real and is it a population that we can reliably identify so that we can write labeling.

DR. KIEBURTZ: Why isn't as important as if.

Dr. Bastings.

DR. BASTINGS: It is a question to Dr. Schapira regarding these combinations available in U.K. Is there any evidence from controlled studies

that metoclopramide provides any contribution to efficacy for these preparations?

DR. SCHAPIRA: Thank you. I have not actually looked at and don't have access to the original data on Paramax or MigraMax. But I think that Dr. Alexander may have in order to answer your question.

DR. ALEXANDER: Your question is whether or not there is data that this combination would be effective in migraine.

DR. BASTINGS: No.

DR. KIEBURTZ: Let me restate the question and make sure I understand it. The question of the addition of metoclopramide to the other analgesic like what we have been going around about today, in a factorial kind of design, what is the evidence of the additional benefit of metoclopramide to the underlying analgesic.

Did I understand your question correctly, Dr. Bastings?

DR. BASTINGS: Yes.

DR. ALEXANDER: There are limited studies.

One study I will show is twenty years old. That is this slide here.

(Slide EB12)

It is a study by Tfelt-Hansen looking at the preparation Migravess which Dr. Schapira noted was aspirin plus metoclopramide. This was a factorial study looking at Migravess, aspirin and metoclopramide, versus aspirin alone versus placebo.

You can see that this is a modest improvement of only 2 percent for a two-hour pain response rate in that study. A good small number of subjects, basically 118 subjects, treating three migraine attacks.

There have been a number of comparative studies between these combinations and even with triptans that have shown generally equivalent results in the treatment of migraine.

DR. KIEBURTZ: Thank you.

DR. SMITH: I want a little clarification on the estimated risk of the TD with the intermittent use because Dr. Bastings mentioned, in

his talk, that there was an estimate of 380 cases per million persons per year and then, in the FDA review, there was an estimate quoted from the NDA of 20 per million.

I am wondering what is the estimate that the company has and what is the basis for their estimate.

DR. ALEXANDER: Thank you for that question because it needs clarification. Back in 2004, when Pozen was preparing for the meeting with the FDA, the type A meeting, the critical-path meeting that you heard about, we were looking at the figure of 1 percent as the figure that was given to us in the not-approvable letter as being the upper limit of possibility. But is still a figure of 1 percent.

That certainly is significant when you consider tardive dyskinesia. So we undertook to try to estimate how much lower the risk might actually be. We looked at spontaneously reported cases in the databases available. You have seen the 87 cases or the 40 cases from the Shaffer

article.

We also looked at estimates of prescriptions or usage over a year's period of time and applied a multiplier for the spontaneous reported rate of, say, 1 percent. If only 1 percent of all incident cases are reported, what would the risk be? It is a conservative estimate.

In that way, we calculated the risk could be as high as 0.002 percent or something like that, just to make the distinction that it is much less than 1 percent. That has gotten carried over into this discussion today and I just want to point out that it is based on estimates or assumptions. The better data are the actual-use data that Dr. Schapira has shown with the use of metoclopramide, we think, in migraine in a large population in the U.K..

DR. SMITH: Let me just make sure I understand. You are basing the estimates, these lower estimates, on reporting rates to adverse-events reporting systems in the U.K. and U.S.? Is that correct?

DR. ALEXANDER: Let me just specifically address the 0.038 percent risk that Dr. Bastings more recently used in this. That is based on an estimate of a risk that was the most conservative that we could come up with based on the data.

DR. SMITH: Okay. Thank you.

DR. KIEBURTZ: I think we will talk about that some more, too, when we address the specific questions. I want to ask one question and then we are going to have to close, and this might go to Dr. Jinnah, if he is still here, or, if you don't know the answer.

I believe Dr. Jung brought this up in part. In stimulant-induced sterotopy or models of tardive dyskinesia, are there animal models, and this was alluded to in at least one presentation, as to whether single or a few doses, or intermittent doses, could induce tardive dyskinesias in animal models as opposed to chronic use. Can you speak to this?

DR. JINNAH: I can. I am familiar with that literature. It is going to be difficult to

translate that literature which is mostly derived from rodents to humans because the types of drugs and the temporal course of drug delivery in rodents to create these movements that are labeled as analogous to TD are quite different.

So whether or not we should be even calling it TD is at question. So I am not sure that answering the question is going to help.

DR. KIEBURTZ: Could you answer it anyway?

DR. JINNAH: Sure.

DR. KIEBURTZ: Here is my question. I understand there are animal models. And I understand that animal models don't represent the human disease. But I think it would be useful to know whether or not tardive dyskinesia--or those movements have been induced with intermittent or few exposures are they are required to have chronic exposures for them to develop in models.

It doesn't necessarily, therefore, mean that the human experience follows that.

DR. JINNAH: Correct.

DR. KIEBURTZ: Let me put it a different

way. My understanding is those models indicate that intermittent or few exposures can induce those changes and reduce the threshold for stimulant-induced stereotopies. Am I wrong?

DR. JINNAH: No. That's correct. Either chronic or intermittent administration, as few as just one or two doses of the drugs, can induce these movements that are called tardive dyskinesia. I should temper that statement with the observation that Reserpine is one of those drugs and Reserpine does not cause tardive dyskinesia in humans, to my knowledge.

So what the movements are, I think, is still really a key part of that answer.

DR. KIEBURTZ: So the specificity and the meaning of these models is unclear.

DR. JINNAH: I think that is true. But, perhaps, Dr. Jeste can comment on the issue of using neuroleptics intermittently in psychiatry because there is some data showing that drug holidays of neuroleptics and intermittent use of neuroleptics in human patients does, in fact,

increase the risk of tardive dyskinesia.

But, again, it is not PRN or intermittent use as we have been talking about. It is more chronic for weeks, months, maybe years with a holiday and then chronic again. So it is a little bit different but the same idea.

DR. JESTE: That actually applies to people with schizophrenia or other psychiatric disorders when you do long-term treatment. People who get the treatment intermittently seem to be a high risk of developing tardive dyskinesia. The theory is that has something to do with kindling, that if you administer something continuously, there is development of tolerance where it is intermediate. Intermittent administration may lead to kindling and increase the risk of TD.

DR. KIEBURTZ: Thank you.

We are going to stop the discussion period at this point. Just to reiterate, to the point of being boring, not to continue any discussions of the presentations not in the public forum.

We will start with the Open Public Hearing

next. All registered Open Public Hearing speakers, please register at the Registration Desk. 1 o'clock is when we will start again.

Let me just thank all the participants from the sponsor, from the FDA and from the committee for bearing with the way we ran things.

We are adjourned until 1:00.

(Whereupon, at 12:00 p.m., the proceedings were recessed to be resumed 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

(1:00 p.m.)

Open Public Hearing

DR. KIEBURTZ: The first part of the afternoon is the Open Public Hearing. I have a statement to read here.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To insure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its products and, if known, its direct competitors.

For example, this financial information may include a company's or group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA

encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So far, we only have one registered speaker for the Open Public Hearing and that is Dr. Cynthia McCormick who can come on up to the podium and address the committee.

DR. McCORMICK: Thank you. Good afternoon, Dr. Kieburtz and members of the PCNS Advisory Committee, Dr. Katz, Dr. Temple.

First let me start with the disclosures and also thank you for giving me the opportunity today to address the committee as a member of the public, which is a new experience for me, and to share with you my thoughts as you proceed into the deliberations for today.

So, in terms of disclosure, since leaving the FDA, I have worked as an independent consultant to regulated industry including upwards of probably

close to 70 companies by now, many of which are in the area of pain therapeutics including a few companies developing drugs targeted to treat migraine. Among these, I have served as a consultant to Pozen.

Today, however, I am speaking on my own behalf and my comments are not driven by my industry consultation but rather by own personal experience. The division has heard these, I think, in some manner but probably not in this context.

By introduction, I am a neurologist and a former federal employee, 17 years a federal employee, most of which was spent at the FDA, initially as a reviewer in the Division of Neuropharmacologic Drug Products, and the remainder as the Division Director in Anesthetic Critical Care and Addiction Drug Products where I had the responsibility, among other things, for therapies to treat various painful conditions.

As such, I have been in the position of approving drugs before. I know that it is not always straightforward and there is a great deal to

consider. I also know that there is a fair amount of discretion in making these decisions and that, perhaps, makes the decision-making even more difficult.

I think I have to say that both approval decisions and not-approval decisions can have important consequences for patients. I believe in the FDA process. I believe in the mission of the FDA and I have enormous confidence in the FDA. With all of its oversight systems of checks and balances, high ethical standards, it does, really, a remarkable job in protecting the public health, both in not approving drugs that are not effective and safe and also in approving drugs that are. The job isn't without its struggles. The recent public criticisms that FDA has had to endure which, in my opinion, are unwarranted, make it even more difficult.

But I am speaking to you today not as a former regulator but as a chronic migraine patient. I know what drugs are available, both for prophylaxis and for PRN treatment of acute migraine

attacks and I have tried most of them. I know the side effects of the medications and I have been able to make informed decisions because the FDA process works and because product labeling is usually fair and very complete regarding the risks of medications.

So, two and a half years ago, while I was serving as FDA's Director of Anesthetic Drug Products, I suffered a serious, potentially life-threatening, adverse event from an approved migraine drug which I took on the day before an advisory committee meeting, much like this one, although the topic was prescription drug abuse and oxycoton which probably explains the headache.

I found myself in the intensive-care unit and I have permanent sequelae from the event. But the thing is that it left me with no realistic treatment options for migraine and I, as many others, consider this a disorder that can be very incapacitating at times.

So consider for a minute what is currently approved for the treatment of migraine. Most of

the approved products are associated with vascular risk, as you might expect, including significant cardiovascular risk. These include the ergot alkaloids, the triptans and, up until spring of this year, one of the selective cox-2 inhibitors no longer on the market.

So, for patients who have suffered a myocardial infarction, or who have cardiovascular risks, these medications really aren't an option. So what is left? Not very much. I think we heard, when we saw the slide with three things on it this morning, well, eliminate one column. So, over-the-counter and off-label medications. Those are my choices right now. So, for people who have no options, any therapeutic gain is significant.

So, when you consider how to deal with what is an acceptable risk in this population, consider the following: the existing medications have risks that are not trivial. Patients who suffer from migraines tend to know a lot about their medications and truthful labeling is absolutely critical and something they expect from

the FDA and something the FDA expects from themselves, as well. Without it, they can't make informed choices about their treatment.

To put into perspective the kind of risks that some patients are willing to take with migraine to get relief, take a minute to consider how bad the disorder can be. It took me several years after the first triptan approval before I was willing to take one.

I listened to the adverse-event profile unfold during the NDA review because I was in the division that reviewed that drug. So when I finally took one, I did it with my eyes wide open, with absolute full knowledge and understanding that there was a cardiovascular risk and what that risk might be. And I was willing to take that risk, obviously, and I did.

But my headaches were so debilitating at that time, and so incapacitating and really impaired my ability to work, that I was willing to take that risk. So that is how bad it can be.

Here we are with an armamentarium that

includes three, now, actually, two classes of drugs that are off-limits for a segment of the population like me, and few options. Right now, you are discussing a drug that has a different kind of side effect. It has been implicated with the potential for having a risk of tardive dyskinesia with chronic administration.

I am a neurologist. I know what tardive dyskinesia is. I have seen it. It is a bad condition. It can be very debilitating. So the question is is that worse than an MI? I don't know. That is what I am asking myself. I think each patient has to make that decision themselves as to what risks are worse than others and what they are willing to take.

It might be, if there were some benefit that I could gain from that drug. But I can absolutely guarantee that, if I didn't get any benefit from the drug on the first administration, I wouldn't be taking it more than once. That is one thing that I think we heard this morning about--that is pretty characteristic of people with

migraine. We self-select our medications. You are not very likely to accumulate a cadre of patients who are continually deriving no benefit and only risk. So that is something to put into the equation.

My message to the committee and to Dr. Katz is the following: please keep an open mind. Migraine can be incapacitating. For a segment of the population, the drugs that are currently approved don't exist. While it would be ideal to have criteria that would give us the perfect drug, patients like me don't expect perfection and would be very happy with any therapeutic effect so long as the labeling truthfully reflects the risks as well as they can be known.

Thank you.

DR. KIEBURTZ: Thank you.

Is there anyone else who would like to address the committee during the Open Public Hearing? Not hearing any, thanking Dr. McCormick for her statement, we will close the Open Public Hearing phase of this meeting.

Committee Discussion and Response to FDA Questions

DR. KIEBURTZ: We will now, as a group, deliberate the questions that were posed. Committee members, just so you are familiar, I believe, just from my seating chart, that Dr. Porter is the only non-voting member.

So, on the five questions, we have to individually vote our opinion about the questions posed. Some of them are multipart so it is going to be a little difficult. We can discuss the question and then we need to come to an answer. At the time you give your answer, or your vote, you can get some clarification as to why you are voting that way.

This will be a chance for the agency to get a clarification of how we are thinking.

Here is the first question. Take it as a given that this has been estimated as an annual incidence--that is, the number of new cases of tardive dyskinesia--at this dose for use of up to six doses per month, so up to 72 doses per year, 380 cases, new cases, of tardive dyskinesia per

million patients per year.

Do you think this is a reasonable estimate? Dr. Fahn.

DR. FAHN: I would like to start. I did some calculations on the margins of the slides that were handed out. The risk for developing--the incidence for developing tardive dyskinesia has been calculated by John Kane and his colleagues at Long Island Jewish who has studying the epidemiological of tardive dyskinesia for decades.

He calculated the risk to be about 5 percent per year, so a person would take--now, these were neuroleptics, but these were dopamine-receptor blocking agents which, of course, metoclopramide is also. The calculation was that 5 percent per year, that if you took it for four years, then you would have a 20 percent risk of getting tardive dyskinesia and so forth.

Multiply 5 percent per year times 72 days divided by 360 days, I come up with a 1 percent risk, not 0.38 percent risk. Now, granted that the drugs that were used in the psychiatric population

are daily doses continuously, so that might have been the risk for 72 days in a continuum. What would happen if it was discontinuous? I think this is the big unknown. I don't think anybody, as we heard all day so far--that no one really knows what these intermittent or periodic risks are and it may be less.

The intermittency, when you stop--for psychiatric patients, of course, and then restart it, the risk seems to go up. But, giving it for migraine is one thing. So I think this a level that is probably too low. I think it, at least from these calculations, is going to be probably closer to the 1 percent risk.

If you want me to address the second part of that question, I would be glad to do that.

DR. KIEBURTZ: Let's just stick with this. I mean, we can have a little bit of general discussion about whether we think it is reasonable or not, and then we are going to have to just each vote about that question.

Dr. Jeste, did you--

DR. JESTE: Actually, unrelated in a way, but one general point I want to make. Since the morning, there has been a lot of discussion of how do we define tardive dyskinesia. I would argue that there is, actually, a standard definition in the DSM IV for tardive dyskinesia. By definition, as Dr. Jinnah said, that is later occurring. The word "tardive" means late occurring.

So, if it occurs in less than a month, it should not be tardive dyskinesia. That doesn't mean it cannot be persistent. So we need to separate out tardive dyskinesia from persistent dyskinesia. Acute dyskinesia can be persistent but we should not call it tardive dyskinesia. I think it is somewhat of an oxymoron to say tardive dyskinesia that develops after one day of treatment, of any drug, for that matter.

The DSM IV definition is minimum 90 days except for older people where it is 30 days or more. One can use different definitions for possible different types but, again, in terms of standard nomenclature, I think we should stick to

that definition. That would be my recommendation.

DR. KIEBURTZ: Dr. Porter.

DR. PORTER: Yes. An epileptologist should never tackle a movement-disorders expert in his own field, but, Stan, I think that you have gone way too high.

I think that, if it were really 1 percent for this particular drug in migraine, we would be seeing 95 patients every year showing up in the U.K. yellow-card system. While I think maybe the U.K. yellow-card system is flawed, I think that it is not nearly that flawed, especially when the dose given in the U.K. is more than twice the dose as proposed for the tablet here in the U.S.

So I think it is--actually, I think that the company's estimate is high and I think your estimate is very high.

DR. SMITH: I want to comment, because my area is pharmacoepidemiology, and I feel that these databases are kind of being maligned and misused. I want to really make sure that that is understood, that the use of reports and divided the number of

cases is, first of all, not what these databases are meant for. It is a gross misuse of them and it is a very dangerous misuse, particularly in this case. If anything, it is probably the lowest ballpark estimate of what the risk might be and it is not even a good estimate at that.

One of the things we are pretty much, I think, in agreement on without even voting is that it is not a simple disease to diagnose, that there is variation in what makes a diagnosis of TD, that part of the diagnosis criteria does include, in some places, the length of therapy which would preclude people from reporting something it if was--as TD, if it was after just one or two uses, so we don't even know. So the reporting rate for that would be substantially lower than what we think.

The drug has been on the market a long time. It is labeled for this so it is not unexpected. So estimating the reporting rate is just--it is just a guess. It is like throwing an arrow. We don't know if it is 1 percent or

10 percent or 1 millionth of a percent. It is a gross unknown and I think this is something we really have to think about whether or not these numbers are based on anything that is reasonable.

DR. LENAERTS: When we consider the risk of tardive dyskinesia or other movement disorders, would it be appropriate, so that is a question to anybody, or a comment, to consider the relative risk of migrainers where, on the one hand, we have probably a relatively younger population. But, on the other hand, we have significantly more women with a 3-to-2 ratio of women to men, and also the fact that the coadministration of tricyclic anti-depressants and the SSRIs which we have seen can give its own risk is particularly common in that population of patients.

If I take the numbers that you showed, on 67 cases of TD, 14 also took anti-depressants which between 20 and 25 percent. Is it appropriate to consider the special population that migrainers represent in that context?

DR. KIEBURTZ: Sure. I think we should.

Dr. Green.

DR. GREEN: I think that dopamine hypersensitivity is right at the heart of migraine pathophysiology and, therefore, it is not clear to me that any data we get from the general population rather than the migraine population is relevant to this question.

I don't know if that impacts negatively, positively, or not at all. But this is a condition of dopamine hypersensitivity. But also the other comment is I agree with several comments that there is a huge need for a medication that is effective in the treatment of migraine that is not vasoactive, a desperate need for that.

DR. KIEBURTZ: Dr. Hughes.

DR. HUGHES: I try to explore the issue of the safety study that the company had done this morning. I think--you know, you have got 300 subjects followed for a year and 1,000 followed for a few months. I think it would be hard to conceive of the idea that the true rate would be 1 percent or more, given that they didn't really see any

events or they saw zero events according to the definition that they were using.

So I would hazard a guess that it is somewhat below 1 percent. But how much below, who knows?

DR. KIEBURTZ: One last comment.

DR. JESTE: I really think it is fair to say we do not know the risk and we will not know the risk unless and until we do a longitudinal prospective study in which rigorous measures are used to find out whether the patient has TD and one has to use a scale like involuntary movements scale, use some fixed criteria.

There are a number of confounds in deciding the incidence of tardive dyskinesia. For example, the drugs that produce TD are also the drugs that are suppress it. So, if we increase the dose, you may not see TD.

It also depends on what other medications the patients are taking. If they happen to be on dopaminergic drugs, for example, that might precipitate TD. If you look at the history of the

neuroleptics in psychiatry, it is worth remembering that it took more than 25 years before the field accepted that there was such a thing as tardive dyskinesia.

People argued that it was a symptom of schizophrenia for many years. The only time that the incidence became clear is when a number of people did longitudinal prospective studies using that. So I really don't think anybody can make a claim for any kind of--whether it is lower or higher, it doesn't matter. We just don't know the risk at this stage.

DR. KIEBURTZ: Okay. So we are going to vote now. I am going to go around the table, which is, this is the proposed estimate, 0.038 percent, as an annual incidence. Do you think it is a reasonable estimate. We don't have a definition of reasonable, but let me operationalize that. If we are proposing 0.04, there is some range around that from 0.01 to--an order of magnitude around that.

But you have a sense of where the estimate is. Go ahead. Dr. Green? It is either yes, no or

abstain. But you can make a comment.

DR. GREEN: The answer is no.

DR. KIEBURTZ: Dr. Jeste.

DR. JESTE: I don't think, really, there are any data to say this is a reasonable estimate at this stage.

DR. KIEBURTZ: So the answer is no.

DR. JESTE: The answer is no.

DR. SMITH: No.

DR. WELCH: No.

DR. LENAERTS: No.

DR. FAHN: No.

DR. JUNG: No.

DR. GOLDSTEIN: No.

DR. SACCO: No.

DR. KOSKI: No.

DR. HUGHES: No.

DR. KIEBURTZ: I will say yes because I think we don't know but, from the evidence, we have some reasonable bounds, as Dr. Hughes alluded to, that we certainly don't think it is 1.0 or higher. It is somewhere under that. We don't have enough

evidence to conclude it is zero, but what is in the reasonable range of between zero and 1.0 and I think this is reasonable.

Dr. Temple.

DR. TEMPLE: Could I ask whether the people who said no think it might be lower, higher or just can't say.

DR. KIEBURTZ: I am going to do a show of hands. How many people think you just really can't say. There is not enough evidence to say, and that is why you voted not. (Show of hands.)

DR. KIEBURTZ: That is seven.

DR. TEMPLE: I interpret that as meaning they think it could actually be higher. Would that be--

DR. KIEBURTZ: Just don't know. Dr. Fahn, do you think it is higher?

DR. FAHN: I think it is higher.

DR. KIEBURTZ: Dr. Lenaerts does too. Three people think-- does anybody think it is lower than this estimate?

(No response.)

DR. KIEBURTZ: Okay. Is that helpful to you?

DR. TEMPLE: Yes.

DR. KIEBURTZ: I am just going to reverse the order a little bit here in the next set of questions because I think one moots the other. So let's just go to the third question here. Is any risk of tardive dyskinesia acceptable for a migraine population? If we conclude that there is none, the middle question, is not--so, just logically, I would like to go with that question. I know Anuja is going to be mad at me for going out of order.

Any discussion about that?

DR. GOLDSTEIN: It is a takeoff on one of Dr. Matchar's slides, actually, where he said 79 percent of sufferers showed an interest in trying a novel product with similar efficacy but fewer adverse events than existing migraine medications.

The point is that this is obviously another imponderable. We heard testimony that some people might take that risk, whatever that risk

could be defined. But it is possible, through decision analysis, to get some bounds for what the people might--what patients might be able, or willing, to accept as a risk for having a permanent or even a transient sequela.

So, right now, we are just--we are making this up as we go along. But there is a way to actually get data to be able to address that point. What I would encourage would be to try to formally get that type of data. The studies are not that difficult to do.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: No; not right now.

DR. KIEBURTZ: Dr. Fahn.

DR. FAHN: I think the risk of getting tardive dyskinesia on the first dose is extremely, extremely, rare and even the second dose and so forth until you start taking multiple doses. So, when Dr. McCormick made her presentation about migraine sufferers would not continue a drug if it wasn't working, that shed a new light on me. I mean, that is an experience--they are not going to

keep on taking this drug.

Therefore, I think the risk, then, is not for the people who it doesn't help continuing to take it. The risk, then, becomes those in which the drug helps and then the drug, as they continue to take it, the risk keeps going up every time they take it.

But, because a drug is beneficial to those patients, then I think the risk is probably worth it for those people. Therefore, even a 1 percent risk in a year, if it helps the patient, that may be something the patient has to decide and they know what that risk is and would take it.

So, therefore, I think the answer to this is yes. Risk is acceptable for the migraine population at least that gets a response to the drug.

DR. KIEBURTZ: Dr. Welch.

DR. WELCH: My answer to this would be yes as well. It depends on the migraine population and the way the drug is used. For migraine patients with severe disability that haven't responded to

anything else, or there are contraindications to using such a medication, then this would be a risk worth taking. So my vote would be yes.

DR. KIEBURTZ: Dr. Green. You don't have to say about your vote yet. We are just doing general discussion. But you can if you would like.

DR. GREEN: Again, in this special population where vasoactive migraine therapies are not an option, it is wonderful--it would be very useful to all of us to have additional options. I would disagree, however, with the comment that migrainers don't overuse, or wouldn't be likely to overuse, something that is ineffective. In fact, it has been my impression that migrainers are less likely to overuse something that is fully effective and less likely to overuse something that is completely ineffective and the things in the middle which give partial relief are the things which put people at risk for redosing.

DR. KIEBURTZ: Dr. Temple.

DR. TEMPLE: Because you skipped to the third question, there is no context here about the

magnitude of the benefit from the thing that puts you at risk. This drug is going to work on people. It is obvious. Naproxen works in migraine just like ibuprofen and aspirin work in migraine. So there isn't any question it is going to work.

The question that was flagged there is how much is it worth to you to get the added benefit of the metoclopramide. That should be kept in mind, I think, even in this part, though.

DR. KIEBURTZ: I think it is pretty obvious we are going to get to the third question because it doesn't look like there is consensus.

Dr. Koski.

DR. KOSKI: I really would like to second that. In the sense that patients, because of the fact that they can get a response from naproxen, are going to get something, or at least a significant portion of patients will get something in response to the drug.

The question is is there something additional that is taking place with the metoclopramide addition. Because of that reason, I

sort of disagree with Dr. McCormick. I think that this would not be a one-time event, that this would be something that people might continue to take.

Certainly patients I have seen, some of them, quite frankly, think if one tablet works okay, maybe they should take two and then, occasionally, maybe I have something--maybe it is coming on and I am always told to take something just as soon as I possibly can. I will take another one then.

So I think there is a great deal of potential for that type of abuse.

DR. KIEBURTZ: Let me just clarify the question, here, too, which is not a product-specific question. Is any risk of tardive dyskinesia acceptable for a migraine population? It is a question that is independent of benefit. That is why I went there first. But it is a very abstract question, as I read it. But maybe I am reading it wrong.

Dr. Jung.

DR. JUNG: Speaking as the consumer

representative, my concern is that there would be adequate patient education information about what actually tardive dyskinesia is, given the fact that, in this room of neurologists, we can't seem to agree how you actually make a diagnosis. How do you anticipate that, in your office, you are going to be able to explain to a patient or be able to show a video, for example, such as was shown earlier, of what a significant risk is.

I think most people can understand the risk of what a heart attack or a stroke is. But to describe tardive dyskinesia and have the worst-case scenario be apparent is not clear to me, that we can actually do that in the clinical setting.

DR. KIEBURTZ: Thanks.

Dr. Welch, did you have a comment?

DR. WELCH: No; I was going to address--

DR. KIEBURTZ: Okay. Dr. Sacco.

DR. SACCO: I think we have other data from other patient populations that obviously have accepted the risk of medical metoclopramide for GERD. So I think it depends on probably the amount

of risk. Any risk is really tricky if it is 0.0001 and the benefit. So it is a risk/benefit ratio but, in my mind, the fact that other patient populations with pain somewhere else, including gastroesophageal reflux, have accepted the risk of the medicine that is out there, then any risk may be acceptable. But it depends on the amount.

DR. KIEBURTZ: Dr. Smith.

DR. SMITH: I want to agree that just to say is there risk without thinking about the benefit, it just can't be separated unless you are talking about cure and a one in a million risk. Then maybe the answer could be yes. But I agree that you have to think about what is the added benefit when you know you are going to add this risk beyond what is already out there.

DR. KIEBURTZ: Maybe I misread this third question. Maybe it is meant to be contextualized on the second question and not stand alone. Is that true?

DR. KATZ: No; I think you read it correctly. We wanted to find out if it is just

drug independent. But, of course, obviously, the amount of risk you are willing to tolerate will depend on what you think the benefit is. That is obviously critical. But we just wanted to sort of get a baseline because, as you say, it moots the rest of it if everybody thinks no risk is acceptable, no level of risk.

DR. KIEBURTZ: So let's vote the question because I think we know the answer to this. Is any risk of tardive dyskinesia acceptable for the migraine population? We will go this way this time to mix it up. I say yes.

DR. HUGHES: Yes.

DR. KOSKI: Yes.

DR. SACCO: Yes.

DR. GOLDSTEIN: Yes, with just the additional comment that, again, there is a way to get the information so that we are not guesstimating. We can get this.

DR. JUNG: With some hesitation, yes.

DR. FAHN: Yes.

DR. LENAERTS: Yes, too, but for the same

remark. It depends on the efficacy. It is hard to take out of context.

DR. WELCH: Yes.

DR. SMITH: A qualified yes.

DR. JESTE: Yes.

DR. GREEN: Yes.

DR. KIEBURTZ: Back to Question 2 which is a little more complex. I think what we are to do here is to assume that the risk of MT100 is 0.04 percent, let's say.

DR. KATZ: That is what the question asks. But it turns out most people don't think that that is a reasonable risk. Some people think it is higher--or a reasonable estimate of the risk. So I am not sure we want to sort of pin our risk/benefit consideration on some risk estimate that nobody believes.

Maybe the best thing to do is just sort of--I mean, everybody has probably got their own personal view of what they think the risk is. You can't tell. I think maybe we should try to talk about what sort of a--let's assume the benefit part

of this question, the 5 to 10 percent contribution of the metoclopramide and then sort of talk about what sort of risk you think would be acceptable.

That is really more or less the question, and whether or not we think we are at the point yet where we think that that is the risk.

DR. KIEBURTZ: Okay.

DR. KATZ: In other words, I don't want to link it to a number which everybody has already decided doesn't mean anything.

DR. KIEBURTZ: The way that we were discussing the last question it got posed around--several people volunteered it depends on how much benefit you are seeing. So let's turn it around and say, in the factorial designs, leaving aside the question of statistical significance, the proportion of individuals as reported as the percentage of individuals who had sustained pain relief at 24 hours differed in the MT100 group versus the naproxen group by between 3--let's say between 4 and 6 percent.

So between 4 and 6 percent additional

subjects had sustained pain-free response.

DR. BASTINGS: It is not pain-free. It is just sustained pain response.

DR. KIEBURTZ: I mean sustained pain response. Thank you for the clarification. We are assuming that is true, that is the true effect, for the purposes of this hypothetical discussion.

DR. BASTINGS: You also need to take into consideration that there would be no benefit at two hours, which is--

DR. KIEBURTZ: So that is the parenthetical statement below which is, if you looked at the comparison of MT100 to naproxen at the two-hour pain response, those differences were not statistically significant. They were numerically different but they were not statistically--Dr. Bastings' presentation showed that in that, in the one study, quite a number of people had a lower relapse rate and that added up to the total difference between the groups.

In the second study he presented, the majority of it was actually in the two-hour

response and there wasn't that much difference in the relapse rate. But the numeric difference, even at two hours, was 3.1, I think, if I remember correctly.

So the comparisons at two-hour pain response are not statistically significant. So, overall, the effect is 4 to 6 percent but the two-hour comparison of pain response is not significantly different.

Have I framed the question correctly? We are changing on the fly here.

DR. KATZ: In our hands, the way we have analyzed it, the studies which we believe were what the protocol said, the contribution of metoclopramide for a sustained response, which was the primary outcome, is not statistically significant overall. It only seems to be nominally significant when you look at the non-nausea baseline subgroup which is partly where this 5 to 10 percent comes from.

There is a 10 percent contribution of metoclopramide in the non-nausea at baseline

subgroup which, again, is normally significant in two studies. We don't think that that is true replication but, in the overall group, we don't think that the contribution, even for sustained response, is statistically significant

DR. KIEBURTZ: I wasn't suggesting that you did.

DR. KATZ: Okay.

DR. KIEBURTZ: Everyone has got this definition here. So the question is what amount of risk would be reasonable for that amount of clinical benefit. So we are not saying is that risk reasonable. We are saying what is reasonable with that amount of benefit, if you can follow the hypothetical situation.

DR. SACCO: I just want to be sure. It sounds like, in the hypothetical situation, we are giving the compound more benefit than what is seen, 5 to 10 percent, the way this question is phrased, and I understand where you may be getting with not-nausea is to--and possibly an exaggeration of the benefit.

DR. KIEBURTZ: Okay.

DR. SACCO: If we take what we got, which was 4 to 6 overall, this question is not phrased as just in those without nausea. So you are giving it the benefit--

DR. KATZ: No; right. It is not. But the range, 5 to 10 percent, includes--so the estimate that was in the overall population and the maximum difference that you saw in the no nausea. We could talk about whether or not a study ought to be done to replicate the no-nausea subgroup of whether another study or studies should be done in the overall, but we just want to know, is there some well-defined population in whom the contribution--to be determined what that is--if the contribution of metoclopramide is in this range, as a ballpark, because that is where the estimates have sort of fallen out. Are the risks, whatever they are, acceptable?

So I think of this range. We could figure out which population we think that range applies to down the road.

DR. TEMPLE: Our assumption is that there is not going to be a bright line between 5 and 10 percent. They are both fairly modest. One is more modest than the other, but that is a reasonable ballpark to think about. If there is a bright line that you have, say so.

DR. KIEBURTZ: Dr. Welch and then Dr. Fahn.

DR. WELCH: Well, let's try and instill some practical clinical reality into the question. Surely what the question is saying is if there is a small subpopulation, and it would be small at this level of 10 percent improvement, that responds to metoclopramide plus naproxen that doesn't respond to naproxen and that that can be significantly proven, and if you have answered yes to the risk of tardive dyskinesia acceptable for a migraine population, the answer would have to be yes for the second part because you have said that you will use this drug, or certainly you would use metoclopramide, in a particular population that has benefit that can't take anything else.

So the issue here is, have you really proven that metoclopramide plus naproxen is, in fact, statistically significantly different in a subpopulation. I would suggest that it has not been proven that 5 to 10 improvement is in the nausea versus no-nausea, and we are going to talk about that later. But, to me, that is not a stable measure as yet.

But, if it was, there is one in ten patients who responds to naproxen plus metoclopramide that wouldn't respond to naproxen, then you would use naproxen because there is nothing else yes, the answer would have to be yes.

DR. FAHN: That is the point I was essentially going to make and that is what I was going to ask the FDA, if this drug were available on the market, if it was restricted to those who were, on naproxen alone, failed and then they still had that 5 to 10 percent chance of getting better with this combination, then I think the answer is yes.

If it is just going to be open and anybody

can take the drug without even trying naproxen alone first, then the risk for tardive dyskinesia is too great for me. So I assume there will be some kind of restriction that they have to be tested first with naproxen alone because, otherwise, I think the risk would be too great. But if it is restricted that way, then I say, this is a worthwhile risk.

DR. KIEBURTZ: Let me just refocus things again. By pursuing this hypothetical question, we are not agreeing that there is a benefit of MT100 over naproxen. We are just saying hypothetically, if it were so. We are not agreeing that we think that that has been shown. So I just want to make that one statement.

Two is I don't think we can assume that we know how the restrictions are going to be. That is not how this conversation, I don't think--

DR. FAHN: I think the point is if more people will be exposed to this, then more people are going to get tardive dyskinesia. But if the exposure is limited to those people in which this

drug may be the only thing left, then it is a reasonable risk.

DR. KIEBURTZ: Dr. Porter.

DR. PORTER: I completely agree. If you look at the history of cancer chemotherapy of these kinds of incremental improvements are what have made a lot of cancers much less a threat than they used to be. I think that we would have to take these little bites when we can get them.

I agree fully with the thesis that this is a drug that, A, has to be proven. I am not sure about this business about whether or not the nausea is or is not related to its efficacy. I agree with that. Certainly, there will be some labeling, I hope, that would be relatively strong relative to the risk we have been talking about.

But I think to reject the drug when it might help some people who have gone through a parade of migraine drugs would be unfair to them.

DR. JESTE: I am not a migraine researcher but, based on my experience with psychiatric patients, just a couple of points here. The one is

that the risk of tardive dyskinesia varies from one patient group to another. Clearly, elderly patients, the risk is 30 percent incidence with conventional neuroleptics compared to 5 percent in younger adults. So something like that will have to be taken into account.

Secondly, all tardive dyskinesia is the same. It can be pretty mild which is not a problem, or it can be pretty serious when it does become a problem. So it depends, really, on what kind of tardive dyskinesia and what population. So those will need to be taken into account in whatever final decision is made.

DR. KIEBURTZ: Dr. Bastings.

DR. BASTINGS: I would also like people to comment, if possible, on the fact that there would be no effect on two hours but yet there would be an effect demonstrated in a sustained endpoint. The sustained endpoint is a measure which includes two-hour pain response. There is a possibility to have a significant effect on sustained response without actually having an effect on the two-hour

pain response which is a particularity.

I would like to have some idea, in that context, if that is an acceptable outcome measure.

DR. GOLDSTEIN: Again, just to interject a little clinical thought that, let's say, if you were a patient and you were having a migraine and you took this and in two hours you weren't having any benefit. Chances are you might, then, take something else. You might just take naproxen alone, for example, or some other nonsteroidal alone. So the question I would have, as these trials go on, from a practical standpoint, would be is that kind of additional dosing factored in to the 24-hour improvement because, if you factor that in as well, then the clinical benefit might even be less or, in that subpopulation of people who don't respond to that second added drug, the benefit might even be greater.

It is hard to know without that information. They may have it but I don't know--we didn't see the data that way. But that, I think, would address the question that you are asking

here. Nothing at two hours; then is there sustained relief. I think you have to see what else was done at that two-hour standpoint to know that.

DR. KIEBURTZ: That would be a relapse if you had to take anything.

DR. GOLDSTEIN: Yes.

DR. TEMPLE: In these studies, as conducted, and acknowledging that SPID and TOTPAR might give you slightly different impressions, but nobody would know the difference between this drug and naproxen as near as we can tell at two hours. So I think the question being raised, and it is part of it, is when you think of somebody with a terrible migraine that won't go away, you think of the early response mostly.

Mostly that is just naive and we should have been thinking about the sustained response all the time. But part of the question is is this modest effect on that endpoint and not on the two-hour endpoint worth a certain amount of risk of TD. We are not saying no, but we want to gain some

impressions of what you think.

DR. KIEBURTZ: This is a very tricky question and we are modifying it en route. But the trickiness of the question lies in how big the benefit is and the fact that the benefit accrues on a synthetic measure, one that incorporates both immediate response and relapse into a single measure when you have benefit on that but no benefit on the immediate measure, if I am--

DR. KATZ: That is right with regard to the contribution of the metoclopramide. It is obviously complicated because you could construct maybe a better 24-hour sustained-response in which you say--right now it is just you are considered a responder if you responded at two and throughout the next 22 hours. But, at two, the drug might not be better than placebo so you wouldn't win on the typical thing.

But you could construct a sustained-response outcome which says you have to beat placebo at two hours and--it is a two-part outcome--and you have to win on the next 22 hours

as well. So you could do that. But it is complicated because it is possible that the drug, itself, MT100 could win on that particular outcome but the metoclopramide doesn't contribute to that particular outcome. So you have to see what would happen if you did that.

DR. TEMPLE: There is no doubt that the whole drug has an effect at two hours. Nobody is doubting that. It is all about the contribution of the metoclopramide.

DR. KATZ: Right. So the question is do you think the metoclopramide has to contribute for the two-hour point as well as the sustained portion of it or is it okay if the drug overall wins at two hours on this new sustained but the metoclopramide only contributes to a part of it.

DR. WELCH: Again, I don't believe that it has been established yet that there is an efficacy so it is an assumption. So now you are talking about what kind of efficacy measures you would like to see. I would like to see a two-hour pain-free sustained. I think that is the rigorous measure

and I think that, to show a difference between MT100 and naproxen, pain free at two hours.

DR. KIEBURTZ: Dr. Bastings.

DR. BASTINGS: I would like also to point out that this does not even include the issue of the effect on relapse or use of rescue medication such as in the factorial studies of the NDA, there was no significant difference for relapse or use or rescue medication either. It is just the combined effect which gives you an effect.

DR. KIEBURTZ: So if you split the combination thing of immediate response and relapse rate, neither of the individual components was significant. But when you combined them, that was the only measure in which you achieved significance.

We are going to vote this question. What question are we voting? Let's vote this question which is, if MT100 were to carry the same risk, would such a risk be acceptable if the only contribution of the metoclopramide is a 5 to 10 percent improvement on the sustained headache

relief with no improvement on the two-hour endpoint.

DR. WELCH: Can you just qualify this question a little bit because the question is in the question. If you put with no effect on a two-hour endpoint, I would have to say no. But if you really said that there is a 5 to 10 percent improvement on sustained headache relief as defined by two hours pain-free and then no relapse, then the answer would have to be yes.

DR. PORTER: 5 percent to 10 percent of patients?

DR. WELCH: Yes; 5 percent to 10 percent of patients. It is not 5 to 10 percent--which is critical here because it is extra patients who can respond who would not have responded as opposed to 5 or 10 percent more pain relief. It is very critical.

DR. KIEBURTZ: Let me just clarify. The question is what the question is, not as you modified. I know that it not the question you want to answer. But this is the question.

So, Dr. Green.

DR. TEMPLE: Just one thing. But it is all about the contribution of metoclopramide.

DR. KIEBURTZ: Right.

DR. TEMPLE: Nobody doubts that the whole drug works in two hours.

DR. KIEBURTZ: It is the contribution of metoclopramide, 5 to 10 percent, on the sustained measure with no effect on the two-hour measure which is not pain-free. It is just pain relief.

DR. GREEN: Okay. Then I would say no.

DR. JESTE: No.

DR. SMITH: No.

DR. WELCH: No.

DR. LENAERTS: No. But I would like to make a comment, if I may, afterwards.

DR. KIEBURTZ: Go ahead. Comment now, please.

DR. LENAERTS: Of course, I just want to clarify that, but we are really not talking about taking people who have not responded to naproxen alone because that would be--it gave the

impression, sometimes, in the discussion as if we were heading that way.

The other thing is even though the outcome of how they do at two hours and how they do between two and 24 are both important. But, as far as my experience and my reading on the subject, it is clear that the weight of the two-hour response is much more significant than that of the two to 24-hour period.

DR. FAHN: I got a little confused now in the discussions. I thought that this was the added benefit of having metoclopramide on top of naproxen, you get another 5 to 10 percent of patients getting better with less headache. So, on that basis, I think that is yes.

DR. JUNG: No.

DR. GOLDSTEIN: No, not as this question was written.

DR. SACCO: I am still confused about the question. But I am going to say yes because I am, first of all, reading it that if MT100 were to carry the same risk, and I am reading that risk of

TD as being 0.038 percent--am I correct in my assumption?

DR. KIEBURTZ: Yes.

DR. SACCO: Which is, I think, lower than--

DR. KATZ: The way I would think of it, or the way I think we would want you to think about it, is assume, again, the benefit portion of this is true, the 5 to 10 percent, not at two hours but on sustained--assume all that is true. But we have already determined that nobody believes 0.038. So why would we want to link it in a risk/benefit sort of consideration.

I would say whatever you think the risk is now. Do you think the risk--

DR. SACCO: See, that's--it is a risk/benefit question.

DR. KATZ: It is. But these are the data we have. So we have to make a decision based on these data. You might decide, well, since we don't know what the risk is, I can't say yes to this, or, since I believe that the risk is pretty low,

whatever I personally think it is, it would be worth that risk. You have to make an individual decision based on what you believe the risk data are.

They are what they are. We can't do anything about that.

DR. SACCO: Because I was looking at these questions as true hypotheticals and reading them very literally, it sounds like, then--my answer to this is conditional on what I believe the risk of TD is.

DR. KATZ: Absolutely. I think is how you have to answer it.

DR. SACCO: So then I revise my answer and I would say no.

DR. KATZ: Let me just say I think everybody should address the question that way and if the previous no's were assuming 0.038, maybe we need to--

DR. KIEBURTZ: We will go back. Dr. Koski?

DR. KOSKI: I think specifically, since

one of the things that I was concerned about had to do with something that Lily actually mentioned and that is if you split up all of these extrapyramidal disorders, you know, whether they come on rapidly, as long as they are persistent, I think they need to be grouped together because that is going to have some impact on the patient. So my response would be no.

DR. KIEBURTZ: Dr. Hughes.

DR. HUGHES: I would respond yes, particularly if it was at the upper end of the range, towards 10 percent.

DR. KIEBURTZ: My vote is no.

Still no?

DR. GREEN: No.

DR. KIEBURTZ: Still no?

DR. JESTE: No.

DR. KIEBURTZ: Still no?

DR. SMITH: No.

DR. KIEBURTZ: Still no?

DR. WELCH: No.

DR. KIEBURTZ: Still no?

DR. LENAERTS: No.

DR. KIEBURTZ: Yes still?

DR. FAHN: Yes.

DR. KIEBURTZ: Still no?

DR. JUNG: No.

DR. GOLDSTEIN: No, again with there being no effect at the two-hour endpoint because the reason for that was that I think those patients would take another rescue medicine where we have heard that there is, then, probably no benefit.

DR. KIEBURTZ: Did you get the information you wanted from the discussion and the voting?

DR. TEMPLE: What I hear is that, assuming that benefit as described, not much or nothing at two hours and something at 24 and longer, and in light of what you will each individually think the risk of TD or persistent dyskinesia might be, you are saying no.

DR. KIEBURTZ: I believe that is what you heard.

DR. WELCH: The reason being is that if you don't have a difference at two hours, then you

can't prove that it is a metoclopramide effect and, therefore, you shouldn't be putting the patient at risk.

DR. TEMPLE: Why can't you attribute the overall benefit at 24 hours to the metoclopramide? That is the only difference between the two groups.

DR. WELCH: There may be other factors in between which you can't stratify for.

DR. TEMPLE: Okay. But presume it is a properly randomized trial and everybody is treated exactly the same way in all other respects, the usual concerns one would always have, I guess we thought if they could actually win in a persuasive way, you would have to attribute it to the metoclopramide and the main question was how valuable is that in light of a certain amount of risk.

But I guess we thought that if they did the study properly in one, you would attribute the difference between metoclopramide-naproxen and naproxen to the metoclopramide. But I think we understood what people were saying.

DR. KIEBURTZ: Okay. To summarize. The vote on Question 1 was one yes and 11 no's with no abstentions. Question 2 is two yeses and 10 no's with no abstentions. It was all yeses on the third part of Question 1.

I think that is the hard part. We'll see. We are going to go on to Question 2; Is there sufficient evidence that the chronic intermittent administration of metoclopramide does not carry a risk of tardive dyskinesia. If we don't have any discussion, we can just vote it. So we are just going to vote it because I don't see anybody who wanted to discuss it.

Is there sufficient evidence that chronic intermittent administration of metoclopramide does not carry a risk of tardive dyskinesia? I note no.

DR. HUGHES: No.

DR. KOSKI: No.

DR. SACCO: No.

DR. GOLDSTEIN: No.

DR. JUNG: No.

DR. FAHN: No.

DR. LENAERTS: No.

DR. WELCH: No.

DR. SMITH: No.

DR. JESTE: No.

DR. GREEN: No.

DR. KIEBURTZ: That is unanimous. There is a subpart question. Is it possible to define a maximum recommended number of monthly doses of MT100 to avoid the risk of tardive dyskinesia? Is there discussion on this, or is there preparation to vote? Looks like we ready to vote. Dr. Green, we will start at your end.

DR. JESTE: It is possible to define the risk but not on the basis of the data that are already there since one can do a longitudinal prospective study and then define that.

DR. KIEBURTZ: Okay. So the answer for now is--

DR. BASTINGS: We mean on the basis of existing data.

DR. GREEN: No.

DR. JESTE: No.

DR. SMITH: No.

DR. WELCH: No.

DR. LENAERTS: No.

DR. FAHN: No.

DR. JUNG: No.

DR. GOLDSTEIN: No.

DR. SACCO: No.

DR. KOSKI: No.

DR. HUGHES: No.

DR. KIEBURTZ: I also vote no. That was unanimous no's on the two parts of Question 2. See, that was easier.

Question 3; do you believe that, based on the existing data on medication-overuse headache, there is evidence that a proportion of patients prescribed MT100 will likely take a number of monthly doses higher than the recommended amount?

Discussion on that question?

DR. GOLDSTEIN: The question again, the first phrase there, is the existing data on medication-overuse headache. I think the data on medication-overuse headache is different than we

might think for patients who take more than they are supposed to take because it may not lead to medication-overuse headache.

I think, again, we can answer the question the way it is written, but I want to find out exactly what they had in mind because, if the question is, do you think there is a proportion of patients likely to take more than the recommended dose, that is a different question than the first phrase.

DR. KATZ: We were just trying to link it to previous evidence of overuse of other migraine treatments. But yes; we are interested to know whether or not you think people are going to take more than they are supposed to.

DR. KIEBURTZ: Right. And not so much linked to the character or anything about what causes medication overuse headache, just the question of--is that clear?

DR. LENAERTS: It would be better stated maybe, on medication-overuse in headache.

DR. KIEBURTZ: Okay. That is the intent

of the question. Discussion on that question? Is it my turn to start?

Is there evidence that a proportion of patients are likely to take a number higher than recommended? Yes.

DR. HUGHES: Yes.

DR. KOSKI: Yes.

DR. SACCO: Yes

DR. GOLDSTEIN: Yes.

DR. JUNG: Yes.

DR. FAHN: Yes.

DR. LENAERTS: Yes.

DR. WELCH: Yes.

DR. SMITH: Yes.

DR. JESTE: Yes.

DR. GREEN: Yes.

DR. KIEBURTZ: Very good. Thank you. So it is unanimous that it is likely that they will take more than the number recommended.

So we are changing focus here entirely no. This one is a little bit trickier question. All currently approved acute treatments of migraine are

indicated without restriction regarding the presence or absence of nausea at baseline.

Given that patients may have nausea at some attacks and no nausea at others, given that, does an indication limited to the subpopulation of migraine patients with no nausea at baseline represent a clinically meaningful and acceptable indication?

Discussion on that? Dr. Green.

DR. GREEN: Well, given the fact that it is so counter-intuitive, I really believe that both doctors and patients will erroneously give the wrong advice.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: I think that patients do intermittently have nausea at various times throughout the course of their headache. I think, because they are given a drug, they wouldn't exclusively use it in terms of the periods when they didn't have any nausea. So just even accepting the data as it is, I think there is a problem with the way a patient would use it.

DR. KIEBURTZ: Dr. Porter.

DR. PORTER: I agree. I think that this drug will be used in patients with or without nausea if it is marketed.

DR. WELCH: Nausea is such a variable. As we have heard, this drug will be used in people with or without nausea without question.

DR. KIEBURTZ: Further discussion? Dr. Green, how do you vote on the question; is it a clinically meaningful and acceptable indication.

DR. GREEN: No.

DR. JESTE: I am not a migraine researcher so I think I should just abstain from answering that question.

DR. KIEBURTZ: Fair enough.

DR. SMITH: I would do the same.

DR. KIEBURTZ: Abstain.

DR. WELCH: No.

DR. LENAERTS: No.

DR. FAHN: No.

DR. JUNG: No.

DR. GOLDSTEIN: No.

DR. SACCO: No.

DR. KOSKI: No.

DR. HUGHES: I abstain as well.

DR. KIEBURTZ: No.

So three abstentions, nine no's as to whether this is a clinically meaningful and acceptable indication. Any questions from your end of the table? Okay.

The fifth question; In a new clinical study, if the sponsor shows prospectively in a new clinical study in migraine patients with no nausea at baseline a significant contribution of metoclopramide on sustained headache relief of 5 to 10 percent--this harkens back to Question 1--5 to 10 percent of patients, a proportion of people--again, this is a proportion of the enrolled subjects who have this response which is sustained headache pain relief, so that is 5 to 10 percent of the patients, no benefit at the two-hour pain research, no contribution of metoclopramide at a two-hour pain response, no contribution of metoclopramide on the relapse rate or

rescue-medication use in the two- to 24-hour period--so, again, this is a 5 to 10 percent benefit on the synthetic measure but not a significant impact on either of the elements that make up the synthetic measure--would the demonstrated benefit outweigh the risks related to tardive dyskinesia?

This is, again, those effects in a group that was enrolled with no nausea at baseline; would this have demonstrated a benefit outweighing the risks related to tardive dyskinesia.

Discussion of this? Dr. Sacco.

DR. SACCO: Again, I think the only thing I would add here, we have a significant contribution. When it says no contribution in the second and third bullet there, I am assuming we are saying no significant contribution, but, again, there may be a trend in those two, that when you add them up, you have a significant contribution.

DR. KIEBURTZ: I would say that is an appropriate clarification. Again, I think that we should clarify that the risk of tardive dyskinesia

is whatever in your heart you think that is since we don't have evidence in that regard--heart, mind. I am not trying to be flip about it. It is what your own best estimation is.

DR. GOLDSTEIN: Clarification. It seems that this question is a compound of all the other questions. So we have answered, for each of these components, in one way. I don't see what question we are answering that is different than what we have already answered.

DR. KIEBURTZ: Okay. But we are going to answer it because that is our job.

DR. GOLDSTEIN: Okay.

DR. KATZ: We will just see if you are being consistent when you answer this one.

DR. FAHN: It is a different question.

DR. KATZ: It is a test.

DR. GOLDSTEIN: I just want to know, are you trying to get--I want to answer the question that you are asking.

DR. KATZ: No, no; it puts everything together. Then, of course, the thing we haven't

talked about is the very last thing. But, no; you are right.

DR. KIEBURTZ: Dr. Fahn.

DR. FAHN: I read this question as different from the first question, Question No. 1, is that here we are saying on contribution of metoclopramide on relapse rate or rescue medication used in that two- to 24-hour period which wasn't in the previous question. So this is now saying, in the long run, you are still going to have to take rescue medicine just as often, and so forth. So, to me, that changes the equation quite differently. It adds another element which the FDA wants us to answer and I think this now adds that other element we have to look at and think about.

DR. KIEBURTZ: There was not a specification before about the no significant contribution on the relapse rate.

Dr. Porter.

DR. PORTER: My problem with this question is that it assumes that this no nausea at baseline is, in fact, something that we really believe the

company has shown. In my understanding, this is pretty much a post hoc analysis. We are not absolutely sure that they can reproduce this.

I think that, to ask this question assumes that they are going to look for this small subpopulation which, in fact, might be a mistake because, if they are wrong on that, then their drug might be good for migraine as whole. I think that we ought to ask the question of ourselves as well, do we think that this is a subpopulation that company should consider as a population that they want to chase because it is a high-risk event. It cuts down the total number of patients available, et cetera.

I am not sure that we are there yet.

DR. KATZ: This question just sort of took as a given that if this was a real reliably identifiable or appropriate subgroup and they were--and the first part says, and they were to prospectively show it again, would all of these things apply.

I think you have already said that you

don't think that the no nausea at baseline is an appropriate subgroup in which to develop the drug. I think that is more or less how I interpreted the last vote, or whichever one it was.

So I think this question does, more or less, incorporate several of the questions you have already voted on and it would seem as if the answer to this question would be obvious. I suppose we could ask, if this is what you saw in the entire population; in other words, they did a study both with and without--you know, the typical population, as they have already done, and basically saw the same results that they have already seen twice, would it be acceptable.

But I think you have already answered that question as well. I think you have answered that they have to show something in two hours. Anyway, I actually think it has already been answered, but if you want to vote on it, you can.

DR. KIEBURTZ: Dr. Temple, did you want to say something?

DR. TEMPLE: Not to get into too much of

study design things, if the company wanted to do further studies to document and say and an effect at two hours and really thought that the no-nausea population was the right place, they could still do a study in the mixed population, make the primary endpoint the effect of the no-nausea population and get data on the other.

DR. KIEBURTZ: Absolutely agree.

DR. TEMPLE: That is all for later.

DR. WELCH: I guess it depends on what the 5 to 10 percent is. If it is used here as what do you think would be a clinically persuasive difference, independent of what the data has been on nausea, that is a different question that really addresses the second question about additional data.

DR. KIEBURTZ: Just staying on the first question, I think this is a pretty straightforward one to vote which I think the comments to date, we know what the answer is going to be. It is essentially a contribution with a new feature about specifying a nonsignificant contribution of the

relapse period.

Is it my turn to start first? Would the demonstrated benefit outweigh the risks related to tardive dyskinesia. I would vote no.

DR. HUGHES: I vote no.

DR. KOSKI: No.

DR. SACCO: No.

DR. GOLDSTEIN: No.

DR. JUNG: No.

DR. FAHN: No.

DR. LENAERTS: No.

DR. WELCH: No.

DR. SMITH: No.

DR. JESTE: No.

DR. GREEN: No.

DR. KIEBURTZ: So unanimous on the no.

If not, I guess our response was presaged by considering if we said no, if we vote no to that first question, what additional data, or desired primary outcome measure, or desired effect on sustained relief, could provide evidence of safety and efficacy?

What I understand here is we can go back up to these bullet points--and now is an opportunity for us, although I am thinking we are not going to take three hours of opportunity to do this, to flesh out some of the things we have been alluding to regarding whether two hours is important. I think we can comment here even about the nausea or not.

So I think a question which has already been posed by Dr. Katz and Dr. Bastings is whether we would like to see a benefit of the two-hour response. Dr. Welch also mentioned a pain-free and a sustained pain-free response. Maybe we can have some discussion on this point.

Do you want to comment at all, Dr. Welch, not to pick on you.

DR. WELCH: I think that having said that we accept that this combination of medication could be used for certain patients, that it behooves us to ask for the most rigorous endpoints in any clinical trial that we can. The most rigorous is a two-hour pain-free sustained over 24 hours.

What patients really want is to be pain-free as early as possible. That is really what the patient ideal is. So, for that reason, I would ask for that particular data given that we do accept that, with this risk in a limited population, that this could go ahead.

DR. KIEBURTZ: Dr. Katz and Dr. Porter.

DR. KATZ: I just have a question because, obviously, we have not adopted as required for the approval of the typical, if there is a typical, acute migraine treatment, the pain-free at two hours. We have had mild or no pain. I just want to sort of flesh this out a little bit more. Do you think it should be pain free at two hours specifically because of the potential risk or do you think that is sort of a generic requirement?

DR. WELCH: I think it is ideal endpoint that the community know us for, the headache community, the IHS regulations or guidelines. That is the first thing. But I think it is the most rigorous endpoint that you can get and I think, because of the risk, that we deserve to see the

most rigorous endpoint tested, if that answers your question.

DR. KATZ: Yes; it does.

DR. KIEBURTZ: Dr. Green.

DR. GREEN: I, like Dr. Welch, was surprised that endpoint, the primary endpoint, to the study wasn't two-hour pain something, anyway, that certainly we would like to see trials going forward with the primary endpoint being, hopefully, two-hour pain free because, among other things, that probably even predicts recurrence rates and certainly, when we talked about drug overuse, if someone is pain free, they are very unlikely to redose.

DR. KIEBURTZ: So the two-hour time point is an important one as assessment of efficacy.

DR. GREEN: Right.

DR. KIEBURTZ: Of those, the pain-free response is perhaps, even more informative than the pain response?

DR. GREEN: Actually, there is another one. There is migraine-free which is pain-free,

photophobia-free, phonophobia-free, nausea-vomiting free, which is even a tougher one.

DR. KIEBURTZ: You can escalate the characteristics of what the two-hour endpoint is but that is an important time point at which to demonstrate the marginal benefit of--I don't mean marginal, small, but the additional benefit of metoclopramide over naproxen.

DR. GREEN: Definitely.

DR. KIEBURTZ: Dr. Fahn.

DR. FAHN: There are three conditions in this area and one of them that we have been talking about is the two-hour one. But I would say if any two of these would be sufficient in my mind that metoclopramide was superior to naproxen alone; that is, even if the two-hour wasn't any more superior pain-free than naproxen alone but they got better at the end of the day and they didn't have any relapses and they felt better, that would be--those two would be fine with me.

So that is what I would look at. One alone is probably not sufficient for the risk but

two out of the three would be sufficient for the risk in my book.

DR. KIEBURTZ: So either--I am just trying to think.

DR. FAHN: The relapse rate was one of the risks. The two-hour time point is another one of the outcomes. The sustained headache relief.

DR. KIEBURTZ: I don't think you could get the components without getting the composite, but I get your point. Two out of the three rather than just one out of the three which is the circumstance now.

DR. SMITH: A little off the endpoint question, but I would like to see that combination be better than a higher-dose naproxen is one question because you could increase the dosage and potentially have the same type of effect for naproxen alone. The other thing is how would it work among people that failed naproxen alone would be another interesting question because, again, you are talking about a very unique risk and so there probably would be a drug that would not be a

first-line so how does it work in people that fail. Would you see that same response?

DR. KIEBURTZ: So one is an issue of comparators, not just to the naproxen dose intrinsic in MT100 but to a higher dose as a comparator.

DR. SMITH: Exactly.

DR. KIEBURTZ: The other question is one of selection criteria in terms of people who failed.

DR. WELCH: A specific trial in naproxen failures. It has been done for triptan failures. Then you might just ease up a little bit on the rigor of your endpoint.

DR. TEMPLE: To do that trial right, you have to randomize those people who, by history or failures, back to this product again and naproxen. So you are enriching it for naproxen failures. That design can work if the effect is decent, large.

DR. PORTER: I think you have to have a little flexibility for the company. I think our

very rigid two hour must be pain-free might be a hurdle too high. I would urge you to think about a little flexibility even though you want to set the standard high for a drug that is not as safe as some.

DR. WELCH: But the company doesn't want to be set a lower standard if the standard for the whole headache specialty becomes that rigorous.

DR. PORTER: How many drugs do you have that meet that standard?

DR. KIEBURTZ: Let's just not get into a--

DR. PORTER: Okay.

DR. KIEBURTZ: Please. Dr. Goldstein, you had a comment?

DR. GOLDSTEIN: Yes. The other point, this compound question that I think still needs to be considered is is the addition of the rescue medication--the question is, if you are taking care of a patient again, that you want them to be able to take a drug and have relief, be able to get back with their work and not be having to take additional drugs. If they require additional

drugs, I think that needs to be factored into the equation.

The second point is, as you design a trial, what the appropriate comparator group is. I guess the question that you have from the regulatory standpoint is the only question that you are really looking at, is whether the metoclopramide component adds to the naproxen but now how the combination would compare with other approved agents.

DR. KATZ: That's the first question, absolutely, is the combination policy of both components making a contribution. The question of whether or not the actual product, how that compares to other products, is usually not one that we consider from a regulatory point of view except when you are worried that the product might be more dangerous than everything else that is out there.

There have been extraordinarily rare occasions when you actually have to show that your product actually beats something else out there in order to get approved because it is so dangerous.

So, yes; in some sense, we always think about that in the back of our minds but we almost never require it because it just doesn't--the circumstances don't support it.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I just wanted to go back to the endpoint question again. I am just trying to understand why the migraine community is basically saying that outcome for clinical trials regarding migraine drugs should be changed. From my understanding and what I have learned today and what I am reading is that pain research, none, pain-free, or mild pain has always been the endpoint.

Is it because we are hearing the risk of this drug or do you think, in general, for every migraine drug to come, the new endpoints should be pain-free. If so, I am just trying to understand why, because I am okay with none or mild pain, but I am continuing to hear you want it changed to be pain-free.

Am I not reading that right?

DR. WELCH: The issue is how do you define mild. What is mild? It is very subjective. So the most rigorous one would be pain-free. The outcome from here on in, I believe, by the community would be to use that.

There are other endpoints that you could choose, but I would be afraid, addressing the issue for the company is, if someone else came up with another drug with a more rigorous endpoint and they were given a more flexible one, that they wouldn't compete well with it.

But I think if you certainly do a trial against naproxen, itself, in naproxen failures, you could let up on your endpoint, again qualifying the study.

DR. KIEBURTZ: Dr. Hughes, you had a comment?

DR. HUGHES: I guess the main comment I have is I would like to see the other side of the equation and get a bit more formal information about the risk of TD in this population. I would hate to see an efficacy trial with whatever

endpoint, or similar endpoints, as has been done with a 5 percent difference and still have considerable uncertainty about the risks of TD in this population.

DR. KIEBURTZ: So addressing the issue of what additional data, you would like more safety data.

DR. HUGHES: Formally obtained; yes.

DR. JESTE: I think there is an opportunity to look at safety in a broad perspective, not just tardive dyskinesia but also the various extrapyramidal symptoms, Parkinsonism, microdystonia, akathisia. This should be done. There are number of examples in which this has been done using standardized rating scales for each of these on a regular basis and continuing that for six months to a year at the very least because really one cannot--100 patients keep on the drug for one month is not the same as 100 patient months. You really need patients to be treated for one year before you can say anything about the incidence of tardive dyskinesia let alone its

persistence.

So what I would strongly recommend in terms of suggested studies would be longer-term follow-up studies, standardized rating scales for Parkinsonianism, akathisia, dystonia and tardive dyskinesia.

DR. KIEBURTZ: Dr. Katz and then Dr. Lenaerts.

DR. KATZ: Maybe a little discussion on this point would be worthwhile because these sort of long-term large safety studies have been done when you are trying to sort of cap the risk or say--you might think about, well, I think 0.1 percent risk might be acceptable given this sort of benefit on an appropriate outcome, so you would have to figure out how many people that would be.

You may talk about thousands of patients followed for a year. I am just wondering whether or not people, again, postulating this sort of an effect on an appropriate outcome, whether or not people think that that would be something that would be necessary, even if they were to show

effectiveness at this level.

DR. JESTE: My feeling is that if we did not suspect tardive dyskinesia with this drug, then I don't think one would ask for longer-term studies. But here there are grounds to think that the drug would be associated with some risk of tardive dyskinesia which we don't know. It could be minimal. But, still, there is clearly some risk.

I think that it behooves on us, then, to have at least some long-term data because some patients will, indeed, be using the drug. And the findings may turn out, may show that, actually, the risk is very low, in which case it will be helpful. I do think that long-term studies will be warranted in a case like this.

DR. KIEBURTZ: Dr. Lenaerts.

DR. LENAERTS: Would the number needed to treat shed light into this and, in that case, is my assumption right if we have, say, in 304 study, rounded out 32 percent versus 28 percent, would it be a number needed to treat of eight? Would that

be correct? Would that be useful to look into that?

DR. KIEBURTZ: I am not sure that that is the right number.

DR. LENAERTS: That wouldn't apply?

DR. KIEBURTZ: For number needed to treat. But, anyway. I am not sure.

DR. LENAERTS: I am just throwing in the question.

DR. KIEBURTZ: Okay. Dr. Porter, you had a question?

DR. PORTER: Just a comment and that is if the risk is, in fact, relatively low in this 0.038 percent category, if you can have any kind of power at all to measure this, it is going to take thousands and thousands of patients, as you already mentioned, unless you are lucky, or unlucky, and you happen to stumble over one early. But you could do 2,000, 3,000, 4,000 patients and still not see it and it could still be there.

DR. KATZ: Right; you could decide up front what sort of a risk you would be willing to

live with. In other words, not greater than 0.1 percent.

DR. PORTER: What kind of power you wanted.

DR. KATZ: Right; and then you just figure out how many people. But, yes; we would have to know what people thought would be an acceptable risk and then you work backwards and you figure out how many people you need to follow. But, yes; it could be, depending on what sort of a risk would be acceptable, it would be thousands of people. Sure.

I am trying to figure out whether that is something you think we ought to do and pick a risk to cap it at, or--

DR. WELCH: That would be extraordinarily difficult and extraordinarily expensive in the migraine population. I think the real issue, that what we are dealing with here, is that if MT100 comes to acceptance and general prescription, that all of us know that, in a population of migraine patients, or chronic-headache patients, whatever that makes up, that they will be taking this drug

on a chronic basis, a long-term basis. It is very difficult to actually reproduce, at any clinical trial, an interaction of someone who has the pathogenic factors of a chronic headache, perhaps with dopamine hypersensitivity and the interaction of using the drug.

So it is an almost impossible thing to do, I would think. But the issue is, given that we know that there will be a subgroup of patients who will take this medication inappropriately, that we really must be sure that it is effective for a subgroup of patients who really need it.

Answering the very eloquent appeal for pain relief in migraine, which is very real because migraine patients will, even if some of them know that they are at major risk for vascular insult, will take a triptan and take that risk. We do know that you can use metoclopramide and Naprosyn separately. In fact, before the triptans, I am old enough here to be a pre-triptan-era prescriber, it was not uncommon for me to combine these two medications in patients that didn't respond to

Naprosyn alone.

So the real reason why we must ask for extreme rigor, I think, with this particular drug is knowing that there will be a population that may overuse this drug with the risk of tardive dyskinesia. But to reproduce that in any clinical trial, I would think it is just impossible.

DR. KIEBURTZ: I would ask questions in a slightly different direction because we have not, in this discussion, gone this way. Just say we don't get more evidence about safety, that we are unable to better estimate with precision then something that we think is between 0.038 and 1.0. Say we can't figure that out. Is there a magnitude of benefit that is greater than this number here, since we voted no to this, that would make people, in that situation of relative ignorance, change that to a yes.

So, if there was a 20 percent--the difference between the naproxen and MT100 group was 20 percent--would that be enough to overwhelm whatever the concerns are about the safety. I

think that is another question that we are being asked about. Or would, no matter what the magnitude of the benefit, those safety concerns would be persistent.

I don't see any clear thoughts on that one.

DR. FAHN: I would just go back to what we talked about before that I feel to be absolutely safe, patients would have to show they don't respond at all to naproxen alone but now would respond to the combination drug if there is a combination drug on the market.

As Michael just said, that before there was a combination drug, you could still prescribe metoclopramide if you think it is going to be added. You try naproxen alone and if it didn't work, okay, we are going to try the two together. You will see. Then, if it doesn't work, then you drop it. If it does work, then there is a certain risk that you tell the patient there is going to be and you can take this combination if you are willing to accept that risk.

I think that is the kind of question I would like to see directed if we were going to look for--in other words, it has to has some restriction on a combination drug that you wouldn't have to have if they were prescribed separately because--normally, when they are prescribed separately, it is an extra step.

Too many doctors will say, well, just take this combination. It gives you both the advantages of naproxen alone plus the metoclopramide. I think that makes the risk too dangerous.

DR. KIEBURTZ: So, to paraphrase, the approach, rather than answering by a bigger benefit or quantifying the risk, is modifying the path to which you get to that drug.

DR. FAHN: I think that is extremely important how you give that path because there shouldn't be--if you are going to take any risk, you ought to make sure that risk is worth taking and, therefore, that you are getting benefit that you wouldn't have had otherwise.

For that particular person, if they fall

within that 5 or 10 percent, 20 percent, or whatever number you want to give a category, why, for that person, they are getting a great benefit and they are willing to take that risk. I think that is okay.

DR. KIEBURTZ: Are you getting answers? Is this discussion germane to the--

DR. KATZ: Yes. There are a number of ideas that we will have to think about but I think they are all relevant.

DR. KIEBURTZ: Okay. This is not a voting question because it is, what additional data would you like. So it is not a yes or no. We can't give a yes or no here. Would someone like to make additional comments? I see two. Dr. Jeste.

DR. JESTE: Going back to safety, I am not suggesting that we need to have huge studies to find out the incidence of tardive dyskinesia. I think one can use that normal involuntary movement scale as outcome for the safety purposes as major. So what you are looking at is really percent increase in the M score. Say, the mean score,

let's say, goes up from 0.5 to 1.5. Those patients will still not meet the criteria for tardive dyskinesia because you need a minimum score of 2, minimum at least 1. So that can be done in a few hundred patients. So it is really not the number of patients that is critical. It is the length of the study that will be important. That can be done in as many patients as are needed for just looking at outcome.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: Again, just from a clinical standpoint, I think the real question is whether the patient taking X medicine as opposed to Y is going to get on with their life later, be able to get back to their life sooner rather than later.

If you just improve pain but they are still debilitated because of the concomitant symptoms, you haven't really done much. So, as a composite measure, I think it would be good to have some measure of migraine-related disability, and I know such scales exist, to be considered as one of the endpoints.

That is what we are really trying to do here. The other thing to consider in terms of some of these trade-off issues--I said it before, but, in terms of additional data, that data can be obtained so we are not sort of guessing these things. We can get finite data to support what risk people with migraine would be willing to take of having these sequelae to be pain-free or without disability at whatever given high proportion.

So, again, I think that those data would be very helpful to inform both the company's decisions as to how to go and for the FDA as well.

DR. KIEBURTZ: To summarize Question 5, on the first part of it, we voted no uniformly on the way it was categorized and then discussed ways where data might be helpful in addressing the question. One is more safety data. Two is the two-hour endpoint seems to be important as to whether that needs to be something beyond the traditional pain response is something that is debated and, also, we talked about ways in which subjects or patients might access the medication

through specific failure of other interventions prior to exposure to this intervention.

I am going to briefly summarize our discussion. Unfortunately, your chair has failed my two-hour response to my migraine intervention so my thinking is a little cloudy. So you will have to bear with me. In addition to Dr. McCormick, there are other people who have trouble responding to their migraine medications.

We concluded that the current estimate of tardive dyskinesia following exposure to metoclopramide, particularly in this setting, is not a reasonable estimate. We talked some more about how we might get some better estimates of that.

Both in the initial question and the second question, that the amount of benefit demonstrated so far, without saying whether that is significant or not, is not sufficient given the perceived risk in the absence of concrete data, the perceived risk given the absence of benefit at two-hour endpoints.

We don't think that there is enough evidence that there is no risk of tardive dyskinesia with chronic intermittent administration nor can we identify a dose that would be below the risk, a number of doses that would confer no risk. We think it is likely that, no matter how the drug is labeled and approved, that people will take it more than whatever the recommended dosage is if there is a limitation on the number of dosages, and did not have support for the idea of individuals with nausea at baseline being an identifiable group of a clinically meaningful and acceptable indication for the treatment of migraine.

I think that summarizes our discussion.

DR. PORTER: Could I just add one comment. I think there is an uncertainty about whether or not the nausea or no-nausea populations have been demonstrated here. The company should not mislead itself by a subgroup analysis post hoc that necessarily takes them down the wrong path.

DR. KIEBURTZ: I think, then, unless there are some comments from Dr. Katz.

DR. KATZ: No. I just want to thank everybody. I think it is particularly difficult to discuss these matters and come up with decisions and advice based on so little data, at least on parts of this. So I really appreciate it.

Also, I just learned that Anuja, this is her last meeting with the committee. So I want to thank her publicly for all her work. And good luck in the future. We are sorry to see you go.

DR. KIEBURTZ: You keep your secrets well, like everyone else here at this agency. Thanks to the committee members for coming, for staying on point, to the sponsor for their presentations and their responsiveness to our questions.

We will adjourn the meeting now.

(Whereupon, at 2:40 p.m., the meeting was adjourned.)

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