UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

ARTHRITIS ADVISORY COMMITTEE

WITH REPRESENTATION FROM THE

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE

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MEETING

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Tuesday, July 15, 1997

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The Advisory Committee met in Versailles III and IV of the Bethesda Holiday Inn, at 8120 Wisconsin Avenue, Bethesda, Maryland, at 8:30 a.m., Ralph D'Agostino, Ph.D., Chairman, presiding.

PRESENT:

RALPH D'AGOSTINO, Ph.D., Chairman
ANDREA G. NEAL, DMD, MPH, Executive Secretary
GEORGE A. BLEWITT, M.D., NDAC
ERIC P. BRASS, M.D., Ph.D., NDAC
KATHLEEN HAMILTON, NDAC
CAGE JOHNSON, M.D., NDAC
MARY ANNE KODA-KIMBLE, Ph.D., NDAC
PATRICIA A. McGRATH, Ph.D., NDAC
LYNN McKINLEY-GRANT, M.D., NDAC
BETH L. SLINGLUFF, A.N.P., NDAC
THEODORE G. TONG, Pharm.D., NDAC
STEVEN B. ABRAMSON, M.D., AAC
DAVID T. FELSON, M.D., M.P.H., AAC
HARVINDER S. LUTHRA, M.D., AAC
LEONA M. MALONE, AAC
FRANK PUCINO, JR., Pharm.D., AAC
LEE S. SIMON, M.D., AAC
HAROLD P. ADAMS, JR., M.D., PCNSAC
DAVID A. DRACHMAN, M.D., PCNSAC
SID GILMAN, M.D., PCNSAC
JUSTIN A. ZIVIN, M.D., Ph.D., PCNSAC
SEYMOUR DIAMOND, M.D., Guest Expert
DEBRA L. BOWEN, M.D., FDA
WILEY CHAMBERS, M.D., FDA
KAREN J. LECHTER, J.D., Ph.D., FDA
MICHAEL WEINTRAUB, M.D., FDA
RUDOLPH M. WIDMARK, M.D., FDA

ALSO PRESENT:

SION A. BONEY, Bristol-Myers
HOWARD HOFFMAN, M.D., Bristol-Myers
RICHARD LIPTON, M.D., Bristol-Myers
REBECCA BURKHOLDER, J.D.
ELIZABETH LODER, M.D.
EILEEN McGRATH, J.D., C.A.E.
JERRY MILLER
LESLIE R. WOLFE
TARA ROLSTAD

A-G-E-N-D-A

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

(8:40 a.m.)

CHAIRMAN D'AGOSTINO: My name is Ralph D'Agostino, and I'm the Chair of the Nonprescription Drug Advisory Committee, and I will be chairing today's meeting. This is a meeting of the Nonprescription Drugs Advisory Committee and the Arthritis Drugs Advisory Committee, with representation from the Peripheral and Central Nervous Systems Drug Advisory Committee. Our agenda today is on Excedrin Extra Strength.

I'm going to now ask the members of the committees to introduce themselves and to speak into the microphone so that the transcriber can make sure that all the mics are working and can be heard. Let's start with George, would you want to begin the introductions?

DOCTOR BLEWITT: Yes. I'm George Blewitt. I'm the Industry Representative for the Nonprescription Drugs Advisory Committee.

DOCTOR McKINLEY-GRANT: I'm Lynn McKinley-Grant. I'm an Associate Professor Dermatology at George Washington University and Washington Hospital Center.

DOCTOR SIMON: Hi, I'm Lee Simon. I'm

from the Beth Israel Deaconess Medical Center in Boston, and I'm a visiting person from the Arthritis Advisory Committee.

DOCTOR LUTHRA: I'm Harvey Luthra. I'm a Rheumatologist at the Mayo Clinic.

MS. HAMILTON: Kathleen Hamilton, the Consumer Representative to the Nonprescription Drugs Advisory Committee.

MS. SLINGLUFF: Beth Slingluff, Carondelet Health Care, with the Nonprescription Drugs Advisory Committee.

MS. MALONE: Leona Malone, Consumer Rep for the Arthritis Drugs Advisory.

MR. TONG: Good morning. I'd Ted Ton. I'm Professor of Pharmacy, Pharmacology and Toxicology at the University of Arizona, and I'm a member of the Nonprescription Drugs Advisory Committee.

DOCTOR DRACHMAN: Good morning, I'm David Drachman, Chairman of Neurology at U. Mass Medical Center, and on the Peripheral and Central Nervous System Advisory Committee.

DOCTOR FELSON: I'm David Felson. I'm from Boston University and a Rheumatologist, and I come from the Arthritis Advisory Committee.

EXECUTIVE SECRETARY NEAL: Andrea Neal,

Executive Secretary to the Nonprescription Drugs Advisory Committee.

CHAIRMAN D'AGOSTINO: Ralph D'Agostino from Boston University.

DOCTOR BRASS: Eric Brass, Harbor-UCLA Medical Center, Nonprescription Drugs.

DOCTOR McGRATH: Patricia McGrath, University of Western Ontario, Nonprescription Drugs.

DOCTOR ZIVIN: Justin Zivin, University of California, San Diego, from the Peripheral and Central Nervous System Committee.

DOCTOR GILMAN: Sid Gilman, Department of Neurology, University of Michigan, from the Peripheral and Central Nervous System Drugs Advisory Committee.

MS. KODA-KIMBLE: Mary Anne Koda-Kimble, Department of Clinical Pharmacy, University of California at San Francisco.

DOCTOR JOHNSON: Cage Johnson, University of Southern California, Nonprescription Drugs.

DOCTOR DIAMOND: Seymour Diamond, the Diamond Headache Clinic in Chicago, Guest Expert.

DOCTOR BOWEN: Debra Bowen, Director, OTC Drugs.

DOCTOR WEINTRAUB: Mike Weintraub, FDA.

DOCTOR CHAMBERS: Wiley Chambers, Divisio n

of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products.

CHAIRMAN D'AGOSTINO: Thank you.

The screech that was in the mic seems to have worked its way out, so I presume that's all right now.

The next item will be the meeting statement by Andrea Neal.

EXECUTIVE SECRETARY NEAL: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

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

In accordance with 18 U.S. Code 208(b)(3), full waivers have been granted to Doctor Ralph D'Agostino and Doctor David Felson. A copy of these waiver statements may be obtained by submitting a

written request to FDA's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note for the record that Doctor Harvinder Luthra's employer, the Mayo Clinic, has an interest in American Home Products, the parent company of firms which manufacture competing products to Excedrin. Although this does not constitute a financial interest in the particular matter, it could create the appearance of a conflict. However, it has been determined that it is in the Agency's best interest to have Doctor Luthra participate in the committee's discussions concerning Excedrin.

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

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

CHAIRMAN D'AGOSTINO: Thank you.

We have two opening comments. Michael

Weintraub?

DOCTOR WEINTRAUB: Good morning. Actually, as one of the people responsible for all of you coming here, I feel very honored and really thankful that you were all able to make it.

I'm going to be discussing a couple of things, I don't want anybody to laugh, but I'm going to discuss some -- history of migraine headache and a little bit about caffeine as well, and, as I said, I don't want anybody to laugh.

Now, migraine headaches has been really very well studied by the Agency and by a number of committees for the government. The appropriateness of a migraine headache indication for OTC analgesic drug products was evaluated by first the National Academy of Sciences, National Research Council, Drug Efficacy Study Group, the Panel on Drugs for Pain Relief, and the Advisory Panel on OTC Internal Analgesic and Anti-rheumatic Drug Products.

In the Federal Register of April 5, 1967, the Agency published a proposed statement of policy and changes in the warning statements for OTC systemic analgesics. In that proposal, the Agency included migraine in the list of conditions that it believed could not be accurately diagnosed by the consumer,

safely treated without medical diagnosis and the supervision of a physician, and conditions in which an OTC systemic analgesic wouldn't be regarded as useful.

Now, that was a conclusion drawn in 1967, and we know that things change with time, and that's one of the aspects of the presentation today, and of the medication today, that we want you to comment and think about.

The recommendations of the Pain Relief Panel, which is the National Academy of Sciences Research Council, said on the effectiveness of an OTC buffered analgesic product containing phenacetin in those days, Aspirin and caffeine, indicated for the pain of mild migraine, were published in the Federal Register of April 20, 1972, and I want you to note, it was the pain of mild migraine.

The panel found the combination ineffective for this indication. It also objected to the use of the migraine indication of an OTC product based on its belief that migraine is a serious condition which requires medical advice and diagnosis. So, in '72 we still hadn't really changed our attitude.

The migraine indication has also been evaluated by the Analgesic Panel under the OTC Drug

Review. The panel's evaluation of label claims for the OTC analgesic products submitted to it were published in the Federal Register of July, 1977. The panel found migraine to be an unacceptable claim for OTC analgesics containing Aspirin and classified the indication in Category II, which in those days was not generally recognized as safe and effective.

The indication was classified with a number of other labeling indications that the panel found to be examples of drug use directions that were unsupported by the scientific data or sound theoretical reasoning.

They also said that the modifying adjectives associating with pain with various physical conditions, or disease entities, or specific physical sites, was not appropriate.

That's basically where we have been for a number of years, for more than 20 years. We still have to -- one of the things you are going to have to do is view the mild migraine syndrome again and make a statement, because, in fact, since we already have a negative statement on the books from an advisory committee, we have three negative statements in a sense, we are going to need you to tell us if the record is correct or not, at least to advise us and

present some information that we can deal with to tell us whether or not a consumer can make the diagnosis, whether or not it needs a physician to adjust the drug treatment, or whether the person may make an error in the diagnosis which could result in an important problem in the future.

Now I'm going to turn to caffeine for a moment. The use of caffeine in OTC drug products has been evaluated again, really, very much in depth, by four OTC advisory review panels. With the exception of the use of caffeine in OTC weight control products, where it was taken out of the weight control products, the panels have found caffeine to be safe for a variety of OTC uses, including its use as an OTC analgesic adjuvant and as a stimulant.

The Advisory Review Panel on OTC sedative, tranquilizer and sleep aid products, and that was called the Stimulant Panel, concluded that caffeine was safe for use in OTC stimulant products at a dose of 100 to 200 milligrams, and they limited the use to every three to four hours or a 1600 milligram per day daily dose. These conclusions were published in the Federal Register on December 8, 1975.

In the Federal Register of July, 1988, July 8, 1988, the Analgesic Panel stated its

conclusion, caffeine was safe for use as an OTC analgesic adjuvant at a single adult dose of 65 milligrams, not to exceed 600 milligrams in 24 hours.

The Agency published a final rule for OTC stimulant products in the Federal Register of February 29, 1988. In that final rule, caffeine was included as a monograph ingredient at the panel's recommended dose, which was 65, not to exceed 600 milligrams in 24 hours, and caffeine products were required to bear a caffeine-specific warning. And, that caffeine-specific warning reads as follows: "The recommended dose of this product contains about as much caffeine as a cup of coffee. Limit the use of caffeine-containing medications, foods or beverages while taking this product, because too much caffeine may cause nervousness, irritability, sleeplessness and occasionally rapid heart beat."

Based on the panel's recommendations that OTC stimulant product should not be used by children under 12 years of age, the final rule also required the additional warning, "do not give to children under 12 years of age."

1988 was a relatively active year for the Federal Register and our documents on caffeine, because on November 16, 1988, we published another

document in the Federal Register. The Agency responded to a comment noting that the recommended dose for caffeine as an OTC stimulant and analgesic adjuvant were inconsistent.

The comment requested an increase of the recommended caffeine dose for use as an OTC adjuvant from 65 to 150 milligrams per single dose. The Agency at that time, in 1988, decided to agree with the comment, and noted that the 150 milligrams was well within the range, dose range, for OTC stimulant products.

Subsequently, the Agency informed industry about caffeine's potential role in analgesic associated nephropathy. That was at a public meeting held on February 16, 1989. The basis for this discussion was proprietary animal toxicity data for an analgesic and caffeine combination submitted as part of an investigation on a new drug application. Thus, the toxicity data were presented in a closed session of the Arthritis Advisory Committee, and the end result was that the committee was not overly concerned by the data, and concluded that more safety information on the combination was needed.

On April 8, 1993, five years later, the Agency's Nonprescription Drugs Advisory Committee met

to consider caffeine's use as an analgesic adjuvant. The animal data were presented to the committee in closed session. The committee concluded that 65 milligrams of caffeine is an effective analgesic adjuvant when combined in a one-to-ten ratio, and that was done in public, however.

The Nonprescription Drugs Advisory Committee further concluded that up to 130 milligrams of caffeine was an effective analgesic adjuvant when used with a combination of acetaminophen and Aspirin up to a single total analgesic dose of 1000 milligrams.

As you know, the Agency's view is that Aspirin and acetaminophen can be considered the same drug for analgesic purposes. That's something we've held for a number of years. However, based on safety concerns about the caffeine-sensitive segment of the population, the NDAC recommended that OTC analgesics containing 65 or more milligrams of caffeine should bear the caffeine and child warnings required for OTC stimulant products. The Nonprescription Drugs Advisory Committee also recommended that the front panel of such products, the principal display panel, should include the statement, "Contains caffeine."

After considering the recommendations of

the Nonprescription Drugs Advisory Committee, the Office of OTC Drug Evaluation, in those days it was an office, now a division, tentatively concluded that caffeine could be considered a safe and effective OTC analgesic adjuvant when combined with Aspirin or the combination of Aspirin and acetaminophen.

However, based on safety concerns, the office issued a feedback letter to industry in April, 1995, concluding only that the minimum effective dose of caffeine, which would be 65 milligrams, should be permitted in a single dose, and agreeing with the recommendations made by the Nonprescription Drugs Advisory Committee for the labeling of these OTC drug products.

And, that brings us to where we stand today.

I've gone through this in a fair amount of detail because we are going to need your opinion also on caffeine as an analgesic adjuvant, although that really isn't one of the main questions before you today. But, I do think we are given by these committees, by your predecessors so to speak, a dual message. The message is that caffeine is an analgesic adjuvant, but that the dose is not exactly clear, it can be as low as 65 milligrams, that may be a dose

that's too low for analgesic adjuvancy, or just on the borderline of effectiveness for analgesic adjuvancy, or that it should be the same as the stimulant dose. So, we have those two sort of cards on the table already.

However, and that's why I've given you this sort of detailed background, I think as both the presentations unfold today, and as the questions are presented to you, I think you'll see where we are trying to go and what kinds of advice we need from the committees.

Thank you very much.

CHAIRMAN D'AGOSTINO: Thank you, Michael.

Doctor Chambers is now going to make opening comments also.

DOCTOR CHAMBERS: Thank you.

On behalf of the various reviewing divisions, I would like to welcome you all and thank you for attending this session.

As you can see from the past couple days and including tomorrow, there's a mix and match of a number of different advisory committees or portions of advisory committees as we discuss different issues. This review, this NDA, also has a joint or co-review in progress. That review consists of components from

the Division of Over-The-Counter Drug Products and members of the Division of Anti-Inflammatory Analgesic and Ophthalmic Drug Products. The different aspects of the NDA review have been divided up within the two different divisions, so we have individual reviewers from each of these two groups providing reviews and sharing them between the two different divisions, and we are attempting to do that also with the advisory committees as we try and share the different comments among different groups.

One of the components that we will not be discussing at all today involves the chemistry review. That is, as any other NDA product that's reviewed, there is chemistry manufacturing information, most of that is confidential information. Any aspects of that review will be shared with the sponsor as it gets completed, but in general the expertise of this group is not of the chemistry and manufacturing, so we do not generally bring those issues before you. That does not mean that if this group were to recommend approval of the product that it would appear tomorrow, those chemistry issues, if there are any, and I'm not saying there necessarily are, would need to be resolved, but you can rest assured that those will all be taken care of prior to any final approval, but

that's a separate issue.

In general, my tendency has been to bring scientific disagreements to advisory committees, and my other kind of caveat to this opening discussion is that I want to say that that's not the case in this particular instance. The scientific reviews that have been done, as you'll see from our presentation, are in substantial agreement with the sponsor, as far as what the data shows. There may be minor disagreements as far as individual numbers of a couple different patients, but we do not believe that they contribute to the overall findings and conclusions of the study.

What we are, in fact, asking you to discuss are some of the general policy issues that Doctor Weintraub alluded to in his opening remarks.

As we go through, if there are any questions of any of the different review divisions, please feel free to ask them and we will try and get the appropriate comments back to you in a timely fashion.

Again, thank you.

CHAIRMAN D'AGOSTINO: Thank you.

We'll now move directly to the open public hearing. There have been five individuals who have come forth and asked to make statements in the open

public hearing segment. I'm going to follow the agenda as it was included in the outside material, the material you can pick up outside. First we are going to hear from the Center of Women Policy Studies, then the National Consumer League, then the American Council on Headaches, then the Wellness Council of America, and the American Medical Women's Association. Each of these speakers have been given an allocated time, and I ask that they stick and adhere to that time. They can use either the podium or one of the mics on the floor, whichever they find more convenient.

We'll start with Leslie Wolfe from the Center for Women Policy Studies. Leslie.

Also, please make sure that you state your name for the transcriber, your affiliation, and who you are representing at this particular meeting.

DOCTOR WOLFE: My name is Leslie R. Wolfe and I am the President of the Center for Women Policy Studies in Washington, D.C. The Center is a national, independent, multiethnic feminist policy research institute, which was founded in 1972. We have conducted research on both women's health decision making and also on workplace issues for women of color, both of which suggest the importance of this

issue because about 75 percent of persons who suffer migraine are women. I have a staff member who suffers really bad migraines, so that's my only personal experience, thank heavens, and it is debilitating for her.

Many women, however, do not work at the Center for Women Policy Studies, and they feel they must hide their suffering from such conditions as migraine, for fear that they may not be treated seriously by co-workers, that their illness may not be taken seriously by co-workers or by supervisors. We are also aware at the Center of data that indicate that headache pain, including migraine, is one of the leading causes of lost work time in this country.

Several of the biological triggers to migraine are, in fact, unique to women, relating to hormonal changes that are connected to pregnancy, child birth, menstruation, menopause, which most non-women do not ever experience. And, all of these in women can be connected to the onset of a migraine.

For women such as my staff member, migraine headache pain can make life unbearable in the workplace, at home or in the community, and she is one of 17 million American women.

In addition, the Center's research on

women's health decision making, which included focus groups, literature review and a national survey, found that women, regardless of race, ethnicity, age, or income level, want to feel in control of their health care, but they want to do it in partnership with their physicians. Women also respond well, as we did message testing, they responded well to thoughtful and respectful health care messages that first reflected the realities of their lives, and also reflected their roles as health care decision makers for themselves and their families.

The data that you are reviewing today contains important health information that we believe can help women manage their health and their work and family lives far better. Given this information, given respectful and complete messages about it, and given effective over-the-counter medications for conditions such as migraine, we are certain that women will be able to effectively manage their pain.

We are especially heartened by the possibility that women will have access to relatively low-cost medication, effective in short-term dosage, for this extremely pressing problem.

We recommend that these committees urge the FDA to move quickly to approve labeling and public

education programs that will raise awareness of migraine among the general public, help them understand the effect migraine has on women, I think specifically employers need to understand that, and to include in the labeling specific dosing information for migraine. We think this will make a major benefit for women in the workplace and in their homes.

Thank you.

CHAIRMAN D'AGOSTINO: Thank you.

The next speaker is from the National Consumers League, Rebecca Burkholder.

MS. BURKHOLDER: Good morning. I'm Rebecca Burkholder with the National Consumers League in Washington, D.C., and I'm here on behalf of the National Consumers League. The League is a National non-profit consumer organization that has represented consumers and workers in the marketplace and workplace for almost 100 years. Assuring that consumers can purchase safe and effective medication is a primary concern to our organization.

I would like to inform the committee that Bristol-Myers-Squibb was one of 93 contributors to the League's health care conference this year. Their contribution amounted to 0.7 percent of our annual operating budget.

The League supports adding an indication for migraine headache to the label of Extra Strength Excedrin. Informing consumers that Excedrin is effective for migraines will provide guidance to the 23 million Americans suffering from migraine headaches. Helping consumers manage migraine pain will improve the quality of their life at home, as well as at work.

Educating consumers on managing migraine pain is important in this age when consumers are assuming greater responsibility for their own health. As more consumers self treat with over-the-counter products, they need guidance on which pain medications work for which ailments. It is important for consumers to know that there are different kinds of headache pain and different levels of treatment for headache pain.

Indicating on the label that Excedrin is effective for migraine headaches will provide consumers with helpful information on understanding and differentiating among pain medications. Studies conducted by the manufacturer show Excedrin to be effective in alleviating migraine headache pain. This information should be conveyed to the consumer.

Because Excedrin is an OTC drug, the

information on the label may be the only information consumers will receive about the product. Therefore, the fact that Excedrin is effective for migraines should be included on the label.

The League does not believe consumers will misuse Excedrin if it is indicated for migraines. The label will clearly instruct consumers to consult a doctor before use if the migraine is accompanied by vomiting or if it is so severe bedrest is required. Consumers are also instructed to consult a doctor after use if headache pain continues or worsens.

Informing consumers that Excedrin is effective for migraine pain will directly affect the quality of life for the 23 million Americans suffering from migraines. Every year, migraine pain costs society at least $5 billion in lost productivity and 270 lost work days for every 1,000 workers.

In addition, migraine has its highest prevalence in individuals between the ages of 25 and 55, the peak years of productivity.

Migraine pain also disrupts life outside of the workplace, causing strain in relationships, missed family time, sleep disruption, loneliness and frustration. Providing information which helps consumers self treat for migraine pain is economical

for both the consumer and the greater society. The average cost to the consumer for the over-the-counter purchase of a bottle of 50 pills to treat a headache is estimated at $5.00. The total cost to the consumer for a visit to the doctor and filling a prescription for 50 pills is estimated at $34.00. Because the majority of migraine sufferers have never been diagnosed by a physician, an OTC migraine indication would be of particular benefit to those consumers.

While the League supports the new migraine indication for Excedrin, it is also encouraged as a manufacturer to continue educating consumers on types of headaches and how to prevent and treat headaches. Common triggers of headaches include stress at home or work, certain foods and hormonal fluctuations. As the increasing use of technology speeds up the pace of life at home and at work, managing stress becomes difficult. Continued consumer education on how to reduce or handle stress is important in preventing the onset of headaches.

In conclusion, we would hope that an OTC label containing an indication for migraines would be in large enough type size for the consumer to read without getting a headache.

The warnings informing consumers when to

consult a doctor regarding migraine pain are useless unless they can actually be read by the consumer.

Thank you for providing this opportunity for the League to present our views on this important issue to the FDA.

CHAIRMAN D'AGOSTINO: Thank you.

The next speaker is from the American Council on Headache.

DOCTOR LODER: Good morning. My name is Doctor Elizabeth Loder, and I am the Director of the Headache Management Program and the In-Patient Pain Management Program at the Spaulding Hospital in Boston.

I'm here today as a member of the governing body of the American Council for Headache Education, otherwise known as ACHE. This is a non-profit, physician/patient partnership which is dedicated to raising awareness, public awareness and professional awareness, of migraine as a treatable biologically-based illness.

The American Council for Headache Education receives revenues from its patient newsletter, from contributions from pharmaceutical companies, unrestricted educational grants, among them Bristol-Myers-Squibb, the makers of Excedrin.

We believe that migraine headache is a very important, under-recognized and under-treated public health problem, and as you've heard it affects anywhere between 23 to 25 million Americans. And, for those people who are migraine sufferers, migraine, as you have heard and will hear, can be a very important problem. It's estimated, as you have also heard, that it accounts for approximately 5.7 million lost or reduced productivity work days per year, and that turns into an enormous societal and economic burden, which as you've also heard primarily falls on people in otherwise productive years of their lives.

Many of these migraine sufferers are already using over-the-counter medications, sometimes inappropriately, and many of them lack access to affordable health care.

My experience as a practicing clinician, whose patients are, I think, reflective of migraine sufferers in general, has shown that they already self-medicate with over-the-counter medications, but that they often lack information about what they are treating, what the other treatment options might be, and what types of symptoms might require a visit to a physician rather than self-medication.

Labeling and public education efforts on

the appropriate use of effective over-the-counter medications for migraine pain are, therefore, of great interest to organizations such as the American Council for Headache Education, and we believe they are key aspects of the proper management of migraine headache pain.

An OTC indication would allow access to directions for appropriate use and access to education, regarding therapeutic alternative options and professional counsel. Appropriate dosing instructions based on the results of well-controlled trials would be an important step in leading to the appropriate use of over-the-counter products.

The data you will see today we believe, if provided to consumers, can be an important step in encouraging this appropriate use of over-the-counter medications. Labeling that recommends short-term use can be an extremely effective tool in encouraging appropriate use of over-the-counter medications.

The physician and patient members of the American Council for Headache Education strongly believe that consumer education is the key to appropriate recognition and treatment of migraine, and we encourage the committee to support measures which would increase access to this information and

information about therapeutic options, and increase the flow of information to migraine sufferers in general.

Thank you very much.

CHAIRMAN D'AGOSTINO: Thank you.

The next speaker is Mr. Jerry Miller from the Wellness Councils of America.

MR. MILLER: Good morning. My name is Jerry Miller, and I'm speaking on behalf of the Wellness Councils of America, or WELCOA.

WELCOA is a national, non-profit membership organization dedicated to promoting healthier lifestyles for all Americans, especially through health promotion at the workplace. Created in 1985, WELCOA today has a membership of 14 wellness councils across the country and 2,500 companies, both large and small, representing over 2 million workers.

Headache and migraine, in particular, can significantly impact the quality of life for headache sufferers, both at work and at home. Because the prevalence of migraine is highest among individuals in their most productive years of life, ages 35 to 45, the impact of this condition in the workplace is substantial. In fact, headache is one of the leading causes of absenteeism and lost productivity in the

workplace, and migraine contributes significantly to the economic consequences.

There are an estimated 270 work days lost annually for every 1,000 people who suffer from migraine. Lost productivity due to migraine in the U.S.A. is estimated at $6.5 billion going up to $17.2 billion. In addition, migraines are responsible for $1.3 billion in lost wages annually.

In today's work environment, employee productivity and individual contributions are more important than ever. Currently, the majority of migraine sufferers use over-the-counter medicines and very often they use these medications in the workplace. Access to new, effective and affordable treatments is critical. We support efforts that will help educate sufferers about the appropriate use of these products.

WELCOA is committed to providing health information and education that can increase productivity, decrease absenteeism and provide a healthy corporate environment. Therefore, we believe it is important that the committees strongly consider new treatment alternatives that will expand therapeutic options, as well as public education and health promotion programs for migraine sufferers in

the workplace and beyond.

Thank you very much.

CHAIRMAN D'AGOSTINO: Thank you.

The next speaker is Eileen McGrath from the American Medical Women's Association.

MS. McGRATH: Good morning. My name is Eileen McGrath, I'm Executive Director of the American Medical Women's Association. AMWA represents more than 11,000 women physicians and medical students. We were founded in 1915, and our organization seeks to further the personal and professional development of women physicians and medical students, and to advocate on women's health issues.

AMWA receives a variety of support from industry, and in 1995 received an unrestricted educational grant for advanced curriculum in women's health from Bristol-Myers. Currently, AMWA receives less than one half of one percent of our budget as support for our foundation from Bristol-Myers.

The American Medical Women's Association is submitting this statement in support of the application of Excedrin ES to be approved as an over-the-counter medication for mild to moderate migraine. As we have a particular interest in women's health, AMWA is concerned about the high incidence of

headaches and migraines among women compared to men, and you've heard that that ratio is 3:1.

We feel strongly that the very real problem of migraines in American women requires new treatment options, particularly, over-the-counter treatment options. AMWA fully supports increased exposure of the public and the medical profession to educational information through advertising and the availability of safe over-the-counter products to increase awareness about migraines.

Migraines affect the lives of more than 20 million Americans each year. An estimated one in six women are affected by the serious, often debilitating disease. Not only are women disproportionately affected, but the disease has a greater impact on their lives, and, particularly, women have reported that their professional development and career and family responsibilities have been affected by migraine.

The currently available treatments for migraine, while effective in many patients, may at times have unwanted side effects. A middle ground is needed for treatment, which improves patient symptoms, enabling a return to functional status, and has potentially fewer side effects.

There is a gap in our armamentarium of medicine with fewer side effects. This gap would be filled by approval of this OTC medication for mild to moderate migraine.

It is important that patients take an active role by seeking a medical diagnosis and complying with treatment and follow-up. The use of over-the-counter therapy, such as Excedrin ES, offers patients a desirable option for the treatment of migraines, but should be made in partnership with their physicians, and I think the labeling would take care of advising patients when they should consult with their physicians.

Many women are unaware of the higher prevalence of migraine among women, and consequently may not take their condition seriously and may not seek treatment. The American Medical Women's Association believes that the availability of Excedrin ES over the counter will help educate women and men about this condition through its accompanying advertising campaign, and will lead women and men to take notice and action against this frequently ignored condition.

The American Medical Women's Association strongly supports additional research into migraines

and other conditions that disproportionately affect women. In order to develop the most efficacious treatment, additional research is needed for a better clinical understanding of the role of hormones in migraine.

We support the application of Excedrin ES and feel that its introduction and accompanying advertising will increase awareness of migraines and provide women with more treatment options.

Thank you.

CHAIRMAN D'AGOSTINO: Thank you.

We'll move now directly to the presentation by Bristol-Myers. Doctor Howard Hoffman is going to lead the presentation. It will consist of three speakers, and then a summary by Doctor Hoffman.

I would like to ask the panel members, the Advisory Committee members and consultants, not to ask questions while the speakers are making their presentation, unless it's a major point of clarification. I've been asked by the speakers, and I agree with it, that it would be best if we heard the presentations and then saved our questions until after the presentations.

Doctor Howard Hoffman.

DOCTOR HOFFMAN: Good morning. Thank you,

Doctor D'Agostino, members of the Nonprescriptio n Drugs, Arthritis and Peripheral and Central Nervou s System Drugs Advisory Committees, Doctor Weintraub , Doctor Bowen, Doctor Chambers, and representative s from the Agency, I'm Doctor Ho ward Hoffman, Executive Medical Director for Bristol-Myers products. It's a pleasure for me and my colleag ues to be here today to present and discuss with you information and data in support of the proposed use of OTC Excedrin Extr a Strength in the treatment of migraine headache pain.

Our presentation will take approximately 75 minutes. We have allocated 15 minutes fo r questions, and request that you hold your question s until after the conclusion of this presentation.

Please note that a number appears in the lower right-hand corner of the slides for you r reference.

CHAIRMAN D'AGOSTINO: Excuse me, is that bold enough, can people read that?

DOCTOR HOFFMAN: Yes, it could be a littl e darker.

The purpose of today's meeting is t o present data supporting the efficacy and safety o f Excedrin ES for the relief of migraine headache pain, and to request endorsement by this committee fo r

regulatory action to broaden the Excedrin ES headache labeling to include the relief of migraine headache pain.

The specific regulatory action for OTC Excedrin ES is to change the OTC headache indication from the current one, which is for temporary relief of the pain associated with headache, to temporary relief of the pain associated with headache, including migraine headache pain.

There would be no change in the dosing and dosing interval, as per monograph, and Excedrin contains 500 milligrams Aspirin in the two tablets, 500 milligrams acetaminophen and 130 milligrams of caffeine. Additionally, warnings for use in headache, including migraine, will be added, these would include see your doctor before use if headache is accompanied by vomiting, and see your doctor before use if headache is incapacitating or requiring bedrest. These will be discussed later in the meeting as well.

This is the agenda for our meeting, we'll be giving you a brief introduction of our subject, Doctor Richard Lipton, Professor of Neurology at the Albert Einstein College of Medicine, and Co-Director of the Headache Unit there, as well as our principal investigator for one of our studies, will be

discussing the background and clinical study results. Mr. Sion Boney, President of Bristol-Myers Products, will be discussing the label comprehension study and education programs, and I will be giving some concluding remarks. At that time, I will -- both me and Doctor Lipton will be available for comments and questions.

We have a number of consultants who have worked with us on this project and are available for questions during this presentation. Doctor William Beaver, Professor Emeritus of Pharmacology, Anesthesiology, Georgetown University School of Medicine; Donald Dalessio, Senior Consultant in Neurology, Scripps Clinic, La Jolla, California, Past President, American Association for the Study of Headache, and the Past President of the National Headache Foundation; Elizabeth Delzell, Professor Epidemiology at the University of Alabama; Joseph Izzo, Professor of Medicine and Pharmacology at SUNY at Buffalo; John Edmeads, Professor of Medicine and Neurology at the University of Toronto; Michael Gallagher, Director of the University Headache Center, Professor and Vice Dean, the University School of Dentistry of New Jersey, School of Osteopathic Medicine, Secretary, National Headache Foundation and

Chairman of the National Headache Foundation Headache Certification Board, also the Chair of the AAS H Medical Curriculum Committee.

Additionally, Gene Laska, Director of Statistical Science and Epidemiology at the Nathan Kline Institute for Psychiatry; Alan Leviton, Professor Neurology, Harvard Medical School, Director of the Neuroepidemiological Unit; Charles O'Brien, Professor and Vice Chairman of Psychiatry, University of Pennsylvania; Marcus Reidenberg, Head, Division of Pharmacology, Cornell University Medical Center; Lorie Rice, Associate Dean for External Affairs, School of Pharmacy, University of California at San Francisco; and Doctor Rick Schnellmann, Professor of Pharmacology and Toxicology, University of Arkansas.

We are here to talk about an important therapeutic option for migraine sufferers. Migraine headache pain indication for an OTC analgesic would offer a meaningful therapeutic option to consumers. As we've heard, migraine is a prevalent condition affecting 23 to 25 million Americans.

The majority of these migraine sufferers, above 62 percent, treat with OTC analgesics off label. OTC analgesics are recommended in treatment guidelines, but what's missing at the present? Right

now, there is no approved OTC medication for the treatment of migraine headache pain, and one that would provide safe, proven, widely accessible, inexpensive treatment options, and appropriate information on dosings and warnings. During this presentation, we will be talking about our program to address these issues.

Doctor Weintraub, in his presentation, talked about headache as a well-established OTC indication and its history, the fact that by 1977 FDA had recognized headache as an appropriate OTC indication, though, obviously, it was used prior to that time for headache. It was clear from the regulatory discussions that headache was self-recognizable, acute and self-limited, and appropriate as an OTC indication.

Similarly, as Doctor Weintraub mentioned, migraine headache pain was excluded or carved out of the OTC indication at that time, and clearly there was not a lot of information about migraine.

What's changed since then? Between 1988 and 1991, the IHS classifications provided tools for new research. New diagnostic criteria were established, and this led to improved diagnosis of headache and facilitated clinical and epidemiological

research, and this allowed us to get additional information on what might be an appropriate population for OTC use.

This epidemiological research found a spectrum of migraine population appropriate for OTCs. As I stated, based on IHS criteria, a number of studies were performed, it was found that migraine affects 23 to 25 million Americans, that migraine is a heterogeneous disorder with a wide range of pain severity and functional disability.

Prior to this time, physicians frequently felt that migraine patients were the most severe kind that would have attacks for several days on end, be sort of tucked away in a dark room, but here we go to more information about the entire spectrum of migraine, and the fact that there were patients with mild disease, medium disease, and certainly the more severe disease.

Additionally, in the surveys of what patients were using to treat their migraines, it was found that greater than 60 percent of migraine sufferers treat with OTC analgesics and, indeed, many migraine sufferers had never consulted a physician for treatment.

Based on some of these new thoughts in the

evolution of migraine and thinking about migraine as a possible OTC indication, we thought about programs to address this, and for us we addressed the issue of why Excedrin ES for the relief of migraine headache pain.

Excedrin is an OTC analgesic that has been marketed for greater than 19 years in its current formulation, with over 30 billion tablets sold. Its efficacy has been well established in a number of pain models, and especially relevant to this subject, the tension headache model.

Caffeine is a proven analgesic adjuvant and caffeine is used in Rx migraine medications, thus, indicating its potential usefulness for treating migraine.

Additionally, what was important to us was to look at the safety profile, so that we could decide on the studies we intended to form.

I'm going to show you two large databases that we looked at before the start of our studies. The first one is our tension headache type pain relief studies. This encompassed four large studies with 1,400 patients in the Excedrin group, 700 placebo patients. As you can see, the serious adverse experiences, there were none reported in these

studies. The adverse events that were seen in these studies are the type that are seen with analgesics containing Aspirin and caffeine. As you can see, abdominal pain was one, dyspnea and nausea in the digestive system, and in the nervous system dizziness and nervousness, things that would not be unexpected. But, overall, the safety experience was excellent, and the type of adverse events were mild and self-limiting in these tension headache trials.

I'm next going to show you some more data from our post-marketing experience. This covers a period from 1984 to April of 1997, and through that time period 17.8 billion tablets were sold. Once again, in this time period there were 2,396 reports, 2,427 events, and only 12 serious events. There were no deaths reported to Bristol-Myers as well.

This is the additional information on that database with adverse events with greater than one percent by body system, again, a denominator of 17.8 billion tablets sold, and 2,427 events. Again, they cluster in the areas where we would expect them to be, in the digestive system, likely secondary to Aspirin, the nervous system, likely secondary to caffeine, and then a scattering of other adverse events.

I think overall, here are our serious

adverse events from that trial, the 12 cases that I mentioned, again, syncope in three, allergic reactions in two, GI bleeds in two, abdominal pain in one, two reactions unidentified, and an esophageal ulcer from a lodged tablet, and one intestinal obstruction. Again, once again demonstrating a very good safety profile.

With this information in hand, and the additional information we had from the epidemiological studies, we talked to headache specialists, investigators and the FDA about what would compose the appropriate program to study Excedrin ES for the OTC treatment of migraine headache pain.

The issues that we brought up were the need to do three single-dose, double-blind, randomized, placebo-controlled, parallel group studies, to look at the efficacy. What was very important was that we confirm that patients studied had IHS diagnosis of migraine and the treated headaches were migraines, to be certain that the patients actually had migraine, and that we study a spectrum of migraine patients typical of a population likely to use OTC analgesics for relief of migraine headache pain and do appropriate label comprehension and education programs.

The FDA questions that we will be addressing today are the following:

1. Is the pain of migraine an appropriate OTC indication?

2. Has the applicant provided adequate evidence, clinical studies, to support the effectiveness of Excedrin ES in an OTC migraine population?

3. Has the applicant provided adequate information to support the safe use of Excedrin ES in an OTC migraine population, and provide other labeling recommendations?

It's now my great pleasure to introduce Doctor Richard Lipton, Professor of Neurology, Epidemiology and Social Medicine at the Albert Einstein College of Medicine, Co-Director of the Montefiore Headache Unit in New York. Doctor Lipton is an expert in this area, and has been involved in the key epidemiological studies done during the past decade on this subject.

DOCTOR LIPTON: Good morning. Over the next 30 minutes or so, I'd like to review three different areas with you. The first is why migraine headache pain is an appropriate OTC condition. The second is the rationale for treating migraine headache

pain with an OTC analgesic, and the third is to review the data that was gathered in the three clinical trials previously alluded to.

As you've heard already, the International Headache Society provided a classification and diagnostic system for migraine and other headache disorders in 1988, and that classification system represented a major step forward for the field. First, it provided operational diagnostic criteria, which allowed uniform diagnosis, both in clinical practice and research, and it also facilitated epidemiologic research by providing a case definition for the symptom-based condition, and also by providing a method for standardizing diagnosis in clinical trials.

The IHS classification for primary headaches recognizes four groups of primary headache, three of which are the most important groups, those being migraine, tension-type headache and cluster, and, of course, today we are focusing on migraine headache. Although the IHS recognizes seven subtypes of migraine, the two that are most important in the population and two subtypes of migraine that were the focus of this clinical trails program, namely, migraine with aura and migraine without aura.

Migraine with aura is the condition that was formerly called classical migraine. It's a form of aura that's preceded by various kinds of symptoms, most often a visual display consisting of positive features like sparking lights or zig-zag lines, and sometimes negative features such as visual loss as well.

Migraine without aura is the more common form of migraine, and in fact represents about 80 percent of migraine in the population.

There are a number of characteristics of migraine that support the notion that it may be an appropriate OTC indication. First, migraine attacks are episodic and self-limited. The median duration of untreated attacks in the population is 24 hours. Second, attacks are relatively infrequent. The median frequency of attacks in the population is about one per month, and 75 percent of people with migraine in the population experience three or fewer attacks per month.

Migraine without aura is defined both by pain features and associated symptoms, and the pain features that are used by the IHS to define migraine without aura are the unilateral location of pain, the pulsatile quality of pain, moderate or severe pain

intensity and aggravation obtained by routine physical activity. According to the IHS, two out of four of those features needs to be present to make the diagnosis of migraine without aura.

Associated features are also required, and the associated features that are used to define migraine are nausea and/or vomiting, or the presence of photophobia and phonophobia, and only one of those two features is required to define migraine. Photophobia and phonophobia are given less weight in the sense that both features are required to define the condition.

Epidemiologic studies have clarified the potential role for over-the-counter treatment of migraine. Certainly, one major strength of these studies is that facilitate the identification of migraine sufferers in the general population, using systematic methods, whether or not people are seeking care. These studies have helped clarify the prevalence and distribution of disease, and you've already heard a fair amount about that. These studies demonstrate that migraine produces a spectrum of pain, and a spectrum of disability, and as a corollary I would suggest that those differences in pain and disability may imply differences in treatment need.

Finally, by evaluating and identifying migraine sufferers in the population, independent of whether or not they were seeking care, that makes it possible to assess patterns of health care utilization and get a handle on how people are treating migraine, not just in the doctor's office, but in the community.

Now, you've heard already that migraine is a highly prevalent condition affecting roughly 17.6 percent of American women and roughly six percent of American men. This slide, from the American Migraine Study, illustrates the one-year period prevalence of migraine as a function of age. What you see is that in all post-pubital ages migraine is more common in women than in men, and that prevalence, as you've heard already, peaks between the ages of 25 and 55, during the peak productive years.

You've heard already that migraine produces a spectrum of headache pain. Here we asked a population sample of migraine sufferers to rate their average pain on a scale from zero to ten, where zero was no pain at all and ten was pain as bad as it can be, and what you see is that there's a fairly wide distribution of pain, though the majority of migraine sufferers have pain that they rate above five, and so the distribution is somewhat right skewed.

When we look at the distribution of disability, an interesting picture emerges. Here we asked a population sample of migraine sufferers how they were affected by their headaches usually or on the average, and what you see is that a third of migraine sufferers reported that they were severely disabled, they required bedrest. Now, that most disabled fraction of migraine sufferers is demonstrably more likely to consult physicians for headache, and also demonstrably more likely to consult headache specialists.

Prior to the conduct of these epidemiologic studies, much of our understanding of migraine was actually defined by the more disabled segment, though certainly some patients with mild to moderate disability consult as well.

The largest group of migraine sufferers fell into the mild to moderate disability group, 50 percent of men and 52 percent of women fell into that group, and there's a group of -- a small group of migraine sufferers, 11 to 15 percent of men and women respectively, who reported no disability at all.

When we examine patterns of medical consultation for migraine an interesting picture emerges. Here the entire circle on these pie charts

represents a population sample of 321 men with migraine or 1,385 women with migraine, and we asked these people who met IHS criteria for migraine whether they had consulted a doctor for headache, and if they had consulted when they last consulted.

The current consulter group consists of people who have consulted a physician specifically for headache within the last year, and you see the 12 percent of men and 17 percent of women have specifically consulted a doctor for headache in the last year. There's a large group that we have called lapsed consulters here. These are individuals who have consulted for headache at some point, but not within the last year, and that group comprises 45 percent of men and 51 percent of women. There was also a substantial fraction of never consulters, 43 percent of men and 32 percent of women never consulted a physician for headache at all, and, of course, we are talking here about men and women with migraine.

Now, when you look at the lapsed consulter and never consulter group, and you ask them why they are not seeking care, a very common reason, in fact, the single most common reason they give, is that they are taking over-the-counter medications which they find beneficial. You know, I also want to add,

however, that there is certainly a disabled segment of migraine sufferers, and among the lapsed consulting and never consulting group there is clearly a group that would benefit from medical care for whom over-the-counter medications would not be the most appropriate treatment.

Current patterns of medication use mirror in many respects current patterns of consultation. Here we are looking at first a group that takes no medication at all, roughly five percent of men, roughly three percent of women take no medication at all for their headaches. The vast majority of people with migraine do use medication to manage their pain.

Two thirds of men manage their migraine headache pain with over-the-counter medications to the exclusion of prescription drugs, and roughly 57 percent of women use over-the-counter medications to manage their migraine to the exclusion of prescription drugs. There's a substantial group, 28 percent of men and 40 percent of women, who use prescription drugs, but roughly half of the people in those groups also use over-the-counter medications.

So, the picture that emerges from the population-based studies is that migraine is a condition where self-treatment with over-the-counter

medications is the norm, not the exception.

What then is the rationale for the OTC treatment of migraine headache pain? Well, as we have said already, headache pain, including migraine headache pain, is symptomatic and self-recognizable, obviously, the way we know that a person has a headache is because they report their painful experience. These attacks of migraine are acute, relatively short lived and self-limited. The attacks are episodic as well.

Migraine headache pain is commonly treated with over-the-counter analgesics, and, in fact, as I've said already, over-the-counter analgesics is the major mode of treatment in the United States.

There's a spectrum of migraine headache pain and disability for which over-the-counter analgesics appear appropriate, both based on the range of pain and disability that we see in population samples, and based on self-report of use of OTC medications.

Finally, I want to call to your attention the fact that migraine is an OTC indication in the United Kingdom. Migraine has been on the label of OTC products in the U.K. for over 40 years. There are more than a dozen marketed products, including two

products which are caffeine combination products containing 65 milligrams of caffeine per tablet, and in that 40-year experience no product has ever been withdrawn from the market for safety reasons.

Why Excedrin for migraine headache pain? Well, efficacy of Excedrin is established in various pain models, most importantly in tension-type headache, so we know this is a medication that works at least for one kind of headache. Excedrin is already widely used for migraine headache pain. In fact, an AASH/Gallup survey, AASH being the American Association for the Study of Headache, an AASH/Gallup survey conducted in 1995 showed that roughly six percent of migraineurs in the United States currently use Excedrin ES as either their first or second choice treatment for migraine, so this is a treatment that's already being used.

Caffeine is a proven analgesic adjuvant in a variety of pain models. Caffeine certainly has a heritage as an ingredient in prescription medications, including Fiorinal, Fioricet, Esgic, Cafergot and so forth.

Finally, as Doctor Hoffman showed you, Excedrin is a drug with an excellent and predictable safety profile, making it an attractive choice.

There were a number of considerations in designing the clinical trials program. The overall program consisted of three single-dose, placebo-controlled, randomized, double-blind, parallel group studies, and these were the three pivotal efficacy studies that I'll summarize for you in a moment. The design of these studies is consistent with the design that was used for approved medications for migraine on the prescription side, most notably Sumatriptan, but also it's quite similar to the follow-up design for many of the triptan drugs that are currently in development.

The design is similar to the single-dose analgesic studies that may be more familiar to some of you, and finally, the study was conducted using IHS guidelines, both for diagnosing migraine, as well as with awareness of and largely following the IHS guidelines for migraine clinical trials that were published in 1991.

There were a number of considerations in developing this program. One of the key issues was ensuring that the study included an appropriate study population for the OTC treatment of migraine. One objective was to include migraine sufferers who would be likely to use an OTC analgesic for migrain e

headache pain, if migraine headache pain was on the label.

We made the judgment that it would be most appropriate to exclude the most severely disabled segment of migraine sufferers from this study for really two reasons. One reason is that the most disabled sufferers might not be appropriately treated with over-the-counter medications, and the second reason was, going into this program we didn't know what level of efficacy we would see, and it actually seemed somewhat unethical to me to study a severely disabled segment with a product whose efficacy was uncertain.

Another consideration was to carefully document the diagnosis of migraine in the patients, and also to document the treated attack was migraine. The reason that's an issue is that people with migraine sometimes experience headache attacks that would be better classified as tension-type headache attacks and we wanted to be very careful to treat attacks that were, in fact, migraine.

The program also included a label development comprehension study, which Mr. Boney will discuss following this presentation.

The clinical trials program consisted of

three independent studies, named 840, 841 and 842. The objective of all three studies was to assess the safety and efficacy of Excedrin ES in alleviating acute migraine headache pain.

The study 840 was a single center study, and I was the principal investigator of that study. Studies 841 and 842 were multi-center studies.

This map summarizes the sites included in the study, and you see that the program included broad geographic representation of the major regions of the United States.

A couple of comments on inclusion/exclusion criteria, which are detailed in your briefing books. Subjects had to meet IHS criteria for migraine with aura or migraine without aura. Attack frequency was required to be one migraine attack every two months to six migraine attacks per month, with moderate to severe headache pain during the previous year. The reason for this frequency consideration was that we wanted to get people with attacks that were frequent enough so that they would be likely to treat in the treatment window, but also we wanted to get as representative a group of migraine sufferers as possible.

We excluded from study two important

groups. We excluded individuals who vomited more than 20 percent of the time, on the grounds that they may not be able to absorb an oral medication, and we also excluded people who usually were incapacitated by their attacks, parenthetically defined as so incapacitated as to require bedrest.

The study was conducted in four phases, which I'll review one at a time, a screening phase, a patient selection phase, an out-patient treatment phase, and then a follow-up visit after treatment.

The objective of the screening phase was to obtain a broad spectrum of subjects for whom an OTC analgesic might be appropriate, and we used two methods, a populated-based recruiting method, which I'll describe further in a second, which is a novel method, and also traditional office practice recruitment where study investigators enrolled their patients from their practice who were eligible and also patients identified by advertising.

The objective of the population-based recruiting method was essentially to use epidemiologic methods to identify a representative sample of migraine sufferers independent of consulting status. And, essentially, what we did was use the phone interview methods that we had developed and validated

for purposes of epidemiologic research to conduct focused screening and recruiting of subjects in a geographic area close to our clinical trial center in Towson, Maryland. We deliberately located our clinic in a demographically diverse area of Towson, which we chose based on reviewing Census data.

We used random digit dialing to contact households that were within a ten to 15-minute drive of our clinic. We administered a validated telephone interview to screen for migraine, and when we identified individuals who potentially had migraine we conducted a follow-up recruiting interview, and in that interview we validated or confirmed the features of migraine in most cases, and also ran a number of protocol-specific inclusion/exclusion criteria.

We then identified potentially eligible subjects to make a clinic visit, and proceeded as one would using ordinary clinical trial methods.

In the selection phase, and this is the initial visit now, an IHS migraine diagnosis was made by a neurologist or headache specialist using a semi-structured interview. The semi-structured interview was designed to ensure that the clinician touched all the critical diagnostic bases for assigning an IHS diagnosis of migraine. The semi-structured format

also allowed the clinician to ask any follow-up questions or probes they deemed appropriate to ensure that the information that was obtained was of optimal diagnostic validity.

Subjects were educated to ensure that the treated attack was a migraine headache and the features of that attack were reported in the study diary, so that a post-treatment determination could be made by the study investigators, and subjects were also educated to complete the self-reporting diary in which they described the response to their headache treatment.

In the treatment phase, patients took two tablets of Excedrin ES or placebo. An effort was made to ensure that the treated headache was a migraine headache, and then subjects self-reported their headache characteristics.

On the final visit following treatment, the diary was reviewed for completeness and the diagnosis of the treated headache was assessed by the investigator, who made a judgment about whether or not the treated attack was migraine.

In addition, at the request of the FDA, an independent neurologist reviewed diagnoses in a sample of study subjects. This review was intended as a

quality check to ensure that the enrolled subjects were migraine and that the treated headaches were migraine. A random sample of ten percent of the case report forms were reviewed by John Edmeads, who is in the room. Doctor Edmeads is a Professor of Neurology at the University of Toronto, and an acknowledged authority on headache diagnosis.

Doctor Edmeads made the judgment that every subject enrolled in the study had migraine, and that the treated headaches were migraine. This, of course, was done in a subgroup that had been previously screened by study investigators, and as I'll show you in a moment, patients did make some errors, although the diagnostic error rate among patients was incredibly low.

We looked at a number of outcome measures that are typical of migraine studies. We looked at a pain intensity measure on a zero to three scale, where zero is no pain and three is severe pain. We looked at pain relief, nausea, photophobia, phonophobia, functional disability, use of rescue medication and also had the subject and investigator complete a global evaluation as well.

The primary efficacy endpoints in this study were two. The first was an endpoint called

responders at two hours. For those of you who don't work in the headache area this may be an unfamiliar endpoint. The definition of a responder is that you have moderate to severe pain at baseline, and experience a pain reduction to no pain or mild pain at some point in time, and the time point that was designated as the primary efficacy time point was two hours.

In addition, we used the Pain Intensity Difference measure, and again designated two hours as the time for the primary endpoint assessment, and pain intensity is defined as baseline pain minus pain intensity at two hours. So, if you start out at a pain intensity which is severe or three and go to pain that's mild or one, that would be a pain intensity difference of two.

Let me review with you the disposition of randomized subjects, again, three independent studies, each with over 400 patients. The pooled sample included 1,357 patients. Of those, 107 did not take study medication for two reasons. One reason was that they didn't have a treatment attack within the protocol window, the other reason was that the protocol was terminated because enrollment objectives had been met.

A total of 1,250 people took study medications, and of those 1,247 were included in the intent-to-treat analysis. Individuals were excluded from the intent-to-treat analysis only if there was no baseline or follow-up measurement, so that it was impossible to derive any estimate of treatment effect.

For the efficacy evaluable analysis, an additional 27 individuals were lost. The major reason for losing individuals in the efficacy evaluable analysis was that the treated attack, in the judgment of the investigator, was not a migraine.

The results of the intent-to-treat and the efficacy evaluable analyses were virtually identical. I'm going to show you the efficacy evaluable analyses on the grounds that this includes the set of patients that were judged by the investigator to have treated migraine attacks.

Looking at the demographic characteristics, and here I'm showing you pool data, though the data is broken out by study in the briefing materials that you were given, looking at the demographic data we see that the mean age was roughly 37 years. We see that there was a fairly wide range of ages, though the majority of individuals were in the middle-life years where migraine prevalence peaks.

We see that there was a female preponderance in the study population, not dissimilar to the epidemiology of migraine itself, and in the study overall roughly ten percent of patients were African American, roughly 85 percent of patients were Caucasian, and there was a small group of self-identified Hispanic and Asian study participants as well.

I want to simply point out that the groups were comparable in their baseline demographic characteristics, suggesting that the randomization was, indeed, effective.

Looking again at migraine headache history, we see that a little less than 20 percent of the sample had migraine with aura, again, similar to the population of migraine sufferers. We see that the mean number of headache attacks per month was 2.3 or 2.4. This is a little bit higher than the mean attack frequency in the population, and the reason for that is that we had protocol-specific exclusions that eliminated people with relatively infrequent attacks.

The pattern of pharmacologic treatment in study subjects is of interest here. One to two percent of subjects took no medication at all. Roughly two thirds of subjects used over-the-counter medications, to the exclusion of prescription drugs,

not dissimilar to the information I showed you for the general population, 12 percent treated with prescription drugs only, and roughly a fifth of subjects treated with the combination of prescription and over-the-counter medications, and again, there were no differences in groups treated with active drug or placebo.

Now we are going to look, not at the baseline characteristics of the population, but at the baseline characteristics of the treated attack. I was showing you information that was captured at the enrollment visit, now I'm going to show you information that was captured in the headache diary by the study subjects at home, at the time they treated their attacks.

Again, we see 20 percent -- a little less than 20 percent of treated attacks were migraine with aura. We see that roughly 60 percent of patients had nausea. We see that the combination of photophobia and phonophobia in the pooled data was slightly over represented in the placebo treated subjects to a statistically significant degree. This difference was not statistically significant for the individual studies, and the statistical results I'm going to show you are adjusted for baseline differences in this

covariate in any case. Two thirds of the patients had moderate pain, one third had severe pain.

When we look at functional disability, recall that we deliberately excluded individuals who were usually severely disabled by their headaches. Despite that exclusion, roughly 30 percent of the sample reported severe functional disability with this individual attack, even though they weren't usually disabled, and a small proportion reported that they were completely incapacitated. So, the subjects enrolled in the study were not treating trivial headaches.

Let's talk a bit about the primary efficacy endpoints. The first endpoint is once again the responder endpoint, which is defined as a proportion of patients who had moderate or severe pain at baseline, who had mild pain or no pain at two hours. We are plotting here the proportion of patients who responded with Excedrin in yellow, placebo in blue, across the three studies and in the pooled data. And, what you see is that from 56 to 64 percent of patients responded to Excedrin, and 31 to 37 percent of patients responded to placebo, the effect size here is impressive, differences were statistically significant in all three studies and, of

course, in the pooled data as well.

Now, looking at this endpoint across multiple points in time, and the time points assessed in the study ranged from 1/2 an hour to six hours, I want to point out that there is some non-linearity in the time post-dose curve here, the intent was simply to make the slide legible. What you see when you look at this slide in the pooled data is that statistically significant differences emerged at 1/2 an hour and were maintained at all time points through to six hours, and that by six hours the pooled response rate was 80 percent, and these are cumulative response rates, by the way, though looking at the hourly response rates the results are not substantially different than our highly statistically significant.

This summarizes the data for the individual studies. My intent here is to simply show you that the data is quite consistent. Results are statistically significant at all time points at one hour and thereafter in all three independent studies.

Looking at the Pain Intensity Difference score, and, again, this is pain at baseline minus pain at two hours, we see substantial and statistically significant effects in each of the individual studies, and, once again, in the pooled data as well.

Using the same style of presentation, here we are going to review the data across all the time points in the study, and once again in the pooled data there was statistically significant differences beginning at 1/2 an hour and maintained through all six hours of the study.

When we look at the individual studies, once again we see that statistically significant differences are present in all three studies at all time points past one hour. The overall Pain Intensity Difference in the population-based study at six hours is 1.6 versus 1.3 in the other two studies, but overall the profile of results is strikingly consistent.

Looking at the secondary endpoints, what I've plotted here is the effect on functional disability, and what I'm plotting is the proportion of subjects with little or no functional disability in the pooled data. The fact that the Y intercept is a 20 percent means that at baseline 20 percent of the study subjects had little or no functional disability, and the increase in this proportion reflects the increase in the number of individuals who have no disability, i.e., improvement in functional status. In the pooled data, there are statistically

significant differences at one hour and at all points thereafter.

And, if you look at the individual studies, once again, the pattern of results from study to study is quite consistent.

This is looking at the proportion of subjects without photophobia. The Y intercept here indicates that the overwhelming majority of subjects had photophobia at baseline, and what you see is that at one hour and all time points thereafter there was statistically significant improvement in this endpoint as well. This slide demonstrates, again, that results were consistent from study to study.

Looking at phonophobia, the results are similar, once again, that statistic there indicates that there were statistically significant baseline differences in phonophobia. The test statistics were done running an ANCOVA, which took into account those baseline differences so the statistical results are adjusted for this difference, and, again, there were significant differences at all time points, and the effect size is substantial. And, again, examining phonophobia, the results were quite consistent from study to study.

When you look at nausea, the relatively

high Y intercept here reflects the fact that 40 percent of patients had no nausea at baseline. The reason for that, I believe, is that we excluded patients who usually vomit and so nausea in this group may have been less severe than it would be in a typical prescription migraine trial. In terms of improvement in nausea, statistically significant differences emerged at two hours, and are present at all time points thereafter, but no differences were seen at early time points.

And, when we look at the pooled data, again, the results are relatively consistent from study to study, though in the population trials statistically significant differences didn't emerge until three hours.

We did a number of subgroup analyses to assess the robustness of these results, and also to get a handle on whether there were subgroups for whom this treatment was not effective. The results I'm going to show you are based on the responder endpoint, and we examined gender, race, age, usual method of treatment, presence of menstruation at the time of baseline treatment, and migraine type.

The diary included a question which was simply, you know, do you have your period today, that

was asked of people who treated their attack, and if the woman said yes we considered the headache to be a mestrually-associated headache.

Looking at these subgroup analyses, the pooled data represents what I hope is now familiar to you, the 59 percent responder rate at two hours. When we look at females versus males, there are differences between active drug and placebo in both gender groups, and those differences are highly statistically significant, and the magnitude of effect looks approximately comparable as well. Looking at Caucasians and African Americans, the effect is statistically significant in Caucasians, in African Americans this difference is not statistically significant, though the patient group, as you can see, was relatively small, only 69 patients received active drug in the pooled data, and the magnitude of the effect was approximately comparable to other racial groups.

When you look at the three age strata that we examined, results were statistically significant in all three age strata.

Again, looking at the pooled data, and now comparing it by treatment status, of those who treated with over-the-counter medications only there was a

statistically significant benefit, of those who treated with any prescription drug, that is, prescription drug alone or in combination with OTC, again, there was a statistically significant treatment effect.

It's interesting to note that there was a 14 percent drop in the placebo response rate in the group that used prescription drugs, so that the magnitude of the effect size here, the difference between active drug and placebo, is actually impressive.

In the group that had menstruation at baseline, again, treatment was effective, treatment was effective in people who had migraine without aura, as well as individuals who had migraine with aura, and the one place where I think you see a significant diminution in treatment in a subgroup is for the migraine with aura group, although the study wasn't designed to make this contrast the difference between the without aura group and the with aura group is significant, even though treatment was beneficial in both groups.

Moving on to a summary of adverse events in the study, overall I think you'll see that the ARE profile here is strikingly similar to what Doctor

Hoffman showed you for the tension-type headache studies, in that the side effects in the study were generally mild and self-limited. Eighteen percent of Excedrin treated patients and 10.8 percent of placebo treated patients had one or more adverse experiences that was a statistically significant difference, and when we looked at AEs that the study investigator judged to be possibly or probably drug attributable, again, there was statistically significant differences. There were no serious adverse experiences in the entire clinical trials program, either for the Excedrin treated patients or the placebo treated patients.

When we examined AEs by body system, when the ARE occurred in more than one percent of the sample we see that there were -- that 1.6 percent of the sample had cardiovascular AEs, that five of those events were tachycardia, again, tachycardia is a well known side effect of preparations of this kind, and in every case the tachycardia was of short duration, self-limited and did not require specific therapy.

There were digestive system symptoms associated with use of active drug. Nausea was more common in individuals who received active drug, and the proportion of people who had nausea as an ARE is

actually similar to what you saw for the tension-type headache study.

It sometimes causes questions about nausea, you know, nausea as an ARE, in a condition which is defined in part by the presence of nausea sometimes raises questions for people. The nausea here was treatment emergent nausea, or an exacerbation of nausea following treatment, and, you know, I think it's a medication side effect.

Abdominal pain did not differ in the two groups. The incidence of vomiting did differ. It's interesting to note that there was actually more vomiting in placebo treated patients. It may be that vomiting is a manifestation of ongoing attack, and that the higher prevalence of vomiting in placebo treated patients reflects the absence of the treatment effect in the placebo treated group.

Dizziness and nervousness were more common in patients treated with Excedrin than in those treated with placebo.

Well, to summarize the results of the clinical program then, first focusing on the study population, it's my belief that the methods we used allowed us to successfully recruit a wide spectrum of subjects with migraine headache, for whom an OTC

analgesic were appropriate.

Certainly, the vast majority of subjects enrolled in the study used OTC medications. The enrolled subjects clearly had a diagnosis of migraine confirmed by IHS criteria, and further, the treated attacks were migraine.

The majority of subjects were already treating their migraine headaches with OTC analgesics, 65 percent with OTCs alone, and 21 percent with OTCs in combination with prescription drugs.

In terms of efficacy, Excedrin ES was an effective treatment for the relief of migraine headache pain. There were significant differences, both on the responder endpoints and the Pain Intensity Difference endpoint, not only at two hours, which was the time point we designated as our primary endpoint, but at all time points from one hour to six hours.

In addition to that, Excedrin was effective in improving the symptoms associated with migraine, including functional disability, nausea, photophobia and phonophobia.

In terms of safety in the context of this clinical program, Excedrin was safe and well tolerated. There were no serious adverse experiences reported at all. The adverse experiences that were

reported were mild, self-limited, and similar to both prior clinical trials and the sorts of symptoms that occurred in the post-marketing surveillance database.

So, in summary then, I think these three studies provided consistent evidence of the safety and efficacy of Excedrin in the treatment of migraine headache pain.

I'd now like to introduce Sion Boney, who is President of Bristol-Myers Products. He's going to discuss with you the label comprehension study, and some educational programs.

MR. BONEY: Thank you, Richard.

Good morning. We are obviously very excited by the results of the clinical trials which Doctor Lipton has just presented to you, affirming Excedrin's safety and efficacy in migraine headaches.

We believe Excedrin can play a very important role in the lives of many of the 23 million Americans who suffer from migraine headaches, and who often turn to OTC pain relievers as an initial line of relief.

Since what we are proposing to you today amounts to a specific change on the label of Excedrin, to include now the relief of migraine headache pain in addition to the headache indication that is already on

the label, and a corresponding warning about when to see a doctor if pain is particularly severe, since that is what we are proposing, the Agency has asked us to study consumers' ability to understand this label change by measuring their comprehension of key label messages on the new label, as well as on our existing label, to make sure that in the absolute there's a high level of understanding and that the understanding is as effective in the new label as with the current label.

So, that's why we did the label comprehension study. I'll present in about five minutes a summary of that study to you, and then I'd like to spend just a few minutes after that talking about our headache education programs directed at consumers and professionals which we have conducted for many years, which we're very proud of.

The objective of the label comprehension program and study was to ensure that the new use warning is effectively communicated, that you should see your doctor if pain is so severe that you require bedrest, and secondarily, to ensure that the other warnings on the current label of Excedrin are not diminished when you add the migraine indication and the new warning.

This I know is difficult to see, but I just wanted to show you, this is the current label of Excedrin. This is the label that would change with the migraine indication, and the way we tested it was in the drug facts format, which as you know is part of the new FDA regulations that we'll be moving to, and we support that format. So, we tested the current label and drug facts. This is the indications section, and the only change is the addition of -- you see that the uses currently are for temporary relief of pain associated with headache and the other symptoms, and it changes to for temporary relief of pain associated with headache, including migraine headache. The change in the warning is, this is the section of the warning that exists on the current label, and on the test label we've added for headache, including migraine headache, that's accompanied by vomiting, you should see your doctor before you use it, and for headache, including migraine headache, is so severe that you require bedrest, that you should see your doctor before using the product, if that is your type of pain.

In addition, we wanted to ensure that the current warnings on Excedrin are not diminished when you add this new indication, and that, again, is to

see your doctor if your headac he, including migraine, is accompanied by vomiting, to ask your doctor after use if the symptoms, including headache pain, continu e or worsen, or if new or unexpected symptoms occur.

The methodology was, we did the stud y among migraine headache sufferers. These were self-report ed sufferers of migraine over the past fiv e years. Forty percent of those in the study ha d actually been diagnosed by a physician with migraine during this time. These were done in malls, in 3 2 locations dispersed across the country. There wer e 906 subjects, 748 random stratified by age and gender , and we added 158 supplemental subjects who were high school non-graduates. This is typically the sensitiv e area when you are measuring label comprehension, is by education. We wanted to supplement with a robus t sample of non-high school grads to ensure that th e communication was consistent regardless of education level.

Five hundred and 76 saw the test label , 340 saw the control. This was an open label study , meaning that just as in real life the person had the label in front of them when the questions were being asked of them, and open-ended, as well as closed-ende d questions were asked. Open-en ded questions were when

the interviewer asked a questi on and records whatever response is given unprompted, and closed-ende d questions, which are always asked afterwards, wer e multiple choice in nature.

And so, to the results. First off, th e new use warning is effectively communicated. Th e question, if your headache or migraine headache is so severe that you require bedres t, what do you do? The correct answer is to ask a doctor before use, and as you can see, whether on an open-ended basis or a closed-ended basis the scores were quite high in the abso lute, which was the desirable outcome. Almos t nine out of ten subjects clearly understood to see a doctor if their pain was so se vere, and that was what we would have hoped for.

This result was true whether you wer e looking at high school grads or high school non-grads , same question, very high levels of comprehension i n the absolute to this important warning.

Now, looking at the current headach e warnings, which we want to make sure were no t dimini shed, if a headache or migraine headache i s accompanied by vomiting, what do you do? Again, the correct answer is to ask a doctor before use, and her e you see, both on an open-ended basis and a closed -

ended basis the scores also were quite high, and the desired outcome here is to attain a high score in the absolute, as well as to ensure that the test label, the new label, communicates as effectively as the current label. And, as you can see, that was achieved, and that is true whether you are looking at high school graduates or high school non-graduates, high levels of comprehension, no difference.

The other warnings, if the symptoms continue or worsen, or if new or unexpected symptoms occur, the correct answer is, ask a doctor after use, and regardless of open-end or closed-end for both of these questions, symptoms continue or worsen, or new or unexpected symptoms occur, again, very high levels of communication on this, both in the absolute and for the new label versus the current label, and this, again, was true whether you are looking at high school grads or high school non-grads, high levels of absolute comprehension and new versus control.

For the purpose of this presentation, in the interest of time, we have shown you just the data for the total population, as well as broken out by education level. We have lots of data broken out by other sub-populations, by race and gender, income levels and so forth. We'd be happy to share any of

this information with you. I can tell you that when you look across all the subgroups there are no important differences in communication among any of them, it is consistently high across all the different sub-populations.

So, in conclusion, the new use warning is effectively communicated. The addition of the migraine headache indication and the new use warning does not diminish the communication or the understanding of the other warnings that are already on the label, and comprehension is consistently high across key demographic groups and education levels.

I'd now like to turn just a minute to our education programs. Two points I'd like to make here. We've been doing these for many years, usually in a situation like this someone in my position would be promising you a lot of education programs that we would do if you approve the new drug or indication we were seeking. In this case, these are programs we have been running for several years. We have escalated our commitment to them year in and year out, and we will continue these programs and continue to increase our commitment to them, regardless of whether we get this new indication or not.

The other point is that there are a lot of

people who are interested in these programs and the education they get from them. We have enrolled over 1.6 million consumers into our headache education program, which we call the Headache Resource Center, we've enrolled over 45,000 health care professionals, including over 35,000 physicians, so there is a high level of interest. We continue to enroll both consumers and health care professionals into this program at a rate of over 3,000 calls on average per week.

There are many messages that we communicate here. Some of the key ones are, the lifestyle factors affecting headache, we encourage people to keep a headache diary, to find out what triggers their headaches, be it certain types of foods, or allergies, or environmental stresses, lack of exercise, these sorts of things. We help people to understand their triggers, to help them prevent future headaches. We teach them various approaches to treating headache, starting first with non-pharmacologic approaches, and if those don't work pharmacologic approaches. If those are used, the appropriate dosing of OTC analgesics, all OTC analgesics, not just our's, when to seek professional consultation and additional information sources that

they can go to.

This is a sort of map of all the differen t programs that are available, which we believ e encourages safe and effective use of all OT C medications for headache. The consumer programs are available to them through adve rtising and other forms of media. In fact, I noticed in this week's People magazine we have a full page ad about our Headach e Resource Center and inviting p eople to enroll and get educational information about how to diminish thei r headaches.

We send a lot of materials directly t o people's homes. We have a quarterly newsletter to th e people who enroll in the program. We send the m workbooks, headache management pamphlets, samples . These materials are also available in the store, a s well as interactive. We have a web site, an 80 0 number, and so forth.

As well to professionals, we have man y different outreach programs, continuing medica l education, newsletters, sympos ia, et cetera. We have a popular Allied Health Program, particularly focusin g on workplace wellness. You heard a lot of comment s this morning about the problem with headaches an d migraine headaches in the workplace, and we have a

popular program which helps co mpanies work with their employees to minimize the occu rrence of headaches and their debilitating nature, which several companie s have asked us to present to them.

We have a managed care program fo r patients and professionals, pr ograms for pharmacists, many different materials which physicians can hand ou t to their patient, a wide range.

These are just some examples of some o f the brochures and newsletters, videos which we mak e available to encourage safe and effective use of OTC medicines. We have included in your briefing boo k which you received from us some examples of th e educat ion materials, and when we get the labelin g comments that you have towards the end of the meeting we would be very happy if you have any comments t o make about any of the educational materials or an y suggestions for how to make them better, we woul d certainly appreciate.

These are just examples of some of th e materials that are made available to professionals an d some of the ways in which they can receive thes e materials.

So, in conclusion, as I said, this is an important education program which we've been doing fo r

several years. We will continue to do it at a very high level, regardless of whether we get the approval we are seeking. The educational programs will be expanded to further reinforce physician consultation when appropriate, to improve the management of headache pain, including the migraine headache pain, by consumers and health care professionals, and to continue to address specific information needs of headache pain sufferers, including migraine sufferers.

Thank you very much for your attention. I'd now like to ask Doctor Hoffman to come back. We will do a brief conclusion, and then we'd be delighted to take any questions that you have.

Thank you.

DOCTOR HOFFMAN: Thank you.

I would now like to summarize the findings of our program and address the FDA questions.

Again, just to review, the requested regulatory action is for the OTC Excedrin ES. Please recall that this is not an Rx to OTC switch, and this is just an additional indication for Excedrin. And, specifically, it's to change the OTC headache indication from temporary relief of the pain associated with headache to temporary relief of the pain associated with headache, including migraine

headache pain.

The FDA questions:

1. Is the pain of migraine an appropriate OTC indication?

2. Has the applicant provided adequate evidence to support the effectiveness of Excedrin in an OTC migraine population?

3. Has the applicant provided adequate information to support the safe use in an OTC migraine population, and provide other labeling recommendations?

The pain of migraine is an appropriate OTC indication. We discussed this during our presentation. Headache pain is a long-established OTC indication, headache pain including migraine headache pain is symptomatic, self-recognized, acute and self-limited, and episodic, and certainly appropriate as an OTC indication.

Many migraine sufferers already use OTC analgesics. As we've mentioned in a number of studies and surveys, greater than 60 percent use OTC analgesics.

Specifically, OTC Excedrin is an appropriate treatment option for the consumer with migraine headache pain. It's effective for the pain

of both migraine and tension-type headaches at the same dose, so there's no need for a consumer to differentiate the headache type. OTC Excedrin has been indicated and used by consumers for relief of headache pain for greater than 19 years. The current labeling, which has been there for a long time, successfully communicates key safety and usage messages to consumers, and the new labeling that we will add will strengthen these warnings.

The clinical studies support the effectiveness of Excedrin in the OTC migraine population. The three clinical trials, 840, 841 and 842, each demonstrated the effectiveness of Excedrin in the relief of migraine headache pain, as I said, in each of the studies, as well as the pooled data.

On this slide now, there is the pooled data for the two prospectively defined primary endpoints, and I'm showing you data from the 1/2 hour point to six hours, with the two hour point being the primary time point. But, as you can see, very robust, clear treatment effect for the Excedrin in this population.

Of note, this information has been submitted to the -- accepted by the Archives of Neurology, and is currently in press.

Excedrin was also effective in improving the symptoms associated with migraine headache in each study and the pooled data. Doctor Lipton showed you data on photophobia, phonophobia, nausea, disability, that was also very positive.

We studied a broad spectrum of subjects for whom OTC analgesics are appropriate. Again, Doctor Lipton mentioned the recruitment techniques used and the population recruiting, which helped enable a group of OTC patients, regardless of physician consulting status.

Additionally, as we said, in any way we looked at the data, clearly greater than 60 percent of these patients were using OTC analgesics.

Additionally, subjects were IHS diagnosed migraine sufferers, and the treated headache was a migraine, again, an important consideration by the FDA at the start of the program.

Clinical studies and post-marketing surveillance support the safety of Excedrin ES in an OTC migraine population. We showed you data on the tension headache model, in our post-marketing surveillance, as well as in the migraine program.

Adverse experiences were mild, self-limited and similar to that expected from these single

components, the Aspirin, caffeine and acetaminophen, and overall had an excellent profile.

With regard to revised labelin g, warnings were strengthened to direct co nsumers to see a doctor before use if the headache is accompanied by vomiting or so severe as to require bedrest. The results o f the label development program demonstrate d comprehension of all major warnings in the test label , and that the addition of migraine headache pain to th e indication section did not diminish understanding of the existing warnings.

The education program, Mr. Boney ha s spoken about this and Bristol-Myers has an ongoing OT C comprehensive educational program for headach e sufferers, and the headache tr eated medical community has already reach 1.6 million consumers and ove r 46,000 professionals, health care professionals.

Bristol-Myers will continue to expand thi s program by adopting more programs, to includ e responsible treatment of migra ine headache pain in an OTC setting.

Finally, conclusion, pain of migraine is an appropriate OTC indication. Studies 840, 841 and 842 demonstrate the effectiveness of Excedrin in a population likely to use OTC analgesics to trea t

migraine headache pain. Clinical studies and post-marketing surveillance support the safety of Excedrin as an OTC product. The labeling and educational programs successfully communicate key safety and usage messages to consumers.

You've heard a number of messages from consumer groups and headache interested consumers early in this presentation that underscored the importance of treating migraine headache pain and providing an option to consumers.

Finally, approval of OTC Excedrin ES for the relief of migraine headache pain would provide consumers with a safe, proven effective, widely accessible and inexpensive treatment option with comprehensive labeling.

Thank you.

I'd like to ask Doctor Lipton to join me for some --

CHAIRMAN D'AGOSTINO: What I think I will do, actually, thank you very much for the presentation, but this might be a good time for a break. Let's take a 15-minute break, and please be back at 10:45, and we'll begin immediately at 10:45 with the questions.

(Whereupon, at 10:39 a.m., a recess until

10:55 a.m.)

CHAIRMAN D'AGOSTINO: We've heard the presentation from Bristol-Myers, quite complete presentation discussing the issue of the OTC population, the clinical trials, and the label comprehension studies. Now, I'd like to invite the committee members, excuse me, I'd like to invite the committee members to ask questions.

Sid, do you want to begin that?

DOCTOR GILMAN: Yes. I have two questions for the sponsor. The first concerns the three studies, the second concerning the labeling of the product. Perhaps, I'll just ask one at a time.

First, with respect to the three studies. You mentioned diabetes mellitus and hypertension as exclusionary criteria, but I did not see evidence that the patients in these three studies were actually examined with a physical examination or neurological examination. A particular study, 840, where you did an epidemiologic study, you did ascertain that patients had a history of headaches that would suggest migraine, but did you actually have a physical examination to ascertain the level of blood pressure, look for papilledema, and do the rest of the neurological exam to be sure you were not dealing with

secondary headache?

DOCTOR LIPTON: Yes, I apologize for not making that clear. The patients in 840, or 840 patients were recruited using the population methods. In the other studies, 20 percent were recruited using population methods, but once patients arrived in the clinic every patient had a history taken by a physician, who did a semi-structured interview, and every patient had a complete general medical and neurologic examination. And, I'm sorry if I didn't make that clear.

DOCTOR GILMAN: Well thanks, I didn't see it in the briefing book either, but I'm glad to know that.

Second question is, as we heard, and I think most of us know, people with migraine headaches frequently self-medicate with over-the-counter medications, often they will take medication every day, whether or not they have pain, and a well-known consequence of this kind of behavior is analgesia-induced chronic daily headaches. There's a large literature about this phenomenon.

The sponsor mentions in the labeling material, do not use for pain of more than ten days, unless directed by a doctor. Knowing that patients

with migraine and other kinds of headaches commonly treat daily, even when they don't have any headache, have you considered adding an additional warning, something to the effect that prolonged use of this product can lead to chronic daily headache?

DOCTOR LIPTON: You know, it's certainly true in clinic-based samples in headaches of specialty practice, for example, that a high proportion of the patients treat headaches every day. For migraine sufferers, in particular, in the community that's actually not a very common pattern at all.

I certainly agree with your point that medication over use needs to be limited, and that medication over use is an issue. You know, my initial thought would be that the advice on the label, not to use the medication for more than ten days without physician advice, would be sufficient, but --

DOCTOR GILMAN: Well, it says for pain more than ten days, it doesn't say, don't use it more than ten days.

DOCTOR LIPTON: I see, so your concern is that people are simply taking the medication on a daily basis for absolutely no reason at all.

DOCTOR GILMAN: That's frequently the case, yes. It's well known, well known among headache

sufferers.

DOCTOR LIPTON: Yes, and I guess my comment would be that I'm not sure that's a common phenomenon, I think it's not a common phenomenon, but to the extent that it is an issue, it's an issue for all OTC analgesics, independent of the addition of migraine to the label. So, I guess, to the extent that that's a serious concern, I think it's a generic concern for all OTC analgesics that should be looked at.

CHAIRMAN D'AGOSTINO: Yes.

DOCTOR ZIVIN: In your trials, you mentioned that you thought it was unethical to treat patients with severe headache problems, and so the patients who had severe migraines were excluded from the protocol. Nevertheless, the label that I saw does not indicate that you have warned the patients that for severe headaches that this drug is likely to be ineffective, or at least was not tested. Can you tell me a little bit about how you plan to deal with that?

DOCTOR LIPTON: Yes, you know, one issue is what's meant by severe, and , you know, when people talk about severe migraine they mean one of three different things. Sometimes they mean severe pain , and patients with severe pain clearly were treated in

the trial, and, in fact, a third of treated attacks had a baseline intensity that was rated severe across the entire program. So, in terms of efficacy for severe pain, I think the program demonstrates it.

A second thing people sometimes mean when they talk about severe migraine is disability, and in the context of this program the exclusion was for people who usually required bedrest, who were usually so disabled that they required bedrest, and those people were not included in the clinical trial, and the label advised individuals who usually require bedrest to not take medication without the advice of a physician. So, there's a compatibility between the inclusion/exclusion criteria of the study and what's on the label.

The third thing people mean by severe sometimes is treatment refractoriness. They mean, you know, I get these migraines, and no medication works. In the context of this particular clinical trials program, there was no exclusion based on medication response at all, just an exclusion based on usually requiring bedrest or vomiting more than 20 percent of the time.

DOCTOR HOFFMAN: Perhaps, if you'd like, we could show you some of the data on the more severe

patients as well.

CHAIRMAN D'AGOSTINO: Would you like it? Why don't we move on. David, do you have a question?

DOCTOR DRACHMAN: Yes. You haven't done the study, but have you looked at the data regarding ergot or the triptans, and how much more or less effective Excedrin is vis-à-vis those medicines.

DOCTOR LIPTON: Yes, you know, as you said, this wasn't a comparative trial, so, I mean, there's no direct way of commenting.

In the 12 percent of patients who took rescue medication, about 30 rescued with Sumatriptan, and I believe approximately another 30 rescued with ergots, but, you know, there's no direct comparative data.

You know, I also want to comment that, because we excluded the most disabled headache sufferers from this trial, the patient population included in this study, or these studies, isn't really comparable to the patient population enrolled in the Sumatriptan trials. The actual magnitude of the treatment effect, the difference between active drug and the placebo, is similar to Sumatriptan, but I wouldn't want to make an inference about that because of the difference in patient populations.

DOCTOR DRACHMAN: The other is sue is that these people were all known to be migraineurs. Now, undoubtedly, a lot of the people out there regar d migraine as being a very bad h eadache, and one of the things we might worry about is that people wit h ruptured aneurism, subdural hematomas, meningitis , brain tumors, and so on may fi gure, well now I've got a real migraine, maybe I'd better try this drug, whic h has that as one of the indications.

I sort of wondered whether a number o f other warnings might not be included in your labeling . For example, headaches that ar e new, that begin after the age of 40, would be one that one would thin k about. Headaches associated with a stiff neck , headaches that awaken one from sleep or are wort h lying down, and headaches that begin following a head injury, now that gets to be sort of a medical text , but one wonders whether you need not include some of those warnings with the drug.

DOCTOR LIPTON: Yes. Certainly, it is an undesirable outcome of people with secondary headache disorders, treat with an over- the-counter medication, and so delay seeking care.

I would point out that headache has been an OTC indication, you know, for many decades, so to

a great extent the problem exi sts already, whether or not migraine is added to the l abel, and my view would be that the incremental risk of adding migraine to th e label is low.

You know, if you are saying that -- yo u know, and there are, essential ly, two ways of dealing with the issue you raise. One is through publi c educ ation, and Mr. Boney has shown you educationa l materials that actually contains all of the warnings that you mentioned and some other ones that you didn' t mention. So, one strategy is through publi c educat ion. The second strategy is to actually hav e the warnings on the box, and what would be the mos t effective method for communicating those messages, yo u know, I'm not sure, but I do t hink the issue that you raise is an issue pertinent to OTC headache i n general, and not just OTC migraine.

DOCTOR DRACHMAN: Well, yes, b ut you know that a year doesn't go by that we don't see several o f these in our emergency room, people with sub - - hemorrhage who have treated it with Aspirin, that's a really dangerous way of treating it. So that, on e wond ers whether simply by using the word migraine , which to the lay public may mean a really ba d headache, you are inviting that a little bit more.

DOCTOR HOFFMAN: I think you bring up a very good point, and both Mr. Boney and Richard have mentioned some of the educational information that's already ongoing, and actually pretty much mimics a lot of the things you just said, and I think it's something that we need to talk about as we get to labeling and see the relative merit of that compared to the current labeling.

CHAIRMAN D'AGOSTINO: We will have labeling recommendations, I think that's going to be quite important.

Doctor Brass and then Doctor Diamond.

DOCTOR BRASS: I have a couple --

DOCTOR DIAMOND: Can I just answer Doctor Drachman for a minute, please?

CHAIRMAN D'AGOSTINO: Please, do, yes.

DOCTOR DIAMOND: I don't mean to interrupt, I'm sorry.

CHAIRMAN D'AGOSTINO: No, please do.

DOCTOR DIAMOND: Okay.

There was a very interesting study about your first question that was done in Europe by Doctor Tfelt-Hansen, and he did this study on 421 people. It's comparable, he used lysine acetylsalicylic acid and metoclopramide and comparing it with Sumatriptan,

and had very effective results with the combination. So, I just want to answer your first question.

I've got my own questions to ask Doctor Lipton and the group, but I just wanted to give you that information. If you want, I'll be glad to give you the article, I brought it me with me because it was interest.

CHAIRMAN D'AGOSTINO: Very good.

Doctor Brass will ask a question, and then Doctor Diamond.

DOCTOR BRASS: I have one question about the study, and then a few questions about the OTC appropriateness.

The study question has to do with rescue medications, and it wasn't clear to me what the protocol content was for rescue medication, what was permitted, what was used, and the group differences in rescue medications.

DOCTOR LIPTON: Right, 12 percent -- in the pooled data, 12 percent of patients treated with Excedrin, and 28 percent of patients treated with placebo rescued.

We asked patients not to rescue if they could possibly avoid it prior to the two hour primary efficacy time point, and, in fact, patients who did

rescue prior to that endpoint were excluded from, you know, the analyses that I showed you.

Can I have the back-up slide on rescue medication, please? This slide actually will summarize for you by class what rescue medications people took. And, of course, you know, one issue with rescue medication is that observation points following rescue are influenced by the effect of rescue medication.

So, what we are looking at is rescue medication for OTC products and prescription drugs for the Excedrin group and the placebo treated group. You see that the placebo group is much more likely to rescue, that the majority of patients who rescued, rescued with over-the-counter products, rather than prescription drugs, which is compatible with what they told us, that they usually treat their migraine headaches with over-the-counter products rather than prescription drugs. And, OTC analgesics was the single, most common category, with acetaminophen and Ibuprofen products being, you know, the most heavily represented products in that analgesic group.

DOCTOR BRASS: Thank you.

One of our concerns, one of the issues we are going to have to deal with is whether patients can

self-recognize and self-diagnose this disorder. And, in that context, I'd be interested in any information you have on screened failures, particularly people who presented as saying I have migraine and I'm eligible for this study, who, in fact, were not for any reason.

DOCTOR LIPTON: Okay. First I'd like to respond to the assumption your question makes, and then I'd like to respond to your question.

In terms of the assumption your question makes, in my view, you know, migraine being an OTC indication does not require that consumers are able to self-diagnose, and my reason for making that statement is that, you know, currently, people with migraine are self-treating with over-the-counter medications, and if someone has migraine and they make a mistake, the concern is that they have a secondary headache, as Doctor Drachman suggested. If someone thinks they have migraine, but they really have tension-type headache and they take Excedrin, or if they make the mistake in the other direction, that's a mistake that does no harm, because if treatment works they are satisfied, if treatment doesn't work they are directed to consult their physician.

In terms of the accuracy of self-identified migraine, in this study people were

enrolled, not based on self-id entifying migraine, but based on our interviewing them about headach e symptoms, and then assigning an IHS based diagnosis.

We have examined, in another stud y actually, in the American Migraine Study, the accurac y of M.D. diagnosis versus IHS diagnosis, and th e accuracy of self-recognition of migraine in th e absence of medical diagnosis.

DOCTOR BRASS: No, I understan d that, but I'm specifically interested in the screened failures in these studies, who the patients, by phon e interv iew, were thought to be eligible, who on exa m turned out not to be eligible.

DOCTOR LIPTON: Okay, yes, I'd be happy t o show you that data. Can I have the back-up slide tha t begins with the recruiting interview process?

While they are looking for it, though, I thou ght your interest was in the accuracy of self - identified migraine, and in terms of that, you know, I would suggest, you know, a better data point i s looking at people who said the y had migraine but have never been diagnosed by a doctor, and then the result s of a clinical assessment, and when we've done that we find that self-identified migraine is relativel y insensitive, the sensitivity i s about 40 percent, but

the specificity is about 85 percent.

And, interestingly, when we compare self-reported physician diagnosis with IHS diagnosis, sensitivity and specificity is about the same.

Actually, the slide I'm looking for is the second of the flow diagrams. I'm sorry that I don't remember the number.

Okay, so this actually summarizes the population-based recruiting interviews that we did. It may take us a little longer than it's worth to go through here, but we completed a total of 50,000 -- approximately 50,000 screening interviews, we identified 4,650 odd subjects who, on preliminary first-cut analysis we thought had migraine, of those 1,043 refused further participation, there were 579 who moved or whose phones were disconnected, there were 86 we were unable to locate.

We then completed recruiting interviews on 2,947 patients, and ended up identifying a study sample of 868 who based on the phone we thought were eligible for study. Of those, 197 either missed or refused to allow us to schedule appointments for them, 671 actually completed clinic visits, and of those 232 screen failed for one reason or another, giving us our enrolled sample of 439 in the population-based study.

And, if you are interested in seeing the reasons for screen failure, if you could put on slide 237, please.

DOCTOR BRASS: I'd also be interested in 236, as to why the phone interview didn't work.

DOCTOR LIPTON: Okay.

Now, this is a slide that shows the distribution of recruitment interviews in the 2,947 people who agreed to be interviewed for the study, and we found them ineligible for low frequency, for diagnosis in 616 out of the 2,947, because they had allergic reactions to study medication in 120, because of health reasons in 220, because of concomitant meds that were exclusions in 253, and for other reasons, and of those 509 other reasons the most common were either that their headaches were severely disabling, or that they vomited more than 20 percent of the time.

DOCTOR BRASS: Do you know if those 616 patients who were excluded based on diagnosis thought they had -- stated they had migraines up until that point?

DOCTOR LIPTON: Well, actually, only -- I actually don't know the specific number, but it's a minority of those individuals who were excluded who believed they had migraine.

DOCTOR BRASS: Okay.

And, can I ask just a couple very quick labeling questions. First, I actually agree with Doctor Gilman's point, that migraine is different, because it is a chronic condition, where patients may be viewing the medication in terms of a chronic condition, whereas, the existing labeling is for episodic conditions, so I do think the chronic use issue is a more important one.

And, my final comment is, I have serious concerns about the "label comprehension study" demonstrating any of the points that it was purported to demonstrate. If, in fact, the points that you have added to the label you truly feel are important for the consumer to understand, then testing their comprehension of it in a cued, open book exam doesn't seem to me to be the way to test whether the consumer, picking up the medication off the shelf, will understand independently and extract that information.

And, I have serious concerns about whether that test has meaningful parameters.

DOCTOR LIPTON: Let me respond first to the issue of migraine as a chronic disease, or migraine as an episodic disease. You know, of course, the most striking manifestations of migraine are the

episodic attacks of pain, and, you know, my personal view is that there's a severe spectrum of migraine where it's best to conceptualize it as a chronic disease where the attacks are frequent, where there's a diminution in quality of life between attacks, but there's also really a spectrum of migraine where the attacks are relatively infrequent, they occur one or several times a month, there aren't disabling consequences, and the most notable manifestations are occasional episodic attacks of self-limited pain that respond to over-the-counter analgesics.

So, I guess my view is a little more complex than your's, though I certainly agree that the chronic spectrum of migraine exists, you know, that's, I don't think, the spectrum that we're talking about. The label comprehension may be --

MR. BONEY: We simply felt that the most effective way to do the research was to try to replicate the real world situation that people are in when they have questions about the product they are taking. In the real world, if they have a product which they are considering using and wondering how to use it or when to use it, they have the label in front of them, they consult that label to make a decision as to whether this is what I should be using now, or

should I be doing something el se. So, we were simply trying to replicate as closely as possible wha t happens in real life.

DOCTOR HOFFMAN: Just one other brie f comment. In terms of the actual labeling requested, it's for the temporary relief of pain associated with headache, including migraine h eadaches. I think your point is a good one, in terms of the spectrum o f migra ine, but we are really talking about tha t headache pain.

CHAIRMAN D'AGOSTINO: Doctor Diamond, do you have questions?

DOCTOR DIAMOND: Yes, I've got som e questions.

Number one, how did you measure you r endpoint, did you use a stop watch, or did you jus t ask the patients to time it themselves, or did you us e the Laska method, or what did you use, Richard?

DOCTOR LIPTON: Yes, no, there was no -- there was no stop watch, and there was no study clock , the patients had a diary card, which is actually i n the packet you have in front o f you. The time points for all the assessments were written on top of th e diary card, and the patient was simply trained t o record the assessments at the appropriate time point

using a clock that they had at home.

DOCTOR DIAMOND: Secondly, do you feel that the six hour relief curve that you showed, that it was due basically to the abortive effect of the medicine? These people were having -- you know, there's all different degrees of migraine, there are people that get attacks that last 24 hours, we do know that the non-steroidals can abort attacks or cut them short, and do you feel that the six hours were actually aborted attacks, or do you think that it was strictly pain relief that occurred?

DOCTOR LIPTON: I don't really have the data to make that differentiation. Certainly, for a number of migraine medications, patients experience pain relief and then develop recurrences subsequently. That wasn't measured in this study, this study was designed as an acute dosing study.

DOCTOR DIAMOND: All right.

And, my other concern I go with Doctor Gilman on, and I'd like to say, you know, the majority of the people that have migraine, and they maybe get two attacks a month, sometimes you have people with six or eight attacks a month, we who have headache clinics, or neurologists who see patients with headache, sometimes see a very skewed population, and

we see a great number of peopl e with daily headaches, the abusers, and all these type of patients.

I don't think that we should mix thes e type patients with what we are talking about righ t now. Doctor Gilman, I appreciate your comments on th e warning, and I think that mayb e on the labeling maybe we should say that if your mig raine is over 48 hours, you should see a physician if your migraine is over 4 8 hours, because if you are dealing with a migraine tha t that's prolonged it's not going to get the benefi t from any continuation of the drug. And, this is m y only objection to the labeling.

DOCTOR LIPTON: Yes, I think that's a well-taken point, and I'm not -- you know, I think th e optimal labeling is something that's going to need to emerge from discussions, and certainly that's a n important suggestion.

You know, just to emphasize the issue tha t you raised, which is really an issue of selectio n bias, you know, I showed you that most people wit h migraine are not currently consulting, but of thos e who do consult most people consult in primary car e settings, of consulters ten to 15 percent se e neurologists, only two percent see headach e specialists, so that group of patients who you and I

see in our sub-specialty practice does not look like the headache sufferers in the communities at all. I mean, I think what you said is really quite important.

CHAIRMAN D'AGOSTINO: Any comments over here?

Lynn.

DOCTOR McKINLEY-GRANT: I guess this is in line a little bit with Doctor Diamond's question, but I just wanted clarification. Did you look at the timing of the onset of the headache to when they took the Excedrin?

DOCTOR LIPTON: Yes, the way the study was designed is that patients were instructed not to take medication until they had pain that was at least moderate, and there was also an algorithm on the front of the diary to make sure that the treated attack was migraine.

The clock started at the time people took study medication, the time from onset of headache to taking study medication wasn't measured in this study, though in studies that look at earlier treatment the general pattern is that earlier treatment is even more effective than waiting until moderate pain with full-blown migraine symptoms take hold, but that's not something we measured here.

DOCTOR McKINLEY-GRANT: Okay.

Did you have plans to include that in the education about taking the medicine?

DOCTOR LIPTON: That patients should --

DOCTOR McKINLEY-GRANT: That who take the analgesics earlier tend to get a better response, and it might be the abortive effect of the migraine?

DOCTOR HOFFMAN: We have information, you know, sort of general, very good information about sort of prophylax in terms of headache triggers and why people that have migraine, what they should look out for. I think that's a good suggestion to look into that, that aspect, there may be something in that program already, but make sure that's clear.

CHAIRMAN D'AGOSTINO: Mary Anne.

MS. KODA-KIMBLE: I wonder if you have any data regarding the efficacy of Excedrin ES in migraine versus garden variety headache. And, the reason I ask this question is because, if it's less effective I would guess that the behavior of the patient would be to rescue, and you've got a pretty good dose of acetaminophen and Aspirin here, and what will they rescue with, and what are the risks of rescuing with a similar medication and over dosing on -- potentially over dosing on Aspiring and/or acetaminophen?

DOCTOR LIPTON: Actually, I lost the connection between the first half of the question and the second half, I'm sorry.

MS. KODA-KIMBLE: The question is, do you have any evidence -- what is the data regarding the efficacy of Excedrin ES in migraine versus garden variety headache?

DOCTOR LIPTON: Well, yes, I mean, there are no direct comparative studies, but there have been well-designed placebo-controlled trials in tension-type headache which show that Excedrin is a very effective treatment for tension-type headache, and those studies were published as a large series by Migliardi a couple of years ago. I don't know if we have back-ups on those or not.

But, I mean, there is a compelling body of evidence of --

MS. KODA-KIMBLE: And, your study did show that there were patients who rescued. I mean, you specifically told them not to rescue, to try not to rescue, but the behavior was, is that patients did rescue if they didn't respond, correct?

DOCTOR LIPTON: Well, yes, you know, first of all, in the context of a clinical trial, of course, half the people are getting placebo, so we have to

permit rescue. Twelve percent of the patients treated with Excedrin took rescue medication. We asked them to try to wait beyond the two hour assessment point, because that was the per protocol primary endpoint time, and almost everyone did.

DOCTOR HOFFMAN: Can I just see slide L-6, tension-type headache Pain Intensity Difference, PID from one to four hours? Okay.

This is the tension-type headache studies that we talked about before, and as you can see there was efficacy at all those time points.

DOCTOR LIPTON: You know, actually, it's interesting to note that the actual magnitude of the Pain Intensity Difference at two hours in this model is quite similar to the magnitude of the Pain Intensity Difference with migraine, though the placebo Pain Intensity Difference is higher here, reflecting the fact that migraine is actually a better pain model than tension-type headaches.

MS. KODA-KIMBLE: I have another question.

You did some epidemiologic studies on migraineurs, generally?

DOCTOR LIPTON: Yes.

MS. KODA-KIMBLE: In that particular study, did you ask about drug taking patterns and

behavior in those patients? I know that you said that they took OTCs, but I'm wondering about Doctor Gilman's question, how many of them had the habit of taking over-the-counter medications on a daily basis or chronically?

DOCTOR LIPTON: We actually asked questions about attack frequency, but we did not ask questions about frequency of medication taking, so I don't specifically have data on that point.

MS. KODA-KIMBLE: And then, finally, I wonder whether the company has any data on caffeine withdrawal headaches, secondary to the chronic use of Excedrin ES.

DOCTOR LIPTON: Well, you know, I mean there's no question that, you know, caffeine withdrawal does occur, and there's no question that a prominent feature of caffeine withdrawal is headache. I mean, that's probably one of the more common causes of the so-called weekend headache syndrome, where people sleep through their morning coffee on Saturday morning and then awaken with a headache.

I'm not aware of any specific data looking at Excedrin. There are obviously many caffeine exposures that are a lot more prevalent than Excedrin in the population.

CHAIRMAN D'AGOSTINO: Doctor Luthra.

DOCTOR LUTHRA: I wanted to kind of just follow up on the same theme that we are talking about. When you say that 2/3s of the patients with migraine are taking over-the-counter medications for pain relief, and they are not seeing physicians, to me it suggests that they are getting adequate relief with what is available to them. And, it becomes important to understand what exactly are they using.

To sort of come back to the study that you have done, in the number of patients in the placebo group did take rescue medicines, did you have any data on what type of medications, other than the broad category, you already showed the data that they took enceds, but do you know what enceds did they take and what percentage of those patients took Excedrin?

DOCTOR LIPTON: The data is available in the OTC group, far and away the most commonly used enced was Ibuprofin, you know, not surprisingly reflecting patterns of use.

There were some patients who took Excedrin as a back-up medication. I think there were five or six patients in the study, I can look it up at the break and give you the information. I don't remember it precisely.

I actually can show you a slide on what people in the community with migraine are currently taking for their headaches, based on self-report, if that's of interest to you.

DOCTOR LUTHRA: I think those would be of interest.

DOCTOR LIPTON: Maybe we could find that back-up slide.

You know, the typical way of studying patterns of medication use is, of course, using IMS or prescription audits, and that misses OTC use, so the way we did this was by identifying migraine sufferers, by interviewing them about their IHS defining features, and then asking them what they took.

DOCTOR HOFFMAN: I think the other point is, there's readily a lot of use of different OTCs. We don't know -- whether -- there aren't any well-controlled programs that evaluate that, and I think that's a key concern that the patients have, that therapeutic option.

DOCTOR LUTHRA: When your studies were being designed, was there any consideration given to having a third arm with another standard analgesic?

DOCTOR LIPTON: The most important reason to do that, I think, would be to demonstrate that the

model was sensitive. You know, in the event that we failed to separate Excedrin from placebo, if we separated some atriptan from placebo that would provide us with comfort about the sensitivity of the model. In this context, I'm not sure that having an active comparator arm would have added a lot of value, though comparative studies are now planned now that there's evidence for efficacy.

CHAIRMAN D'AGOSTINO: Doctor Felson and then Doctor Tong.

DOCTOR FELSON: I guess I wanted to sort of lead in from Harvey's question about use of other analgesics. It sounds like the other analgesics people -- OTCs that people are using are GI safer than what you are proposing, Advil, Tylenol, and I'm concerned this is a chronic recurrent condition, and one of the elements of the treatment here is plain Aspirin, which we know to be among the most dangerous of non-steroidals in terms of GI side effects.

I'm wondering about -- I'm worried about chronic use of this, and its potential effect on ulcers and bleeding, and I realize there's a labeling thing here that says something about that, but I'm still quite concerned.

DOCTOR LIPTON: I mean what you say is

true, that the most commonly used -- actually, the most commonly used drug for migraine in the United States is acetaminophen, and various Ibuprofin and Aspirin combinations are also widely used. Caffeine combinations are widely used as well, it's, you know, six, seven, eight percent, I don't remember the precise number.

In terms of -- you know, in terms of the GI safety --

DOCTOR HOFFMAN: Yes, I have one other point, which is, we've got to step back to, obviously, Excedrin is an OTC that's been out there for at least 19 years at this formulation, and longer, and has an excellent safety profile, so I think we have to just think about this, this isn't a new entity, in terms of comfort. Clearly --

DOCTOR FELSON: But the truth is --

DOCTOR HOFFMAN: -- clearly, there's --

DOCTOR FELSON: -- this is a recurrent chronic condition, as many people have stated, so they are going to stick the bottle of Excedrin for treatment of their recurrent migraines in their cabinets, and they are going to continually draw from that.

DOCTOR LIPTON: Let me just make one

comment, and that is that the distribution of attack frequency as for tension-type headache and migraine are actually strikingly similar. So, you know, I'm not sure -- I'm not sure that in terms of frequency of use that migraine poses any incremental risk over tension-type headache in terms of profile. But, you were going to address GI safety, I think.

DOCTOR HOFFMAN: Well, that, too, but, again, in these studies there was about two patients that had 2.4 episodes a month, and the general group that we are talking about might be even less, so you remember we are capturing a little more of the severes to help in our efficacy trials.

DOCTOR LIPTON: Which is more of the frequent -- less of the disabled.

DOCTOR HOFFMAN: Right. In terms of GI safety, the data that we've shown you has shown over the time that we've collected data five GI bleeds that resulted in hospitalization, but no deaths, and, again, I think we know about Aspirin, we know about acetaminophen, caffeine, we have a good handle on them over their OTC use for many years. So, I think we have to look at the excellent safety we've seen in this condition, and certainly one where there is no other approved therapy.

DOCTOR FELSON: It's hard to believe that all of potential GI events were captured by those reporting, even a small percentage probably. One might get around this problem by suggesting in the labeling that people take this medicine with food, which admittedly may be difficult for some migraine patients, but that would lower the risk.

DOCTOR HOFFMAN: Right now the label talks about, again, if you've got ulcer disease or if you've got GI upset, that you should talk to your doctor. So, there are some of the mono graph labels, but those are great point.

CHAIRMAN D'AGOSTINO: Doctor Tong.

MR. TONG: In the product information we've been provided, I see Excedrin Extra Strength comes tablets, caplets and geltabs. Are you comfortable with the information you've given us that it applies to all three forms, or did the study patients only get the tablets, or did they get all three?

DOCTOR HOFFMAN: There was a biostudy that linked them. I don't have all the details, but I could get that for you, but as far as I know a biostudy was done to link all the information.

MR. TONG: Do you feel that there may be

differences here that might affect the impact on migraine?

DOCTOR HOFFMAN: None that --

MR. TONG: The rapidity of onset?

DOCTOR HOFFMAN: -- not based on our previous biostudies on this product.

MR. TONG: In this conversation around the table, we've used the word Excedrin, and in the OTC world we worry about label extensions. We have Excedrin PM. We have Excedrin Aspirin Free, and Excedrin Extra Strength, which is the topic of our discussions. How do you approach informing and advising patients that these are different Excedrins? You have Excedrin Aspirin free related to what Doctor Felson was asking, we get patients who say, 500 milligrams of Tylenol is equal to 250 of acetaminophen and Aspirin, and would that be equally effective for my particular migraine problem?

MR. BONEY: It's a good point. This, obviously, would only be a label change on Excedrin Extra Strength, and we do have an Aspirin free Excedrin product which has not been studied. We would be interested in, perhaps, studying that subsequently, but it would be clear as we market the product that it would only relate to this formulation, which is the

subject of the discussion this morning.

MR. TONG: So, you would say that the geltabs and the others are all going to have the same label?

MR. BONEY: Oh, yes, we -- when you look at all the chemical and pharmacokinetic characteristics of the geltabs, and caplets, and tablets, we've done, and certainly we can give you the data on this, that show that they are truly equivalent and with no differences between them, so, yes, it would be labeling that would appear on the different forms of Excedrin Extra Strength, but this labeling would not apply to Excedrin PM or to Aspirin Free Excedrin.

CHAIRMAN D'AGOSTINO: Lee.

DOCTOR SIMON: To expand a little bit longer, to pursue the issue of active comparators versus the effectiveness in this particular product, given the placebo response rate, and given the fact that you've predicated your presentation on the fact times have changed and we are better able to classify patients with these kinds of diseases, that given the fact that caffeine and Aspirin in this particular product run certain specific risks associated with toxicity, that it seems to me that I'm not yet

convinced that active comparators, as simple as Ibuprophen or acetaminophen alone will not give you equally as good responses with much more safety, and given the high incidence of the placebo response rate, which all of us who take care of chronic patients see in clinical studies, and I'm not surprised about that, I'm a little concerned that you have not presented any data about active comparators such as Ibuprophen or acetaminophen. And, I presume you are going to rely upon older data that demonstrates that the combination of acetaminophen, Aspirin and caffeine is a better effector in migrainous relief or headache relief than any one of those products alone, although I have to admit I'm somewhat ignorant of those particular studies, and I feel a little uncomfortable given the fact that you've predicated your presentation on this new way to classify patients, which may make a difference in patient response compared to studies from previous times.

And, given the toxicity, or potential thereof, I wonder how you can justify that.

DOCTOR LIPTON: Okay. That's kind of a complicated question. I mean, first let me address the IHS criteria that were the basis of this study. The IHS criteria were published in 1988. Since 1988,

they've been the basis of virtually every migraine clinical trial and virtually every epidemiologic study that's been conducted in the United States and in Western Europe. So, our data about Sumatriptan and other gold standard migraine drugs are, in fact, predicated on this classification system. It's a classification system for a symptom-based condition, it admittedly contains some arbitrariness, and there are individuals who fall on one side or the other of a boundary, but, you know, it's an incredibly useful tool, and it's the tool we used.

You know, in terms of the need for comparator studies, you know, my take is that this program of research demonstrates that the drug that was studied, or the combination that was studied is a safe and effective treatment for migraine. There may well be other safe and effective treatments in the world. I'm certainly interested in seeing data on them. I'm not sure that it is the obligation of the study sponsor to study all of those treatments before coming forward with this comparative data.

You actually had a third question and I lost track of it. I'm sorry.

DOCTOR SIMON: No, what I was really wondering was why an active comparator that may be

potentially safer, based on the constituent parts, could have been used to justify the continued use of the combination under these new criteria, which are appropriately to be used.

DOCTOR LIPTON: So, your question is really why wasn't the factorial design -- why wasn't a factorial study conducted.

DOCTOR SIMON: Right.

DOCTOR LIPTON: You know, I guess the answer to that is that, you know, caffeine is a well known analgesic adjuvant. There have been, you know, numerous studies that have demonstrated its efficacy as an analgesic adjuvant across a broad range of pain models, and in addition to that the focus of this program was on adding a new indication to a currently marketed product, so the question that the study asked was, is this marketed product that's already used for tension-type headache, that's already used for migraine in fact, safe and effective in migraine, and the program was designed to answer that narrow question, based on the established efficacy of caffeine as an analgesic adjuvant among other things.

CHAIRMAN D'AGOSTINO: Patricia.

DOCTOR McGRATH: Thank you.

I'd just like to know, you had presented

data on some of the subgroup analyses and I wondered if you had done those on pain intensity, the two levels, and on frequency at enrollment into the study, since it varied from about one attack every two months up to under six a month if you had look at differences in efficacy as a function of frequency and intensity.

DOCTOR LIPTON: Yes, can we have the back-up slide that shows treatment effects as a function of baseline pain intensity?

CHAIRMAN D'AGOSTINO: Let me add a third slide that you might look at. The subjects were not supposed to be functionally disabled, yet 30 percent were. It would be nice to see the slides of those who were not functionally disabled, because that's what your label is supposed to be directing on, and then also those that were, how much of the study is being driven by them.

DOCTOR LIPTON: Let me respond to that in a second. What we are looking at here is a proportion of respondents in a group that had moderate pain at baseline and in a group that had severe pain at baseline. If you look at the two hour time point, which is the time point of primary interest, the overall response rate was higher in the group with moderate pain than severe pain, though at least part

of the reason for that is that this endpoint is defined as the proportion of patients who make a transition from severe or moderate pain to mild or no pain.

So, if you have moderate pain and you have a one point change in your pain scale, that's a response, whereas, if you have severe pain you need to have a two point change in your pain scale to have a response.

Nonetheless, what this slide shows is that active drug was effective in comparison to placebo at this endpoint at one hour and all time points thereafter, I believe.

In terms of the question about treatment effects by frequency, I'm not sure if we did that analysis. I guess we did not do that analysis.

In terms of the question about disability, recall that the exclusion criteria was that we excluded you from the study if you were usually severely disabled with your attacks. So, if you were defined as disabled more than 50 percent of the time, so that if 48 percent of the time you were severely disabled you could still be enrolled in the study, and by chance some proportion of patients who weren't usually severely disabled, but were sometimes severely

disabled, would have severe di sability on the treated attack, and that's what the baseline data reflects.

We do have a back-up that looks a t treatment response in a severely disabled subgrou p defined by multiple criteria, and maybe we could show that slide as well.

CHAIRMAN D'AGOSTINO: Do you also have on e in the mild and moderate, thou gh, isn't that what the label is going to really focus on?

DOCTOR LIPTON: Well, actually, the --

CHAIRMAN D'AGOSTINO: The claim.

DOCTOR LIPTON: -- label, when someon e makes a decision to buy a product to take for their headache, they are not buying it generally for th e individual headache. So, what the label says is that if you usually require bedrest don't buy this product without consulting your doctor. It doesn't say, if o n any particular attack you happ en to be disabled don't take it, and, in fact, the clinical trial include d peop le with a broad spectrum of disability and th e treatment effects reflect aggregate responses across that spectrum of disability.

Okay, what I was looking for was the back - up that had the most severely disabled segment. Okay . This is not exactly what you asked for, but I thin k

it's at least partially responsive. To be included in this analysis you had to have severe baseline pain intensity, moderate to severe disability, headache aggravated by physical activity, nausea, photophobia and phonophobia, so we were trying to find the most extreme migraine subgroup we could and look at treatment effects.

What happens is kind of interesting, because across the studies the placebo response rate falls as we select the most disabled segment, but overall if you look at the pooled data the magnitude of the treatment response comparing active drug with placebo is roughly 25 percent, and in the aggregate data it was roughly 30 percent. That difference is statistically significant from the pooled data, but not for the individual studies, and the reason for that is the small sample size, as you see reflected in the numbers under the bar graphs.

CHAIRMAN D'AGOSTINO: Thank you.

I'd like to move on now to the FDA presentations and thank the Bristol-Myers presenters for their presentation and for their responses to our questions.

For the FDA, we have two presenters, and we'll start off with Doctor Widmark, the Medical

Officer at the Division of Anti-Inflammatory Analgesic and Ophthalmic Drug Products.

DOCTOR WIDMARK: Doctor D'Agostino, members of the Advisory Committee, ladies and gentlemen, most things that have to be said have been said already by all the previous speakers. So, in order to make it not boring for you I will deliver this speech with an accent.

(Whereupon, laughter.l)

CHAIRMAN D'AGOSTINO: And, it will sound more profound.

DOCTOR WIDMARK: For us it was interesting to find out whether those three studies that had different investigators, multiple investigators, and were spread all over the country, as you have seen from the geographical distribution of the sponsor, whether those trials resulted in dissimilar patient populations, study populations, or similar.

Here are the three studies which have been presented already by the sponsor. Study 840, one investigator, study 841, ten investigators, ten different investigators on site, and study 842, ten investigators in nine investigational sites. There was a diversity of people involved in this, and they followed all the same protocol.

Now, let's find out the demographics of the population in the three different studies. By the way, I cannot read that slide, maybe you can, but it's too far away for me.

As you can see here, we have gender, race and age, and as you can see the distribution is amazingly similar, with some slight differences, they are not identical.

This is already the efficacy, the two hour readings, and I have put all the Excedrin treated patients for the three trials on one side and the placebo treated patients on the other, and, again, you will find that these numbers are very, very similar. That is a good feeling it gives us, because we know that these protocols were followed the same way in all the three studies, because at the six hour efficacy you will find out that there is a high placebo response, around 40 percent, that's in all migraine trials, in all headache trials you will find a placebo response around that high number. You will find, again, that similarity persists even after six yours.

This is a composite of the adverse drug reactions that were reported by those patients.

And, if you go through this you will find out that there are a few side effects in the Excedrin

ES treatment groups that are characteristic for th e side effects of Aspirin, aceta minophen, and caffeine.

I would not dare to say that this is a comple te safety profile of this drug, it's only on e dose, and from one dose one cannot get a profile.

These are the conclusions. Si nce I can't see them, but you can read them, you will find ou t that we agree with the sponsor that they hav e demonstrated efficacy. What the sponsor did no t mention, because they probably didn't think of it, is the fact that I agree with a previous advisor y committee conclusion that it would be safe to put a warning on all caffeine-contai ning products, contains caffeine. That is important, because there are peopl e out there who just cannot tolerate caffeine.

By the way, they cannot tolerate 6 5 milligrams either, so 65 milligrams is not safer for them than 130. But, those who cannot tolerate should know without having to read th e fine print, it is all in fine print on this label, that that medicatio n contains caffeine.

Then, I have another issue which I would like to bring up, it occurred to me here when I heard the presentation by Doctor Lipton, and I believe it, that an untreated migraine attack can last up to 2 4

hours, untreated. A treated migraine attack should not last that long. However, the labeling is for ten days, for four doses for days, that I don't believe should be applicable to headaches and migraine in general.

If the medication is taken, not when the patient has already a full-blown migraine attack, but at the very beginning, because they know it's coming, these medications should work, and if they don't they should immediately go and see a doctor to be diagnosed what they really have, and if they need -- if they have real migraine they might need prescription medication.

That's all I have to say, and we -- actually, I recommend approval of this drug for the indication of pain associated with migraine headache.

If you have any questions, please do so.

CHAIRMAN D'AGOSTINO: Yes, why don't we take some questions, if there are any.

Let me ask one question about the active comparator. Would that have been a good idea in the studies, and do you think the studies are deficient by not having it?

DOCTOR WIDMARK: I don't think so. A prescription comparator would have been an unequal

comparison, like comparing a revolver with a -- rifle. So, that is not what they could use.

They could have used Ibuprofen, but it would mean that they are developing a drug which is a competitor's drug, and one can not blame a company for not being interested of developing a competitor's product.

CHAIRMAN D'AGOSTINO: Sounds reasonable.

DOCTOR WEINTRAUB: Doctor D'Agostino?

CHAIRMAN D'AGOSTINO: Yes.

DOCTOR WEINTRAUB: I wonder if I could say something.

CHAIRMAN D'AGOSTINO: Please, do.

DOCTOR WEINTRAUB: One of the beauties of working at the FDA is that individuals are allowed their own opinions, and can argue those opinions. Unfortunately, I was going to try my Swedish accent so I could compete with Rudy, but, you know, in certain cases we do ask for comparative agents to be tested with the drug in question. So, we don't -- in all cases it is not true that we don't like comparative agents, and we may even take a competitor's drug, and sometimes ask for it to be tested against the test agent.

So, you know, while Rudy has his own

opinions here, I just wanted to make it clear that this is not a standard that we have set for the whole Agency.

CHAIRMAN D'AGOSTINO: Thank you.

Are there other questions?

DOCTOR McKINLEY-GRANT: I had a question, I guess it's more information, about the caffeine warning, which I agree, but about caffeine addiction, and I know this must have come up, you know, when you discussed caffeine, but in terms of the caffeine being in the analgesics, and, you know, the whole thing of caffeine withdrawal, has there been any discussion about that?

DOCTOR WIDMARK: I believe everything can be addictive, if you overuse it. Addiction to caffeine, it exists, I am addicted to caffeine, but I don't go out there to buy Excedrin Extra Strength, I go and make a cup of coffee.

I don't want to minimize your concerns. They are, I believe, important and for real, but I don't have a solution for them. If you have --

DOCTOR DIAMOND: You know, abusers will be abusers, and you'll find them with all kinds of medicine, as well as caffeine alone. I just want to mention that in a cup of coffee, depending how big a

cup and how strong a cup of coffee you are drinking, there's anywhere from 80 to 12 0 milligrams, it varies that much, in a cup of coffee. So, for somebody who is doing two cups of coffee and a coke and something else, they are really doing it.

DOCTOR McKINLEY-GRANT: Yes, I guess my - -

DOCTOR DIAMOND: And, I just want to say that the people are discussing a self -- we ar e talking about self-limited, ep isodic migraine, we are not talking about people with daily migraine attacks here. So, I don't think it really is a concern.

DOCTOR McKINLEY-GRANT: -- I guess m y concern was with, you know, Doctor Gilman's commen t about the chronic analgesic headaches, because th e caffeine withdrawal, you know, the patients commonly will get very severe headaches after caffein e withdr awal, and it's my ignorance, I don't know ho w much caffeine you need to deve lop caffeine withdrawal symptoms.

CHAIRMAN D'AGOSTINO: Leona, d id you have a question?

MS. MALONE: Yes. I just have a point of confusion from a consumer's viewpoint. Normally, wha t I've heard from friends who suffer from migraines , they have been told not to take caffeine, you know, t o

avoid anything with caffeine, and here I can see their confusion as they are reading the label, where it's directed towards efficacy with migraines, and yet it has caffeine. So, again, it's the old thing, you are told to avoid something, and then you are told to take it.

DOCTOR WIDMARK: There was a Doctor Arnold Friedman at Montefiore Hospital. I believe he was your teacher. He developed Fiorinal, and his advice to migraine patients was, you don't really need any medication, several cups of coffee will take care of you. He was a very big proponent of just coffee drinking.

I don't know why your friends are advised to avoid caffeine. There might be a reason, I do not know.

DOCTOR DIAMOND: The National Headache Foundation, which I'm former Executive Director of, the warning is, excessive amounts of caffeine, not to avoid caffeine. Caffeine, you know, historically goes back to the 1700-1800s, when it first became discovered people reported its relieving headaches. But, the excessive use of it is contraindicated because that's when you start getting the rebound.

DOCTOR McKINLEY-GRANT: Okay.

CHAIRMAN D'AGOSTINO: Doctor Gilman.

DOCTOR GILMAN: Yes, I had a simila r response. The reason for that recommendations is so that people will not experience the rebound headache that comes when you stop taking caffeine, so fo r people with chronic headaches we often have them go t o fully decaffeinated coffee very slowly, over a lon g period of time, then when they are caffeine free they may well have no headache. If they do have headache, then taking caffeine is often effective.

CHAIRMAN D'AGOSTINO: Justin.

DOCTOR ZIVIN: I guess I don't understand why the caffeine is in the medication in the firs t place. The sponsors have said that it's an adjuvant, that's a pretty vague term and I'd like to get a little bit more specific about that.

Specifically, the FDA has suggested that one reason it might be in ther e is to do something to cerebral blood flow, but there's no strong evidenc e that migraine headache is asso ciated with alterations in cerebral blood flow, or at least the literature is extremely confusing at this point.

The other thing is that it may or may not have something to do with alterations in absorptio n rate, and I have no data on that one way or the other .

And so, I guess my question is, why is it there, and if it is there, does it really need to be there?

CHAIRMAN D'AGOSTINO: Can someone from the sponsor respond to that? Please identify yourself.

DOCTOR LIPTON: I'm Richard Lipton. You know, the caffeine -- first of all, the definition of an analgesic adjuvant is a compound which by itself doesn't produce analgesia, but which when given in combination with other analgesics enhances the analgesic efficacy.

And, caffeine, you know, there is a large literature showing that caffeine is an analgesic adjuvant, and there's certainly a long tradition of using caffeine in prescription drugs. You know, my belief is that the mechanism is not a primary mechanism on -- a primary effect of absorption. I mean, Gene Laska and Al Sunshine, who are actually in the audience, 12 or 13 years ago published a metaanalysis in JAMA that included over 10,000 patients, showing that the contribution of caffeine added a relative potency of 40 percent, so the addition of caffeine to analgesics made it as if you were giving 40 percent more analgesic, and that's, you know, what's meant by an analgesic adjuvant.

In terms of the specific mechanism in

migraine, you know, I would ha ve to say that it isn't really known, although I would also add that I'm not sure that the mechanism for non-steroidal anti - inflammatories, or even the me chanism for Sumatriptan is known. I mean, there's been substantial progress in understanding the mechanisms of migraine , hypotheses related to neurogenic inflammation, bu t those hypotheses have been recently challenged, s o it's hard to specify how a drug works in a condition whose fundamental mechanism isn't known.

DOCTOR ZIVIN: And, I wouldn't argue with that point, but then the issue is, wouldn't you want to test the drug with and with out the caffeine to see whether there was any difference, since the caffeine seems to be the cause of some concern?

DOCTOR LIPTON: Well, the rationale fo r not doing that was really twofold. One argument i s that caffeine was an established analgesic adjuvant, there's a huge literature that it shows it's a n analgesic adjuvant across a broad range of pai n models, actually, one study including migraine, and i t seemed unnecessary to reprove that which wa s established already. The second issue was, again , that this was not -- this is n ot an Rx to OTC switch, this is a label extension where the issue is, does a

marketed product already approved for other forms of headache, and already used for migraine, is that marketed product safe and effective in the treatment of migraine, and for that reason a factorial study wasn't done.

CHAIRMAN D'AGOSTINO: One last comment from Doctor Gilman.

DOCTOR GILMAN: With respect to Doctor Zivin's question concerning blood flow in migraine, there actually are a good deal of data available in the literature concerning the pathophysiology of a migraine event. Perhaps, the most dramatic was one published in the New England Journal of Medicine about two years ago by Mazziotta at UCLA. This was a positransmission tomography study showing changes in cerebral blood flow. There's a lot of information suggesting that the pathophysiology of migraine is related to spreading depression, which is a slow spreading depolarization across the cerebral cortical mantle, accompanied by big shifts in potassium ion.

Along with that, there are changes in cerebral blood flow that change actually as people's fortification spectra change, which are visual scotoma phenomena.

And, the Mazziotta study showed a single

case studied with repeated blood flow measurement, showing that there was change in cerebral blood flow across cerebral cortex in a distribution and time zone that suggested spreading depression.

So, I think there's a lot of evidence that there are changes in blood flow with migraine events.

CHAIRMAN D'AGOSTINO: Doctor Diamond.

DOCTOR DIAMOND: Yes, just one thing. There have been studies, one by Ward, and one by myself, where we, not in migraine, but in tension headache studies, where we did a separate capsule with caffeine, and we found caffeine, for the first hour and a half, as effective as any of the non-steroidals in both these studies, where we did this separate capsule. So, caffeine does have an effect.

DOCTOR ZIVIN: I don't really want to get into a lengthy discussion of the effects of caffeine on cerebral blood flow, but the fact is that there's at least as much literature, if not more, suggesting no effect, reducing blood flow, or increasing blood flow during migraine headaches, so it's pretty complicated.

DOCTOR DIAMOND: Okay.

CHAIRMAN D'AGOSTINO: I'd like to move to the next speaker. Now we are going to hear from the

Division of Drug Marketing, Advertising and Communications, Karen Lechter of the FDA. Karen is already up at the podium. Thank you.

DOCTOR LECHTER: Good morning. I'm Karen Lechter with the Division of Drug Marketing, Advertising and Communications. This review was done in conjunction with Doctor Rosemarie Neuner, of the Over-The-Counter Drug Products Division.

I'm going to speak briefly about the Label Comprehension Study in a little more depth than you've heard already.

The purposes of the Label Comprehension Study were to determine whether consumers would understand when to consult a physician when using Extra Strength Excedrin, whether the information about use for migraine headaches is sufficiently clear, and if the addition of the migraine information interferes with comprehension of the label.

Specifically, the communication objectives, or the messages that were tested were the following: consult a doctor before use if your headache is accompanied by vomiting, or if it is so severe as to require bedrest. Consultation with a doctor after use is recommended if symptoms continue or worsen, or if any new or unexpected symptoms occur.

All the participants had used a non-prescription analgesic in the past six months to treat a headache and all said that they had suffered from migraines within the past five years. Forty-one percent of those had had their migraines diagnosed by a physician. The proportion of those diagnosed by a physician increased with age.

The protocol did not call for a confirmation of the migraine diagnosis, either by confirmatory information from the doctors or by quizzing the participants as to their knowledge of different types of headaches to determine if they could distinguish migraine from other types of headaches.

There were two versions of the labeling. The front of the package was the same in both cases. For the new product that you are considering today, the uses included headache, including migraine headache, and in this slide the underlying portions are found only in the test version of the label, not in the control version.

In the section, ask a doctor before use if your -- the other two statements appear -- if your headache, including migraine headache, is accompanied by vomiting, or your headache, including migraine

headache, is so severe you require bedrest. You might note that the bedrest warning is not included at all in the control label.

The main questionnaire contained five open-ended questions. These are questions for which there are no suggested responses, the participant has to come up with their own answer. For most of the open-ended questions, there were corresponding closed-ended questions. These are questions for which there are choices to choose from when answering, such as multiple choice or yes/no types of questions.

There were seven closed-ended questions dealing with the communication objectives and one additional question asking what products had been used in the past five years. I won't be discussing that particular question.

Mall intercepts were conducted in 32 geographically dispersed locations around the country. This means that people in the mall were approached to participate and if they appeared to satisfy the requirements of the study and were willing to participate they did become part of the study. This was supplemented by additional persons in the low education category to have sufficient numbers for analysis.

Altogether, there were analyses done on 503 who saw the test label, and 245 who saw the control label. I believe these numbers do not include the low education persons.

For purposes of analysis, the participants were divided into two education groups, those with a high school education, and those without a high school education. They were also divided into three age groups, 18 to 34, 35 to 49, and 50 and above. Participants were asked to read the labeling as though they were deciding whether or not to purchase the product. Then, an interviewer asked them the questions on the questionnaire. As some of you noted earlier, the package was available for them to look at during this questioning period.

When asked the open-ended question about the purpose of the product, 89 percent who saw the test label and 95 who saw the control label correctly stated it was for headaches. However, most of these responses were non-migraine responses. Only 23 percent of those who saw the test label responded that migraine was one of the indications.

This may have been due to the fact that they considered headache to be a general category and it wasn't worth mentioning migraine. Perhaps, another

type of question, a multiple choice question or a checklist, might have tapped into the migraine understanding of the participants a little better.

Participants were asked in open-ended question about what the label says if symptoms continue or worsen. These results are found at the top of the slide here. As you can see, 88 and 89 percent of those seeing the label answered correctly that they should see a doctor.

Significantly more of the high school graduates, 91 percent, provide correct responses here than the non-graduates at 80 percent. However, this difference was not found in the corresponding closed-ended question. The results of that question are found down here.

For the multiple choice question about what to do if symptoms continue or worsen, again, 88 percent and 85 percent who saw this label correctly said to ask a doctor.

Participants were asked what the label says to do if new or unexpected symptoms occur. In the open-ended question, again, 89 and 87 percent correctly said to see a doctor. For the test label for this group, the more educated participants scored better again at 90 percent than the less educated at

83 percent, and the youngest group scored worse at 79 percent than the middle-aged group at 93 percent.

For the closed-ended question, 91 and 87 percent gave the correct responses. There were no differences here based on educational level, however, for the youngest age group who saw the test label, that's this group, 92 percent gave correct responses, compared with those who saw the control label in the youngest age group at 81 percent.

Participants were asked what the label says they should do first when they have a headache or a migraine that is accompanied by vomiting. For the test and control labels, the numbers were 86 and 87 percent saying to consult a doctor. There were no differences here between the high school graduates. For the test label, fewer in the youngest age group, 81 percent, provided a correct answer than those in the middle-aged group.

For the corresponding multiple choice question, 89 percent and 91 percent chose the ask a doctor response. There were no differences here between education groups or age groups.

Apparently then, all the age groups understood that if these symptoms become more severe that medical intervention is appropriate.

Participants were asked what the label says to do first if the headache is so severe that they require bedrest. Now, remember this was not information that was contained on the control label, so it's not surprising that there's a significant difference here on the open-ended question, as well as on the closed-ended question, and the response is to consult a doctor.

On the open-ended question, fewer high school graduates, 49 percent, than non-graduates, 61 percent, stated they should consult a doctor.

For the control label, the youngest age group said to consult a doctor less frequently, at 40 percent, than the middle-aged group or the oldest group, which were at 59 and 60 percent.

On the related multiple choice question, more who saw the test label again said to consult a doctor than who saw the control label.

For the control label, the high school graduates said they should consult a doctor 63 percent of the time and 73 percent of the non-graduates. Technically speaking, for this question on the control label the correct response on the multiple choice question was none of the above, because the question asked, what does the label say you should do if you

require bedrest. The label was silent on this issue, and, therefore, it's not surprising that the high school graduates actually said more often that none of the above was the correct choice for the control label.

Participants were asked a closed-ended question about when, according to the label, they should not use Excedrin, and their choices were if you are allergic or have asthma, if you have ulcers or bleeding problems, both of the above, none of the above. Both of the above are correct here. There were no differences between the labels on the question, approximately 80 percent got this one correct.

This question assesses the participant's comprehension of the Aspirin monograph warning. You might note that even those who did not get the both of the above answer correct, there were some who did get partially correct responses by answering the other questions correctly.

However, I want to say about this question and several others that follow, the type of question may induce what is a called a yeah saying bias, because all of the responses that were available, except for the none of the above one, could have been

partially or totally correct.

The next question here asked them when they should consult a doctor before use. Again, the responses were correct at about 80 percent. Again, both of the above was correct. There was a none of the above choice. All of these other choices were partially correct. If you look at the numbers who got all or some of this correct it goes above 90 percent again, but again the yeah saying bias may have come into play here.

A similar question was asked, what to ask a doctor after you have been using Excedrin Extra Strength. Equal proportions of both labels again, again around 80 percent, got the both of the above response correctly. There were more people who got partially correct responses, and, again, the none of the above choice was the only incorrect one. The yeah saying bias may again have been in play here.

Overall, this was a very simple study. The questions were very straightforward and did not require interpretation of the label. It measured very superficial understanding of the label. Responses to the open-ended questions were supported by similar questions in the closed-ended group. However, there are aspects of this questionnaire that may have

induced a higher correct response rate. For example, the fact that four of the open-ended questions, which were presented one after another, required the same response, to ask a doctor, may have induced a response set by which subjects or participants would tend to say, ask a doctor for any question, regardless of what the question was.

In addition, the closed-ended questions contained those three in a row I just mentioned, where they had a choice of none of the above, or all of the above, the correct response was always all of the above. This would have induced another type of response set.

It would have been better had there been questions interspersed among these that had other correct responses, and it would have been better had there been additional choices within each question for which a different response was appropriate, other than both of the above.

None of these questions asked the participants who may have had contraindications whether they would use a product or whether they should see a doctor before using the product to determine the effectiveness of the warning section for the class labeling. This would have been useful

information.

Further, as I mentioned earlier, the study did not determine whether the participants truly did have migraines. However, I do not believe that this affected the results of the comprehension study.

The differences that were significant among the education or age subgroups, particularly found in the open-ended questions, usually found that the less educated persons gave correct answers less often, and that the youngest age group, 18 to 34, gave correct answers less often.

A warning statement on the label consistent with that specified in the Code of Federal Regulations for OTC Stimulant Products should have to appear on this label. This warning was not tested in the study, nor was the alcohol warning tested.

In conclusion, potential users who are probable migraine sufferers seem to understand the migraine specific elements of the label, as well as the more general elements of the label, although only a small percentage mentioned that the product was to be used for migraine. This understanding in general was at a rather superficial level.

The inclusion of the migraine specific information in the test label did not seem to

interfere with understanding of other parts of the label.

The design of the questionnaire may have increased the proportion of correct responses to some of these questions.

This concludes my remarks.

CHAIRMAN D'AGOSTINO: Thank you.

Are there any questions from the advisory committees? Doctor Gilman.

DOCTOR GILMAN: I just had a question about that next to last slide you showed. You had an entry there saying "red swollen," red swollen what, head? What were you asking them?

DOCTOR LECHTER: I don't recall what the label said on it.

DOCTOR LIPTON: Area of pain.

DOCTOR GILMAN: Scalp.

CHAIRMAN D'AGOSTINO: The painful area is red or swollen.

Are there other questions?

Thank you very much.

It's a good time, I'm looking around with the light, I don't know if I'm missing hands, it's a good time, obviously, for our lunch. We will not have a closed session when we come back, because there have

been no questions that have been raised that we need to go into a closed session. I have 12:15, why don't we come back at 1:15, and we'll have the charge to th e committee at that time.

(Whereupon, the meeting was recessed a t 12:25 p.m., to reconvene at 1:15 p.m., this same day. )

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:26 p.m.)

CHAIRMAN D'AGOSTINO: What I'd like to do now is to ask Doctor Bowen to give the charge to the committee, and then we'll go on to the discussion and questions.

Doctor Bowen.

DOCTOR BOWEN: This is an unusual application, even for our Nonprescription Drugs Advisory Committee members. As has already been mentioned it is not an Rx to OTC switch, in fact, the drug itself has already -- is currently being marketed OTC.

The drug has been marketed for other pain relief indications for a number of years under the OTC drug monograph, and that monograph has not yet been made final. So, this application raises several interesting policy and regulatory issues for FDA, as alluded to by my colleagues, Doctors Weintraub and Chambers.

However, the applicant has submitted no clinical efficacy trials and a specific new drug application for a specific new OTC indication. That indication is the pain of migraine headache. So, today we are asking you to focus only on that request,

in your opinion, has the applicant convincingly demonstrated that the product can be used both safely and effectively in an appropriate OTC target population for the pain of migraine headache.

CHAIRMAN D'AGOSTINO: Thank you. Are there any other comments to be made by members of the FDA to elaborate further on that?

If not, then I'd like to have some time for general discussion with the committee, and then move on to the specific questions. Maybe a way to begin this is to ask Doctor Diamond if he would review somewhat his opinion on the presentations and the general questions. We will go to the specific questions, but if you'd just sort of start the discussion by giving us your general feel on what you've heard today and what you've been reading.

DOCTOR DIAMOND: From what I've read and what I've heard today, I think there's been adequate discussion of the different problems that might be involved in this approval. I think that an understanding is necessary by this committee that there are all degrees of migraine and there is a population that can be served by the over-the-counter analgesic drugs.

I think that we should also understand

that there is a population of migraine sufferers that go to specialty clinics such as mine, and such as neurology clinics, and neurology practices, which may be a more recidivist type population. But, in the group that has episodic migraine, I think there is a place for over-the-counter drugs in the mild to moderate cases of migraine pain.

I do feel that these drugs, in spite of their pain-relieving factors, may have some abortive qualities as well, in other words, they might abort or really cut short the migraine attack, and this has been shown in numerous studies, particularly abroad.

I think that we have to address some labeling concerns which I have about the drug. I personally feel that there should be some labeling that if the migraine persists over two days that the person should seek professional help, and I think that this should be specifically on the label, because migraine is not a ten-day disease, and the way the label -- present label says, it can be used up to ten days. If they are going to go for a migraine indication, they certainly should specify -- it might be all right for their tension-headache patients, but if you are talking about migraine, and it's over 48 hours, I think that you need some more specific

definitive treatment.

I think that the studies that they presented were very well run and are very adequate, and I have no criticism with the studies per se. I would have liked to have seen some comparison studies, but we don't have those, and this was not the charge I understand of what they were doing.

I think that the issue of caffeine, I agree with Doctor Widmark that those that are going to abuse it are going to abuse it, it is not an issue in this particular use that we are dealing with, especially if we put the labeling the way I suggested it for migraine.

And, basically, that's my opinion.

CHAIRMAN D'AGOSTINO: One of the concerns that I have, and let me voice my concerns before I open up the discussion, or it's a question I want answered, is it a concern, is it possible that there will be a population of individuals who shouldn't be taking the OTC medication who are very serious and the delay that results from them taking the medication could, in fact, be quite serious for them?

DOCTOR DIAMOND: And, I think Doctor Drachman brought up the same point earlier in the discussion, and, you know, we see many -- clinically

I see people who I put on -- who give a very typical migraine history, and on occasion you'll get an aneurysm that one misses, but this happens in practice, in the practice of medicine as well, and we can't go running MRAs and angiograms on every patient, so it's going to happen whether it's going to happen.

I don't know any way that we can stop it from happening by any labeling or anything that we're going to do. We are saying, or they are saying that it's for a mild to moderate migraine, and certainly the pain of a ruptured aneurysm is going to be a severe, unbearable pain like the person never had before, and I wouldn't call this a mild to moderate pain.

So, in addressing that issue, that's the best I can say.

CHAIRMAN D'AGOSTINO: That's good.

We had before us in previous meetings a lipid-lowering drug, and there was concern that the physician should be the one involved in looking at that on a yearly basis or what have you, and turning it completely over in an OTC fashion might be a problem, but I think from what you are saying that we can't really draw an analogy at all between that and this particular condition.

DOCTOR DIAMOND: No, not whatsoever.

CHAIRMAN D'AGOSTINO: We are in the point now, we are ready to go to the questions, but before we do I wanted to know if there's any, and invite any comments, general comments that the advisory committee members and consultants may have. Are there any general comments that we should talk about or address? Cage?

DOCTOR JOHNSON: Well, I want to second what Doctor Drachman, and Doctor Diamond and yourself have expressed, that I'm a little concerned about the layman's ability to make the diagnosis of migraine, and I speak, not as a professional in this case, but really from personal experience.

A migraine has a very fairly well-defined spectrum of symptoms, and yet, I think, as has been expressed earlier, the layman, the person to whom this particular application is directed, does not know that definition, he doesn't know the IHS criteria for the diagnosis. And so, they may utilize this agent for severe headaches of any etiology, whether they be subarachnoid hemorrhage, or brain tumor, what have you.

On the other hand, the current situation exists that this product is marketed for headache,

irrespective of what the diagnosis is, so I don't see that -- although this is a concern, I think the situation is such that there is no way really we can have any better impact on the utilization of this agent in the community than is already going on.

CHAIRMAN D'AGOSTINO: Any other general comments? David.

DOCTOR DRACHMAN: I appreciate all of the insights from the neurologists about migraine and its difficulty in self-diagnosing. I want to bring the perspective again of toxicity from a rheumatologist, non-steroidal use perspective, and wonder seriously if the introduction and marketing of this agent for the unique treatment of migraine, when other over-the-counter agents aren't so available, will actually have a detrimental effect on public health.

I think that the net effect here is to sell a drug for the use in migraine that's probably equally potent to other over-the-counter analgesics that people are already using with some efficacy, and to have them use a drug which is substantially more dangerous than what they are using, and I think we have to be careful here.

Perhaps, we can deal with some of these concerns in the labeling, but this is plain Aspirin,

and non-steroidals were in some cases introduced in order to get around the side effects of plain Aspirin. We give people single intericoated Aspirin per day in order to save them from the risks of smaller doses of plain Aspirin than this. So, I think we have to be concerned about people who take this repeatedly, when they might as well be taking acetaminophen, or Advil, or some form of low-dose ibuprofen that may, in fact, be safer for them.

CHAIRMAN D'AGOSTINO: Thank you.

Yes, Beth.

MS. HAMILTON: From a consumer perspective, I find myself also wrestling with how significant or not significant the need is to have a consumer be able to distinguish between a migraine headache and some other form of headache.

I respect the presentation made by the sponsor, and they clearly made a point of saying that there wasn't a need to differentiate for purposes of authorizing use of Ex Excedrin ES for migraine, but it occurs to me that there might be other reasons that the need for a consumer to differentiate might be present.

Two thoughts. One is the ten day, consult a doctor if you haven't had relief in ten days, and I

am impacted by the comments of our medical practitioners here, who suggest that a failure to have relief within 24 or 48 hours from a significant headache, I don't want to confuse the issue by suggesting that a migraine is the same as a serious headache, but to suggest that someone that doesn't have relief from a migraine within 24 to 48 hours, but still has a severe headache, I 'm concerned that we've suggested they don't need to seek medical aid for another ten days.

On the other hand, I recognize that the general use of the product for a headache may be associated with flu or cold. Ten days might be a perfectly reasonable period of time to let the person be grappling with that, so I raise it as a concern, I haven't fully resolved it myself.

I also want to raise the issue of consumer education. The material presented to us from the sponsor presents some impressive consumer education materials, but while their sort of clinical presentation says there's no need to differentiate between a migraine or another kind of headache, their education materials clearly attempt to do that. And so, it suggests to me that there is some significance to those differences that I'm also wrestling with, if

there are those differences, maybe we need to have more information about those, and to be assured that we are providing consumers with the kind of information that they can effectively utilize to make those self-diagnosis decisions.

I found the general consumer ed materials not helpful in that regard. I read them really carefully, and I don't know the difference between a migraine headache and a tension headache, from having read the materials.

CHAIRMAN D'AGOSTINO: Yes, sir.

DOCTOR GILMAN: I was going to hold these comments until we talked about labeling, but since this is under discussion now let me float them out before you currently.

Keying off Doctor Drachman's comments, and then the subsequent comments that we've heard, we have the concerns about the diagnosis of migraine, and then we have the concern about serious causes for headache. And so, we could address the issues of labeling to, you know, undercut the problems that they raise.

So, we could say, or recommend saying, headache, including migraine headache, if diagnosed by a physician, that's one option for taking it out of the consumers' hands. Second, we could add to the

list, ask your doctor before use if, there's a long list, not very long, there's a list of items there. We could also say, you do not have regular headaches and you are experiencing the worst headache of your life, which is commonly the case with subarachnoid hemorrhage, you have a fever or stiff neck with your headache, Doctor Drachman had concerns about subarachnoid hemorrhage, and I might add at this point that the mortality from each subarachnoid hemorrhage is one third, in other words, 33 percent of people will expire with their first subarachnoid hemorrhage, and with each subsequent subarachnoid hemorrhage another third will expire. It can be a lethal disorder.

In addition, the longer one waits after a subarachnoid hemorrhage for definitive diagnosis and neurosurgical treatment, the greater are your chances of expiring for particular times on the early days after the event.

The fever or stiff neck is with respect to the possibility of meningitis, and Doctor Drachman mentioned those two, I think you were thinking of brain tumors also, David, but I would suggest that we at least think about these items now.

CHAIRMAN D'AGOSTINO: That's a good

comment. One of the reasons I am asking for a general discussion now is because if we plunged into the questions, I was concerned that we would have issues like this, and it would color the way we would answer to the first few questions. If we raise these issues, and get a sense of where we may place them in our discussion, I think it will help a lot.

Cage, do you have a question?

DOCTOR JOHNSON: Actually, no, I have a comment. In order to put this whole field into perspective, I think you have to realize that like other chronic diseases probably 20 percent of the patients are very severely affected by the disorder, and are under the care, in the vast majority of cases, of a qualified professional. Eighty percent of the patient population may or may not be seeing a physician, and may be self-managing these.

In my own family, my wife, she has migraine clusters, and they sometimes will last a week. And, her brothers and sisters also have migraine. None of them saw a physician until just recently when I kind of leaned on them a little bit. They were self-treating, self- diagnosing, they didn't even diagnose migraine, they had headaches, they took an analgesic and went in a dark room and slept it off,

and didn't seek a physician.

I think the target audience for this preparation is really that patient, the non-patient so to speak, the person who is not under the care of a physician for this particular disorder.

And, I think you have to keep that consideration in mind. We are concerned about those few individuals who would have a serious medical disorder that might seek relief using this preparation initially, but I think the vast majority of the individuals using it are going to be in that mild to moderate migraine suffering group, who aren't under the care of physicians and for whom this is probably a reasonably appropriate medication, despite the, I think, real concerns about toxicity, and I think we can't consider the non-steroidals and their renal toxicity as purely safe agents either.

So, I think you have to balance both of these issues when talking about the population that we are talking about, which is the American people, not patients in our offices.

CHAIRMAN D'AGOSTINO: Eric.

DOCTOR BRASS: I think we have to be careful not to fall into a trap in this discussion, in terms of the appropriateness of this agent, and for

this indication for over-the-counter use.

I'm thinking specifically if t he safe use of this product is truly dependent on some nuance in the label we are doomed. There will be no nuanc e extracted. We spent all day yesterday talking about legibility. We do not have any data on th e photophobic, nauseated patient trying to read 4. 5 print. If this is in the medicine cabinet whe n somebo dy has the worst headache of their life, the y are not going to read the label to make sure it i s excluded from the worst headache of their life. And so, I think we have to re realistic in terms of what we really want to convey.

The second point is that I think trying t o convey it is made difficult by the nature of th e indication for the product. Y ou are trying to put in directions for taking this pro duct for migraine, when the label also includes menstrual discomfort, and tha t one set of instructions and warnings is trying t o cover both uses. And, I think that is going to be an extreme challenge in trying to get any of th e specificity in there.

So, I think when we view it from th e broader question of, is this product and thi s indication appropriate for ove r-the-counter, the more

we get into nuance and subtlety the more trouble we are getting into.

CHAIRMAN D'AGOSTINO: I don't think we'll take comments from the sponsor, unless asked specifically.

Yes, David.

DOCTOR DRACHMAN: First of all, the question in my mind is, who is not using Excedrin because they have migraines? I mean, is there anybody out there who says, I've got a migraine, I better not use Excedrin SE, ES, Extra Strength, whatever, but in any event, the point is that, what exactly will change.

And, as I think about it, that probably won't change, so what will? Undoubtedly, the sponsors will or should, I suppose, say they are going to advertise that this is now good for migraine. When they do that, then the premo non nocare, first do no harm, is the rule that I think we want to be very careful about, since most people, not neurologists, or headache specialists, don't know a migraine from any other headache, the issue there is that they really regard migraine as being a very severe headache. So that, here, within the advertising, the labeling in large letters so they can read it, even when they have

one of these, it should say, not what it is you use it for, but what it is you don't use it for, and what the risks are.

That, I think, would be what I would like to see, you know, not here's a migraine, here's a tension headache, know the difference, but rather, in very large print, the worst headache of your life, and headache with a stiff neck and so on, the subdurals, the subarachnoid hemorrhages, the meningitis, that's what we want to make sure they will not use it for.

CHAIRMAN D'AGOSTINO: Thank you.

Other comments on that? If not, I'd like now to move to the questions. Again, keep in mind as we go through these questions, I think we've experienced before a trap that we answer the first with sort of thoughts on how we are going to look at the other questions, and then suddenly find ourselves not being able to really maneuver the way we felt we should.

So, I'm under the impression that we've had our general discussion and we've sort of touched on all the issues that are covered in these questions, and now I want to turn specifically to the questions and start off with number one.

Number one says, "Is the pain of migraine,

an appropriate OTC indication?" And those in the audience, the questions are in the package of the agenda if you haven't seen them already, so, "Is the pain of migraine an appropriate OTC indication?"

Again, I think that what we are talking about here is for mild to moderate, is there a population, an OTC population, that can recognize this condition, take the medication appropriately and get safe and effective results from taking the medication. We are answering it in the small, in the sense that we are not saying all migraine headaches, we are not saying also that there's possibilities for misuse and what have you. Those we can take, hopefully, care of later, but right now, is there an appropriate OTC indication, and I'd like to ask Doctor Diamond to give us his thoughts on that first.

DOCTOR DIAMOND: If you're talking about mild to moderate migraine, yes, there is a population that can be served, and I think the population is out there, and they are out there using over-the-counter drugs now, and will probably enhance the use of the drug they are trying to get approval for.

Certainly with this approval there will be, as Doctor Drachman said, a certain amount of promotion with it, and it will probably enhance its

use.

My only question is, I don't think, as long as the advertising says mild to moderate, I don't think it's going to take away from the people who would come normally to a physician for the problem.

CHAIRMAN D'AGOSTINO: Cage, do you have a comment?

DOCTOR JOHNSON: I'm kind of mixed on this one, because I don't see where the addition of this indication is really going to change what's going on in the population of people with headaches.

CHAIRMAN D'AGOSTINO: The question is, is there an appropriate OTC indication, as opposed to are people misusing or doing it anyway.

DOCTOR JOHNSON: No, I'm not thinking about misusing at all. At this moment I'm undecided.

CHAIRMAN D'AGOSTINO: Mary Anne?

MS. KODA-KIMBLE: Yes.

CHAIRMAN D'AGOSTINO: This is not the vote, it's good to make the vote strong, I was just trying to get comments.

Sid, did you have any comments?

MR. PUCINO: I think the data are very clear, I would rephrase the question and say, is the pain of migraine an appropriate indication for an OTC

medication, to get rid of the jargon in the question. Other than that, I would say yes.

CHAIRMAN D'AGOSTINO: Frank?

MR. PUCINO: Yes, I agree the data looks pretty consistent with all thr ee studies, and I think there is a population that would benefit from th e drug, and I would vote that it could be used for that .

CHAIRMAN D'AGOSTINO: Thanks.

Justin.

DOCTOR ZIVIN: I agree.

CHAIRMAN D'AGOSTINO: Okay, ag ain, we are falling into the vote, but what I'm trying to get a sense of -- and, we'll do a vote by hand, but I'm jus t trying to get a sense of if there's any objection s before we take the vote, we se e where they are coming from.

Patricia.

DOCTOR McGRATH: I have no objection s before we take the vote.

CHAIRMAN D'AGOSTINO: Eric.

DOCTOR BRASS: I have nothing to add t o the discussion.

CHAIRMAN D'AGOSTINO: You may say, why is he going through this, well, I thought I was at this point yesterday and I said, let's take a vote, an d

then I was asked about a discussion.

What about David now.

DOCTOR DRACHMAN: No question at all. They showed that very clearly in their studies.

CHAIRMAN D'AGOSTINO: Great, any other comments?

Then why don't we take a vote on this, and I think an indication for an OTC medication is appropriate. Now, we have to make sure we understand who is voting. The consultants do not vote, and the industry liaison does not vote, so all those in favor of question one, a yes vote, is that all right? Doctor Diamond is a consultant, and George is the industry liaison, everyone else, except for the FDA people, are voting members. So, we have lots of votes. All those in favor please raise your hand. Any opposed? Any abstentions?

What is the vote, 17 and zero in favor, very good.

Now, the second question is, "Has the applicant provided ..." -- now we move specifically to the particular material in front of us, "Has the applicant provided adequate evidence, clinical studies, to support effectiveness of this product in an OTC migraine population?" Are there any comments

and discussion on that questio n? Many were answering it as they went along with the first vote.

Yes, Patricia.

DOCTOR McGRATH: I just maybe wil l introduce this now. I think we've all used words tha t are similar to what Doctor Weintraub used this mornin g when he talked about mild migr aine, and I think there may need to be discussion on the effectiveness i n terms of a population with mild or moderate headaches , as opposed to delibitating. And, I also think there may need to be more caution used with respect t o children's use.

For our pain clinic, we see ch ildren with headaches as the biggest out-patient population, and all of their parents have tried a variety of OT C products. And, I do think that the first one tha t specifically has migraine in the title and in th e marketing may be one that is l ooked at very carefully for children, despite the proposed labeling for not t o use it unless directed by a do ctor for children under 12.

So, I think maybe we need to talk abou t that at some point, and I would also, again, as kind of a repeated theme over the year, urge industry t o really look at products in the marketplace for people

under 16 years of age as not just over 12 year old's get migraines.

CHAIRMAN D'AGOSTINO: When you say we should talk about it, are you thinking of in the labeling making it more specific?

DOCTOR McGRATH: Yes.

CHAIRMAN D'AGOSTINO: Because their study design and their analysis did do an intent to treat, and did do it for at least the recruitment for the population that they are ultimately claiming for, so it's the specifics of the label.

Yes, Eric.

DOCTOR BRASS: Yes, I would also like to follow up on this mild to moderate thing, because it is no where in the indication, nor the label, that it says for mild or moderate migraine. It's by exclusion, if you read the warnings, and that non-mild, non-moderate is specifically bedrest or vomiting, so the advertising, the indication, whatever else context you want to put into it, if you expect to see mild to moderate that is not going to be there. So, I think that should be removed from the discussion.

CHAIRMAN D'AGOSTINO: Well, but I think in some of the other analgesics, though, the studies are basically mild/moderate for over-the-counter use, they

don't appear in the label, but it's the type of medication that is put in the over-the-counter, so I think we are in the same spirit as that.

Other comments over here?

DOCTOR McKINLEY-GRANT: I would like to see, perhaps, a study, because it sounds like there hasn't been clear evidence, but a study that somehow they could put this on the label saying that the earlier you treat a migraine, the shorter the duration of that. I mean, I don't know that we can say that now, but it would be helpful if the industry could do a study that would support that.

CHAIRMAN D'AGOSTINO: Other comments?

Then we have the question before us, have they supplied adequate evidence to support the effectiveness of this product in an OTC migraine population, understanding, again, it's OTC, and it's mild and moderate, with the caveats that have come up and the points that have been already raised, with those taken into account, all those in favor of the second question, please raise your hand. Any opposed? Any abstentions? Seventeen, zero again.

Now, the next one talks about the safe use. "Has the applicant provided adequate information, clinical studies and prior marketing

history, to support the safe use of this product in an OTC migraine population?"

Yes, Eric.

DOCTOR BRASS: I have a residual concern here that I haven't resolved in my own mind, and that is that the studies were all one-time, single-dose studies. And, clearly, the directions are not that, and, clearly, our expectations for use are not that, and, clearly, our experience even with rescue type medications are that repeat dosing will occur.

So, in terms of the true safe marketplace use, I do have a residual concern, though that is partly offset by the market experience, I think the studies by themselves that were presented today, the three studies, do not provide complete reassurance on the safety and actual use.

CHAIRMAN D'AGOSTINO: Are there other comments on that? Yes, Beth.

MS. SLINGLUFF: I would have to agree. The Label Comprehension Studies that were submitted, in terms of appropriate use and heeding of warnings, was a very limited survey. Again, you know, there's obviously years and years of marketing experience here with this particular product, and I think that if we were trying to answer questions of safety what we'd

really be looking at is that data, we wouldn't really be looking at the data that was submitted with the submission.

Doctor Brass has pointed out, and I would concur, that, you know, the issue of what happens when people need rescue medication, how would they be advised on a label what would be appropriate to take, what would not be appropriate to take.

Some of the other issues that we've dealt with in labeling with previous submissions in this committee have dealt with the problem of people mis-dosing, either too many tablets too frequently, too many times in a 24-hour period, too many times over time, and that's been a far greater issue than, do you know that you need to call your doctor if you are vomiting instead of taking this pill.

CHAIRMAN D'AGOSTINO: Is that another question, Lee?

DOCTOR SIMON: I absolutely agree. I'm very concerned that, in fact, we have not seen data about its safety of use, and I'm less impressed with the marketing experience and, perhaps, some other people around here, mainly because we know that a significant number of people have GI toxicity, and they end up either stopping the drug, self-treating or

having other issues go on, that is of some significance. I'm concerned that the warnings are not strong enough as listed in the insert to make me feel comfortable that I have seen enough information to know how safe this really is in multiple-use circumstances.

CHAIRMAN D'AGOSTINO: There's two ways of addressing that. One is to go to the labeling and make the labeling very explicit and very strong. Another is to do more studies. Are you suggesting that the labeling could do it?

DOCTOR SIMON: I feel that it's possible that if we're very aggressive about the labeling it would help me feel comfortable with that.

CHAIRMAN D'AGOSTINO: David.

DOCTOR DRACHMAN: I am unaware of anything regarding true migraine patients that would in any way make them less safe to use this medicine than people with menstrual cramps, or those with tension-type headache, where this drug is already approved and there are, I guess, 19 billion doses that have already been sold, meaning five for every man, woman and child on the planet.

So that, from my point of view, I can't see anything about this group of patients that would

be risky. I do see things about people who think they have migraine, who don't, that could be risky, and there I think would be labeling issue.

But, as far as migraineurs being in more trouble if they use this drug than all of those other folks, I don't see it.

CHAIRMAN D'AGOSTINO: Eric has a comment on this.

DOCTOR BRASS: Yes, I just want to respond, because I agree with seeing no data, and in the absence of data I resort to common sense. And, common sense that these people will have more severe headache, be more tempted to take additional medication beyond the label indication during that first 24 hours of their migraine than somebody who just got off the phone with their mother in law.

CHAIRMAN D'AGOSTINO: Ted, do you want to comment?

MR. TONG: I'll go on the record also adding my concern to the chorus of concerns that have been raised here. Unfortunately, I'm unable to offer a solution.

I know we have the advantage, when we are talking about an Rx to OTC switch, we talk about post-marketing surveillance, and there seems to be a lot of

interest on the sponsor's part to see that, to convince us that this was the right move.

I don't know if this is possible, given the circumstances here. I do get very tired, you know, usually waiting six months to see data of post-marketing coming out of the Wall Street Journal about how much, you know, in terms of the company that, you know, sells the product, but not the kind of details that we are talking about here, the concern of what is actually happening and, you know, the impact of the promotion, and the advice, and all the so-called learned intermediaries that are out there assisting our patients and making decisions on OTCs ought to also have knowledge and experience with this.

So, I think the labeling isn't going to be the only solution, but it's going to be a couple of other approaches.

CHAIRMAN D'AGOSTINO: Labeling and post-marketing surveillance can be addressed, and certainly post-marketing surveillance, that would be routine, wouldn't it?

Wiley, do you have a comment?

DOCTOR CHAMBERS: Doctor Chambers, this is an NDA, it falls under the same categories of any other studies where there are switches. You can have

pre-marketing studies, you can have post-marketing studies. They are all -- you can make recommendations as you see fit.

CHAIRMAN D'AGOSTINO: Cage?

DOCTOR JOHNSON: I want to follow on on the concern about repeated doses, because I think this is, particularly, the over-the-counter market, we are always concerned about whether the individuals taking these drugs will utilize more than the label says, and I'm sure that does occur on occasion.

But, I seem to recall one study that was presented at one of these meetings that showed that, in fact, in the over-the-counter market most people under-dosed, rather than over-dosed, by a big margin. So, I think it's a concern, but it's a concern for a very, very small proportion of the population, and the vast majority of people are not going to be affected, even though I think in this particular case, because of the biologic behavior with migraine, that this may be an indication that is at special risk for excessive dosing.

But, I think if you are really severely affected by migraine, and, you know, you take one or two of these and it doesn't work, I think you are going to move on to something stronger. That's been

my experience.

CHAIRMAN D'AGOSTINO: I'd like to focus the question here in terms of how we respond to it. If we think that the safety data that has been presented is inadequate because of the need for post-marketing surveillance, the need for attention to labeling, but in the safety, and we worry about the multiple dose, again, with the post-marketing surveillance and the labeling we can address that.

And so, the question I'd like to have at that, if there's ways that we can correct it, our concerns, that one would still tend to vote on the yes side of this, if there's such strong feelings of individuals that the safety data presented is just inadequate to make a judgment, and we can't make generalizations from other populations that have headaches and so forth, then one votes that way accordingly.

Before I take the vote, what I'd like to do is just give a quick run around the table so people would sort of voice their way. I think, Cage, you've voiced yourself fairly well on your concerns.

Mary Anne, do you have an opinion that you'd want to voice on this?

MS. KODA-KIMBLE: I noticed in the

labeling comprehension present ation that the FDA made that there was -- and I know there are som e limitations to the study -- but there was a multiple choice question in which they said, what would you do -- I think I'm recalling this -- if your headach e didn't go away, and one of the choices was to tak e more Excedrin. And, most peop le chose, see a doctor.

Nevertheless, we did have some subjects i n the actual study which rescued , despite the fact they were explicitly told -- advised against it.

It's just an observation, it's not a recommendation.

CHAIRMAN D'AGOSTINO: Sid, do you hav e comments on this?

DOCTOR GILMAN: Yes, I do. The question before us is really a very int eresting one. Restated it is, have we seen data suggesting that for thi s particular indication this will be an unsaf e medication, as opposed to previous experience fo r other indications, and the reason for asking tha t question is because people with migraine have mor e severe pain probably than people with other kinds of symptoms for which this is used.

To answer that question, I agree about th e notion of common sense, Doctor Brass, but how could w e

acquire that information? That would require a couple of double-blinded, well-controlled, long studies to have available to us, and we would have to hold up this kind of approval in the meantime, and yet, the sponsor has demonstrated quite convincingly that this is a pretty reasonable indication for this symptom, set of symptoms.

So, I prefer to go in the direction of post-marketing surveillance and very careful labeling. I think we are going to need to put a lot of effort into the labeling issues here. So, I think we have no evidence suggesting that it is unsafe, but we still don't know what consumers are going to do, and even a carefully controlled set of studies prospectively may not still tell us what consumers actually will do with this product.

So, it's almost an insolvable problem at this point in time, at least to do our job and come away.

CHAIRMAN D'AGOSTINO: Frank.

MR. PUCINO: I'd like to reiterate that it would be nice to have a post-marketing surveillance, or at least have the data from the European studies, using it in migraines.

My concern right now would be probably for

the patient who is at greatest risk, the elderly patient, the patient who has renal or hepatic compromise, things that you don't see listed in the labeling. Also, the use of other agents that Doctor Koda-Kimble brought up, Tylenol-containing products, caffeinated products, salicylates, non-steroidals, other things that may compound these concerns.

CHAIRMAN D'AGOSTINO: Justin.

DOCTOR ZIVIN: I'd just like to point out the fact that this drug has three active ingredients, all of which have been around for a very long time. Aspirin goes back better than 100 years at this point. Even the combination has been around for almost 20 years.

I think that if there were any really substantial safety issues with this drug they would have already become apparent, and I think that the excessive concern for this drug, for this patient population, is -- I don't see a justification for it at this point. And, I'm interested in acquiring further information, but I don't see that at this point I have any reason to believe that this is any less safe than lots of other things that are marketed.

CHAIRMAN D'AGOSTINO: Patricia? Eric? David Felson? No.

DOCTOR DRACHMAN: There is a no tion that I believe is floating about that people with migraines get many more headaches than those with tensio n headache. Doctor Diamond, would you like to comment on that?

DOCTOR DIAMOND: Actually, you know , there's been a lot of literature on transforme d migraine, and where they go from migraine to chronic tension headache, but, you know, I'm an old timer , I've been doing this a long, long time, and I thin k people were looking for some salvation. A small grou p of very difficult patients whe n they talk about these conditions, it's not the general population that we'r e talking about now, the population that we would us e this drug for.

Of course, in your clinics, in my clinic, and in every neurologist's clinic, you are going t o see these people with the mixed headache syndrome, th e real rough ones, but they are the exception, they are not the common thing that we are talking about here.

DOCTOR DRACHMAN: Yes, so the point reall y is that migraines are less common than the commo n garden variety of muscle contraction headache. Th e worry that the drug would be abused more, used mor e frequently, is not one that I have, so I would g o

along with Justin Zivin's view that we have a lot of experience that I don't see any reason why those with migraine would use more of the drug than those with all the other indications, and I am not concerned.

CHAIRMAN D'AGOSTINO: Thank you.

Ted? Beth?

MS. SLINGLUFF: I just want to briefly clarify my comments earlier. While I don't -- while I am not particularly persuaded about particular safety issues or appropriate use by the current data that's been presented, I am very reassured by the long marketing history of use of this drug. And, on the basis of that alone, I think that this can safely be marketed in an OTC population for the indication.

I do think that there are some labeling concerns that I would have, but I think they can be addressed at that level.

CHAIRMAN D'AGOSTINO: Kathleen.

MS. HAMILTON: I'm satisfied that there aren't any safety issues associated with the proper use of this product. I'm inclined to agree with the suggestions that the FDA do whatever it is procedurally we do to request post-marketing information on the possible misuse, over-use of the product for migraine sufferers, but I would also like

to request that we get similar data for misuse or over-use for other headache sufferers as well, so that the data is put in some context.

CHAIRMAN D'AGOSTINO: Harvey.

DOCTOR LUTHRA: No comments.

CHAIRMAN D'AGOSTINO: Lee.

DOCTOR SIMON: Well, I'm sorry, but I'm still very uncomfortable, and I apologize for my intransigence about this. I actually am really relating to the question, which was particularly relating and asking, do I see safety data regarding the way this drug is used, and I don't. I see safety data regarding a very, very, very carefully done clinical study, which we all know is not really applicable to humans in the real world, and I think that we have written words here in the product labeling that suggest the drug could be used up to ten days.

That's not what I've seen, I've not seen safety data about that, and I take issue with some of my colleagues, in that as an arthritis physician there are plenty of patients that we don't see in the hospital that have significant toxicity from Aspirin, who develop GI bleeding and other problems and are not any less or worse sick than someone with migraine.

I am just responding to the issue at hand, which is, I do believe these things can be handled in a post-marketing way and in the labeling, but I do not believe that we have seen any safety data that reflects the real use of this drug in the real world.

CHAIRMAN D'AGOSTINO: David Felson.

DOCTOR FELSON: Yes, I also will second the intransigence. I'm deeply worried about using plain Aspirin, which I don't use in my patients, without labeling concerns or some other concerns that tell patients how potentially dangerous that is. I don't honestly care whether it's available for other indications, it should have been there for other indications too, to be honest, and it's not something I'd let my patients do ever at this point. It's too dangerous.

And, for someone who said there's no evidence that this is a potential problem, given the large marketing history, boy, you know, this is the most common death from rheumatic disease, is GI bleeding from non-steroidal anti-inflammatory drugs, and even worse from plain Aspirin. I mean, it's just, I think there's got to be something built into the labeling here, or more data here, about the safety of this before it is widely used for the unique

indication of migraine.

CHAIRMAN D'AGOSTINO: Lynn, do you have a comment?

DOCTOR McKINLEY-GRANT: I would just recommend the post-marketing study about repeated dosing, and I guess pattern of use, as opposed to assuming that it's misused, but I think just looking at the pattern of use of patients who have migraines.

CHAIRMAN D'AGOSTINO: I don't know if the FDA has been paying attention, but you see what we are facing.

DOCTOR WEINTRAUB: We have been paying attention.

CHAIRMAN D'AGOSTINO: Good.

DOCTOR WEINTRAUB: You know, the company, we can ask the company about doing actual use studies, either before or after the approval, if we do get to an approval, and there are some other things we can do, too. One thing is, we can ask for two different kinds of labeling, because there are two different kinds of indications, and I started earlier in the day marking down, when I got to the letter M in marking them down I figured that was it, so I haven't marked anymore, but I'm sure I could get to Z, you know, 26 letters worth of difference between the drugs, because

the indications and the drugs.

So, we'll have to approach that with the company, of course, but it may be -- that may be the best thing, and you can rest easy that we'll try.

CHAIRMAN D'AGOSTINO: Good.

I do hear in the committee some individuals who are feeling very strong about the particular drugs and the safety not available, but I think the general tone is that many of these can be handled by labeling and post-marketing, and I want to just make sure I'm conveying the sentiment of the committee.

Mary Anne.

MS. KODA-KIMBLE: I just want to say that I'm not sure this is specific to migraine. I think it's specific to pain generally, and tolerance to pain. I mean, what do people do after a pain doesn't go away for half an hour, do they take another Aspirin, or Tylenol, or do they take a different analgesic?

So, in some ways I think it's a bit unfair to say, okay, migrainers, I think it really is, what is the behavior, the analgesic-taking behavior of people who are in pain? There may be cultural differences here, there may be gender differences, et

cetera, et cetera, and I'm not so sure that it's so specific to migraine.

And, anybody who has had premenstrual pain, there are levels of intolerance to that kind of pain as well.

CHAIRMAN D'AGOSTINO: I am going to ask you for a vote on this, and I would like to tone it as, will it be unsafe, I think that that sense, do we have data that would indicate that it would be unsafe, and also, if it's a positive response to the question, we are going to pick up labeling and post-marketing and so forth, so a positive would say the data that we sort of expect at this point in time is there, and do we have an indication that it will be unsafe is the thing that should drive the negative, as opposed to other type of concerns. Is that all right?

DOCTOR SIMON: Could you then just restate then what we are voting for?

CHAIRMAN D'AGOSTINO: Yes. What I'm saying is that, we have to decide what this means, when we say do we have adequate information, some adequate information can be that we'd like to see post-marketing surveillance, others would be that the labeling can be straightened out. So, I'm saying, when we look at this, we say at this point in time the

sponsor has made a presentation, they have the history of the drug, the drug has been around, the drug components have been around for a number of years, we have safety data on that. We have these three studies We have the comprehension studies, all of those have supplied information about safety. Do we think that with that information in its totality will there be any reason to think the drug is going to be unsafe, not that we would like to see even more information, but do we have any belief at this point to say that it's inadequate safety data that's been presented, the safety data is inadequate. All right?

All those in favor of the question three as it has been sort of rephrased, please, raise your hand, if we think yes. All those opposed? Any abstentions? Fourteen and three is the vote, 14 yeses, three no's. Again, I think the discussion on that was more important than the particular vote, so that we have a sense of what the feeling is of the individual members with regard to the material in terms of its safety, and what it is that we can do beyond the safety data that we already have, and this is where we come into the labeling recommendations. I think that we can mix in the labeling recommendations in question four, not only labeling

recommendations, but also othe r studies that we think would be appropriate to get at some of the concerns w e have.

DOCTOR WEINTRAUB: Excuse me, Ralph.

CHAIRMAN D'AGOSTINO: Yes.

DOCTOR WEINTRAUB: I just wanted to check , Andrea, do you have the question? Do you fee l comfortable with your phrasing of the question?

EXECUTIVE SECRETARY NEAL: No, I don't . I'm comfortable with the count.

DOCTOR WEINTRAUB: The count, but not the question.

CHAIRMAN D'AGOSTINO: What I'm trying to do, Michael, and we can go over it again, what I' m trying to do in number three is, I'm trying to hav e the question read that at the moment there's a safety data that has been presented, there may be more w e would like, but is the data that has been presented, is it adequate for us to vote yes on this question.

DOCTOR WEINTRAUB: Okay, that' s fine, and Doctor Chambers is correct, I can get it off th e transcript, too, so we are all right.

CHAIRMAN D'AGOSTINO: No, it's important that we understand.

Sid.

DOCTOR GILMAN: I voted in favor of the answer to this question as being yes, however, the applicant has provided adequate information to support the safe use of this product, as tested in their population of people with migraine. So, I voted yes.

We could put an addendum, if you will accept this, the company, or the sponsor, has not, however, provided evidence that this will be safe for prolonged or very frequent use. In other words, there is no information on that question which would get around the various concerns raised.

CHAIRMAN D'AGOSTINO: Well, this is what I was trying to get at, we could do post-marketing research to get at the prolonged use. Those would be ways of addressing that particular issue.

DOCTOR GILMAN: Well, I'm just suggesting that we, as a committee, could, perhaps, make an addendum to this. We could answer question number three, put a postscript, by the way, we've only seen data concerning safety on a single intervention with this medication, we have no experience or information on how it may be used with migraine patients and, therefore, we recommend post-marketing surveillance as an outcome and careful labeling.

CHAIRMAN D'AGOSTINO: I think we are

saying the same thing. I'm suggesting in the response to question four, that we talk about labeling and any other things that we think are appropriate, and certainly the post-marketing surveillance has come up a number of times, and I think that that message is quite clear to the FDA, that we would like post-marketing surveillance.

And, it is, just to clarify the question three one more time, it was trying to not limit the possibilities of added items in the post-marketing surveillance and the labeling type of items.

So, let's take the labeling first, and we can go back to even other things beyond the post-marketing surveillance, what labeling recommendations would we make, Sid?

DOCTOR GILMAN: Well, let me return to a suggestion earlier, actually, this morning. We could, under warnings, add, prolonged daily use of this product can lead to chronic daily headache, which I think would be a very helpful admonition to people who are inclined to take it when they are headache free, sort of chronically or prophylactically, people get a little bit superstitious about taking or not taking medication, and if it relieves headache then many people think, well, maybe I better take one to avoid

having a headache, and then before you know it, the patient is taking headache medication every day, and then winds up with daily headache. It's very common, actually.

That's one suggestion. Let me float out two other suggestions for the items under, ask a doctor before use if. I have two there. One would be, you do not have frequent headaches, and you are experiencing the worst headache of your life. The second would be, you have a fever or stiff neck with your headache.

CHAIRMAN D'AGOSTINO: Mary Anne.

MS. KODA-KIMBLE: I wonder if we could suggest a change in the request to indicate headache, including mild to moderate migraine headache, as opposed to asking them to diagnose it by exclusion, just say it, mild to moderate. I don't know whether that would be understood by the consumer.

The other issue I have is one that Doctor Tong raised before, and that is, on the front of this label the package, it has a gold seal sort of that says, "the headache medicine," and I'm wondering whether that gold seal occurs on all other Excedrin packages, and how that might be confused if we add this particular indication. I don't have the other

Excedrin packages before me.

CHAIRMAN D'AGOSTINO: Does anybody have an answer to that? Is that on all of the Excedrin?

CHAIRMAN D'AGOSTINO: It is not on all of them, it is on Excedrin Extra Strength and the Aspirin-Free Excedrin products, it is not on Excedrin PM.

CHAIRMAN D'AGOSTINO: Thank you.

Eric, did you have a comment?

MS. KODA-KIMBLE: Can I just finish?

CHAIRMAN D'AGOSTINO: I'm sorry, finish, yes.

MS. KODA-KIMBLE: When you look at this package, all you see is Excedrin. Extra Strength is just really buried, and if you look at the end thing, it's almost impossible to see Extra Strength, so I would just ask the manufacturer to take that into consideration.

Further, I think when we consider labeling, I think we consider patient information that is put out, and to the extent you could help the consumer differentiate between mild and moderate migraine and severe migraine, I think that might be useful.

CHAIRMAN D'AGOSTINO: Eric.

DOCTOR BRASS: My first comment on labeling is to the Agency, and specifically, as I indicated this morning, I have concerns about the value of the comprehension studies that are being done.

I would encourage, if the Agency is going to ask sponsors to perform such study, that the Agency develop some standards or expectations that actually measure something meaningful from the consumer side. Otherwise, I think we are just spending money for show and not accomplishing much.

DOCTOR WEINTRAUB: Actually, Eric, we are in the process of setting up the standards and doing it. You know, this has been a learning experience for us, too, and we are getting better at it.

DOCTOR BRASS: Okay.

The second comment I would make is also indirectly related to labeling, and it follows up on something Ted mentioned this morning, and that I would hope that the Agency would review the bioequivalency data on the other formulations, to ensure that, in fact, there are no differences in rate of absorption of any of the components between the tablets, capsules, et cetera, before the labeling was generated. I thought that was a good point that Ted

raised.

I remain concerned that as we try to develop a label with sufficient warnings and directions, that are specific for the migraine indication, we will make the entire label completely incomprehensible and useless. Again, we are talking about adding relatively sophisticated ideas, which will take up sizeable amount of space, and whether or not if those things are really going to be necessary to permit the safe use of the product, whether or not we are not talking about a completely separate label for this indication, and not melding it into the headaches, oh, by the way, migraine, too, kind of approach, because I think all the points that have been raised are valid, I just don't know how to phrase them in a way that can be put onto this kind of label that will allow the consumer to differentiate when they are buying it for a migraine versus arthritis, versus menstrual pain, in a way that's meaningful.

And, finally, I would not be enthusiastic about trying to do the mild to moderate thing, simply because I don't think the consumer will understand it, and that you are asking them to make a gradation judgment without any standard of comparison.

CHAIRMAN D'AGOSTINO: Frank, you had a

comment.

MR. PUCINO: Keeping in mind the limitations of size on the label, under the do not use, instead of just saying if you are allergic to Aspirin, allergic to Aspirin and any other over-the-counter pain medication, because of concerns of cross-sensitivity.

Under the ask your doctor before use, it mentions any other medical condition, including diabetes, gout, arthritis, I'm probably as concerned about liver disease or kidney disease, and make mention of those if you are going to make mention of any of these.

And then, in terms of your headache, including migraine headache, as Doctor Gilman suggested, diagnosed by a physician might be helpful, and avoiding a mild to moderate possibly, and then finally under ask your doctor after use, it says, symptoms including headache pain continues over -- maybe to say, over a 24 to 48-hour period, something to limit that duration.

CHAIRMAN D'AGOSTINO: David, and then David Felson.

DOCTOR DRACHMAN: My point, put in warning, before using for migraine, call 1-800-FOR-

PAIN, or something like that, so that you could give the whole message.

CHAIRMAN D'AGOSTINO: David Felson.

DOCTOR FELSON: In the wish list of label changes, and I guess I have to ask for PK data here, but in terms of directions, I would say two tablets with food every six hours while symptoms persist, that's a much safer way of taking this than two tablets with water. But, people are obviously searching for immediate relief, and I guess I'd like to know whether they get bloodstream levels as quickly if they take it with food.

DOCTOR DIAMOND: You are going to cause a lot of problems, because nausea and vomiting are the prominent symptoms of migraine.

CHAIRMAN D'AGOSTINO: Justin.

DOCTOR ZIVIN: I'm less concerned about the fine print than I am about the main message, and I don't see any problem with putting on as many caveats as the committee thinks is important, but there's only about three things that the patients are going to pay any attention to, and most of those are going to be the things that they can read without their glasses on while they've got a headache, or when they are in the store looking at the thing and they

don't have the headache, and they aren't looking at it particularly carefully.

And, that's why you already have on the label that this is for minor arthritis, and so I don't see any reason why you couldn't put on as well the idea that this is for mild or moderate migraine, and that would at least get the main point across, and then that would alert people to having the idea that they ought to look a little bit further into what that means.

CHAIRMAN D'AGOSTINO: Any other comments? Leona.

MS. MALONE: Yes, I just think the three ingredients should be a little larger, easier to read, darker print, something.

CHAIRMAN D'AGOSTINO: Beth, did you have a comment also?

MS. SLINGLUFF: Just a quick one. I don't have any additions to specific warnings, but, perhaps, the way to format, deal with this by format, is to simply have a separate boxed section on the label that deals with all of the issues around using it for headache and headache pain, and qualifiers around the type of pain, so it's separate and distinct from the other warnings section.

CHAIRMAN D'AGOSTINO: Lee, do you have a comment?

DOCTOR SIMON: Maybe I missed this, maybe it's been said already, but less than ten days of use, it should be much shorter than that if we are just dealing specifically with migraine, but that raised the issue of dual labeling, I guess, is what Mike was referring to before.

I would think that somebody that doesn't get better in 48 hours with this should be going on to see somebody under those circumstances, and we certainly shouldn't leave ten days on here, at least for this indication.

DOCTOR WEINTRAUB: I think what we've heard, and what we've heard actually this morning and early in this period, was that there needs to be a separate label for this medication which is under NDA. We'll have to deal with the company on that.

CHAIRMAN D'AGOSTINO: Kathleen?

MS. HAMILTON: I want to support the recommendations to include the mild to moderate information. I think that's helpful.

Also, with respect to Doctor Gilman's suggestion to include language that suggests, prolonged or frequent use may actually exacerbate a

headache problem, it seems to me that that's going to be very confusing to the consumer.

And so, I wonder if a more general language would be useful, and also then, obviate the need to have a list of considerations, to, perhaps, say prolonged or frequent use may present health risks, consult your physician, something more general.

CHAIRMAN D'AGOSTINO: Other comments? Cage.

DOCTOR JOHNSON: There are actually a couple good things about the label. I like the bolding for the very important warnings, although I prefer the mixture of capital and non-capital, and I like the idea of adding the other ingredients.

Unfortunately, it's in a green background, white print, and I can tell there are letters there, but it is totally illegible.

CHAIRMAN D'AGOSTINO: Sid.

DOCTOR GILMAN: I should respond to the issue of modifying my suggestion about chronic data on headache. It's really not other health risks that my comments address, it is chronic daily headache.

The problem that we see all the time in departments of neurology, and in private practice of neurology, is people who come in with chronic daily

headache and then you take a history, what medications are you taking, and patients will take two Tylenol, and five Aspirin, and some Excedrin every day. What you do is progressively wean them off those medications, very slowly, and then you find out where you are.

Usually, within tow to three weeks, these patients' headaches go away totally, so it's not a general health risk issue. Their general health may be fine, and if there's going to be potential for renal disease that ought to be addressed separately, but this is a very specific problem that's very, very common and totally unrecognized.

CHAIRMAN D'AGOSTINO: Any other comments?

Well, I think the FDA has received a number of suggestions, and hopefully they'll come back some time and tell us how they've incorporated them in their discussions with the sponsor.

I think, in general, that the committees are impressed by the studies. We do think that there's an appropriate OTC population or an indication for an OTC population. We do have concerns about safety. The data has a completeness to it in the sense of the studies had supply data, and there's a long history of the particular drugs, but the

prolonged use in the migraine population for OTC indication is of concern, and we are asking for the post-marketing surveillance, and we are asking for a number of indications and a number of changes, excuse me, on the labeling, or suggestions to the labeling that would try to address these concerns.

Are there other issues that the committees would like to bring up?

If not, then let's have an adjournment of the meeting. Thank you very much.

(Whereupon, the meeting was concluded at 2:41 p.m.)