FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE

ARTHRITIS ADVISORY COMMITTEE (AAC) AND THE

DRUG SAFETY AND RISK MANAGEMENT

ADVISORY COMMITTEE (DSaRM)

Wednesday, April 25, 2018

8:00 a.m. to 2:00 p.m.

Day 2

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

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C O N T E N T S

P R O C E E D I N G S

Call to Order

Introduction of Committee

DR. NEILL: Good morning, everybody, and welcome to the second day of our committee meeting. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so.

I would also like to identify the FDA press contact, Tara Rabin. If you are present, please stand, Tara. I don't see Tara. Sorry.

My name is Richard Neill. I'm the acting chairperson of the Arthritis Advisory Committee and I will be chairing this meeting. I will now call the joint meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee to order.

We'll start by going around the table and introducing ourselves. We'll start with the FDA to my left and go around the table. Dr. Hertz?

DR. HERTZ: Good morning, Sharon Hertz, director for the Division of Anesthesia, Analgesia,

and Addiction Products.

DR. RACOOSIN: Good morning, Judy Racoosin, deputy director for safety in the Division of Anesthesia, Analgesia, and Addiction Products.

DR. PRATT: Good morning, Valerie Pratt, the deputy director for safety in the Division of Non-Prescription Drug Products.

DR. LI: Good morning, Bo Li, statistical reviewer, Office of Biostatistics, Office of Translational Sciences.

DR. HENDRIX: Craig Hendrix, clinical pharmacology, Johns Hopkins.

DR. CUNNINGHAM: Melody Cunningham, pediatric hematology, oncology, and pediatric palliative care, University of Tennessee, Memphis.

DR. ROUMIE: Christianne Roumie, associate professor, internal medicine, pediatrics, Vanderbilt University, and the VA Tennessee Valley.

DR. FARBER: Good morning, Neil Farber, general internal medicine, professor of clinical medicine, University of California San Diego.

DR. PARKER: Ruth Parker, Emory University

School of Medicine.

DR. BOUDREAU: Denise Boudreau, Kaiser Permanente, Washington and the University of Washington.

DR. RICHARDS: Good morning. This is Steuart Richards, adult rheumatologist, VA Pittsburgh Healthcare system.

DR. OLIVER: Good morning, Alyce Oliver, Medical College of Georgia, adult rheumatologist.

LCDR SHEPHERD: Jennifer Shepherd, designated federal officer.

DR. NEILL: Richard Neill, family physician from the University of Pennsylvania, home of the back-from-the-dead Philadelphia 76ers.

DR. TCHETGEN TCHETGEN: Eric Tchetgen Tchetgen, professor of statistics, Wharton School at UPenn.

DR. SCHMID: Chris Schmid, professor of biostatistics, Brown University.

MS. ROBOTTI: Suzanne Robotti under MedShadow Independent Health News and DES Action USA executive director.

MR. DUBBS: Bob Dubbs, retired attorney, West Palm Beach, Florida.

DR. WARHOLAK: Terri Warholak, University of Arizona College of Pharmacy.

DR. MEISEL: Steve Meisel, director of medication safety, Fairview Health Services in Minneapolis.

DR. LEWIS: Julia Lewis, nephrologist, Vanderbilt.

DR. SOLGA: Steve Solga, adult hepatology and gastroenterology, University of Pennsylvania.

DR. OHMAN: Magnus Ohman, cardiologist at Duke.

DR. BLAHA: I'm Michael Blaha, director of clinical research, Johns Hopkins Ciccarone Center for Prevention of Heart Disease.

DR. HO: Good morning, Michael Ho, cardiology, VA Eastern Colorado and University of Colorado.

DR. ROSENBERG: Good morning, Yves Rosenberg, branch chief, Division of Cardiovascular Sciences, National Heart, Lung, and Blood

Institute.

DR. CHUNG: Hi, I'm James Chung. I'm the industry representative. I'm from Amgen in the U.S. medical organization. I'm a rheumatologist.

DR. NEILL: Welcome to you all. For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting. In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topics at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these

proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you. Now, I will pass it to Lieutenant Commander Jennifer Shepherd, who will read the conflict of interest statement.

Conflict of Interest

LCDR SHEPHERD: Good morning. The Food and Drug Administration is convening today's meeting of the joint Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

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

The following information on the status of

the committees' compliance with the federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208 is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with the federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of

these committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves supplemental new drug application 20998 for Celebrex, celecoxib capsules, submitted by Pfizer, Incorporated, which includes the results from the PRECISION, Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen trial, the cardiovascular outcomes randomized controlled trial that compared celecoxib to ibuprofen and naproxen and determined whether the findings of the trial change FDA's current understanding of the safety of these three NSAIDs.

In order to interpret some of the PRECISION findings, the committees will also consider the

clinical implications of the drug interactions between each of these three NSAIDs and aspirin in patients taking aspirin for secondary prevention of cardiovascular disease.

The topics to be discussed during this include both a particular matter involving specific parties and a particular matter of general applicability. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C., Section 208(b)(3) to Dr. Ruth Parker.

Dr. Parker's waiver covers her spouse's ownership of two healthcare sector mutual funds. The current aggregate value is between 0 and $100,000. The waiver allows this individual to participate fully in today's deliberations. FDA's reasons for issuing the waiver is described in the waiver document, which is posted on FDA's website at www.fda.gov/advisorycommittees/committeesmeetingmat

erials/drugs/default.htm.

Copies of the waiver may also be obtained by submitted a written request to the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland 20857, or a request may be sent via fax (301) 827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. James Chung is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. His role at this meeting is to represent industry in general and not any particular company. Dr. Chung is employed by Amgen.

We would like to remind members and temporary voting members that if the discussion involves any other product or firms not already on the agenda for which an FDA participant has a

personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

Clarifying Questions (continued)

DR. NEILL: Thank you. So I'm going to use the chair's prerogative to rearrange our agenda very slightly. We have scheduled at 8:30 a.m. an open public hearing and we'll commence with the open public hearing at 8:30.

Before that, I am aware that industry has gathered some data based on some of the questions that were incompletely answered yesterday, including at least two; one related to a slide containing a report of deaths and 30-day in follow-up period; the other, I believe, containing data related to statins.

So what I'm going to suggest is that,

industry, if you are ready, we'll listen to that information and do so with an eye towards the presentation and any clarifying questions ending by 8:30. Thank you.

DR. PRESSLER: Good morning. Milton Pressler, Pfizer. Actually, there are two things that we wanted to bring before the committee in response to its questions yesterday. And the first is slide AH-11.

This is with regard to the question on the dispensed dose, the dose. And the numbers that appeared to be replications, its turns, it's due to rounding, so that if you look at the average dose for ibuprofen and rheumatoid arthritis patients, it's 68.88 times 3 with an 82.19 standard deviation. If you look down two rows for osteoarthritis, it's 681.67. Those rounded both to 682.

So that's a rounding matter. And then I think that Dr. Meisel asked us a question about statins. And we tried to provide that. AH-10 up, please. So this, Dr. Meisel, is related to your

question about statin use and it was this factor in the outcome.

So at the top panel is celecoxib versus naproxen with statin use at baseline. Without statin use in the lower panel is celecoxib versus ibuprofen, with statin use and without statin use.

Approximately 50 to 60 percent of the patients were on statins. And again, that's not surprising, given that this is a higher cardiovascular risk population. But thank you for allowing us to just introduce this into your deliberations.

DR. NEILL: Thank you. So Richard Neill. For point of clarity, I misunderstood. Thank you. The additional data was not about the missing carriage return in the death slide, which I think we settled yesterday, but rather about this rounding error, not error but rounding phenomenon, which shows that these weren't randomly similar, but rather was a matter of significant digits.

If there were additional clarifying questions that any of the committee had regarding

these two specific issues, I'd be happy to entertain those now for industry. Dr. Meisel?

DR. MEISEL: Steve Meisel from Minneapolis. On the statin question, do you have any data or differentiation about people who may have started statins after baseline?

DR. PRESSLER: Milton Pressler, Pfizer. The answer is probably, but we don't have it here with us. We can look at the slide again to see what we have here, age 10 up, please. So this is baseline data. Yes.

But suffice it to say there's an absolute wealth of information in this dataset, so perhaps in the future, we will. Slide down.

DR. NEILL: Thank you. Dr. Richards?

DR. RICHARDS: Steuart Richards. Just to clarify, on the mean dose of the non-steroidals, you stated that it was, I think, 682 three times a day. Yesterday, you also mentioned that those were lower doses than the maximum prescribed dose. And I think you said the naproxen specifically you could go up to 1,500 milligrams a day.

But I don't believe those are doses for chronic use for osteoarthritis as opposed to the celecoxib, the 100 BIDs, a chronic dosing regimen for osteoarthritis. So I just wondered if you could clarify that because it seems as though you are comparing apples to oranges there.

DR. PRESSLER: Milton Pressler, Pfizer. So what's being shown was the maximum approved dose that's in the label for naproxen and ibuprofen. Now, I can tell you what I remember about the label.

The understanding is that, if patients do not respond to 500 milligrams twice daily of naproxen, the dose can be escalated to 750 milligrams twice daily, but maybe turn to Stan in terms of it may not be commonly used, but it was a matter of what was allowed versus what was used in the study.

DR. COHEN: Stanley Cohen, Dallas. I would have to go back and look at the label. You may be correct. I'd have to check. But as you know in practice, the most commonly used doses are about

1,000 milligrams of naproxen and 1,600 to 2,400 milligrams of ibuprofen.

DR. HERTZ: While we get that, this is Sharon Hertz. While we get that microphone going, I would like to point out the labels are in the background package.

DR. PARADES-DIAZ: Alberto Parades-Diaz from Bayer. The usual dosage in osteoarthritis is 500 milligrams twice daily. Naproxen has a particularity that, if you increase the dose more than 500 milligrams, the drug will be fast eliminated.

So in general, you do not need more than 500 milligrams twice daily. Thank you.

DR. NEILL: Thank you. Dr. Parker?

DR. PARKER: So I have the label. I just looked it up. So this is for naproxen, just to put it on the record. So for naproxen, it is for the dosage and administration for rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

It looks like it's listed for Naprosyn tablets as 250 or 500 twice daily; for the Anaprox

DS, 275 or 550 twice daily, or the EC Naprosyn is 375 or 500 twice daily.

DR. NEILL: Thank you

DR. MALONEY: Alison Maloney, Bayer, and just one addition to that label at the bottom. Where you're reading it actually says it can be used up to 1,500 milligrams for 6 months.

Open Public Hearing

DR. NEILL: Thank you. Seeing no other clarifying questions, I'm going to begin the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency of the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you

may have with the sponsors, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance of the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully, and treated with dignity, courtesy, and respect. Therefore, please speak only when

recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. WOLFE: I'm Sid Wolfe, Public Citizen Health Research Group. I have no financial conflict of interest. I drove myself out here this morning. Labels are important. The conduct of PRECISION, of the study, was limited because of the FDA's labeling requirement which says that, for osteoarthritis, you can't go over 200 milligrams once daily or 100 BID, and most of the patients in the study had osteoarthritis.

But the reason I put this up is just to note that, although 200 a day is thought to be the upper limit that osteoarthritis patients should be exposed to, for rheumatoid arthritis, again, that's part of the protocol of the study. It could go up to 200 BID. For ankylosing spondylitis, you could go up to 400 a day if the lower dose didn't work.

And, for acute pain, AP, you could start out with one day of 600.

This is relevant because the dose response curve in terms of cardiovascular problems with this drug is serious. This is from the CNT study, which I think was presented and discussed by Dr. FitzGerald and others at the meeting four years ago.

If you just look at the top part of the graph, those are sequential doses starting at 200, then 400, and then 800. These are from placebo-controlled, randomized, human trials showing that whereas at 200, the rate ratio is really close to 1.

It goes much higher, even though not quite statistically significant at 400 to 1.29, then up to 2.96. And in small print up there is a significant trend unlike the bottom part of the chart, which is Vioxx, which obviously was taken off the market because of the cardiovascular problems, but did not have a dose response trend that was at all significant compared to celecoxib.

This is now from a paper published after PRECISION was published by Patrono and Baigent. Baigent, Colin Baigent is one of the principal investigators in the CNT study, whose slide I showed before. And by way of comparison, what you can see on the top is the previous information about risk as a function of dose with celecoxib and, for ibuprofen and naproxen, mostly 1,000 as measured before and then at a lower dose of 440.

What you can see is that, by its design, the PRECISION design, you wound up with doses of these that would not really arguably -- and they didn't -- show any difference in the hazard ratio. This, I think, raises a sore point with Steve Nissen because I noticed that, in reading the transcript of the 2014 meeting, he objected to Dr. FitzGerald's characterization of the study.

This was before the results were known because it hadn't been finished yet. And these are just the comments he made in a paper about a little over a year ago after seeing the results, "Patients were not at high CV risk," even though it was

stated explicitly that these were to be high-risk patients, "As reflected by an annual rate of serious cardiovascular incidence of about 1 percent," yet the mechanism is conditioned by underlying cardiovascular risk.

There's no dispute at all that, for these drugs, this one, the others also, as a function of what your baseline cardiovascular risk is, it will magnify whatever effect if there is any caused by the drug.

Second point he raised, that it didn't compare daily doses of the three COX inhibitors achieving equivalent levels of COX-2 inhibition as indicated by lower analgesic effects, renal adverse effects, and blood pressure changes in celecoxib-treated patients than naproxen- or ibuprofen-treated patients.

These were just calculations that I did based on, A, the Pfizer briefing materials, page 229, and the supplement to the PRECISION study in the New England Journal. And the point here was that there was a significantly higher chance,

finding that people on celecoxib would leave the study because of the clinical benefit, and the phrased used in the study is insufficient clinical response as the stated reason for leaving.

So this is one of the examples of not having coequal COX-2 inhibition. That's one way of looking at it, but just not having equal doses in terms of these are arthritis patients and you're trying to make them more comfortable.

These were some briefly additional points made by Dr. FitzGerald in his study, in his analysis, called ImPRECISION. A third constraint was that, of about 8,000 patients per arm, randomly cited, 5,000 had stopped taking their therapy by the end of the study, 30 percent loss to follow-up and so forth. And he just points out that this makes it more difficult to have a valid conclusion of non-inferiority.

Another point made was that it was designed to address differences in the likelihood of an NSAID interaction with low dose, aside from the fact that there wasn't a randomization to aspirin.

This is pointed out as early as 2005, I think, in a Science article, "Both ibuprofen and naproxen interact to undermine sustained cardioprotection of aspirin. However, COX-2 is not extant in platelets risking an intrinsic bias in favor of celecoxib."

Then this is just a repeat of something said earlier, "The trial is not powered or designed to address the report comparative cardiovascular safety with high-dose naproxen, either because of the high dose, of not being a really risky population, cardiovascular, and also because the recruitment was such that it showed changes to the parameters on evaluating the study."

This is another. It was January of 2017, Dr. FitzGerald's paper. This is something published in August of 2017. And Colin Baigent again mentioned, as the author of the CNT, one of them, the question in this little analysis was, to what extent do the initial information from PRECISION might alter our current mechanistic understanding and/or clinical practice.

After reviewing the defects, many of the same ones that Dr. FitzGerald had delineated a few months earlier, he says, "It's unfortunate that such a large trial will not be useful in informing guideline committees, regulatory authorities, or practicing physicians on how to manage OA or RA patients at truly high cardiovascular risk when they need NSAID therapy."

This was just going back. The bottom part is that several members of the advisory committee, during that meeting, just based on the design of the PRECISION study, had doubts whether or not something new that could be translated into some new FDA regulation or clinical practice would happen.

This again was Dr. FitzGerald during the meeting, so ibuprofen, naproxen, but not celecoxib may interact to undermine the platelet inhibitory effects, something we talked about before.

So where does that leave us? Instead of answering or discussing the questions as framed, I agree with Drs. Baigent and Patrono and

Dr. FitzGerald that this study does not provide reliable information sufficient to change the labeling on the drugs or alter clinical practice.

We had petitioned to ban celecoxib back about a decade ago and it was based really on the same findings of those studies, the adenoma prevention study and so forth, showing that it had a sharp dose response curve. Now we know even more about the sharp dose response curve and that, if it's so dangerous that you can't use more than 200 milligrams a day, it has a low margin of safety and I think, if anything, the drug still should come off the market.

But I think that the main point of this meeting is not that. The main point is, do we have new information. I mean, it was a very laborious study, well done if you agree with the original design, and I think it's unfortunate that we are, in my view, not learning anything important that we didn't know before. Thank you.

DR. NEILL: Thank you. The open public hearing portion of this meeting has now concluded

and we will no longer take comments from the audience.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments. Dr. Judith Racoosin will now provide us with a charge to the committee.

Charge to the Committee – Judith Racoosin

DR. RACOOSIN: Good morning. Yesterday, you heard about the evolution over the last 13 years of our understanding of cardiovascular risks with the NSAID class. Over that time, we have gleaned knowledge from randomized controlled trials, meta-analyses of randomized controlled trials, observational studies, assessments of biological plausibility, and now a large cardiovascular outcomes trial.

Real-world challenges had to be faced along the way. The PRECISION trial was designed against the backdrop of anxiety about the use of COX-2 selective NSAIDs and non-selective NSAIDs, weighing the willingness of investigators to participate in

the trial.

Due to issues with lack of efficacy and/or the emergence of adverse events, patients often discontinued study medication and didn't always stay in the trial to be continued to be monitored. Slower than expected APTC event accrual resulted in modifications needing to be made to the trial design and statistical analysis.

Pfizer was not always as rigorous as we would have liked them to be in the conduct of the trial. In particular, they did not capture some information that would have been helpful for interpreting the results; for example, information on adherence, closer tracking and analysis of the use of rescue therapy for pain, and the specific reasons for patients discontinuing from study treatment.

Despite these challenges, the PRECISION trial was completed and we ask that you consider the data that you heard yesterday and the open public hearing comments you heard this morning to address the questions we have for you today.

Regarding the aspirin interactions for celecoxib, ibuprofen, and naproxen, we concur with Pfizer that celecoxib does not appear to have an interaction with aspirin. For ibuprofen and naproxen, we acknowledge that, while patients are taking round-the-clock treatment, these non-aspirin NSAIDs appear to function like aspirin in inhibiting COX-1 and inactivating platelets.

We also acknowledge that there did not appear to be a difference in the APTC outcome between celecoxib-treated patients taking aspirin and those taking ibuprofen or naproxen and aspirin.

We remain concerned about the washout period, though, when ibuprofen or naproxen serum levels decrease to the point where they are not inhibiting COX-1, but may still be interfering with aspirin accessing COX-1.

The patients who are likely most vulnerable to the adverse effects of the interaction that emerges in the washout period were not enrolled in PRECISION, namely those who had recent MI, revascularization, or stent placement.

In order to optimally guide clinicians through prescription labeling and patients through OTC labeling, we ask that you consider the data you heard yesterday and the comments you heard this morning to address the questions we have for you today regarding the interactions between aspirin and non-aspirin NSAIDs studied in PRECISION.

Now I'm going to read through the questions. The first group of questions are about the PRECISION trial. Number 1, discuss whether the data from the PRECISION trial support a conclusion of cardiovascular safety for celecoxib relative to ibuprofen and naproxen, taking into consideration the outcomes of the APTC events and hypertension.

Number 2, discuss limitations of the PRECISION trial that may interfere with interpretability of the cardiovascular outcome results, including the comparability of the dosing regimens and any other concerns regarding study design or conduct.

Number 3 is a voting question. Has the PRECISION trial demonstrated comparable

cardiovascular safety for celecoxib as compared to naproxen and ibuprofen? Please provide an explanation for your vote.

Number 4, discuss whether the secondary and tertiary endpoints of the trial; for example clinically significant GI or renal events and all-cause mortality; can be relied upon for comparing the risk across celecoxib, ibuprofen, and naproxen, given the definitions used and the lack of a pre-specified hierarchical statistical plan.

The next group of questions are about the interaction between aspirin and non-aspirin NSAIDs studied in the PRECISION trial. Number 5, discuss whether there is a clinically significant interaction between aspirin and celecoxib, aspirin and ibuprofen, or aspirin and naproxen.

Number 6, if you have concluded that there is a clinically significant interaction with aspirin for one or more of the non-aspirin NSAIDs presented, discuss whether there are patient populations, for example, patients with recent MI, revascularization, stent placement for whom the

risks of the aspirin-NSAID interaction potentially outweigh the benefits of the non-aspirin NSAID.

Number 7, discuss whether any of the interactions between aspirin and non-aspirin NSAIDs are of sufficient clinical significance to warrant description in prescription labeling.

Number 8, these last two questions refer to OTC products. Which of the following regulatory actions based on material presented and discussed at this advisory committee meeting should be taken with respect to naproxen non-prescription labeling and comment on your rationale?

So again, this is a voting question; A, no change to the current naproxen drug facts label, see FDA briefing document, appendix 1, for an example; B, include a warning regarding the interaction between aspirin and naproxen, and C, include a contraindication of use for naproxen when taken with aspirin.

Question 9, again, a voting question; which of the following regulatory actions based on the material presented and discussed at this advisory

committee meeting should be taken with respect to ibuprofen non-prescription labeling, and comment on your rationale; A, no change to the current ibuprofen Drug Facts label; see FDA briefing document, appendix 3, for example; or B, include a contraindication for use for ibuprofen when taken with aspirin. Thank you.

Questions to the Committee and Discussion

DR. NEILL: Thank you. We'll now proceed with the questions to the committee and panel discussions. I would like to remind public observers that, while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

So if we could have question 1 up, I'd like to describe the process by which I think this will be most helpful. In the first group of questions related to PRECISION, there's a little bit of an overlapping issue. You'll note that the questions address some of the presentations by both FDA and industry yesterday.

If you have clarifying or if you need clarifying information from FDA or from industry, I would appreciate you considering that before your question or before your comment. Lastly, I would say that my intent is to try and ensure that everybody on the committee participate, even if your participation is limited to, yes, my comments have already been made and I cede my time.

Having said that, I'll read the first question. Discuss whether the data from the PRECISION trial support a conclusion of cardiovascular safety for celecoxib relative to ibuprofen and naproxen, taking into consideration the outcomes of cardiovascular thrombotic events, Antiplatelet Trialists Collaborative Endpoint, and hypertension.

If you'd like to lead us off, raise your hand or turn your card up and we'll record. Dr. Roumie?

DR. ROUMIE: So we've seen a lot of data in the last 24 hours and, unfortunately, while the PRECISION trial was a very large trial with very

good intentions to understand the comparative effectiveness of these three medications, I am really not sure that I know anymore than I did based on the data that was based in 2014.

So really, what I've seen is, there's a very, very low event rate and, for an enriched cardiovascular population, I'm shocked that there was a 1 percent per-year event rate. Actually, it seemed lower than that.

So I don't know that the results of PRECISION truly reflect the patients that we see in practice and the underlying co-morbidities that would be reflected in the populations that would take these medications.

So I'm not really reassured in the non-inferiority trial design as well as the low event rates and the comparisons to a very high dose of ibuprofen and Naprosyn over a very short period of time, which is not really, I think, the underlying basis of what we were trying to capture in that trial.

So I am left wondering whether or not that

really has added any information from a prescriber standpoint. I am not really reassured by the data.

DR. NEILL: Dr. Lewis?

DR. LEWIS: I have a couple comments. When I look at the inclusion and exclusion criteria, I think this is a high cardiovascular risk population that was enrolled. I don't think there's any question about that and I think the baseline characteristics reflect that as well.

The 1 percent rate reflects the fact that our cardiology community -- and there were, I guess, 766 sites in the United States -- continues to make advances that keep cardiovascularly high-risk people alive longer and with less events.

I guess we're all going to die of suicide, homicide, and cancer. But it is an event-driven trial. So again, we waited until they got all those events. So again, I think actually that's pretty good evidence.

The other complaint that they moved the confidence intervals, the point estimates, or whatever, they achieved great and consistent point

estimates and upper-limit confidence intervals, way better, actually close to what they initially intended.

So I actually also will say that I have a strong bias that one large clinical trial that's randomized, et cetera beats the meta-analysis of a bunch of small trials, hands down. So I think that I'm going to withhold some of my comments that I do think there are some limitations to what we're interpreting and what we're seeing.

But I think they have done and I applaud them for it -- have advanced our knowledge that Celebrex, 100 BID, compared to ibuprofen and naproxen at the average doses that we saw in the briefing documents is equally cardiovascularly safe.

DR. NEILL: Thank you. Dr. Blaha?

DR. BLAHA: Thank you, Dr. Blaha, Mike Blaha. Yes. I'm also generally supportive of the conclusion of relative cardiovascular safety to ibuprofen and naproxen.

I echo Dr. Lewis in saying that, as opposed

to me saying that I didn't learn a lot from the randomized controlled trial, I actually think I didn't learn a lot from anything before the randomized controlled trial, didn't learn a lot from these studies that weren't designed for the purposes of assessing cardiovascular safety and the comparison in multiple groups that were perhaps not like the patient that we treat traditionally with NSAIDs for pain.

So actually, I think a lot from the randomized controlled trial that I did not know from meta-analyses of smaller studies. So I think it's worth unpacking I guess what this discuss question is, too. Of course, this doesn't say cardiovascular safety relative to placebo.

It says cardiovascular safety relative to ibuprofen and naproxen, which in my opinion is what was tested in this randomized controlled trial and also thought it was interesting that, in this question, it not only says cardiovascular and thrombotic events, but it says, "and hypertension," which I actually found a fairly persuasive part of

this trial and very relevant to my practice and everyone's practice.

So when you unpack these components of this question, cardiovascular safety relative to ibuprofen and naproxen for cardiovascular thrombotic events and hypertension, I would say I am, like I said, generally supportive of this particular claim as written. I support this conclusion and I learned a lot from this randomized controlled trial and I would just reiterate again I did not learn a lot from anything before the randomized controlled trial.

DR. NEILL: Thank you. Dr. Farber?

DR. FARBER: So I think there are some issues regarding the study, as with any kind of study like this in terms of crossover, some of the other issues that we've discussed. One of the things I think we need to point out is that this was a non-inferiority trial.

I'm used to non-inferiority trials being to see efficacy of a particular drug, to see whether drug A is as good as drug B. And this was designed

differently than what we're used to or at least what I'm used to in that it was designed to see if drug A, meaning celecoxib, is no more dangerous if you will than ibuprofen and naproxen. I think, to some degree, it showed that with caveats in terms of how reliable are the data.

But I think we have to put in perspective that we're not talking about safety. We're talking about the fact that celecoxib was not more dangerous, if you will, than ibuprofen or naproxen.

DR. NEILL: Thank you. Dr. Tchetgen Tchetgen?

DR. TCHETGEN TCHETGEN: I actually want to echo Dr. Farber's comments. Non-inferiority trials, while it's a randomized trial, are susceptible to certain sorts of bias, one of them being non-adherence, non-compliance, or discontinuation during the course of the study, switching back and forth between treatment arms, or use of other medication not considered in the trial.

All of these issues were present in the

PRECISION trial. I don't think they were addressed to the full extent that I would have liked to see it addressed. There are statistical methods to deal with non-compliance and non-adherence.

The effect of such complications are in fact biased towards supporting non-inferiority, in which case the bar to demonstrate that these biases are not present is much higher than in standard placebo-controlled randomized trial for superiority where the bias will in fact lead to more conservative tests.

Here, it in fact leads to anti-conservative inference. And so that concern remains for me. There was some evidence that was presented that the discontinuation were balanced with respect to baseline characteristics. I don't think that's particularly compelling because there was a lot going on post-randomization.

There are a lot of risk factors for discontinuation that oppose randomization factors that would also be related to the endpoint. None of those were accounted for. There wasn't

very -- the data was not particularly well collected on adherence, as was mentioned a number of times.

I would have liked to see a lot more about those data. An imperfect randomized trial is just as good as an observational study and there are a lot of methods for observational studies that should have been considered to further assess the robustness of this trial.

DR. NEILL: Dr. Rosenberg?

DR. ROSENBERG: Thank you, Dr. Rosenberg, NHLBI. I do acknowledge as a clinical trialist all the limitations, statisticals and otherwise, that have been discussed and definitely need to be taken into account in the interpretation of the results of the trial.

However, we never look at one clinical trial in a vacuum. We look at it in the context of other research, other trials, meta-analyses, and look at the consistency of the results of the whole and within subgroups and with different type of analysis.

So within this context, I did learn a lot from PRECISION that, for the specific limited relatively now recommendations we have to make, I think, are very helpful. So I definitely think that we cannot extrapolate to other population at higher risk or with the use of higher doses.

But within the context of the trial and what was studied, looking at how consistent the results are, we, especially within the aspirin/no-aspirin subgroup, which go in the opposite direction of what I would have expected if there was a significant problem, this all to me looks fairly reassuring that it's not an excess cardiovascular risk, again as for the patients evaluated in this trial at the dose tested.

DR. NEILL: Thank you. Dr. Parker?

DR. PARKER: So I reiterate, Dr. Rosenberg, what you just said. I was going to underscore that I think what we're able to understand needs to really relate to the dose used in the study, which was the 100 milligrams twice a day predominantly for people with OA, osteoarthritis.

I note in the full label for celecoxib that it comes in capsules that are 50, 100, 200, and 400 milligrams and that the dosing, dosage and administration in the label recommend including for OA 200 milligrams once daily or 100 milligrams twice a day.

The PRECISION trial used 100 milligrams twice a day for 90 percent of the people that were a part of it, given with osteoarthritis. So I think we need to be very careful to limit our comments and our thoughts about the trial to the dose and the formulation, as they were used in the trial.

We need to be very careful that there's full disclosure of that information for people who are prescribing it so they understand what we really do know and what we don't know. Any findings that we have really are related to the 100 milligrams twice a day, which was used in a large trial with the caveats that exist with it.

But given that the medication is available with 4 different sized capsules and the label

itself as it currently stands also states taking 200 milligrams once. That's not what was looked at in this trial and, were you to take 200 milligrams at once rather than 100 milligrams every 12 hours or BID, whatever that happens to mean to the people who took it, our findings would be limited specifically to that, which was what's done in the trial.

So I think we need to be really careful that that information is clearly conveyed.

DR. NEILL: Dr. Warholak?

DR. WARHOLAK: So I'd like to echo some of what Dr. Parker and Dr. Tchetgen Tchetgen said. Is that even close to right? Okay. So a couple of things, I really appreciate the Herculean effort of the PRECISION trial. It took a long time. There was a lot of work that went into it. But that said, there's certain things that I'm a little worried about.

When I was first reading the documents for the materials presented, I just was at full stop when I saw the dose of the celecoxib because, in my

mind, it's not comparable to the other doses that were studied.

So that's the first thing that concerned me. And then I was thinking, as Dr. Tchetgen Tchetgen said, the validity for the randomized controlled trial; the most biggest threat to the validity of a randomized controlled trial is differential experimental mortality.

I believe we have that here. In addition, we don't really know why people dropped out. So I would have liked to have seen a lot more reasons for dropout, especially compared in the arms. In addition, I would have liked to have seen a lot more information on the other confounders that were introduced post-randomization such as the rescue meds, et cetera, and comparisons amongst the groups.

I'm not convinced that I saw that.

DR. NEILL: Dr. Ohman?

DR. OHMAN: Magnus Ohman. So this is an interesting dynamic. So if I was a scientist and I said, okay, I'm going to do a non-inferiority

trial, how do I stack the deck in my favor. First of all, I will have a lower event rate than projected. I would use a comparator that has a high event rate for the issue that I'm looking at.

Then I would have a high dropout rate because, if I do that, we're going to go back to null pretty much and the statisticians in the group will probably give you a much better explanation for this.

So here we are, PRECISION trial has all those three characteristics in its favor, including confidence intervals that are fairly wide. So on this basis, I want to congratulate the FDA, actually, for including Naprosyn.

It turns out that, in documents that we haven't had here but were shown a few minutes ago, actually, ibuprofen has the highest event rate. It has a hazard ratio of 2 for cardiovascular events against placebo, which makes it really pretty risky in this setting based on the meta-analysis by Baigent .

So in a way, the good news is, we have

Naprosyn, which didn't have the same signal in the trial, so we had a reasonable comparator, at least in one of the groups. So the PRECISION investigators should be congratulated because this is one of the biggest challenges when you have an after-the-approval fact doing a large phase 4 randomized trial where patients' preference of what they'd like to do really plays in.

The best example of this is actually in diabetes, where we've now, since the cardiovascular events have been incorporated, actually learned a lot. We even found that some anti-diabetes medication actually lowers mortality. So how good is that?

So now we're back to where we are here and I would say that this is the best data we have. I think all of these agents are risky. They fall on the gradation of where they are. I'm hard-pressed to say which one is the winner other than to say they all have cardiovascular events.

For the PRECISION investigators, I'd also like to give some advice for the future, if there

is ever a future in this field. It would have been so wonderful if they had embedded a platelet function study in the middle of the overall trial to anchor the information that we're looking at because, in a way, we would have been a lot smarter about this aspirin/no-aspirin question, because it would have been embedded in the trial. We could have interpreted that information, at least with some level of comfort as opposed to having it separately.

So my thinking here; this is the best we have. They did a really good job with what they had. And we've given a lot of information that I think would help us because all of this is going to come back to that label that Dr. Parker read, "Ask a doctor."

So when I go to clinic, the other day after tomorrow, I'm going to be, "Ask the doctor." What am I going to do? So I think we have gained an awful lot based on this, but it's not pretty. Thank you.

DR. NEILL: Dr. Schmid?

DR. SCHMID: As a meta-analyst, I'm going to have to come to the defense of meta-analysis here a little bit. Big trials are very useful, but they're also very homogenous in terms of what they're looking at.

So one of the advantages of meta-analysis is it does allow you to look at heterogeneity. So I actually found online a meta-analysis. It's not particularly well done, but it was from last year, looking at this topic. And there's about, I don't know, 25 randomized controlled trials here, some of which have thousands and thousands of patients enrolled, so I don't think we can just say that there's a meta-analysis of tiny little studies.

There's about 5 or 6 here that have more than 10,000 patients enrolled. A lot of them are looking at arthritis patients, but a lot of them are looking at other kinds of patients, which we obviously don't have any information about here, and they look at very different types of doses.

I haven't really looked at this in detail, so I don't know how much heterogeneity can be

explained by these various things, but one of the things I'm really bothered by here is that I'm being asked to vote on a question here or discuss a question which is talking about safety for drugs, which presumably are being used by lots of people for lots of different reasons and at lots of different doses.

Yet, the information that we're talking about in this trial is for only two indications at very particular doses, as we've been discussing. So it's going to be hard for me to know how to judge that question when I'm making a very general conclusion about labeling a product which is used very widely by lots of people for lots of reasons and, yet, most of the information here is coming from particular indications with particular doses.

So to the extent that we could discuss that a little bit, it would help me a lot in terms of how to vote.

DR. NEILL: Ms. Robotti?

MS. ROBOTTI: When I asked to speak, I was going to ask for a discussion on dosage, but

fortunately, Dr. Parker brought that up and several other doctors, including Warholak, you, followed up on that, which gave me more clarity and confirmed my concerns, that this product is over the counter.

Your doctor's going to tell you to take Celebrex or take celecoxib. And he's going to say, "Use it, 100 milligrams two times a day," and you're going to go and say, "I'm going to go buy 400 milligrams because I really hurt," and we don't know what that is going to be like.

We have no idea. So why is it? Maybe it shouldn't be on the market. Don't panic. I'm really not going to suggest that, although maybe we should. So I'm struck by what we don't know from this study.

DR. RACOOSIN: I'm sorry. I don't mean to interrupt, but I just want to make sure you're clear.

DR. NEILL: Please put your name into the --

DR. RACOOSIN: I'm sorry. Judy Racoosin, FDA. There's no over-the-counter formula or

marketed over-the-counter version of Celebrex. Just the labeling that Dr. Parker is referring to, and I'll refer you all to page 199 of the FDA background package is where the Celebrex label -- it sounded to me like you were talking about an over-the-counter formulation and there is not one of Celebrex.

MS. ROBOTTI: I totally misspoke. So I got that. But to go on, I am concerned about all the reasons why people left this trial. When you look at the reasons for treatment discontinuation that were given to us and add up the percentages, it adds up to 70 percent.

So we don't know all the reasons why people left. And looking at the adverse event as a reason for leaving the trial, not to mention people died. That's 23 percent, so people are really having a problem with these drugs. This is all the drugs, 25 percent on average.

So I have a problem with what's missing. And thanks, I guess. Really appreciate the comments by Dr. Parker and Warholak.

DR. NEILL: Dr. Ho?

DR. HO: Michael Ho. I guess I'm thinking about the question in kind of two contexts. One is really about internal validity of the study and then I think a lot of the comments have focused on external validity of the study findings.

I appreciate a lot of the comments about the limitations of the study for PRECISION. But for me, I mean, I think the study was helpful in highlighting additional information that, really, the event rates, when you look at it, while low, there's really not a signal of increased risk with Celebrex.

What was reassuring to me was the sensitivity analysis that looked at the additional events that were needed to reach that pre-specified margin. So for me, that was very helpful. And I think we just need to interpret it within the study design and the doses that were given.

To me, the external validity is a different set of issues. Thank you.

DR. NEILL: Dr. Chung?

DR. CHUNG: James Chung, industry representative. I know there have been comments about the dose across the three NSAIDs. And of course, there's a very important and complex issue, there being dose response for various physiologic processes, which may in the aggregate contribute to cardiovascular outcomes.

But I find it reassuring that, if you look at the pain outcome as though there may be some limitations to that, they're remarkably comparable. And so what you may have is actually doses that are of clinical relevance that are used when physicians are given the ability to use it to treat their patients.

DR. NEILL: Dr. Solga?

DR. SOLGA: Hi, Steve Solga. I just want to comment on the cardiovascular risk consideration and invite more of the cardiology colleagues to chime in on this. I think I already have a sense for it.

As an internist, I recognize this group that was studied as a high-risk group and the low event

rates is indeed due to the fact that cardiology care perhaps has been getting better and we're left with 1 percent.

The criticism of the study and the circulation of the quarters that this was not a very, very high-risk group strikes me as unhelpful. There are reasons why folks in very, very high-risk groups aren't studied. It's not merely potentially unsafe. It's that the physiology changes as people get a lot sicker and results end up being ungeneralizable when patient populations are very, very heterogeneous.

As a hepatologist, I'm accustomed to managing risk in patients as they transition from mild cirrhosis to moderate and severe and their ability to manage medication risk changes individually and daily.

There are very few medicines that I can prescribe in a moderate- to severe-risk patient with cirrhosis that has been well studied. And so what I end up having to tell patients is, we have to prescribe with the liver you have, not the liver

you want.

Then when they pass and they do all the time, every single patient death is individual and different than the last. So it strikes me as almost a silly criticism to say, gosh, maybe we should have studied a very, very high-risk group and we're left with not that today. I find the patient population that was studied very appropriate.

When these lessons are adapted to folks who are very hot from a cardiology standpoint, you're just going to have to put on your physician cap and think about the risk-benefit to the individual patient.

DR. NEILL: Dr. Boudreau?

DR. BOUDREAU: Denise Boudreau, two things. One, I agree with what's been said about dose. And while it's an issue of generalizability, I think it's really important in this context of medications that are used for a variety of different indications, and populations, and doses.

So the way these questions are worded -- and

I know we're not voting yet, but even the way the question is worded to vote seems very general to me, given what the trial was. And it's interesting because it's not uncommon when we vote on efficacy that our votes are specific to dose and yet nothing is mentioned here with regards to dose or even the high-risk population, whether it is or isn't. I'll defer to clinical colleagues there.

The second thing is with regards to if I was to take dose out of this, generalizability, and just think about internal validity. As an epidemiologist and to Dr. Tchetgen Tchetgen's points, I have concerns around the way or the lack of things like discontinuation, crossover, switching, loss of follow-up were not handled in the analyses, that there are methods available that could have perhaps teased those things out a bit.

DR. NEILL: Thank you. We are going to discuss dose a bit in the next discussion question. Dr. Hendrix?

DR. HENDRIX: I'm Craig Hendrix. So I found the study was very helpful. I think all the

limitations that have been mentioned are correctly pointed out. I think that the agency can deal with these by circumspection with regard to the treated population in the study, cardiovascular risk however that's defined, as high or very high.

The dosage; these are statements that were supported previously. I think one of the useful things in the analysis is that, because the event rate is so low and the sensitivity analysis that was done showed that there would be a requirement of very large numbers to flip this, that whatever the magnitude of difference is that might have been missed with the limitations in the study design, the overall impact is really small.

I think, in addition to that, what FDA stated as their largest concern, which as a pharmacologist was theoretically my biggest concern, was the switching back and forth with the regimens.

With all the switching back and forth with the prescribed randomized drugs and the other NSAIDs to which they were switched, that didn't

seem to give a very high event rate. Again, the situation that was of most concern, there seemed to be plenty of that, but the event rate was surprisingly low, given the inclusion/exclusion criteria for the population, so I thought that was also somewhat reassuring, given the FDA's stated concern in that area. Thanks.

DR. NEILL: Dr. Meisel?

DR. MEISEL: Steve Meisel. So I'm struck by a couple of things. I'll hold my dose question for later or comment for later, but I'm struck by the fact that, every time there's a major trial like this, it answers one question, but brings us four more.

Sometimes, we can become paralyzed by the answers to the questions that we don't know and haven't asked yet. And we sort of lose sight of what we have learned from this. And despite all the criticism that I think are valid about the crossovers, the dropouts, and everything else, this also reflects the real world. This is real world practice of what happens out there.

People are on aspirin; some aren't; some get started on statins; some are not; some are on statins to start with. They switched from drug A to drug B because of efficacy reasons. All of that reflects real-world medical practice. And with all of that, when we still see very little difference in the cardiac outcomes, to me I find that reassuring.

Yes, there are lots of unanswered questions and there's lots of critiques we can make of the details in the study, but by gosh, we had 24,000 patients in the study. I mean, that's quite a large trial and to see such little difference here, I think, is to me reassuring.

DR. NEILL: Dr. Cunningham?

DR. CUNNINGHAM: Thank you. I agree with a lot of what has been said and particularly focusing on the patient population treated in terms of their arthritis as well as the dose. We talk a lot about the high dropout rate, but I just want to point out that it's really consistent through all of the different groups. And so it's not as though one

had a much higher dropout rate, where we would say, well, this was not as good of a medication.

When they looked at the anti-arthritic efficacy and I think someone else had pointed that out, they really looked very similar. So I think we are talking about comparable doses from the arthritis and pain effect. And I think that's all I have to add.

DR. NEILL: Dr. Richards?

DR. RICHARDS: Steuart Richards. I just wanted to reiterate the concerns people had about restricting it to the 100-milligram twice daily dose. The other reassuring thing I thought was that you were not seeing an increase in the rate of events as the trial progressed.

It seemed to be more or less consistent throughout. That's always a concern when you're looking at a safety event over something that can happen, not just in the short term, but in the long term as well.

Also, just to reiterate, although the dropout rate was high, I think this is typical of

what we see in a lot of trials of patients on rheumatic therapies, particularly when you're dealing with things such as pain. So it's a little probably unreasonable to expect people to stay in a pain study or stay on a medication for pain that's going to be going on for over 2, 3, 4 years.

So I think that dropout rate is not unexpected. I think, certainly, we would have liked to have seen more information and details about the reasons for dropout, the reasons for the adverse events. And because patients would be switching, more information about stopping medications, more information about the adherence, I think, would have been helpful.

DR. NEILL: Dr. Oliver?

DR. OLIVER: Alyce Oliver. I gleaned a couple things from this study. One, I agree with the comment that it did show that Celebrex is not more dangerous than the other to non-steroidals. Certainly, there wasn't a placebo group to show how poor they would do.

Dr. Richards beat me to the comment about,

in terms of the high dropout rate and the improvement of the visual analog score of only 10 out of 100, that we do a really poor job of controlling our patients' pain. And we see that as rheumatologists.

As we continue to move away from opioids, it doesn't look like non-steroidals are doing the trick, either. So it is something to look at.

DR. NEILL: Thank you. A number of the committee members have asked to make additional comments. And for those of you that are counting, I'm impressed, given the number of committee meetings that I've been to you that each of you, save one, has already made a comment.

I'm going to ask Mr. Dubbs if he wants to weigh in before we look to members who have already made comments to weigh in.

MR. DUBBS: I really don't have anything to add.

DR. NEILL: I still have Dr. Lewis, Rosenberg, and Tchetgen Tchetgen. Dr. Lewis?

DR. LEWIS: I want to talk a little bit more

and then ask some questions about the discontinuations. First, I will say that, having personally designed case report forms, they are very confusing to the coordinators, even when we try very hard. And I think more and more drug companies are trying to do one case report form for all studies across specialties.

That's going to worsen this problem of confused study coordinators not having enough disease-specific or even, whatever, study-specific questions to give us more information. I don't know what these case report forms actually look like. I don't know if there's more detailed information somewhere and they got lumped together. That would be great if that was true.

I will say that I can applaud them. We keep saying they've lost all these patients. Well, there's only 8 percent loss to complete follow-up, I mean, people that they don't know anything about. Everybody else might not like the reason or you might say there may be other reasons behind it, which is a design in the case report form problem,

but someone knew. Someone asked. Someone said what's going on? So I actually think that's great.

I was reassured -- and I'm not a statistician -- by the FDA's excellent presentation, where they, both in their briefing document and during yesterday, where they reassured us that, even if you gave worst-case scenario to the people who discontinued, still it would be highly improbable that Celebrex would lose.

However, Dr. Tchetgen Tchetgen and some of our other colleagues keep alluding to other kinds of analysis that could be done. So I wonder if there are other analyses. That would be really good. Could the FDA do them? Do they have the information to do them? What are those analyses? I mean, maybe you guys could have a more specific discussion and you could better inform your decision because only one of the aspects of your decision is going to come from what we say today.

So if there really are these better things you could do to look at the data, we'll do it.

DR. NEILL: Dr. Tchetgen Tchetgen, you're

not next on my list, but Dr. Rosenberg, if you'll cede a moment, do you want to address this question? And then you also had another comment I think you wanted to make.

DR. TCHETGEN TCHETGEN: Sure. I think the two are actually related along that, so thank you for that. So I wanted to make a distinction between dropout and discontinuation or lack of adherence or switching. So those are two types of complications that arose in this trial.

My understanding of the statistical analysis that both the sponsor and the FDA did with it, the tipping point analysis, was under a hypothetical situation where both of the comparators where the number of event rates was held constant and they are trying to figure out how many more cases you would have had to see in the active arm, the arm of interest, to pass or to break non-inferiority.

That's a very conservative analysis. I would agree with that. And that's actually very compelling that, in fact, in terms of dropout, we may not be as concerned about that.

My main issue is with discontinuation, switching, and lack of adherence because those that were not obviously were not random events, the patients who discontinued, not necessarily in terms of baseline characteristics, but rather in terms of post-baseline characteristics might be very different from the patients who should have stayed on the trial.

The analysis, either the modified analysis or analysis that would condition on or stratify by remaining in the trial, could induce selection bias due to that confounding factor. And there was no effort to address any post-randomization confounding arising in this trial.

So that was my main concern. I'm not aware of what data on risk factors post-randomization were collected that might be predictive of discontinuation, that might be predictive of an endpoint.

Those factors can be incorporated. There are techniques such as extension of the analysis that was done for inverse probability weighting by,

I think it was, 4 aspirin at baseline. A similar analysis could be conducted to incorporate time-varying confounders.

There are such analyses anyway. I think I could maybe stop there and I don't know if FDA would like to respond to that comment.

DR. NEILL: Dr. Li?

DR. LI: Bo Li from FDA. I agree with Dr. Tchetgen Tchetgen about the limitation of that sensitivity analysis. It's an ITT analysis. It took into account those patients who drop out of the study. We did not do a similar analysis like how to flip the result for those who discontinued treatment.

Those are 70 percent. But if you look at the discontinuation from treatment, I think there is, either in the briefing document or in our clinical reviewer's presentation, Dr. P.'s presentation, there is a reason collected for that.

For the adverse events, it's, like, 25 percent balanced across the arms. And if you look at the general safety analysis from our clinical

reviewer, you will see that either the serious adverse events or the adverse events collected are treatment emergent. So they are collected on treatment or on treatment plus 30 days.

So they are pretty balanced. Either it's related to CV or it's other, GI adverse events or others. So although I did not do that, I do not have 100 percent sure -- but I think, if a similar analysis was done, but this analysis just relies on the predictive power of those adverse events, which are considered associated with APTC events.

But I believe, if we do a similar thing on the mITT on-treatment analysis, you will still see maybe a large number needed to flip the results of the on-treatment analysis.

But I think, for aspirin, yes. So that's my understanding. I did not do the analysis, but yes. If you look at the briefing document, those adverse events are pretty balanced on treatment, too.

DR. NEILL: So before we move to Dr. Rosenberg, Dr. Lewis, the question that I heard

from you was whether, given the concerns that were raised about the statistical analysis that might be applied, Dr. Tchetgen Tchetgen, Dr. Li, or sponsor had approaches that would help. I'm not sure whether you were also asking were any of those actually performed.

DR. LEWIS: Actually, I am interested in knowing whether the sponsor performed any of them. The FDA has told us they didn't. And then I was just wanting to hear more of a discussion rather than just leave it there, that inadequate analysis was done and there's more to know.

If there's more to know, you guys should. I mean, nobody can do it today.

DR. HERTZ: So this is Sharon Hertz. I need to redirect us a bit. We shouldn't be having additional discussion or information presented at this point. Once we finish with the open public hearing and start with the questions, we really need to hear from you folks and then we'll take that advice back.

So if you tell us there are things to look

at, we will go back. We'll see what we've done. We'll see how what we've done fits your suggestions. If there's more that can be done, we'll think about that.

Similarly, the sponsors have gotten their opportunity to present and, if they have more analyses they want to submit, we're here and we'll look at them and take those into consideration as well.

DR. NEILL: So we're also in the next discussion question going to have the opportunity to address more general concerns and perhaps we can reserve that conversation for that question along with other suggestions. Dr. Rosenberg?

DR. ROSENBERG: Yes. Maybe commenting on this issue briefly, I think all of this analysis can be very informative, but they're only just second reanalysis that need to be considered with a lot of caution.

I mean, the FDA is the first one who suggests that's not what they base their decision on. So last point on this is, although I'm pretty

convinced it's informative censoring that has occurred there, the level of between the reasons of drug discontinuation and crossover that was observed or that we suspect, I do still have a hard time to believe that could completely reverse the results, put this trial on its head, so that they will show they would have an impact in completely reserving the result. That's my comment.

The question or comment I had was related to the question that we're supposed to vote on. My experience with this kind of question is that, even if it's not specified, we vote based on what the current labeling, approved labeling is based on what the drug is approved for at the current dose and for the appropriate population.

So that's in this context that I will vote and the FDA doesn't agree or has any comments they can make on that. But that's at least the way I interpret it.

DR. NEILL: Dr. Hertz?

DR. HERTZ: Hi, Sharon Hertz. So this happens every committee. We write these. We go

over these questions like you don't even know and still we don't have it as clear as could be. The way we worded it; has the PRECISION trial demonstrated; we meant for the conditions studied. So when we get to the vote, when you think about the question, it is limited at the doses under the conditions of the study.

DR. NEILL: Thank you. Dr. Cunningham?

DR. CUNNINGHAM: Just in that regard, we were told when looking at the secondary and tertiary endpoints, that they were to be interpreted descriptively. And I think it's just interesting, though, the hypertension data was compelling, that that's rolled into part of this discussion and I don't think it ought to be rolled into how we think about this or how we vote.

DR. NEILL: Dr. Racoosin?

DR. RACOOSIN: Judy Racoosin, FDA. The ambulatory blood pressure monitoring substudy did have a pre-specified statistical plan, sorry. I just wanted to clarify that. That's why that's included in this question.

DR. NEILL: Dr. Lewis?

DR. LEWIS: So I just have a question for Dr. Hertz, because I think I understand this, what we're supposed to do, that actually the current labels say that they have all equal risk, which is the conclusion of some of this trial. So what we're really talking about is better informing physicians by actually describing this trial or some excerpt about this trial in the label. Right?

DR. NEILL: I'm actually going to use chair prerogative to redirect at this point because what we're discussing now is question 1. And as we go through the remainder of the questions for the PRECISION trial, we will have opportunity in the very next question to discuss some concerns and we're not voting.

In fact, I feel very good. I'm going to give this committee props because you all contributed and I thank you. And I feel like that's what staff and sponsor are looking for, the general input related to the specific discussion questions that we're going through. They do go

through those in great detail. Excuse me. Dr. Meisel?

DR. MEISEL: [Inaudible – off mic].

(Laughter.)

DR. NEILL: No, you are not excused for the rest of the day. We have eight more questions, three of which are voting.

So I'm going to give a brief summary of what I've heard. I am a family physician. And with regard to the issue of discontinuation and dropout, I have a reflexive response when a student is present, shadowing me, and a patient asks, "Do I need to be on this the rest of my life," and my reflective response has become, the answer to this question is never yes. The answer is, until we know better or until something better comes along, and something better always comes along or at least that's what the commercials are going to tell you.

As a consequence of that, my observation has been that patients frequently stop, discontinue for all of the different reasons that medical anthropologists, and health economists, and

pharmacy industry look at why patients do or don't take medicines.

I'm not concerned by an absence of attention in this trial to the fact that, that type of discontinuation or switching doses occurred, nor am I as concerned that there was inattention to drop-out.

With regard to the committee was discussion, what I have heard generally is that the committee feels, with regard to the specific question, that celecoxib relative to ibuprofen and naproxen seems non-inferior specifically with regard to these APTC and hypertension endpoints with many different, very specific cogent well-thought-out concerns, which we'll discuss now in the second question again.

Let's move to the second question. Yes, Mr. Dubbs?

MR. DUBBS: I'm just thinking about what the word "safety" means. And when we say non-inferior, does that mean it's safe? Or are the others all the same issues, and this one is also, and it's not

any less, but it's not necessarily safe?

DR. NEILL: I'm also going to use chair prerogative to explain to you how I would like to structure this discussion. With regard to the first question, the first discussion question, you'll notice that we and I went through very deliberately try and assure that everybody was able to make a comment first, which by preventing respondents in the immediacy of a comment in some respects limits discussion.

That's deliberate on my part. I think, as we go through the other discussion questions, I recognize and I'm willing to allow us to play out individual issues that are new for which there are new points to be made as they come up.

In that regard, if you get my attention while we have a list of speakers, I may ask you is it specifically with regard to this. If not, we're going to move on. So Dr. Blaha, is it with regard to this specific issue?

DR. BLAHA: I'm not sure I fully understood that issue. I had a separate question about

question 2. I couldn't tell if we moved to question 2 yet.

DR. NEILL: I'm not to question 2 yet because Counselor Dubbs asked whether safety was non-inferiority. If there are no other comments about that -- Dr. Farber?

DR. FARBER: So that's a really good question and that's what I tried to bring up earlier, that this being a non-inferior trial, you can only say that, basically, celecoxib is no worse, no more dangerous than is naproxen or ibuprofen. What is safety? I mean, basically, I think that may be something the FDA needs to eventually define, but --

DR. NEILL: Unfortunately not the subject of the discussion of this committee today.

DR. FARBER: Right, and I'm not going to go there.

DR. NEILL: For those of you that wish to stay behind, maybe you want to grab a beer together and go over that.

DR. FARBER: I'm not going to go there, but

only to say that, basically, since there was no placebo arm, and legitimately not, you can't say whether this is safe or not. You can only say that it's no more dangerous.

DR. NEILL: In my practice, the question is, is it as safe as walking across the street to come to my practice? Which, because there's not a light and the orthopedics practice is in my building, not that I'm imputing any intent; it's a dangerous event. But because it's familiar, people misattribute the risk attached to that phenomenon and misattribute risk to things like these medications, very important question.

Now, let's move to question 2. I'm going to read question 2. I'd like the committee to discuss limitations of the PRECISION trial that may interfere with interpretability of the cardiovascular outcome results, including the comparability of the dosing regimens and any other concerns regarding study design or conduct.

Before I open to committee discussion, I'm going to try and list some of the concerns that

have already been raised. And I'm confident I will be incomplete. I heard some concern and also some committee members being reassured by whether or not the baseline cardiovascular risk of the patients was high or not.

My sense was that, if the committee were to be weighed, that it was slightly in favor of reassured that these were high-risk patients, it was defined, et cetera. We have already begun a discussion of whether or not, given the original design of the trial, there were statistical methods that could have been applied after initiation that might have addressed some of the concerns that arose with regard to dropout, discontinuation, adherence, and switching.

I heard concerns about dosing, which I think is specific to this question, both that we and FDA limit any conclusions that we may draw about the study results to the study dosing, which has been noted repeatedly for celecoxib, had been limited, could not be increased or accelerated.

I heard some discussion of study selection

for OA/RA patients self-dosing for those meds that were available in OTC settings.

We have discussed and in the question 1 discussion, the concern about event rate and adjustments that were made to the upper limit confidence levels were raised. And with regard to dosing, I heard a very specific comment about not just the average or total daily dosing, but the frequency of dosing. I would also remind the committee that, yesterday, we saw a lot of data about the timing and ordering of dosing when it came to aspirin, celecoxib, ibuprofen, naproxen, one before the other, twice per day, three times per day, et cetera, et cetera.

So having already heard those concerns now, I'd like to open the floor to the committee. If you have a comment or question, please raise your hand. We'll start with Dr. Blaha.

DR. BLAHA: Mike Blaha. I'll make a quick comment about the cardiovascular risk since I do come from a cardiovascular background. I'll say I'm reassured by the cardiovascular risk of these

patients. The event rates are going down.

We see lots of patients that have a lot of 10 percent ASCVD risk over 10 years, which we consider high enough risk to treat with preventative medications. So I think that it's overplayed in my opinion to criticize the trial based on the fact that the patients weren't high enough risk. They have risk.

But the comments I want to make actually have to do with dosing because I'm sitting and thinking about dosing quite a bit and it's very interesting. And I was trying to take the approach of someone who doesn't know a lot about pain medication dosing. And I'm trying not to pay attention to the fact that one drug is 100 milligrams and one is a higher dose because, of course, the milligram numbers don't matter. What matters is what the drugs do.

So taking out that the numbers are bigger in one arm, I'm just looking at what the drugs do. And I'm acting as if there's an indicator of the effect of that drug and comparing them, just as if

I was looking at a blood pressure drug. I would be comparing not the milligram dosage of the drug, but whether the blood pressure came down in the same in both arms or if the LDL came down or if the A1c came down.

At least what I saw from a non-pain specialist is that these doses produced equivalent pain lowering. So I think the doses seem comparable to me. Let's finish that thought. So I didn't have a lot of concern about the dosing, I guess especially because it's within the range of the recommended doses.

So I didn't have as much of a concern, I think, as others, since it seems like the indicator of the effect of that drug for its intended purpose, pain, seems similar. And maybe I guess some of the pain specialists can fill me in there, but at least as far as looking, it says a drug that produces an effect and is the effect equivalent across the drugs. I actually from what I saw, and as I missed it, was equivalency.

DR. NEILL: Before I go to the next speaker,

I would note that, in my practice, everybody knows that 500 milligrams works better than 50 without regard to what the medicine is. And if it's prescription, it works better than OTC, even when they are identical medicines off the same manufacturing line.

DR. BLAHA: Right. I'm allergic to the 2-milligram, but I can take the 4-milligram dose.

DR. NEILL: Dr. Meisel?

DR. MEISEL: Thank you. Just to clarify from FDA, the reason that OA has a dose of 200 milligrams a day or 100 BID, whereas RA has a higher potential. The reason that was the design -- correct me if I'm wrong -- is because higher doses offer a higher risk, but no added value. Is that correct?

DR. HERTZ: My understanding of the labeling is that it reflected the clinical trial results from the original applications for those indications. So we saw a little bit for the OA trial, that there wasn't a dose response for efficacy, so the dose was different than for the

RA.

DR. MEISEL: So again, to me, that's reassuring. All the concerns about the dose escalation for naproxen and ibuprofen; there are ranges there where you do add efficacy at higher doses that don't exist for celecoxib, at least for the OA population.

So I am unconcerned about the dose questions in this space. I really am. Now, what happens in clinical practice? I'm sure that there are some OA patients who end up on 200 BID or whatever. I'm sure that happens in the real world. I don't know if FDA has data to that effect, probably not.

But at least in the doses studied for the reasons that are given and the fact that they had comparable pain relief, to me this is a non issue.

DR. NEILL: Dr. Rosenberg?

DR. ROSENBERG: Yes. It's another comment regarding the dose and comparability. When I look at the subset of limited sample size I acknowledge of the RA patients, we use, I think, about 40 percent higher dose if I remember well. The

results seem fairly consistent with the overall results, so that, to me, is fairly reassuring, that this dosing issue is not really a major concern.

DR. NEILL: Dr. Farber?

DR. FARBER: So one of my concerns, you had mentioned, actually, was timing. And correct me if I'm wrong, but I don't remember us discussing if there were any data about when the patients took their aspirin in comparison with their particular NSAID or celecoxib.

DR. NEILL: If we had or if that was in the PRECISION trial, would it be a current for you, the absence of data regarding the timing?

DR. FARBER: Right. It would be, and the reason being that -- and we'll get to this a little later. I'm not sure how much celecoxib is involved in the interaction with aspirin, like the other NSAIDs are.

But if there were a possibility -- and there may be a different kind of effect, but if there were some kind of interaction, if for example the patients who were on celecoxib happened to take

aspirin, all of them took aspirin a half-hour before the celecoxib, whereas all of the patients who were on NSAIDs, meaning ibuprofen and naproxen, took the aspirin together with their ibuprofen or naproxen. You would expect to see no difference if for example celecoxib had more events.

DR. NEILL: I think Dr. Roumie and Dr. Lewis both have a comment about this specific issue of timing. Dr. Roumie?

DR. ROUMIE: Yes, they did mention that it was part of the protocol that the aspirin was to be taken two hours prior to the study dose, but we didn't see any data on if people complied with it, but it was mentioned.

I think my second comment is, while much of the committee has convinced me that there was some benefit to the trial. I still keep going back to that the risk of Celebrex and celecoxib in many prior trials and in the information up to now was a dose response risk.

So the risk for events happened at much higher doses. And to say that we are narrowly

looking at this one dose because, as you mentioned, one is good, two is better, three much be great.

DR. NEILL: That's the American way. Dr. Pratt, I think you wanted to speak to this question?

DR. PRATT: Right. This is Valerie Pratt, FDA. I just wanted to add on to Dr. Roumie's point. As was already expressed at this meeting, I understand that patients were advised to separate the ibuprofen and the aspirin dosing by two hours.

I understand, as you pointed out, that data was not presented about whether or not that advice was actually adhered to by the patient. And I will further point out that, as I understand it, it was again not clarified if the patients were taking immediate-release release or enteric-coated aspirin, which as displayed in the slides yesterday have different half-lives.

DR. NEILL: Dr. Lewis, you were next on my list anyways.

DR. LEWIS: Yes. So I was going to just clarify what you already have, that yes, it was

part of the protocol. I think showing adherence to it, unless you did a MEMS thing or something, would be asking the patient, which is semi-worthless, but not semi-worthless, but it would be not real accurate.

But I don't think there's any reason to believe since this was a double-blind trial with three dummies and they worked hard at it, that there would be a differential not following the instructions between the three groups, so it doesn't worry me.

DR. NEILL: Dr. Parker, did you have a specific comment about this?

DR. PARKER: [Inaudible – off mic].

DR. NEILL: We're going to come to you then in a minute. Dr. Cunningham?

DR. CUNNINGHAM: Mine was just in reference to Dr. Blaha's comment. So we look at fentanyl and we look at morphine. Right? And morphine's in milligrams. Fentanyl's in micrograms. Probably most people don't know that. Well, most of our patients don't know that C means a whole lot. But

I think we can't look at the absolute numbers, although I think our patients do.

DR. NEILL: In Philadelphia, they're all in bags.

(Laughter.)

DR. NEILL: Dr. Parker?

DR. PARKER: So difference in dose; the other just question, concern in my mind related to when I thought about the baseline characteristics of the population and looked at the description in the intention-to-treat population. My understanding; it's similar across, but the mean BMI for the study populations is about 32.5.

That's big, whatever word you use around that. And so I don't know a lot about it. I only know the mean as I saw it reported in the PRECISION trial in the New England Journal, so I don't know a lot about that, but it does come into my mind when I think about not big, given that 32.5 was the mean BMI across the three arms in the study.

I'm thinking about whether or not the dose in terms of the metabolism of the drug and in a

population that's consistently that size versus the members of the population that aren't that size and whether or not that could impact anything comes to mind.

DR. NEILL: My suspicion is that that's a lower than the mean in the United States adult population about this specifically, good, about BMI, and then afterwards it'll be Dr. Richards and Dr. Ohman.

DR. LEWIS: Yes. So actually, you should come to Nashville. That's not actually that big a BMI there. But having said that, I think that we have almost no data and neither will they on any drug. And I know, as pediatricians, you guys do it all the time.

But as adult physicians, most drugs, we have no idea in the BMIs of 40 versus -- I mean, it's just bad. And it may be one of the reasons obese people have such poor outcomes in many medical things. We may be underdosing their antibiotics or whatever, but I don't think it's a precise complaint of this drug or this study.

DR. NEILL: Dr. Parker?

DR. PARKER: Actually, I think in many trials, there's greater variability. I think this relates to the prevalence of OA, and who has OA, and who you're going to see a lot of, and the patient cohorts, so I understand what you're saying.

DR. NEILL: Dr. Richards?

DR. RICHARDS: Just to go back to the dosage equivalents based on their pain response, it's actually a 100-millimeter pain scale and the decrease was about 13 millimeters, which is pretty small. And that may be because there wasn't a washout period.

Certainly, that would be within the range of a placebo. Many of the trials for pain -- and I should clarify I'm not a pain specialist. The placebo would actually get more of that, but they may have had a washout period, but it is reassuring that the decrease in pain was similar across the groups.

DR. NEILL: Dr. Ohman?

DR. OHMAN: Magnus Ohman here. This is not a dosing comment. That is a reference to Dr. Li. Is that a lot?

DR. NEILL: Certainly.

DR. OHMAN: So I recognize that you had done sensitivity analysis and I'm going to just try to explain, at least from my simple mind, how tenuous this is, because if the trial had gone to the 762 events and if we actually said that there were then on average 52 extra events, the number of additional events that need to be changed may actually be proportionally lower out of the total endpoints by a fair bit.

So I'm not too sure. This is a very complicated issue, but it speaks to the challenge when trials are underpowered. And I'm sure you can do Monte Carlo simulations, sensitivity analysis with all the variables that you need to do. And maybe that is hopefully something that you can carry out.

But I think it's very tenuous when the proportion of missing events, potentially missing

events had a trial been adequately size for what it set out to do. That's maybe the biggest issue that I see.

DR. NEILL: Dr. Boudreau? I'm sorry. Dr. Li, did you want to respond to that?

(Dr. Li gestures no.)

DR. BOUDREAU: Dr. Boudreau?

DR. BOUDREAU: Denise Boudreau. Getting back to the comment about BMI, I think we're all very aware that one of the limitations of trials is generalizability. And my question yesterday around age, and race, and gender was similar in that there's a lot of generalizability issues potentially with this trial.

We've talked a ton about dose, but dose specifically related to clearance for older individuals. Someone mentioned biomarkers and just probably lack of data on whether the effects that we see in the specific population would extrapolate to other populations, is all.

DR. NEILL: Thank you. So I've heard from committee members that wish to make a comment.

Before I recognize you, Dr. Lewis, specifically with regard to question 2, for committee members who have not commented, do any of you wish to add or have anything new to add to the lists of concerns regarding study design, or conduct, or dosing?

(No response.)

DR. NEILL: Dr. Lewis?

DR. LEWIS: I want to clarify my concern about dose. I'm not concerned about whether it's a low dose of this and ibuprofen is a high dose, or the pain scale, or any of those things. I do think that I had read the paper that Dr. Wolfe showed in his slide about the potential dose effect of Celebrex in cardiovascular risk.

I was around in the Vioxx time and I do strikingly remember that a concern was that Celebrex just was a lower dose than Vioxx and that's why it didn't have as much cardiovascular risk. So for me, if I was going to try to inform the public, I think it would be important to inform them of the mean dose of this trial being 10 BID.

To just put the range that the patients could get, I think, would be potentially misleading in a potentially unsafe way.

DR. NEILL: Thank you. So I'm going to again applaud the committee because one of my measures of success has to do with the efficiency, one measure of which is speed with which we can generate the themes related to the specific question in front of us.

I will point out that, not yet being 10:30, which is the time for our first break, we have already, I think, had a good discussion of both questions. Now, this is my imperfect assessment. And I just want to do a check because, if any of the committee members feel that either the process we're using or the speed is limiting in some way, themes, questions, or concerns that need to be raised for FDA, I would be anxious to hear your thought.

If there are none, we're going to proceed to number 3, which is a vote.

(No response.)

DR. NEILL: I'm sensing the committee's okay so far. So number 3, question 3, is a vote. I'm being asked whether I summarized. I did not summarize. Rather than reiterate the list that I did not write down at the beginning, but which I'm confident our capable transcriptionist will record for the minutes, I'm going to point out that the additional important issues that were raised that I did record are concerns about how we advise FDA about what clinicians should say about dosing, that we restrict our advice to the dosing as in the PRECISION trial.

There were concerns about the generalizability specifically with regard to the average weight and size, the BMI of patients. There was additional discussion of timing. And there was some elaboration about the statistical methods that were used. Did I forget?

(No response.)

DR. NEILL: So that's my summary. Let's move to question 3. This is a vote and I think I have some script that I'm going to read. We will

be using an electronic voting system for this meeting. Once we begin the vote, the buttons will begin flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote.

If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the screen. The designated federal officer will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and their vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in this same manner until all questions have been answered or discussed.

Are there any questions about the voting method that we'll use? If not, I'm going to allow the committee to pause. There are two parts of

this that are important. One is, we will vote. This involves pushing a button. As important and perhaps more is that, after we vote, we will go around, starting at staff end of the table, all the way around to state your name, and read your vote in, and at that point remark if you want to about why you voted how you did on the specific question. Dr. Parker, you have concerns or a question?

DR. PARKER: I just had a clarifying question. So I would like to know, has the PRECISION trial demonstrated comparable cardiovascular safety at a dose of 100 milligrams a day for osteoarthritis for celecoxib as compared to Naprosyn and/or ibuprofen? Or is this a carte blanche, if you will, cardiovascular safety for celecoxib without specification of dose, patient population as we previously discussed, if I could just have clarity on what I'm voting for? Thank you.

DR. NEILL: My understanding is that this is within the context of the PRECISION trial, not how we might generalize the results of the PRECISION

trial to patients who walked into our office with OA or RA. Am I clear about that?

DR. PARKER: I think that the question should state that specifically so that the recorded vote would accurately reflect what it is that we're asked to vote on, because I think those are two very different things.

DR. NEILL: While I appreciate the comment, there's another reflexive response that I have when I hear the word "should," which is a moral term and it reminds me of the first time I was in a meeting with you in 1999 and I made the mistake of asking how do we change this.

The response of one of the staff was, very politely, "Run for Congress." So while I agree with you, I think it's informative and I think that the staff will hear our comment after we vote.

With that in mind, I would encourage us as a committee to vote and, if in your explanation of your vote you want to explain how and why you voted the way you did because here's how it should be, I would encourage you to do so. Now's your time.

You don't even have to run for Congress. Okay?

(Laughter.)

DR. NEILL: Any other questions or clarifying questions about the vote that we're about to take?

(No response.)

MR. DUBBS: Does it matter if you use your right or left hand?

DR. NEILL: The question to me was whether it was important to use left or right hand. It is not important. So we're now open to voting. So now, committee members, please vote. I beg your pardon. I need to read the question for the record.

Vote, has the PRECISION trial demonstrated comparable cardiovascular safety for celecoxib as compared to naproxen and ibuprofen? Please provide an explanation for your vote. Now, please vote.

(Voting.)

LCDR SHEPHERD: For the record, the vote is 15 yes, 5 no, 1 abstain, 0 no voting.

DR. NEILL: Thank you. Starting on my left,

I'd like to start with Dr. Hendrix and we'll go around the table this way.

DR. HENDRIX: Craig Hendrix. I voted yes. I have no additional comments to my prior comments on question 1.

DR. CUNNINGHAM: Melody Cunningham. I voted yes for the equivalent cardiac risk for OA and RA patients receiving 100 milligrams BID.

DR. ROUMIE: Christianne Roumie. I have been convinced by the committee that the trial did add value. I believe there is comparable cardiovascular event rate at the 100-milligram dose. So my vote was yes in that context.

DR. FARBER: Neil Farber, I voted no. I think my major concern is the word "safety" and the fact that I don't think it proves safety because of the fact that it perhaps demonstrated non-inferiority, but not safety necessarily.

Also, even apart from that, if I were reviewing this study for a paper as a peer reviewer, I would have a lot of comments that the committee said and would send it back, saying you

need to do these before we could publish it.

So I think there needs to be some spiffing up of the statistics before we can say that this is a yes vote.

DR. PARKER: Ruth Parker, I voted no, similar concerns about, yes, it did prove the non-inferiority, but I have concerns about whether or not that's the same as safety and also because I felt like, without further clarity in the question, my vote could be misinterpreted.

DR. BOUDREAU: Denise Boudreau, and I voted no for methodologic concerns, both design and analysis that have been discussed.

DR. RICHARDS: Steuart Richards. I voted yes with the caveat that we're mainly looking at the 100 milligrams twice-daily dose and also that the FDA will follow up on a number of the recommendations that were made in prior discussions.

DR. OLIVER: Alyce Oliver. I voted yes. I share the concerns about it being called a safety trial.

DR. NEILL: Richard Neill. I voted yes because of those constraints of the question which asked about comparable safety. I believe that it showed comparable safety to the other study drugs, which is not to say safe. And in practice, as I consider how I might counsel patients who are asking, I will recall that, among this group, there are some specific times when these medicines are not a good idea.

I frequently have that conversation because so many of my patients are on aspirin and have high cardiovascular risk. So having said that and given the limitations of the question, this is why I voted yes.

DR. TCHETGEN TCHETGEN: Eric Tchetgen Tchetgen. I voted no for the reasons that I stated before. I had concerns about primarily post-randomization events such as switching, discontinuation, which were likely to make the arms comparable irrespective of the actual effects, differential effects of the drug post-randomization.

DR. SCHMID: Chris Schmid. I voted yes with the caveats that the recommendations are limited to the doses and indications in this trial. I do share the concerns about the design of the study, but I felt the results were strong enough that the comparability of these particular drugs was probably shown.

I do want to add that I do believe, for the overall question here of safety, I do think there needs to be consideration of other studies, whether it's a meta-analysis or something. I don't think this one trial answers the question.

MS. ROBOTTI: Suzanne Robotti. I abstained because I objected to the phrasing of the question. It was unclear what message we would be sending. I found the similarity of the results to be reassuring within the study, but it didn't demonstrate safety. It showed no increase in harm.

Also, my comfort there is undermined by the issue that the dosages did not seem to be equivalent across the board. The range of dosages was not tested for Celebrex and I'm not confident

that the medical community will restrain itself when prescribing in response to patient pain in real life.

So voting yes would have sent an unclear message and voting no didn't address those issues.

MR. DUBBS: I voted no.

DR. NEILL: Make sure and state your name.

MR. DUBBS: Robert Dubbs. I voted no because of the discussion we had on safety. As a consumer, the word "safety" is a very positive, strong word and there's so much relativity to it in this study that I'm bothered by the use of "safety".

DR. WARHOLAK: Terri Warholak and I voted yes. And I still have the concerns about the study design, especially not adjusting post-randomization. But it is a real-world study and it does provide some real-world evidence that 100 milligrams of celecoxib twice a day is no more risky than ibuprofen or naproxen.

DR. MEISEL: Steve Meisel. I voted yes with the caveat that the question is sort of framed in

the background by the FDA as Dr. Hertz described before within the context of the PRECISION study. I think, although I appreciate the differences with the term safety and non-inferiority, I think it's a little semantic whether something is non-inferior for the safety outcomes or whether it is safe.

I think that, within the context of the question, to me, I see no evidence that celecoxib is any worse than the other agents in this class based on the outcomes of this study.

DR. LEWIS: Julia Lewis. I voted yes. I believe the transcript will safely hold enough of my comments to inform the FDA about why I voted yes.

DR. SOLGA: Steve Solga. I voted yes. I think the question was really quite clear. This was about comparable cardiovascular safety only. This is not a question about whether NSAIDs are good or bad in some global sense versus placebo versus pain and immobility.

It was about comparable cardiovascular safety. And as Dr. Hendrix pointed out earlier,

you'd have to change a whole lot of numbers to reach any other conclusion, so I feel quite comfortable in my yes vote.

DR. OHMAN: This is Magnus Ohman. I voted yes, but with the caveats that this is not perfect science. This is actually fairly unsteady science, but this is the best we have. And I think that what reassured me was that the point estimate in the two comparisons that we saw was on the right side of where we would like to see it, but I have already expressed my other concerns.

DR. BLAHA: Michael Blaha. I voted yes. I agree with Dr. Solga. I personally didn't have too much difficulty with the terms comparable cardiovascular safety in this case. In terms of an interpretation of that, I think it's a fairly straightforward term that I think applies to the results of the PRECISION study.

In my opinion, as a randomized study, I don't have too many concerns myself about post-randomization or events or things that appeared to be equivalent, at least from what we've seen across

the arms in this randomized study.

So I voted yes, that indeed I believe that the PRECISION trial demonstrated comparable safety for celecoxib as compared to naproxen and ibuprofen.

DR. HO: Michael Ho, I voted yes. For me, I was comfortable that the PRECISION study demonstrated comparable safety within the doses that were used in the study.

DR. ROSENBERG: Yves Rosenberg. I voted yes. I'm the last one, so I can summarize all the other comments if you want. For the same reason that said it's comparable safety, that's an absolute within the context of what is currently approved for prescription for the prescribed indications.

So within this context, I really am fairly confident that there's no really little chance of this drug being more harmful than the others in terms of its cardiovascular profile despite all the limitations of the trial. It's the consistency of the results with previous science and within the

trial is fairly strong.

DR. NEILL: Thank you very much. Having seen the vote and heard the comments from the committee, were there any other final comments about the vote that would introduce new themes or concerns that haven't been addressed in the first two discussion questions?

(No response.)

DR. NEILL: Seeing none, I'm going to use chair prerogative to send us on break. We're going to take a 15-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break, amongst yourselves, or with any member of the audience. We will resume at 10:28 a.m.

(Whereupon, at 10:11 a.m., a recess was taken.)

DR. NEILL: Welcome back from break. We're now going to resume discussion of the questions brought to the committee and we'll resume discussion with discussion question 4, if you could display the question.

I'll read the question and then we'll proceed as we did with discussion question 1. Question 4, discuss whether the secondary and tertiary endpoints of the trial, for example clinically significant GI or renal events, all-cause mortality, can be relied upon for comparing the risk across celecoxib, ibuprofen, and naproxen given the definitions used and the lack of a pre-specified hierarchical statistical plan.

If you have comment, I would encourage you to flip your name plate or raise your hand until Lieutenant Commander Shepherd recognizes you and then we'll go in that order. And before I call the first person, because I'm feeling good about this committee and will note that, before the scheduled time for the first break, we've made it through three questions.

I'm going to allow that, if committee members have pertinent question or additional information, to respond to a committee member comment at that time, do your best to try and get my attention and I'll try and do that and, yet, at

the same time, keep us on track so that no concerns or other themes aren't squelched. Okay?

Does everybody understand that? So if it seems a little more freeform this time, that's because it may be. Let's begin with Dr. Lewis.

DR. LEWIS: Being the only nephrologist on the committee and there I guess were no nephrologists in the planning, I want to make a comment about the renal outcome.

First off, I agree totally with Dr. Smith (phonetic) from the FDA's excellent discussion in the briefing document that this did not distinguish well between acute renal failure or progression of chronic renal failure. The outcome they used blurred those things.

I also want to point out that I think the renal events are estimated since study drug was discussed if anyone's creatinine got greater than 1.7 or their BUN 2 times normal, which was actually the entry criteria, that they had to be less than that.

So someone could just have a very slight

decrease in kidney function and be discontinuing study drug. Also, their definition of a renal event, which was a creatinine greater than 2 and an increase greater than 0.7, you really couldn't almost get that without having your study drug discontinued.

It would only occur in people whose serum creatinine was less than 0.9 when they entered for doubling and less than 1 when they entered for the creatinine greater than 2. So the renal events are underestimated on study drug because clearly stopping, I mean, certainly when I do a consult and someone has acute renal failure or even progression, I say to stop the drug and I think it helps. So it's underestimated.

However, I think that, that would likely be equivalent in all three groups and I'm not quite sure that I think that there's a reason it would be informative or hurt one group more than the other.

I think it is reassuring that the adverse events for renal failure, which of course are not the adjudicated definition ones, seem similar

between the groups. But I just did want to highlight that I think we underdetected renal events probably on study drug.

DR. NEILL: Dr. Lewis, I have a clarifying question. Do you believe that the renal events as described can be relied upon for comparing the risk across the three groups, however imperfect?

DR. LEWIS: Yes. That's what I said. I don't think that it affects the relative renal events between the three groups. I think it's just we should know that, because of that discontinuation rule, we might be missing some events and I don't know what would have happened if study drug had continued.

DR. NEILL: Thank you.

DR. LEWIS: I only saw the patients every 6 months, though.

DR. NEILL: Dr. Meisel?

DR. MEISEL: Steve Meisel. Are we able to ask a clarifying question?

DR. NEILL: You can ask and I would encourage that, if you have questions or

observations that you believe might be further informed by sponsor or FDA, that you point those out, but will also note that this time is our time and that that discussion that you may wish to encourage, or explanation, or additional data is something that we will note for the record so that FDA can earn their tax dollars.

DR. MEISEL: Very good. So my focus here is on the GI effects. First of all, just an observation that, when you do a study design to look at X and then you pull out data about Y, Z, A, and B, I think that's highly risky to make conclusions out of because it's easy to come up with the wrong conclusion, that this study wasn't designed to come up there.

So anything with GI, and renal, and mortality, and all of that, I think, has to be taken with somewhat of a grain of salt. For the GI effects, I also want to note that everybody or virtually everybody was on a PPI throughout the entire course of this.

Maybe for the high-risk cardiovascular

patients, that's a part of standard practice, but I suspect that it isn't in the large population, that errors are on a PPI all the time. PPIs have their own independent risk of mortality and other sorts of things that we need to be concerned about.

I think it's relatively easy to present data to support what it is you're trying to prove as opposed to letting the data speak for themselves. So the data we saw yesterday on the GI effects showed an appearance of benefit for celecoxib versus the others, but as I look at figure 28 in the briefing document from Pfizer, there was the risk per year and celecoxib was 0.34. Naproxen was 0.34 and ibuprofen was 0.45.

To me, those are identical numbers. They actually are identical for naproxen and celecoxib. Even though the narrative subsequent to that seems to suggest that this supports the meta-analyses that found a benefit for celecoxib.

I think the data here speak for themselves at .34, .34, .45; are pretty telling that there isn't much of an advantage, particularly when

everybody's on a PPI to start with.

So I think all of the non-cardiovascular hypertension data needs to be taken with a grain of salt and I wouldn't take any conclusions from the PRECISION trial for that.

DR. NEILL: So again, a clarifying question for you, both about the fact that study participants were on a PPI, but also about comparing the GI risk specifically. Given your expert opinion, which with all due respect we all know sits at the bottom of the strength of recommendation taxonomy as strength of evidence, given your expert opinion, do you feel like the data such as it is allows you or can be relied upon for comparing the risk? Would you rely upon it to compare the risk for GI?

DR. MEISEL: I would not.

DR. NEILL: Helpful, thank you. Dr. Warholak, did you want to speak to that specifically?

DR. WARHOLAK: Yes. I'd like to agree and just say that just like would be usual in this type

of situation, these are hypothesis-generating kinds of issues, not hypothesis-testing.

DR. NEILL: Very helpful. Dr. Cunningham, did you wish to speak to this?

DR. CUNNINGHAM: Just in response to the patients, all the patients being on PPI, I think in practicing palliative care, if I had a patient on very high-dose NSAIDs, they would be on a PPI, just like if I put someone on scheduled opioid and I didn't prescribe a laxative. I would be the one who would be disimpacting that patient.

(Laughter.)

DR. NEILL: Dr. Farber?

DR. FARBER: So in regards to all of these events, I'm not a statistician, but the study wasn't really set up to be able to see a significant difference or even non-inferiority for these tertiary endpoints. So I don't think you can rely on them.

However, I think it raises the concern that there should be studies done to specifically look at this because of the fact that there's

significance in the study, even though it wasn't set up to do that. And I think these are important enough issues that need to be looked at in separate trials.

The one other thing I would comment on is the fact that the study was based on changes in creatinine rather than changes in GFR and I would defer to Dr. Lewis, but I don't know how much difference that would make.

It might if you have patients of varying ages, for example.

DR. NEILL: Dr. Lewis, do you want to respond?

DR. LEWIS: Yes. So actually, I created the eGFR or I'm an author on the paper. It just looks at creatinine, age, race, gender. Yes. So gender generally doesn't change. Race doesn't change. Age doesn't have an impact for over a decade. So really, it's in short-term studies and this was 10 years, so age made a little bit of difference.

It's really delta creatinine, so I don't have a problem with creatinine.

DR. NEILL: Thank you. Dr. Tchetgen Tchetgen?

DR. TCHETGEN TCHETGEN: Yes.

DR. NEILL: I'm sorry. Excuse me a second. Did either of you have comments specifically about this?

(FDA gestures no.)

DR. NEILL: Dr. Tchetgen Tchetgen?

DR. TCHETGEN TCHETGEN: Eric Tchetgen Tchetgen. I just wanted to say that, in light of the warning that the FDA put out during their presentation, that these were not pre-specified analyses. I would caution against relying on these analyses to draw any conclusions except maybe as exploratory analyses.

There was a very large number, numbers of p values given to us that were not planned and not adequately controlled for.

DR. NEILL: Dr. Chung, did you have a comment about that specifically?

DR. CHUNG: Yes. I just wanted to note that these secondary endpoints, I think, are pre-

specified and I think are of medical importance of clinical interest to the physicians. And so such a thing is important to communicate.

DR. NEILL: Dr. Tchetgen Tchetgen and then Dr. Hendrix?

DR. TCHETGEN TCHETGEN: Right. While the endpoints were pre-specified, the hypothesis testing that generated the p values were not pre-specified in terms of how the study was planned, that you cannot take them at face value as adequately controlling of type 1 error.

So I agree with you that, in fact, these analyses may have been pre-specified, but the actual statistical control of the type 1 error was not.

DR. NEILL: Dr. Hendrix?

DR. HENDRIX: So I just wanted to clarify. The pre-specified is -- there's two adjectives here. I'm trying to understand which is which. It's the hierarchical, which is the complaint. They were not hierarchical, but they were in fact pre-specified. So that's just to clarify.

DR. NEILL: So the irony of me trying to clarify is not lost on me, but I believe the endpoints were pre-specified, but the statistical plan was not designed a priori to answer the questions related to the p values or the significance of the data that arose. Like many exploratory studies, when presented with a large dataset, academics generate p values and they were generated here.

Without disparaging the hard work over many long years, I think that's an adequate reward so long as it gets published. Just don't try and publish in Dr. Farber's journal, who's tougher than the New England Journal.

But what I'm hearing is that the absence of that pre-specified statistical plan for those pre-specified endpoints ought engender caution. For the statisticians on the committee, is that fair?

DR. TCHETGEN TCHETGEN: That's remarkably accurate.

(Laughter.)

DR. NEILL: I'm going to sleep well tonight.

(Laughter.)

DR. NEILL: The next is Dr. Blaha?

DR. BLAHA: Yes, Michael Blaha, first of all to say that I think it's important to note again; I'll just say for the record that blood pressure results I guess are in question 1 and the other things that we're discussing here are on question 4.

That's important, I think, because their blood pressure was a pre-specified analysis and clinically important results. And I'm going to set that aside because I think that's important to discuss of course the topic for question 4.

First all, I'll just say I think that this is a very important question. It's very important data because all of us, when we give NSAIDs, are thinking about these things. When I give an NSAID, I'm not just thinking about cardiovascular risk. I'm actually primarily in many cases concerned about GI risk, kidney, and so forth.

So I think this is critically important contextual clinical data, extremely important and I

don't want to lose sight of that. And I think it's a major contribution of this trial. And at least there were common definitions used and this was a randomized trial, so I don't have concern for differential bias amongst the groups with the application of these definitions.

But like any randomized controlled trial that has a primary endpoint and secondary and tertiary endpoints, we should take secondary and tertiary endpoints with some grain of salt. I think this is no different than any clinical trial, whether it's a lipid-lowering trial or whatever that looks at other endpoints.

So I think this is critically important. I think it's important contextual data. I think it should be considered like a secondary or tertiary endpoint of any clinical trial and that's important. And the lack of a hierarchical plan is something to be factored in.

I guess the only thing I struggle with are the words "relied on." I think we can rely on it in a greater context for comparing risk, but I

can't exclusively rely on these secondary and tertiary endpoints. But I think they're critically important and, perhaps for my clinical practice, as important as anything else in this trial.

DR. NEILL: As a non-cardiologist, I'll observe the use of the term "with a grain of salt" coming from a cardiologist when discussing NSAIDs is a non-trivial event.

DR. BLAHA: No more than 3 grams of salt per day.

(Laughter.)

DR. NEILL: Any comment related to Dr. Blaha's? Next, I have Dr. Rosenberg?

(No response.)

DR. ROSENBERG: Yes. It's a follow-up. In fact, I have many of the same comments as Dr. Blaha. You can try to attach that [indiscernible], by the way. I really don't care very much about the hierarchical statistical plan in this context. We view all these endpoints really as additional information and really the p value doesn't matter.

I mean, we look at the consistency of these with what we know already and, for the GI at least, I thought these specific class of drug was developed specifically to address the GI question, so this seems a little paradoxical that we're still discussing here. I think it's very, very well demonstrated. Benefits are demonstrated already.

So altogether, within this context, I think this is valuable information. Also, I do agree that you cannot rely on it in a vacuum. It's within the context of all available information that you consider that. It's basically mortality; then I would be extremely cautious about the whole interpretation regarding mortality.

DR. NEILL: Thank you. Dr. Solga?

DR. SOLGA: Dr. Solga. Yes, to me, this is more hypothesis confirming than hypothesis generating. There's a small ocean of information that COX-2 inhibitors are more GI friendly than the COX-1 inhibitors. That was really the inspiration for the development.

So as a gastroenterologist, I would pipe

that into the conversation. And like Dr. Meisel, I'm quite concerned about confounders. We mentioned PPIs and their safety issues. I think that's very, very important. As a gastroenterologist, I'd also include aspirin or non-aspirin use as being essential to understand age of the patients, prevalence of background Helicobacter pylori, which has changed over time. So there are a number of issues that the data can be considered in the context of and perhaps there are some learning lessons from the GI signal here.

But as many others have said, that's not what the study was about.

DR. NEILL: Thank you. Dr. Ohman?

DR. OHMAN: Magnus Ohman. You would think that the three cardiologists sitting online here, or four cardiologists, may actually be singing from the same hymn sheets. But I want to point out one issue here that I think is important to recognize with these non-cardiovascular events.

In the presentation and in subsequent publications, the PRECISION group have talked about

major non-steroidal anti-inflammatory agent toxicity. And they have actually added in cardiovascular events with renal events and serious gastrointestinal events.

Now, we in cardiology are quite happy for net clinical benefit, which is a term that we use, but it only works if those events that are non-cardiovascular have similar weighting for clinical consequences to the patient.

So in that regard, I think the individual components are of interest, the renal ones, the GI ones because they do depend on what we already know, as my colleague here on the left mentioned. And so I think they should be noted.

Somebody mentioned the New England Journal of Medicine. They d this all the time. They present actually non-cardiovascular outcomes in a cardiovascular outcomes trial where there is a significant p value. So I think, in full disclosure, that is something that should be done, but it shouldn't be combined into sort of a net clinical composite outcome because I think that's

an unreasonable weighting of the individual events.

DR. NEILL: Thank you. Dr. Richards?

DR. RICHARDS: Steuart Richards. Yes, I think I agree that it certainly is exploratory and we shouldn't make any definitive conclusions based on these secondary results. It's interesting that the celecoxib had a lower blood pressure. Now you're seeing less renal disease and I'm not sure if there's a direct correlation between that, but I think those two bits of evidence are kind of supportive.

The interesting thing for the GI aspect is that the patients that were supposed to be on a PPI and I think 1 of the questions we had from the clinical standpoint is, if we used a non-COX-2 inhibitor with a PPI, is that just as safe from a GI perspective as a COX-2 inhibitor alone?

If you're taking these results at face value, they're saying no, so I think it's certainly something that probably needs to be looked further into.

DR. NEILL: Thank you. Mr. Dobbs?

MR. DUBBS: Prefacing this with full disclosure, though, when I was in college, I got a D in statistics. I have to say that I'm bothered by the terms relied upon when we're dealing with secondary and tertiary issues because I'm concerned that the robustness, thorough irrefutability when you talk about secondary and tertiary, I just feel uncomfortable saying you can rely on that without that being the focus and the depth in which a study could be made of those points specifically.

DR. NEILL: Dr. Lewis?

DR. LEWIS: So I just want to comment. So on the renal events, I want to make it clear I think that this is not a renal study. I wouldn't want to communicate a message that we know a lot about renal events. Again, low blood pressure would make you more likely to have acute renal failure and maybe less likely to have progression of chronic renal failure, but we can't tell the difference in the outcomes of which occurred, at least by the data that was presented to us and the way they were described.

I said yesterday, but I'll just say, for me, the killer is that it isn't a pre-specified hierarchical statistical plan. It's really a big deal that it's not that and therefore, in and of itself would make me not rely on this.

However, the renal events in particular, I again want to emphasize I think are not a standard way to look at either acute or chronic renal failure because they're conflated and all the other issues that I brought up earlier.

DR. NEILL: Thank you. Dr. Cunningham?

DR. CUNNINGHAM: So I believe that they cannot be relied upon because they didn't have a pre-specified statistical plan and I didn't state that when I spoke earlier.

I also think that even the events are not clearly necessarily delineated. So I put on my hematology hat and I see we're talking about iron deficiency, anemia of GI origin. Well, I think we all assume with NSAIDs that there's macroscopic or microscopic bleeding and that leads to it, but we forget that these are patients with chronic

inflammation.

I mentioned hepcidin yesterday. And I think of that as a GI etiology for iron-deficient anemia, because you internalize your ferroportin when your hepcidin is high and you don't take in the iron that you eat.

So I don't even think that the actual events are clearly delineated. I think they're food for thought and food for further study.

DR. NEILL: Dr. Richards?

DR. RICHARDS: Just in terms of the chronic inflammation, I think the majority of the patients, 90 percent, were osteoarthritis and although there may be some mild inflammation, with OA, I don't think we should look at it as being a systemically inflammatory disease, where it's going to cause a significant anemia or there are complications, which you certainly can see in patients with RA.

DR. NEILL: So before I summarize the discussion related to this question, I want to ask members of the committee who have not had an opportunity to contribute to this discussion

whether they have any specific new issues. And Dr. Hendrix?

DR. HENDRIX: Yes, Craig Hendrix. I just wanted to reinforce what Steve said. I find these to be -- I'm not sure exactly what "relied upon" means, but I would find these to be useful, informative, confirmatory in the larger context.

Since this is one of the last comments, it won't incite riot by the statisticians, but it's always remarkable to me how much weight is put on -- the motivations here to me seem clear. There was a definition, however imperfect, in a number of these other categories that, by labeling them secondary and tertiary and not having a hierarchical statistical plan somehow negates their usefulness.

I always see those more as sort of the priorities of the questions, but not necessarily usefulness of the data coming out of that. And I know that that's a minority opinion in the room, but as someone who is a trialist, and I just give drugs, I measure concentrations, and we don't argue

about statistics very much because there's no other way to get the drugs.

So it's always significant if we can measure it. But I just wanted to say that I do find these useful, just to say that out loud in case there's similar opinions that were looking for someone to sort of go along with them.

So I've said it. Thank you for letting me say it.

DR. NEILL: Dr. Blaha and then Dr. Ho?

DR. BLAHA: Yes. I just have a brief comment and I appreciate what Dr. Hendrix just said, but also, I think it's important when we're thinking about secondary and tertiary outcomes, to think about things that just happened to pop out of analysis or things that are clearly pathophysiologically related to the drug we're giving.

I think it's relevant to me that kidney and GI outcomes are exactly what we're thinking about when we give NSAIDs and there's a lot of prior data in this regard. So I'm no expert in either area,

but I'll say that greater context matters a lot to me here.

DR. NEILL: Dr. Ho?

DR. HO: Yes, Michael Ho. I mean, for me, I think these results were helpful as well because I was thinking what if they found the converse of it, that there was harm? We would be talking about how this would inform the discussion. So to me, I think the findings were consistent and helpful in the broader context.

DR. NEILL: Dr. Tchetgen Tchetgen?

DR. TCHETGEN TCHETGEN: I actually disagree. I think, even if we found significant effect, the same warning would apply, that multiple looks at the data in a manner that was not statistically planned ahead of time opens you up to misinterpretation of the findings.

I don't even know that there's anything to argue about related to that. I think these are useful data to have and to look at. The question is whether or not they can be relied upon for comparing risk and I don't think they can for those

very simple reasons.

DR. NEILL: Dr. Chung?

DR. CHUNG: Yes, just a comment that we're looking at a whole body of evidence, of which this is a very important part. So if you look at the GI effects, for instance, the whole mechanism upon which this is based, the endoscopic studies in the past, and other studies.

So if you put it in that context, I think these results are very significant.

DR. NEILL: So I'm going summarize what I've heard in terms of discussion about this question by constructing an analogy and I'm going to ask each of you for a moment to put yourself in Nepal.

We're about to climb Mount Everest. Many of you know that you begin by going across the Khumbu icefall, which moves and has crevasses. And at the beginning of every season, there are ladders and ropes put across by well-intentioned, very experienced guides, which then gets revised as you go along.

I view the comments about this question as,

have we done a study which allows us to know with some certainty which of those ladders is going to support us, however heavy we may be, however big a pack we may have, however much Motrin we may have taken that morning.

Are we going to make it or are we going to fall into the crevasse? And the role of statistics in the pre-ordained statistical plan in my mind has to do with, in some respects, the engineering that goes into assessing the risk. You can choose whatever ladder you're going to choose and you may find, when you get there, things look a little different and you didn't plan to do this ladder or that ladder.

But we did plan, because of the inclusion in our team of some very rigorous statistical engineers, that this one or two or three paths, if found, would be reliable. And I think what I'm hearing from the committee is that, with regard to the APTC and cardiovascular endpoints, there is, I think, wide if stronger ability to rely and, for these pre-specified endpoints, without the

statistical engineering in place beforehand, we risk relying upon.

Now, as a family doctor or as a Nepalese guide, you're going to get there or you're not, but it's a deadly phenomenon. Well, let me clue you in as a family doctor. My big challenge with all-cause mortality is, it turns out with very rare exceptions we all die.

It's a matter of the length of the study, isn't it? And this is a phenomenally well done study in terms of both length and the data that we have. And I don't think that we disagree amongst ourselves that the presence or absence of the specified statistical plan is going to be the determinant in whether we get across.

It's only going to allow, once we're there or not, for the statisticians to say told you so. Is that fair enough?

(Laughter.)

DR. TCHETGEN TCHETGEN: Perfect.

DR. NEILL: I have a simple mind, so I have to think in these kinds of pictures. Actually, let

me just look at my notes because I want to make sure that I summarize for the staff in a way that's going to be useful for them. I don't think you guys are going to Nepal.

I heard concerns about underestimates of renal effect and that we perhaps can't rely upon either renal or, for that matter, GI events, especially given the swamp of all the other things that were going on over the course of the 10 years in this study.

We also heard a little about data that wasn't presented at this meeting, but that exists and was referenced by some of our experts related to the GI effects specifically.

While not perhaps pertinent to the discussion of this question, I think it provides important context for the context of the questions being asked. I heard dissing of statistics. I heard defense of statistics. Listen, don't try arguing against science and statistics is science.

I heard in a number of different ways that we ought not over-conclude about our ability to

rely because of these reasons. Were there other additional themes? So I'm seeing Dr. Farber. Anybody else? And Dr. Roumie. Dr. Farber?

DR. FARBER: Just the fact that, since there is doubt, at least to some degree, about these data, but that they point out the significant risk that could be associated, that there need to be more studies to look at this.

DR. NEILL: Dr. Roumie?

DR. ROUMIE: I kind of agree with many of the points that have been brought up. I agree as a clinician that an overall event rate among these outcomes is helpful, but the multiple pairwise comparisons that then took place and the bajillion Kaplan-Meier plots that we saw with p values makes me as a methodologist cringe because of course something's going to be statistically significant. There's a billion comparisons up there.

So I think we would have gained more by just kind of looking with the eyeball test at the event rates and saying, is this believable? Is this something that we'll add in the overall clinical

picture?

I do think that it has been brought up that the two composite GI and renal events are kind of conflated event rates, where there is a chronic component mixed in with an acute component.

So you're not exactly sure what that outcome is as far as acute GI bleed with this chronic blood loss, anemia. They're both important. They're both significant events from the patient standpoint. I don't know that it is super clean to put those two together.

DR. NEILL: Thank you. Dr. Parker?

DR. PARKER: So the only other thought I had about this was just to keep our review of it and thinking about it, remember that as part of PRECISION all patients were on a PPI. They were on Nexium. And when I look to the current professional label for celecoxib, I don't see anything in the label about mandatory concomitant or recommended concomitant prescribing of a PPI.

So it makes me think about that and so I just raise that again as we think about anything we

draw from this to be very careful about knowing the details -- and there are a lot of them -- of what we do and don't know based on a complicated clinical study.

DR. NEILL: I'm going to direct my attention to staff and ask whether you believe, given the issues as have been discussed for this question, would staff find it useful for additional discussion about the issues that have already been brought up?

(Dr. Hertz indicates no.)

DR. NEILL: Thank you. So I'm going to consider question 4 discussion closed. And rather than re-summarize what I summarized once before, unless I get advice, I'm going to instead move us on to the next set of questions.

The next body of questions, 5, 6, 7, 8, and 9, all relate to the interaction between aspirin and non-aspirin NSAIDs. And they're designed to generate discussion and there will be some votes later related to that issue.

Question 5, discuss whether there is a

clinically significant interaction between aspirin and celecoxib, aspirin and ibuprofen, or aspirin and naproxen. And Dr. Blaha, could you lead us?

DR. BLAHA: Sure. I'll make a very simple remark here. I think that you always have to distinguish what we learn from a mechanistic study from a clinical outcomes study. So I'll say that there appears to be interesting pharmacodynamic interaction that we've seen.

I appreciate that data. It's interesting. But I'm going to define clinically significant as something that bears out in terms of clinical events and a randomized trial. I have to say that I see no evidence of a clinically significant interaction beyond a very interesting seen in pharmacodynamic studies.

DR. NEILL: Clarifying question; between aspirin and any of the 3?

DR. BLAHA: I didn't see any strong evidence of a clinically significant interaction on clinical outcomes between aspirin and any of the drugs.

DR. NEILL: So again, allow me to clarify

before moving on because I'm a simple family doctor. If I were to send my patient to you as my cardiology consultant, they have an MI, and I've told them keep taking them both, how would you respond?

DR. BLAHA: I guess let me clarify. I didn't see any evidence of a differential interaction between these combinations.

DR. NEILL: One of the challenges as a chair that I have is that I don't always see whether there's need to clarify the question until we start answering, but now I recognize like every other question there might be need to clarify.

So these five questions, I guess I would encourage us to consider whether the interactions exist within the PRECISION data that we've been asked to look at and, given your expertise, experience, and reading, whether there's a greater context. This helps me and hopefully will help staff.

DR. BLAHA: I'll clarify my thoughts even further. I think there's lots of situations where

there's a mechanistic reason to think something's true that doesn't always bear out in trials and we all as clinicians try to factor that in.

So don't get me wrong. I'm very persuaded by the pharmacodynamic data. I think there's probably a steric hindrance at the molecular level here that's relevant. And I factor these kind of interesting physiologic factors in on individual patients for me.

But I'm answering the question I guess as, do I see evidence presented today of a clinically significant interaction that varies between these, that impacts patient outcomes? I didn't see strong evidence of that.

That's not to say that, if I were writing a label, which I don't write a label, if I was writing a guideline, I would say that there is interesting pharmacodynamic evidence of an interaction seen in pharmacodynamic studies. However, there's no solid evidence of a clinically significant interaction on patient outcomes. That's my long answer.

DR. NEILL: Thank you for letting me push you on that. Dr. Roumie, did you want to speak specifically to this?

DR. ROUMIE: I did. While we may not see a clinically significant interaction reported in the PRECISION trial. We never saw data on that. So you don't know when the patients -- if they actually did follow those directions of take it two hours before. So again, as you know, clinical practice is a free-for-all.

We don't know that every clinician will use that same sort of recommendation for their patients and I would argue that many don't actually tell patients how to space out their medications.

DR. NEILL: Go ahead, Dr. Blaha. Make sure and mention your name.

DR. BLAHA: Mike Blaha. So I don't mean to belittle this, because I tell my patients to get off NSAIDs and I try not to use NSAIDs if I can help it. So I mean, I try to avoid it entirely. But if my patient has to be on one, I'm just responding to, do I see clinically significant

interaction? I just didn't see the data.

However, trust me, my cardiovascular patients; I don't want them to take an NSAID if possible.

DR. NEILL: We're going to go to Dr. Ohman and Dr. Ho. Dr. Ho, I didn't know if you wanted to speak specifically to this comment first.

DR. HO: Yes, Michael Ho. I mean, I guess to the point about aspirin, I mean, I'm just not sure about the data because they were all patient reported and I'm just very skeptical about consistent use or adherence with patient-reported data about aspirin use. I mean, you can imagine that they just took it the day of their study visit and they reported that they were using it.

I don't know what the question was, so I'm skeptical of the aspirin data use.

DR. NEILL: Thank you. Dr. Ohman?

DR. OHMAN: Magnus Ohman. This is a follow-on to the discussion. This is one of the more tricky parts of regulatory medicine because, while we want to sometimes rely upon pharmacodynamics,

and genetics, and a lot of other things, we all doctors know that biological specimens sitting around this table are a lot more complicated.

So for that reason, if the question is clinical, I'm going to focus on clinical. But that doesn't mean that there has been displayed very nicely pharmacodynamic effects, as pointed out by both presenters. We really have no clue what that means in the bigger picture.

So from my vantage point, the question really should be framed in two levels; is there pharmacodynamic, yes/no; are they clinically, yes/no. So as it's stated here, the interaction p value to remind you is .4 and .29 for comparing Naprosyn and ibuprofen with and without aspirin with celecoxib.

So to me, I have to say I would have wished that there were two questions. I guess we can't have that, but that's how I see it.

DR. NEILL: Thanks, Dr. Ohman. Dr. Farber?

DR. FARBER: So I'm going to rephrase all of the discussion a little bit if you will. It's

clear that there are pharmacodynamic effects and interactions mainly between aspirin and NSAIDs. That's been demonstrated between aspirin and celecoxib.

But it's also clear that there are cardiovascular effects of all three of these drugs. Whether that's because of the interaction between the drugs and aspirin, I have no way of knowing that. I don't think anybody has any way of knowing that because there are other possible etiologies. I mean, it could be the vasoactive effects of the medications or it could be changes in doses.

For example, celecoxib, when you get up to much higher doses, starts having significant cardiovascular effects, more so than at lower doses. Is that because it's more of a vasoactive effect or is that because it starts having COX-1 effects? I don't know.

So I can't say that there is clinically an interaction. I can say that for all three, there's cardiovascular effects that need to be looked at.

DR. NEILL: Thank you. Dr. Oliver?

DR. OLIVER: Alyce Oliver. Actually, I agree. I was going to say something similar that Dr. Ohman said, that the question really does emphasize clinically significant, so that gives me a different answer, that I did not see a clinically significant interaction with the PRECISION trial.

I do find the pharmacodynamic studies far more interesting, particularly when on the short term there's a washout of the NSAIDs and we do see changes there. I do think it was difficult with the PRECISION trial to know if they were taking the aspirin. And there certainly seems to be an interaction of non-steroidals with aspirin depending on when they're taken. And I think that needs to be explored clinically.

DR. NEILL: Dr. Cunningham, I moved a little quickly. I thought you might have had a comment about Dr. Farber's. Go ahead.

DR. CUNNINGHAM: Thank you. Yes, I had a comment about this discussion. So if we're looking at clinically significant -- and I do think the pharmacodynamic studies are very

interesting -- when we looked at our post-study events, they looked at them in a 30-day window.

I think it would have been far more interesting from a clinical standpoint to look at them in a 3-day period because that's when we see the pharmacodynamic and the washout information. So that might have helped to inform this question.

DR. NEILL: Dr. Hendrix?

DR. HENDRIX: So I would revise that briefly and say it would be interesting to look at a 1-day window because I think that's where the consistent differences were there in the pharmacodynamic data.

But I would caution that all the statisticians will be all over you so that you not overinflate your impressions from that and say that would be a very exploratory, exploratory analysis if one were to do that because I'm sure that no one conceived of that ahead of time.

The comment I was actually going to make is that I think it's true that the pharmacodynamic data -- this is sort of odd that I would be the one saying this -- I thought was very useful to

understand the timing issues, and the study that Dr. Gurbel presented was very useful in understanding that.

It also seemed to be very sensitive -- the pharmacodynamic in terms of the thromboxane effects were very sensitive to the dose level. And I think it's hard to predict and those doses were lower than the doses used, at least the starting doses that were used in the PRECISION trial.

So extrapolation from one to the other is fraught for that reason and I'm not sure what I would even expect it to be as you got to higher concentrations, that there might be a delay in the washout effect or it might be ameliorated all together because the concentrations are so much higher and protective because of higher concentrations of all the drugs.

Except for the celecoxib, they are protective. But there's this discordance between those two readouts, which was striking and in some ways the most interesting thing because I think so much is made of those in vitro tests, which is why

I asked about those results specifically, to see if they're in concordance in the PRECISION trial if they are also discordant; that is, if there are less than 95 percent of the inhibition of the thromboxane 2, to just pick one because they can do that in the archive samples to see if there's a discordance, which would be very helpful to go back to all of that old data that's been used to raise these questions.

This is highly relevant to the over-the-counter prescription issue and maybe I'm getting ahead, but these seem to be grouped for that. So I didn't see evidence of clinically important. And it really questions, given the size of the larger study and, again, with all the caveats, how important all the pre-clinical data is except to perhaps even rule out the importance or to put in context this is one of I don't know.

Can you list 5, 10, 15 important variables in a multifactorial, very complicated system, only a number of which were pointed out?

DR. NEILL: Dr. Rosenberg?

DR. ROSENBERG: Yes, thank you. I do agree that we hope the samples will be put to good use and try to elucidate that question. In terms of clinical relevance, I don't think we're really much more advanced than when we were before this meeting and before the trial results were available except that I'm still puzzled by the analysis stratified by aspirin use.

I think it's a valid analysis. It was stratified in a double-blind context. There's no expectation that there would be major differences in aspirin use. I understand the concern about the timing. That's important.

But I still would like the experts to comment on why the results are counterintuitive. I mean, we would expect that we have more difference between celecoxib in the aspirin you open [indiscernible]. We kind of see the trend going the other way, so I don't understand that.

DR. NEILL: I'm trying to reconcile one of the principal scientists of the National Heart, Lung, and Blood Institute asking for the experts to

comment.

DR. ROSENBERG: Thank you. I appreciate that. I'm not a pharmacologist, certainly not in this area.

DR. NEILL: Very humble. Dr. Lewis, was it about this specific comment, please?

DR. LEWIS: It is. And actually, it's a little bit of an echo of your comment, but really, I mean, I actually want them to think about it seriously. I found these aspirin results to be un-understandable to me. It did make me go back and learn a lot about aspirin and COX-1 and platelets, which I hadn't thought about in a long time.

In the end, it doesn't make sense because it isn't just that on aspirin they're all equal, where celecoxib should have won. It's also off aspirin. It's the opposite of what you'd expect. I mean, maybe aspirin doesn't work through platelets.

So I was hoping you cardiologists would tell me that maybe it's reactive oxygen species and maybe it something through COX-2 or do you two think the data just wrong? I mean, by the way, all

the pharmacodynamic data that we've had, and that we've read, and that I read, since there's no correlates of these interactions with any cardiovascular outcomes study, this is the closest thing to it with all its flaws and I'm really confused by it.

DR. NEILL: I would be willing to come back for that meeting, but that's not this meeting. The question here is whether there is a clinically significant interaction between each of these three.

What I'm hearing you say is, it's not clear that it's clinically significant from these, but there should be some more studies and they should be designed this way. I'm probably hearing incorrectly.

DR. LEWIS: [Inaudible - off mic].

DR. NEILL: We're going to go to Dr. Meisel. Did you have a comment specifically about this issue?

DR. MEISEL: Yes. I think maybe, to frame it in a little different way, we know that aspirin

acetylates platelets and we know that at least ibuprofen and naproxen interfere with that. And we know that aspirin improves cardiovascular mortality. What we don't know is whether the acetylation of platelets is the reason why it improves mortality.

Therefore, assessing the clinical impact of the interactions is impossible.

DR. NEILL: I would additionally suggest things that I don't know; namely whether each of those things is a first-order kinetic process, whether when taking aspirin, given its short pharmacokinetic half-life, the population of platelets, which in their destruction and production is not a first-order kinetic process, but changes with regard to inflammation and all manner of things that the hematologists will tell me about, and given that I don't know whether having taken a single dose of aspirin and thereby poisoning the population of platelets in my body for the next 90 minutes, whether the introduction of my new platelets and their platelet production

rate is what contributes to that never-can't-quite-get-100-percent efficacy.

If so, why are we only dosing aspirin once per day and where is that long-acting aspirin? Because all we need is for the aspirin to be there when every single little platelet knocks on the door to come out into the blood to, like, poison it.

We've seen no data from these studies that answer those questions, either. And yet, my patient is going to ask, "Should I take them together? Should I take one first? Should I not take one? What if I've had a heart attack?"

DR. MEISEL: Right. It underscores the danger of taking the laboratory evidence and translating it into clinical practice.

DR. NEILL: Absolutely. So I think both Dr. Farber and Dr. Ohman may have comment about this specifically. Let's go Dr. Farber and then Dr. Ohman.

DR. FARBER: There is yet another layer in terms of what Dr. Meisel was saying in terms of we

don't know what the effect of aspirin does in terms of -- we know at a pharmacologic level it affects platelets, but does that translate into clinical aspects?

We also don't know the effects of these drugs on patients clinically. Is it through interference with the interference of platelets? Or is it a vasoactive effect? Or is it something totally different?

We know it has a clinical effect, but whether it's through platelets, whether it's an interaction with aspirin, that we don't know.

DR. MEISEL: Or is the statin effect because we're lowering cholesterol? Is it because of other things? It's the same kind of --

DR. NEILL: So that was Dr. Meisel.

DR. FARBER: We know that statin has more than one effect.

DR. NEILL: That was Dr. Farber for the transcriptionist. And Dr. Ohman, I'll allow you to make the last comment and then we're going to move on to Ms. Robotti.

DR. OHMAN: Magnus Ohman. So I want to respond to Dr. Lewis's comment because I think this is really what the fundamental issues are regarding pharmacodynamic studies. In any of the pharmacodynamic studies we've looked at, we looked at platelet aggregation and thromboxane B2.

But you heard from Dr. Gurbel yesterday when asked a question, are there other effects, collagen effects, ADP effects. And he didn't give an answer, but he alluded to the fact that there could be other pathways, so while we have pharmacodynamic effects that are laid out here very clearly, they only represent two aspects really of the platelet.

Then the second part is that much of the work has been done with regular aspirin, not really with enteric coated, and that's another variable that enters into this whole picture. And we don't really know the pharmacodynamic effects of that, not from what I saw presented.

So there's many issues here and that's why I said clinically significant and pharmacologically. It would have been a great pharmacological

discussion had that been the question.

DR. NEILL: Thank you. So I still have Ms. Robotti, Dr. Schmid, Mr. Dubbs, and Dr. Richards. Thank you for allowing me to indulge in delaying your participation a bit. Ms. Robotti?

MS. ROBOTTI: Suzanne Robotti. There's clearly an interaction with all three drugs. The washout period in the PRECISION study seems to clearly indicate that. What the clinical significance is of this, I don't know. I don't think that the study tells us that.

This PRECISION study; that's exactly the point I've been wanting to make. PRECISION study did not break up enteric versus IR. I think that's very significant. The only studies we saw in preparation for this meeting also focused only on IR aspirin, not enteric.

The unanswered question is the efficacy of enteric. Well, there are many unanswered questions; sorry. An unanswered question is the efficacy of enteric aspirin when used with NSAIDs, even with a two-hour window before it.

DR. NEILL: Dr. Schmid?

DR. SCHMID: Yes. I don't know if this is beating a dead horse, but just looking at the clinical data that were presented, all we really know is whether patients used at baseline and whether they added during the study.

The vast majority who were using at baseline continued to use and there were a few people who started during the study. And we don't really know when they started from the data that we got.

So I mean, my problem I guess is that pharmacodynamic studies are very much focused on the timing as being the important thing. We really don't know anything about the timing from the clinical data, so in terms of it being clinically significant from this study, I don't think we really know anything from this study.

We do know something more from the pharmacodynamic studies and we know stuff from previous studies that have been done, but there may be more data here if the timing was looked at more carefully, but then really, as several people have

mentioned, we don't know whether people actually complied and how they complied.

So in my mind, I don't really think we know enough at this point to make any kind of decision.

DR. NEILL: Mr. Dubbs?

MR. DUBBS: As a layperson and having learned the medical terminology today, I think it's irrefutable that there's an interaction. I think it's most likely significant, but I have no idea if it's clinically significant.

DR. NEILL: Dr. Richards?

DR. RICHARDS: I was just going to point out that these are patients who are probably on a lot of baseline medications to start with. They were diabetic, hypertensive, had cardiac disease, and then we're giving them this double-blind medication. And now we're trying to look at whether they were taking aspirin, PPIs, statins as well.

So I think that all gets into the mix of things. So some of this data are difficult to interpret in terms of what effect specifically

aspirin had on the results.

DR. NEILL: Thank you. Any additional comments or responses that I didn't catch from earlier? Dr. Lewis?

DR. LEWIS: I do just have one comment. So I do really think this is very complicated, but I would not say that I would feel comfortable using the data or using it to inform physicians that Celebrex seems to have less cardiovascular events in patients without aspirin, which we've seen in a slide, but I wouldn't say that that would be something I would give a strong weight of evidence to, but I'm very baffled by it.

DR. NEILL: It doesn't further the conversation, but from my perspective as a clinician, when I'm asked by patients, which one should I do, and given the context of more milligrams is better and prescription is better, et cetera, it's notable perhaps that part of the calculation that goes on in my mind is whether or not the prior authorization I'm going to need to do to get Celebrex is worth the work and effort of

explaining to the patient what is correctly described as a very complicated issue.

Again, it doesn't really add anything, so sorry about that. So I'm going to try and summarize what I've heard from the group. I have heard overwhelmingly that the group feels we are challenged to identify a clinically significant interaction among each of these three pairs or any of these three pairs, that while there are clear pharmacodynamic effects that were demonstrated, the magnitude of those effects and their relation to a potential clinical interaction or clinically significant interaction is difficult to conclude, that that difficulty is informed by challenges in some of the study design and the exploratory nature of the data.

In a few instances, some of the conflicting data, also specifically the doses and the actual formulations, for example, of immediate release versus enteric coated, Nexium in my mind versus omeprazole; why this. Also, some questions raised about timing.

So in general, we can't reach a conclusion that these are clinically significant. There may be some signal there. As is so often the case, more research is needed. Are there any committee members that would like to augment that summary of the discussion? Dr. Farber?

DR. FARBER: Just to add I agree that we can't say there is a necessarily clinically significant interaction. We can say that there is some kind of clinically significant effect of all of these drugs on the cardiovascular system.

DR. NEILL: Very important. And Dr. Chung?

DR. CHUNG: Differences of PD effects were discussed. I don't know if it was brought up; perhaps worth noting that there does appear to be differences in the PD effects between the COX-2-specific and the non-specific NSAIDs as regards to some of those assays, experiments.

DR. NEILL: Dr. Parker?

DR. PARKER: So the only other comment I would have relates to looking at the professional label around celecoxib and the language there

because of the complexity of this and what we may know and so much of what we're not exactly clear on, the current language in it. There's no consistent evidence that concurrent use of aspirin mitigates increased risk of serious cardiovascular or thrombotic events.

I think paying close attention to the language used there, to make sure that it really captures the nuances of the conversation we just had; I think that language could be clearer and more helpful, not that a lot of people sit around and read the professional label, but it has very big implications.

So I think really paying attention to making sure how PRECISION's findings and the discussion that was just had are reflected in the specifics of that language will be very important.

DR. NEILL: Very helpful. So we're going to move now to question 6, a discussion question. I'm going to read the question. If you have concluded that there is a clinically significant interaction with aspirin for one or more of the non-aspirin

NSAIDs presented, discuss whether there are patient populations; for example patients with recent MI, revascularization, stent placement; for whom the risks of the aspirin-NSAID interaction potentially outweigh the benefits of the non-aspirin NSAID.

Having read the question, staff, my summary of the preceding question is that we have concluded there are not clinically significant interactions with aspirin for one or more of the non-aspirin NSAIDs.

I'm briefly trying to imagine the benefit of discussing the hypothetical if there were, but I'm looking for guidance from staff for how deep a dive you'd like us to go into this, where normally we would, if no, go to question 7.

While staff is deliberating, I'm going to recognize Dr. Farber, then Dr. Rosenberg?

DR. FARBER: This is Neil Farber. And I would ask FDA staff if they perhaps wish us to change the question and, instead of saying "the interaction", discuss whether there are patient populations for whom the risks of any of these

agents, rather than the interaction, potentially outweigh the benefits of the use of these agents.

DR. NEILL: Again, chair's prerogative; without changing the question and without knowing how staff will respond, I think I'm considering, given that question and looking, that it may be helpful for some of us to comment on specific subpopulations. And so without regard to whether staff wishes us to proceed, we'll entertain those comments in the context of overall, no clinically significant.

I see Dr. Rosenberg, then Blaha, then Roumie.

DR. ROSENBERG: Yes. It's a general comment. As you pointed out, we really don't, from the prior discussion, know or cannot conclude whether the interaction that's been studied from a pharmacological point of view is clinically significant or not.

However, from a clinician point of view and managing some of those populations, maybe some of the other cardiologists can comment, but we usually

based a clinical decision on the best available knowledge and trying to minimize potential harm to patients.

In this context, I assume one would be extremely careful in using an agent in a situation where there is potential harm, meaning decreasing the effectiveness of agents that would reduce risk of complications, that this is very high post-PCI, et cetera if there is indeed an indication in that direction.

So from a clinical point of view, again, I would assume that we would be very worried about the concomitant use of those medications in those very specific instances. So I don't know this comment is helpful, but maybe others want to add to that.

DR. NEILL: Thank you. Dr. Blaha?

DR. BLAHA: Yes. I think these are great comments. I agree with what Dr. Farber said. I was going to say essentially the same thing. If you take the word interaction out, it's actually an interesting question, although maybe outside of the

wheelhouse of this discussion.

But I agree with what Dr. Rosenberg said completely. And I think I stated my thoughts earlier. It really gets a little bit, I guess, to the NSAID versus placebo question. I'd prefer none of my high cardiovascular risk patients take an NSAID because there's probably some cardiovascular toxicity risk versus placebo.

So what I say to my patients, I would say to my patients, my high-risk patients, in fact all the ones that are mentioned here, I would say to them, "I would prefer if you avoided an NSAID," but I wouldn't say the mechanism of that is because of an aspirin-NSAID interaction, which sounds very complicated to patients when we don't even understand it that clearly.

I would just say to them, "I'd prefer that my high-risk cardiovascular patients who have actually had recent MI, revascularization, or a stent placement to avoid an NSAID if at all possible because there's a signal for potential cardiovascular harm with the NSAIDs."

I think I've said that piece, but I wouldn't say it's because of an interaction and it depends on when you take the dose. If you take it this way, it might be okay and not this way. I think that adds layers of complexity that we can't see clinically.

DR. NEILL: Is that clinical advice that you would give influenced by the data that you've heard yesterday in one direction or the other?

DR. BLAHA: I think the data that I heard yesterday specifically informed my discomfort from commenting on how I would use this aspirin-NSAID interaction to guide any part of my clinical practice, the interaction itself.

So it caused me to cross out the word interaction here in the question and, based on the data that I heard, that informed my answer.

DR. NEILL: Dr. Hertz?

DR. HERTZ: This is Sharon Hertz. We have a lot of information already in the labeling about populations at risk and I don't really think we have a lot of data from this study to further that

conversation right now if we did take the word interaction out.

So perhaps we can reframe it in the context of, we have a clinical study with somewhat surprising results. We have the pharmacodynamic studies. If we were to decide that there was an interaction based on additional data that could be collected, or are there additional information that should be collected, maybe more of that kind of a conversation?

DR. NEILL: Thank you. So I still have Dr. Roumie. Then we're going to come back to Dr. Farber and Dr. Rosenberg.

DR. ROUMIE: So my comment was based on the clinical data in the PRECISION trial that we saw. It is very difficult to answer question 6 based on the design of the trial, where people who had those conditions; MI, revascularization, stent placement; were taken off of the NSAIDs or told to come off the NSAIDs.

So I think it becomes very difficult to understand that kind of underlying question which

we're trying to get at, which is, is there a different risk profile for that subgroup of patients once they have a cardiovascular event such that, if they take their aspirin, either the results are negated or it's a timing issue.

I don't know that the clinical data that we received helps us to answer that question because of the underlying design of the trial.

DR. NEILL: Thank you. Dr. Farber?

DR. FARBER: So I think a lot of the answer to question 6, either if you're going to include a possible interaction or not a possible interaction, aren't really affected by the PRECISION trial. It's all the other data that we have seen and experienced over the years.

Basically, what I will do clinically and I think basically is prudent is to say to patients exactly what Dr. Blaha said in terms of -- and I prefer you not to be on an NSAID, but I would expand it beyond this population to any population who's at high risk.

That includes patients with cardiovascular

disease with ongoing ischemia, or congestive heart failure, or diabetics, or patients with CKD, et cetera. I would include all of those patients where I look at them and say, "I'd rather you not be on an NSAID at all."

DR. NEILL: Dr. Rosenberg, I think you'd had a comment about one of the prior.

DR. ROSENBERG: I think the comment is no longer relevant, but if you allow to continue this discussion, to respond to what Dr. Farber said, I'm not sure I completely agree based on PRECISION and all the data I know. The EMA has gone this way saying, for celecoxib, don't choose patients with cardiovascular disease.

I don't see anything in the data that tells us not to go this way, knowing that patient cardiovascular disease like in PRECISION have a relative, limited risk, so it depends on the individual patient risk and the individualized decision with the patient, but not making a broad statement like that may go, I think, beyond the data

DR. NEILL: So allow me to ask a clarifying question. You see nothing in the data or what you see is small if present?

DR. ROSENBERG: I cannot answer the question. I don't see any -- probably is the latter. I don't see anything that will raise my concern enough to say don't use in patients with cardiovascular disease.

DR. NEILL: Dr. Ohman?

DR. OHMAN: Magnus Ohman. So I find it's very interesting because these patients, A, were excluded from the PRECISION trial. Number 2, if for whatever reason there were a number of patients who had any of these events while on the PRECISION trial, which probably happened given what we saw, but the numbers are going to be very, very small.

But what I might recommend to the FDA is to visit the cardiorenal panel because, in fact, all these agents; aspirin is no longer used on its own. It's actually used as dual antiplatelet therapy. And all those agents; clopidogrel, prasugrel, and ticagrelor; have recently gone through an approval

process where I know for a fact that concomitant medicines were collected ad nauseam.

So you should be able, between dosed trials -- there's nearly 100,000 randomized patients -- to ascertain if there is a signal here even if it's non-randomized but using some of the techniques that Dr. Tchetgen Tchetgen pointed out that you can do in non-randomized trial data.

So I think that would be your best strategy to try to get to this question. I don't know that anything else has been presented here that would make me talk about clinically significant issues.

DR. NEILL: Thank you. Dr. Solga?

DR. SOLGA: I agree with all of that except a cardiorenal panel. The COX-2s; the ambition was to make them more renal friendly and more GI friendly. There's a whole lot not discussed here today about GI and liver issues germane to the topic. I would advocate for a gut renal and a separate liver renal panel. It's not all about the heart.

DR. NEILL: You're making me worry about

when celecoxib will go over the counter and it'll come to NDAC, too, but you guys clarify it first before that does, please. Are there any other themes related to the discussion of this question?

If you've concluded that there's a clinically significant interaction or you can omit the interaction with aspirin. Dr. Ho?

DR. HO: Michael Ho. I guess I just wanted to echo Dr. Blaha's comment about trying to avoid these drugs in patients with recent MI and revascularization because most of them will be on dual anti-platelet therapy so that I would be concerned about the risk of bleeding in these patients by adding NSAIDs to their regimen.

DR. NEILL: Staff? Dr. Racoosin?

DR. RACOOSIN: Yes. I just want to reassure everyone that, I mean, we have quite a bit of information about this population in our labeling. So between the box warning about cardiovascular, and avoiding it in patients post-CABG as well as information that we added in 2014 about patients who are post-MI having a higher risk in the first

year after their MI, and also the contraindication for using it in post-CABG, I just want to reassure the panel that we have many of these things covered in our current labeling, recognizing that not everyone is poring over labeling all the time.

But we have tried to capture the data that we've been able to review for these high-risk populations to this time. So I think that's consistent with what you're describing, that you clinically counsel your patients in that regard, that we have the support of that, the data that's consistent with that in labeling.

So recognizing that we have addressed many of those things, but we were trying again to go a little bit further here, trying to understand the impact of the aspirin interaction, but also recognizing what we've [indiscernible], which is that on a clinical level that this impact of aspirin interaction hasn't really manifested itself in PRECISION.

DR. NEILL: Dr. Blaha?

DR. BLAHA: It sounds like a mechanistic

question then because the patients you're describing would all be on aspirin. And you already have it in the label. So it seems that the only thing that's being added is this is the mechanism. And I think that, at least for me, clinically speaking, I would feel uncomfortable saying that that's definitely the mechanism.

DR. NEILL: Thank you. So thank you. That was a robust discussion about a question that is a little confusing, so much so that my brain is in a place where I'm not going to be able to summarize the responses for staff. Sorry.

Having said that and recognizing that it's now 11:51, we will now break for lunch. We will reconvene again in this room one hour from now, at 12:51. Please take any personal belongings you may want with you at this time.

Committee members, remember that there should be no discussion of the meeting during lunch, amongst yourselves, with the press, or with any member of the audience.

Thank you. See you back here at 12:51.

(Whereupon, at 11:51 a.m., a lunch recess was taken.)

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

(12:51 p.m.)

DR. NEILL: Welcome back from lunch. I'd like to reconvene this meeting. We have already discussed six questions, including five discussion and one voting question earlier. There are three remaining in the book.

However, after discussion with staff, I am using and with their advice have decided to omit question 7. That means that we are going to now address questions 8 and 9, both of which are voting questions.

You'll recall from the earlier voting question that I asked the committee to vote and then polled each voting member to comment on their vote and to explain it. And unless there are strenuous objections, I am proposing that we use the same process.

I will also draw your attention to what had not initially gotten my attention. These voting questions are not yes/no, but are lettered such that, when you vote, you will select a letter on

your voting pad that corresponds to the letter of your one answer.

While there are three choices for question 8 and two for question 9, you'll choose one of those. Okay? Are there any clarifying questions about the process that we're going to use, Dr. Lewis and then Dr. Rosenberg?

DR. LEWIS: The labels include a contraindication for use of naproxen with aspirin and ibuprofen with aspirin now. So are you asking us, is this for GI effects? I know it's not for cardiovascular.

DR. NEILL: Actually, Dr. Lewis, I'm going to hold that because I'm not yet ready to clarify the question.

DR. LEWIS: Sorry.

DR. NEILL: But if there are any questions about the process that we're going to use, so Dr. Rosenberg and then Ms. Robotti, and Warholak?

DR. ROSENBERG: Yes. A technical question; in our keyboards here, A is for Attend, so do we press it if we want A? Do we press A?

DR. NEILL: That's correct.

DR. ROSENBERG: Thank you. Ms. Robotti?

MS. ROBOTTI: Suzanne Robotti. Are we going to be discussing before we vote? I mean, we normally don't, but I would think we would.

DR. NEILL: That's not my proposal, but instead propose that we discuss after we vote in order to get everybody's discussion within the context of how they voted.

This is a point where I would re-emphasize that, A, I'm willing to reconsider if it's the sense of the committee, but B, both the vote and the comment are important for the process that staff and industry use. Ms. Robotti?

MS. ROBOTTI: I'm sorry. I should have done this over lunch. I did not pull out the naproxen label to have it in front of me and maybe I'm the only one who needs a moment to look at it.

DR. NEILL: Absolutely. It's in the FDA briefing document and I could probably pull up the page number in just a minute.

UNIDENTIFIED SPEAKER: Could we have it

posted for a little bit?

DR. NEILL: Staff, can we have the naproxen non-prescription prescribing information posted or maybe the briefing document? It exists over a couple of pages and so I realize it may be challenging.

DR. RACOOSIN: We can get you the page

DR. NEILL: Thank you.

DR. PRATT: This is Valerie Pratt, FDA. Do you have the slides from yesterday's FDA speakers? Jenny Kelty's slides has the OTC labels as background.

DR. NEILL: So while staff is pulling those up, Dr. Ohman?

DR. OHMAN: Magnus Ohman. Thanks for that clarification. I have one question. How do I vote if I like to have a change in label, but not necessarily the two options given? Do I abstain? And abstain; well, that doesn't flash on my thing.

DR. NEILL: That is an excellent question. You choose an imperfect response closest to the one that you hate the least and then, in your comments,

you explain which answer you would love the most if you were FDA staff.

DR. OHMAN: Just like the board exams.

(Laughter.)

DR. HERTZ: So this is Sharon Hertz. I just want to say that, from the first vote, when I heard concerns about the vote with a subsequent explanation not being a very palatable option, we look at the why much more than the what because we always get members of our committees who will even vote opposite yes or no, but have the exact same explanation for why.

So sorry we don't always anticipate fully the ramifications of our questions, but what I would suggest as an option is, if you want to change, but you don't think the change that you would like is there, pick a decision and then just tell us what change you'd like when we go through after the vote. And we'll pay very strong attention to that.

DR. NEILL: So before I go down to this end of the table, I think I think, Dr. Meisel, did you

have an additional comment?

DR. MEISEL: No.

DR. NEILL: No. And then let's go to Dr. Rosenberg, Chung, and then back to Dr. Schmid.

DR. ROSENBERG: Sorry. I was not finding the complete appendix on my laptop, so I just want to make sure that we can see the whole thing on the screen, especially if there's any reference to aspirin here. I believe not, but I just want to confirm.

DR. NEILL: Dr. Chung?

DR. CHUNG: I just think that it may be helpful for the committee perhaps to have a definition by the FDA of warnings and contraindications.

DR. PRATT: Sure. Let me try and address those. This is Valerie Pratt. I will refer you to the October 2011 FDA guidance for industry warnings and precautions, contraindications, and box warning sections of labeling for human prescription drug and biologic products.

It describes, "The warnings and precautions

section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are as serious or otherwise clinically significant because they have implications for prescribing decisions or for patient management. A drug should be contraindicated only in those clinical situations for which the risk of use clearly outweigh any possible therapeutic benefit. Only known hazards and not theoretic possibilities can be the basis for contraindication."

I note that document refers to prescription labeling. In the absence of an OTC labeling guidance, we would harmonize ourselves with the general concepts expressed in prescription labeling guidance with the corollaries that, A, we do have a different structure and format and, B, obviously the intended user or reader of the OTC label is a consumer, i.e. a person picking the product up off the shelf without a healthcare intermediary.

Dr. Rosenberg, did you have another question I can address for you?

DR. ROSENBERG: I wanted to make sure that we have all the warnings on this slide or there is no other slide because I didn't see here anything related to aspirin.

DR. PRATT: One second. Please advance the slide. Again, this information is also in your briefing document.

DR. NEILL: So the committee will observe that the Drug Facts label exists over three slides and staff have advanced each of the three. We can in the course of or before the vote and, if there's more discussion, go back and forth between these. Dr. Parker, did you have a clarifying question?

DR. PARKER: I do. I understand this is an over-the-counter product and it's an over-the-counter product for which there is a black box warning on the prescription product and I was not aware what kind of guidance there is about the black box warning content and how that is presented in the Drug Facts label for an over-the-counter product for which there is a prescription black box warning. And I assume these are already aligned

with whatever that is, but I wondered if, in looking at this, this is really culled out the same.

It doesn't really fit with the vote, but to me, it's such a big issue for the public. And so I wanted to put that on record. So that's one comment.

The other one relates not exactly, but it does relate to the question itself and that has to do with the exact wording of the current warning that was up there, that you see in the Drug Facts label about, for example, the stomach bleeding warning and its wording in the black box versus how it is worded in the Drug Facts label using language like "may cause" versus "causes" and how that's interpreted without the learned intermediary.

So this really is sort of at that bridge and I felt like this issue related, so that's why I'm putting that on the table.

DR. PRATT: Sure. This is Valerie Pratt, FDA. I'll address your two points. With regards to your general question about the box warning,

there is no direct equivalent in the OTC label. Off hand and at my immediate fingertips, I don't have the OTC guidance document to refer you to. But what I can say is that you will notice that it's a hierarchy in the drug facts label.

There is also a more recent trend that actually goes back to the monograph examples, too. Sometimes labeling is put as elevated text at the top of the label. For instance, if you go back to the top of the first example slide for naproxen, slide up one more -- there should be one more; above that, before that; stop, thank you -- uses are put at the top. You can see the format there.

Then there are the warnings. Uses are at the top according to the format. Then there are the warnings. You can see that these warnings have been given priority allergy alert, stomach bleeding alert, and the newer heart attack alert. That's heart attack and stroke warning alert.

Then you move into the equivalent of contraindications and, if you can, go to the next slide, please. Then these are also classified as

warnings, but different flavors, I'll say. So what I would advise you is, I acknowledge that the text of the question does not specify what precise language or location in the Drug Facts label, but feel free in your open comments, where you can provide your rationale for voting, to describe your opinion on what type of language or location, understanding the format we are working within.

Regarding your second question about the difference in language between the box warning, which states that, off hand, I understand it as "NSAIDs cause," et cetera versus the OTC label. Again, if you can, go slide up, please, next slide, previous slide.

There we go. So this one says, "NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. This risk is higher if you use..." I believe you're referring to text that has a "may" in it?

DR. PARKER: If you look at the text, sorry, about stomach bleeding warning and, if you could, you could put it side by side with a black box

warning for the same product in a prescription dose, where the word may is not a part of it.

This relates specifically to how "which may cause" is interpreted by the average lay consumer versus "increases," which is used under the heart attack and stroke warnings because the whole thing with the OTCs is there's no learned intermediary. You should be able to self-select the task at hand without someone in between you.

In the black box warning, for stomach bleeding warning, the word "may" is not in there. It is for the OTC here. And so it's nuanced, but I think it actually matters in terms of the task for someone self-selecting and choosing correctly.

DR. PRATT: A first point of clarification is, again, the OTC label does not have an equivalent to the boxed warning, but what I hear you're saying is that you're acknowledging that text or verbiage and word selection are key to conveying the inherent meaning that you're trying to express directly to the consumer.

What I hear you saying is that one should be

cautious about using the word "may" because it may or may not imply causality.

DR. PARKER: I would say the general public would take "may" to mean "has permission to," may I go to the bathroom, but it also means possibly. Can has a different meaning. Might is past tense. But just how dose someone interpret these words? What do they mean in the ordering for a risk factor that ends up in a black box with a prescription of the same medication, how that's conveyed in an over-the-counter setting when there's not a learned intermediary? That's what I was -- yes.

DR. PRATT: Dr. Parker, I recognize the advice you're providing as the OTC labeling expert for this committee. The other additional point I wanted to make is that please be aware that, when slight differences in text are present on the labels, it is often actually due to differences in data.

There may be scenarios where the data says "cause" on a prescription label because it was based upon a study that was used at prescription

doses, whereas the same text may not be appropriate in OTC setting.

DR. NEILL: Thank you for that. Dr. Blaha and then Dr. Schmid?

DR. BLAHA: Mike Blaha. I didn't have any further comments beyond the discussion.

DR. NEILL: Thank you. Dr. Schmid?

DR. SCHMID: I just had a question, Chris Schmid. So I think what I'm being asked to vote on is whether we should be adding an interaction warning between aspirin and either naproxen or ibuprofen.

As I read the current labels, there is such a warning for ibuprofen, but not for naproxen. Is that correct?

(Crosstalk off mic.)

DR. PRATT: This is Valerie Pratt again. As expressed in the FDA briefing document, there is language in the OTC Drug Facts label regarding the interaction between ibuprofen and aspirin. Off hand, I'm going to paraphrase.

I believe it's use of ibuprofen may reduce

the benefit of aspirin. To answer your question, there is no direct equivalent language in the naproxen label at this time because the new study information was presented during this AC and that is part of the reason why you are being asked to opine on the label going forward.

DR. SCHMID: Great. So that's what I understood. So this is appendix one and appendix three. So the appendix 1 has the warning for ibuprofen, appendix 3 does not have it for naproxen. So I'm a little confused as to what I'm voting on for the ibuprofen since it's already there.

I see, for the naproxen, I'm voting to whether to put the warning in, but for the ibuprofen it's already there, so what am I voting on there?

DR. MEISEL: Question 9 is a different question.

DR. NEILL: So identify yourself. That was Dr. Meisel for purposes of the transcriptionist. Dr. Pratt?

DR. PRATT: This is Valerie Pratt. So I recognize there's a difference in the question between 8 and 9. Question 8, which refers to naproxen, you have three options, no change to current naproxen label. Option B is include a warning. Option C is include a contraindication. This differs from question 9, in which you have two options; option A, no change and option B, include a contraindication.

The phrasing of the question 9 acknowledges that there's already a warning present in the ibuprofen Drug Facts label.

DR. NEILL: Thank you. So this was helpful for me to hear in advance of the voting and it brought to mind two stories that inform both the process that I use and perhaps what we've experienced as a committee and hopefully are going to inform how we discuss these votes in a moment.

When I was in the ninth grade, I showed up for my first algebra class and Mr. McGuire said, "Are there any questions?" Being ninth graders, we were mute and he gave us a test and we all failed.

We never came back without more questions and without something. You guys had the same class because you all had questions. That's very appropriate. I'm sorry if I'm channeling Mr. McGuire, but I find it helpful to clarify the questions that you then have because, if you attach stakes to the vote or to the comment, it focuses the mind a bit.

The second story is about politics. We're here in Washington, D.C. and it's the old joke. The chief of staff is talking to the politician and saying these people want you to come and give a talk. The politician says, "Well, how long do they want me? If they want me for two hours, I can do it right now, but if they want me for five minutes, I'm going to have to prepare for two weeks."

Well, that's why we got the briefing materials all this time in advance and, for the record, we can leave that there and remember it. And if I am fortunate enough to chair another meeting in the future for us, you can hold that back up to me if I haven't done my own preparation.

So let's move on now to question 8, which is a voting question. I'm going to read the question. Then I'm going to read the scripted instructions on how to vote. After that, we will vote. After that, we will go through and poll members for how they voted and why. Question 8, which of the following regulatory actions based on the material presented and discussed at this advisory committee meeting should be taken with respect to naproxen non-prescription labeling? And comment on your rationale.

Choice A, no change to the current naproxen Drug Facts label, see FDA briefing document, appendix 1, for example. Choice B, including a warning regarding the interaction between aspirin and naproxen. Choice C, include a contraindication of use for naproxen when taken with aspirin.

If there is no further discussion on this question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the

button firmly. After you've made your selection, the light may continue to flash.

If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

LCDR SHEPHERD: For the record, the vote is option A, 7, option B, 12, option C, 2, 0 no voting.

DR. NEILL: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote and, if you want to, you can state the reason. Actually, in this instance, I would encourage you, please state your reason for why you voted as you did into the record. And we're going to begin on the right with Dr. Rosenberg; shaking things up a bit.

DR. ROSENBERG: Yves Rosenberg, NHLBI. I voted B, include a warning based on the review of the study yesterday. Also, we really don't have any data as discussed early on all the clinical significance of those interactions.

I believe there is much data about potential for an interaction based on pharmacologic data that there is for ibuprofen and, therefore, I don't see why there should be any difference in the labeling of those different NSAIDs. I think it will make it much clearer for the patients. That's all NSAIDs that potentially have this risk and they should be aware of it.

DR. NEILL: Thank you. Dr. Ho?

DR. HO: Michael Ho. I voted for B and, similar to Dr. Rosenberg, I think the data on the pharmacokinetic shows a potential interaction that we're not sure if it's clinically relevant, but we don't have any evidence that it's not a class effect at this point in time.

DR. NEILL: Thank you. Dr. Blaha?

DR. BLAHA: Yes, Michael Blaha. I also voted B for much the same reasons as my predecessors here. From my understanding of the word warning here and my understanding of the differences between naproxen and ibuprofen and the fact that the label also already includes a warning

for ibuprofen, I don't see a reason, a rationale to have a different warning or lack of a warning between these two drugs at this time based on the pharmacokinetic and pharmacodynamic data that I saw.

So I was very conflicted answering this question because I don't think there's good evidence, as we talked before, about a clinical significance of this, but I think including a theoretical warning for both of these drugs is one way of going and I just wouldn't make a distinction between the two drugs at this time.

DR. NEILL: So just a point of clarification for me; with regard to the naproxen label, you would include a warning about the naproxen risk. Rather, could you clarify what the warning would be?

DR. BLAHA: I mean, I'm conflict here. I think I might have answered differently if the warning wasn't already in the ibuprofen label. So I'm asking it in the context of the regulatory environment, I guess, that's already there. But

I'm having a hard time justifying to myself saying that the warning should be in for ibuprofen, but not for naproxen based on the pharmacodynamic data that I saw.

So I guess my wording would be something to the effect of, I guess a class effect term was used, but I'm not sure you would use that term here. But I would say that there's a theoretical pharmacokinetic interaction between aspirin and naproxen that one could be made aware of.

But that's the best I can answer the question.

DR. NEILL: I'm looking at Dr. Parker and wondering how she would respond to class effect and pharmacokinetic on a consumer-facing label.

DR. PARKER: With a smile.

DR. NEILL: But thank you. I'm asking for the wording because I'm hopeful that, for any of us who want to clarify the labeling, given the task before FDA staff to do this, if there are suggestions, however imperfect, for the precise wording, it gives them a sense.

DR. BLAHA: I'll clarify. My opinion right now is, I think it would be unnecessarily complicated from my understanding of the data to have different warnings at this point between the two drugs. So the wording, I guess, would be left up to the FDA, but I don't see a rationale to have different warnings at this time between the two drugs on a pharmacokinetic or pharmacodynamic basis, which I guess is the only basis we have.

DR. NEILL: Very helpful. Dr. Ohman?

DR. OHMAN: So I voted for A, no change to the current label. The rationale is that, if we stick with clinical and we are talking to patients, we are sticking with clinical. And there are clearly pharmacodynamic issues at hand, but I don't see any clinical issues at hand when you look at the PRECISION trial, which is sort of an indirect comparison.

Now, to the outside of the vote, this is not the vote that I wanted to make, really, because I think this boils down to, are we talking pharmacological or are we talking clinical? And

we're lumping them all together, which makes it impossible to answer the question correctly.

So that's my issue. And I'm going to come back and talk about ibuprofen in a minute, but actually having asymmetry in the labels when there's a lot of uncertainty is a challenge, but there is some issues that I will address later on in the second vote.

DR. NEILL: Thank you. Dr. Solga?

DR. SOLGA: I voted B and then switched to A. I voted B for all the reasons Dr. Blaha voted for B. I felt the consistency between the two NSAIDs in discussion, Naprosyn and ibuprofen, was important.

Then I switched to A because too many warnings are too many warnings. I think the warnings in the package label currently are clear, simple, short, and well established. I'm not sure that adding an additional warning that's not clearly well established serves the public at large.

DR. NEILL: Thank you. Dr. Lewis?

DR. LEWIS: I voted A. I think that we saw from the PRECISION study, but it's not that different, that close to 50 percent of people who are on aspirin who are at cardiovascular risk also take non-steroidals. And I would worry that, if something was in there about not taking them together, they would give up their aspirin.

So I think, at the most, what I would put in there is something about talk to the doctor. You're not asking us to opine on what should be in what the doctor reads, although currently what the doctor reads says don't take them together because of GI effects.

But that's why I voted the way I voted. And we can't even figure out the aspirin story.

DR. NEILL: Thank you. Dr. Meisel?

DR. MEISEL: Hi, Steve Meisel. I voted B for all the reasons that Dr. Blaha described. I think it's a theoretical warning. I think we have to think about this globally. This should be for naproxen and for ibuprofen, but I wouldn't word it the way we have it with ibuprofen, either, because

this is theoretical. It's a pharmacodynamic issue.

We don't know about the clinical impact. I think we have to think about how we phrase this in a way that is going to be most useful to both providers and to patients. And I don't know that the language that is currently in the ibuprofen accomplishes that.

But I do think it's a class effect and we need to recognize that at least a theoretical risk is there that has not been disproven by the PRECISION trial.

The other comment that I'd make about the labeling here goes back to a comment that Dr. Farber made yesterday about, if somebody's having symptoms of a heart attack, you don't stop and call your doctor. You do something else.

I think the language of that part of the labeling probably needs some work as well.

DR. NEILL: Dr. Warholak?

DR. WARHOLAK: This is Terri Warholak and I voted for A, but to be honest, like many of the others, I went back and forth several times before

finally landing on it. And if we had waited another minute or so, I probably would have ended up on B again, but the basic thing is, I do believe that there might be somewhat of a class effect here.

However, I'm not sure the data that I've seen thus far shows me that -- it looks like naproxen may have a difference. I'd want to know more about that. I'd want to evaluate the differences between them before adding this. And I feel like, in absence of better evidence, I just went with A.

DR. NEILL: Thank you. Mr. Dubbs?

MR. DUBBS: Bob Dubbs. I voted B and I go back to a comment I made yesterday, which I mentioned to Dr. Neill, that I don't think these studies address the issues of age, gender, race, minority, and to have a broad statement without having really analyzed whether, for instance, a 60-year-old female Native American would have a problem different than a Caucasian or a black (phonetic). I think further study is needed.

So I would think that a patient should be advised to discuss the use before taking the medication. So a warning would be appropriate.

DR. NEILL: Thank you. Ms. Robotti?

MS. ROBOTTI: Hi, Suzanne Robotti. I voted C because it seemed the strongest. I believe that the OTC labels for both drugs should be changed to address a continuous and especially long-term use.

All three of the drugs in the PRECISION trial give only about 30 percent pain relief to about 30 percent of those people who take it. I note that the reasons given for treatment discontinuation is 25 percent for adverse events and that does not get an answer from everybody who quit it.

Also, I'm not clear as to whether that includes SAEs or just AEs, so the number might well be larger. In any case, they're bad enough that people stopped taking the drug. That means I have a significant question about the risk-benefit of these drugs when used continuously.

I think that this should have a warning that

they have a very limited benefit for long-term or chronic pain relief and particularly for those with CV risk. Also, the interaction between naproxen and aspirin is unknown and might interfere with the benefit given with aspirin.

I would take a moment to point out that this is a very large study and yet no subgroup analysis was done. That's not pertinent to this question, but I'd be remiss in my duty in not mentioning that at some point.

The fact that OTC drugs don't have black box labels is one of the many reasons why the general population has the impression that OTC drugs are safe and are harmless or harm free.

I do believe the general population understands the concept of black box labels, but they're only on prescription drugs and therefore give the wrong impression. I think the general population believes that OTC drugs are safe when used at will because they can.

I think that that's extremely harmful to the general population. What have I said wrong today?

Sorry. Okay. Thanks. So I would not make a distinction between the two labels on this issue. Thanks.

DR. NEILL: Thank you. Dr. Pratt?

DR. PRATT: Nonetheless, it is necessary to make the distinction between the two labels. The drugs are indicated for slightly different uses and for different durations. While I acknowledge that people do use prescription and non-prescription drugs for longer than recommended, the Drug Facts label clearly does not recommend chronic use and recommends a duration of use no more than 10 days.

So just recognize, for the individual you described, that is off-label use.

DR. NEILL: Thank you. Dr. Schmid?

DR. SCHMID: Chris Schmid. I voted B basically for the reasons others have stated, that I don't think there's really any difference in the data we've seen between ibuprofen as regards its interactions with aspirin and so therefore I believe the labeling should be equivalent.

Since we have a warning label on the

ibuprofen, I believe there should be a warning label on the naproxen. I don't think there's really enough data yet to indicate clinically whether this risk is clinically significant or not, so I wasn't willing to go any further than that.

DR. NEILL: Thank you. Dr. Tchetgen Tchetgen?

DR. TCHETGEN TCHETGEN: I voted A for reasons that have been stated before.

DR. NEILL: Thank you, Richard Neill. I voted A. I acknowledged the concern over some of the specific risks, but believe that the current Drug Facts label for naproxen reflect that risk with a precision that approximates what we know about it, both in its effect size and frequency.

I also harbor a patient experience, I mean, a physician-patient experience that suggests the challenges in relying upon Drug Facts labels to convey significant risk, to wit nicotine, which has a pretty big black box and people still do it, albeit very different condition, and supplements, which are not under NDAC or these similar type of

regulatory affairs, but all of which carry a beautiful little box, which I can point to when my patients bring them in, and I can say, you see this box here? What this says is that it doesn't do any of the things. It has not been proven to do any of the things that the company who's selling it to you can't claim or else they would make a specific health claim. But they're going to make you think they are.

The last thing I'd say about the challenge in the labeling is, my understanding is that the monograph process is still going on. It started in 1972 and that, if I'm pushing members to come up with specific language, it's because, if it takes two weeks to come up with a five-minute speech, it's taken decades to try and get monographs.

To try and get these warning labels is going to take even longer. And starting from any place is going to be faster than from something better, more general. Dr. Oliver?

DR. OLIVER: Alyce Oliver. I voted B. I think that the data showed that Naprosyn and

ibuprofen are similar and, as such, the labeling should be the same on Naprosyn as ibuprofen.

DR. NEILL: Dr. Richards?

DR. RICHARDS: Steuart Richards. I also voted B, but I vacillated between A and B. And I think I went with B because, in terms of the warning, I'm thinking more of a discussion with your doctor instead of a definite interaction because I think the data presented today is kind of confusing on that and to expand on that in an OTC preparation is kind of difficult.

So I think it's more that, if you're on aspirin, have a discussion with your doctor about how to take the naproxen with the aspirin instead of a specific risk regarding increased cardiovascular risk.

DR. NEILL: Thank you. Dr. Boudreau?

DR. BOUDREAU: Denise Boudreau. And I voted B based on the pharmacodynamic data that was presented yesterday and I think a class effect is reasonable.

DR. NEILL: Thank you. Dr. Parker?

DR. PARKER: Ruth Parker. I voted B for same reasons that have been previously expressed. I do want to reiterate Dr. Richards's comment about the language about how this is expressed in an OTC label. I have always had concerns and still do for an OTC setting to say, ask a doctor or pharmacist before use if, because I know how hard that really is to do.

Given the limits of what labels can and cannot do, I think getting to the best possible language with whatever is put in the limited real estate is incredibly important.

I like the idea of being more specific to a person who would be picking this up, who might read the Drug Facts label and make a decision based on it to say, if you are taking aspirin for your heart health, talk with your doctor before you decide whether or not to take this medication, something that actually puts it into a more actionable framing.

But I think that would deserve some attention, but I think sort of putting it under,

give a call, go ask somebody, is always the limitations of what they can do.

DR. NEILL: Thank you. Dr. Farber?

DR. FARBER: Neil Farber. I voted for C. I actually was considering voting for B because I think a warning would be sufficient if the language were changed as Dr. Parker had said. My concern is, though, that the way the warning is stated, I'm not so sure physicians have the requisite knowledge always to be able to inform their patients adequately.

I'm not so sure that a patient either would ask their physician because of the power differential in the patient-physician relationship or because of the time constraints that the physician has, that the physician would be able to answer coherently.

Because of that, I think my feeling is there needs to be the extra layer of protection on the part of for the patient and so I voted for C.

DR. NEILL: Thank you. Dr. Roumie?

DR. ROUMIE: Christianne Roumie. I voted B

much for the reasons that have been stated as well as overall need for consistent messaging to patients across classes of drugs and the education that's provided have a consistent message as referenced by Dr. Parker.

DR. NEILL: Thank you. Dr. Cunningham?

DR. CUNNINGHAM: Melody Cunningham. I voted for B, also I think for the reasons that have been stated and also really focusing on the mechanism of action of those drugs being the same, the naproxen and the ibuprofen.

Then from a standpoint of how I would word it, from consistency's standpoint, I would say we should word it just as it's worded in ibuprofen. On the other hand, if we want to highlight it more, we have heart attack and stroke warning. I might have something that said aspirin warning and then went on to explain that the naproxen could decrease the effectiveness of the cardioprotection of the aspirin, although I would do the same for ibuprofen again for consistency.

DR. NEILL: Thank you. Dr. Hendrix?

DR. HENDRIX: Craig Hendrix. Since you've made comments about Philadelphia, I'm going to make one comment about Baltimore. So H.L. Mencken once wrote, "A foolish inconsistency is the hobgoblin of little minds." And that's just foreshadowing for the next vote, which will seem to be foolishly inconsistent perhaps on my part.

So the biomarker data is very rich for naproxen based on what was presented here. It's far richer from what I can see than the ibuprofen data. So they're not necessarily equivalent. There's more in one than the other and there's dose- and time-specific differences.

The clinical data presented in PRECISION was helpful here in not showing a clinically significant difference, though the specific analyses looking at interactions with naproxen specifically with and without aspirin were really not part of that.

So I don't have a reason to change what's in the label. The label already includes language that says, assuming that they read this -- but

that's the only reason why we're talking about it -- mention to your doctor if you're taking aspirin.

It also says that you will mention if you have any of these other conditions. So there are warnings about concomitant conditions that may be relevant. There is a warning about informing your physician or care provider that you're on aspirin.

So I didn't have reason to modify this based on the data that was presented here, either the biochemical data -- and I'm letting the clinical data somewhat trump that and not recommending a significant change in the label because of the biochemical data, which is yet to be confirmed one way or the other in alongside the clinical data from the PRECISION trial, which will be very useful perhaps to this point.

DR. NEILL: Thank you. So just to be clear, the naproxen label does not include the ask a doctor if you're taking aspirin. Ibuprofen does, which is I think part of the inconsistency.

DR. HENDRIX: Excuse me, Craig Hendrix.

DR. NEILL: Please.

DR. HENDRIX: So I think I'm looking at the right one. It says, "Notify your doctor if you take other drugs containing prescription or non-prescription NSAIDs, aspirin, ibuprofen, naproxen, and others," although it's in the section under the stomach bleeding warning unless I'm reading the wrong one and I'm trying to page back and forth.

DR. NEILL: No, you're reading the correct one. It's under the stomach bleeding warning as opposed to the subsequent ask a doctor or PFS or ask a doctor before use if, ask a doctor or pharmacist. And this gets to some of the challenges in both being consistent, which I think have been appropriately raised by many of the folks who raised concerns, acknowledging the caveat that there may be data that support some differences in the labeling between the two.

So thank you all for your comments. Without being able, because I wasn't writing furiously to go through all of the rationales for voting, what I've heard among those who voted A to make no

change was that a panoply of lack of concern that there was clinical significance to the data that we saw that warranted change to data.

Those voting B and, to a certain extent C, many different rationales, including data, the consistency between the labels to a certain extent, and Dr. Parker, I'm referring to your comments couched within the context of overall logic and legibility.

Then there were some important and I think distinct comments among the members that voted C related to some of the safety concerns and how those are or are not reflected in the OTC label. Were there any other questions or clarifying comments from the committee before we go on to question 9?

(No response.)

DR. NEILL: So hearing none, if you could display question 9, I'm going to read question 9 and then it will give us a chance to have any clarifying questions about the question or the process, or if you need the label displayed again,

we can do that. And then we're going to come back and vote.

Question 9, vote, which of the following regulatory actions based upon the material presented and discussed at this advisory committee meeting, should be taken with respect to ibuprofen, non-prescription labeling? And comment on your rationale.

Choice A, no change to the current ibuprofen Drug Facts label, see FDA brief document appendix 3 for example; Choice B, include a contraindication for use of ibuprofen when taken with aspirin. So that's the question. Do committee members have any clarifying comments or questions about the question? Dr. Ohman?

DR. OHMAN: Magnus Ohman. I'm confused because really no new data on ibuprofen was ever presented. So I have to assume, doing the boards again, that I have to pick the least favorite of whatever it might be because we have seen no new data except in a trial comparing another agent.

DR. NEILL: I guess I would suggest that we

saw data from Dr. Gurbel and from PRECISION that included ibuprofen in comparison in studies that were designed for reasons other than answering the question that's necessarily in front of us here. And that's different than there being no data, the pertinence of the data, or its applicability or generalizability to this.

I might agree, it is limited, but I think that that's part of the reason for the question and the discussion. Staff, did you care to comment? Dr. Pratt?

DR. PRATT: Sure. This is Valerie Pratt, FDA. I acknowledge the ibuprofen label already contains a statement regarding the interaction between aspirin and ibuprofen and that information was put in based upon FDA review.

This was brought to today's discussion because it relates to the topic at hand, has not been previously discussed at an AC, and in the setting of the clinical data now available, we wanted to hear the group's opinion.

DR. NEILL: So I have a clarifying question

for staff. In the briefing material, we have the Drug Facts label both for adult and pediatric. To what extent do the comments and advice that you receive from the committee influence decisions about both, given my assumption that we're being asked about the adult Drug Facts label?

DR. PRATT: As I stated before, differences in labeling often pertain to the data available at the time the decision was made. At the time that decision was made, it was felt the data regarding the interaction between ibuprofen and aspirin was relevant to adult formulations and, hence, that information is included in the adult Drug Facts label and not in the pediatric versions.

More recently, as a result of the last cardiovascular AC, where data pertaining more to the prescription doses was discussed, that was showed to be basically chronic and additive over time.

Therefore, given that concept, the heart attack and stroke warning was included both in adult and pediatric Drug Facts labels.

So that explains why the labeling is as it is. Pertaining to the question at hand, again, I think you should vote to choose the answer that best is in line with your opinion and, again, when you go around the table, please elaborate on your opinion regarding that point.

DR. NEILL: Thank you. Any other clarifying questions or discussion before we vote?

(No response.)

DR. NEILL: Great. Seeing none, let me read the voting instructions again. We'll be using an electronic voting system for this meeting. Once we begin, the buttons will flash and continue to flash even after you've entered your vote. Press the button firmly that corresponds to your vote.

If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in and displayed on the screen, at which time the designated federal officer will read the vote from the screen into the record.

Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason that you voted as you did and I would encourage you to do so. We're now ready to vote.

(Voting.)

LCDR SHEPHERD: For the record, the vote is option A, 17; option B, 4.

DR. NEILL: Thank you. We're going to begin to my right with Dr. Tchetgen Tchetgen, who twice today was cut off right before breaks and unable to speak. We're going to go around the table towards Dr. Rosenthal (phonetic) and then come back from Dr. Oliver towards staff. Dr. Tchetgen Tchetgen?

DR. TCHETGEN TCHETGEN: Dr. Tchetgen Tchetgen. I voted A just because I thought there were no new data really that would require such a change being warranted.

DR. NEILL: Thank you. Dr. Schmid?

DR. SCHMID: Chris Schmid. I voted A for the same reason.

DR. NEILL: Ms. Robotti?

MS. ROBOTTI: Suzanne Robotti. I voted B for the reasons that I gave above. I believe that the CV risk should be made distinct on there. Also, in my reading of the preparation material on the labels for both naproxen and ibuprofen and in my re-reading carefully quickly just now, I saw no limitation on how long the drug should be taken.

I think that it might well be on the packaging. It wasn't on the labels that were given to us to look at. At least, I couldn't find it. And I think that should be very clear and that long-term use should be considered very carefully.

DR. NEILL: Thank you. Mr. Dubbs?

MR. DUBBS: I voted, excuse me, B, and for much the same reason as I had indicated in 8, there is a lack of information on the various impacts on age, gender, race, minority, which I would have liked to see.

I'm a little upset that I didn't have the option of warning as one of the selections to make for the voting, which I think would have been better and I would have felt more comfortable

because then I would have decided that the warning should be, discuss it with your doctor based on your age or gender, da da da, before taking this medication.

DR. WARHOLAK: This is Terri Warholak and I voted A for reasons stated by my colleagues previously.

DR. NEILL: Thank you. Dr. Meisel?

DR. MEISEL: Steve Meisel. I voted A as well. I think the warning that's currently present, "Ask a doctor or pharmacist before use if you're taking aspirin for heart attack or stroke because ibuprofen may decrease this benefit," is about as clear as you could get and allows for additional information to come in that will change a doctor or pharmacist's suggestions.

I'll just repeat what I've mentioned before. I think some of the other elements of the labeling do need some work, particularly if someone's having an active heart attack. You don't call it in and see if you get a call back. But for this specific question, I think this is as clear as it can get.

DR. NEILL: Thank you. Dr. Lewis?

DR. LEWIS: I voted A. However, I think, because I didn't have an option to say this, that the current wording is extremely poor. There's a lot of cardiovascular risks that you would be assigned aspirin for other heart attack or stroke. So I think it's misleading.

Furthermore, I can't find it in what the doctor reads that it decreases the benefit of aspirin. I see GI effects. I see some vague statements about adverse effects if they're given together, so I think, yes, that's why I voted, but I think that this should just read under, "Ask doctor or pharmacist," and it should say, "If you're taking aspirin and ibuprofen, talk to your doctor."

It's a very complex question. The GI bleeding seems to be more important because that's what's in the doctor's label.

DR. NEILL: Thank you. Dr. Solga?

DR. SOLGA: I voted A and I agree with Dr. Farber that, ask your doctor or pharmacist,

only works if all the barriers are removed and the knowledge base is there. And there's a lot of obstacles to be overcome, but I still feel that expending warnings on package labels is not necessarily a good mechanism.

I agree with Dr. Lewis's point on question 8 that there's a potential concern that folks will stop taking the aspirin if they really feel like they need the ibuprofen and that there will be more harm than benefit from having made that intervention.

DR. NEILL: Thank you. Dr. Ohman?

DR. OHMAN: Magnus Ohman. I voted B, include a contraindication for the use of ibuprofen when taking aspirin for the simple reason that there's a better agent called Naprosyn. If you take the data that we haven't seen today from the meta-analysis by Baigent and others and you look at it against placebo, the hazard ratio for ibuprofen is 2, so twice as high for any cardiovascular risk.

If you couple that with what we saw in the PRECISION trial, where in some of the curves it

actually looks like ibuprofen performed the worst of all the three agents tested, you get a clear message that in fact that may be your worst agent to take, so I use that as a rationale for saying you shouldn't really use it if you have any cardiovascular issues. You should go with another agent.

Actually, in other settings, the Agency has gone that far and even pointed that out, of course not in the OTC label.

DR. NEILL: Thank you. Dr. Blaha?

DR. BLAHA: Yes, Mike Blaha. For this specific question as asked, I voted A, no new information to change the current label.

DR. NEILL: Dr. Ho?

DR. HO: Michael H. I voted A just for same reasons as previously mentioned.

DR. NEILL: Dr. Rosenberg?

DR. ROSENBERG: Yes. I voted A as well. However, I think, if the naproxen is going to include a label with some kind of warning, it's an opportunity to consider changing the label as you

try to harmonize both of them so they say the same thing. Also, Dr. Ohman has a good point, that it might not be the first-choice agent, but that's another discussion.

So to make sure it's clear or clearer if possible, first and foremost, aspirin shouldn't be discontinued before they talk with a physician. I think that's something that's very important. I agree that potentially people in a lot of pain say, well, if there's a problem, I'll stop my aspirin.

They don't understand the consequence, potential consequence, so I think it would be very important to clarify, include that in a revised warning label for both of those agents.

DR. NEILL: Thank you. Dr. Oliver?

DR. OLIVER: Alyce Oliver. I voted A. I didn't see any new data that would have changed my opinion on the labeling.

DR. NEILL: Dr. Richards?

DR. RICHARDS: Steuart Richards. I voted A for the reasons previously given, particularly those of Dr. Rosenberg.

DR. NEILL: Dr. Boudreau?

DR. BOUDREAU: Denise Boudreau, and I also voted A for reasons previously given.

DR. NEILL: Dr. Parker?

DR. PARKER: Ruth Parker. I voted A, similar reasons. I'll just add for the record that the one thing that I did think about as a result of hearing about PRECISION was, particularly with people who escalated their dose, we don't exactly know what they took and it highlights to me the importance of making sure people actually know what they're taking. And I just note that, in the Drug Facts label, it's really important to make sure people know the active ingredient of the drug they're taking because of the risk of how much you can be taking inadvertently.

We know that that's not something most people are able to do.

DR. NEILL: Thank you. Dr. Farber?

DR. FARBER: Neil Farber. I voted B for the same reason as in question A. Yes, there is a warning, but I have concerns about how much

information the physician would have to be able to give to the patient and also concerns about the patient-physician interaction where the patient would actually ask the physician and whether the physician would have enough time to discuss it with the patient.

DR. NEILL: Thank you. Dr. Roumie?

DR. ROUMIE: Christianne Roumie. I voted A for many of the reasons stated, but for a while I debated for the same reasons that Dr. Ohman voted B, which is that ibuprofen did seem to show a larger risk.

But I think it is really important to show consistency in the warnings at the patient-facing material. And there are better choices than the ibuprofen, but because I think the patient educational component needs to be consistent, that discussion can then be had with their physician.

DR. NEILL: Thank you. Dr. Cunningham?

DR. CUNNINGHAM: Melody Cunningham. I also voted for the reasons that were stated. And just to circle back to the questionnaire that was done,

it was a vanishingly small group of patients and not a diverse enough group of patients.

I pulled out my math brain and, if we say that you sell 173 million packages, if you presume that only 1 person was taking from that package, you've questioned 0.0007 percent of the potential users. And it's just so small that I don't think we have really any idea how the general public is taking this. And I think it's an important question.

DR. NEILL: Thank you. Dr. Hendrix?

DR. HENDRIX: Craig Hendrix. I voted A for most for the reasons stated. There wasn't sufficient information either of the biomarkers, PK, and then the clinical data raised issues about how important this was, so there wasn't enough to move it up or down in terms of risks to modify the label from the current language.

DR. NEILL: So Dr. Neill. I voted A. The only thing I have to add -- my perception of the use of both of these medications, but ibuprofen specifically, is that because of its inclusion as

an ingredient in many combination medicines as well as individual, my sense is that we by default end up balancing the pros and cons, risk to a group of patients with osteoarthritis who may have co-existing cardiovascular disease against.

That may be a very immediate risk in an elderly patient who's already had a bypass. We weigh that against what might be potentially a very distant risk among a much larger group of patients taking it from a shorter period of time.

While the data that we saw from sponsor and the analysis from FDA was very instructive in terms of informing the pharmacodynamic interactions, I think the discussion that the committee had about the extent to which those interactions rise to the level of clinical significance, especially when considered in that great milieu, which is the CVS Rite Aid shelf that has these OTC products, was insufficient in my mind to warrant a label change.

So I think that was a very good discussion. We've gotten through all of the questions and it's now just before 2:00. I want to give the committee

a chance. If there were questions, concerns that you either had about data from yesterday, while I would not entertain clarifications of data, if you wish to raise the question for purpose of getting it into the record, especially if it's something that's new or novel, hasn't been discussed, now is the time to bring it up.

(No response.)

DR. NEILL: Hearing none, staff, any other instructions from you that would warrant our keeping the group any longer? Otherwise, I'll consider an adjournment. Yes, Dr. Ohman?

DR. OHMAN: Magnus Ohman. I'm sorry. I don't want to hold anybody from a flight or anywhere, but I did have one suggestion for the agency. And as we have a lot of data now, I think it would be very helpful if you had some internal resources to perform a network meta-analysis with all of these studies, building on the Baigent analysis because, actually, in that way, you can sort of try to homogenize this sort of finding and shed some interesting light on this, which is quite

complex because there are variations in populations and so on.

So my hope is that that's going to be the next piece that you put out.

DR. NEILL: Thank you. Any other comments from FDA?

DR. HERTZ: I just want to take this opportunity to thank everyone for being willing to come, leave your busy schedules. We know you're quite busy. And this really has been a very interesting discussion and we greatly appreciate your assistance and advice.

As I said, you may have noticed, we're typing furiously here. I'm not typing a letter. I'm actually capturing what's being said because we will refer back to this in our deliberations. So thank you very much and safe travels.

Adjournment

DR. NEILL: Thank you. Panel members, please take all of your personal belongings with you as the room is cleaned. Anything left on the table will be disposed of. Please drop off your

name badge at the registration table on your way out so that they can be recycled. We will now adjourn the meeting. Thank you.

(Whereupon, at 2:00 p.m., the meeting was adjourned.)